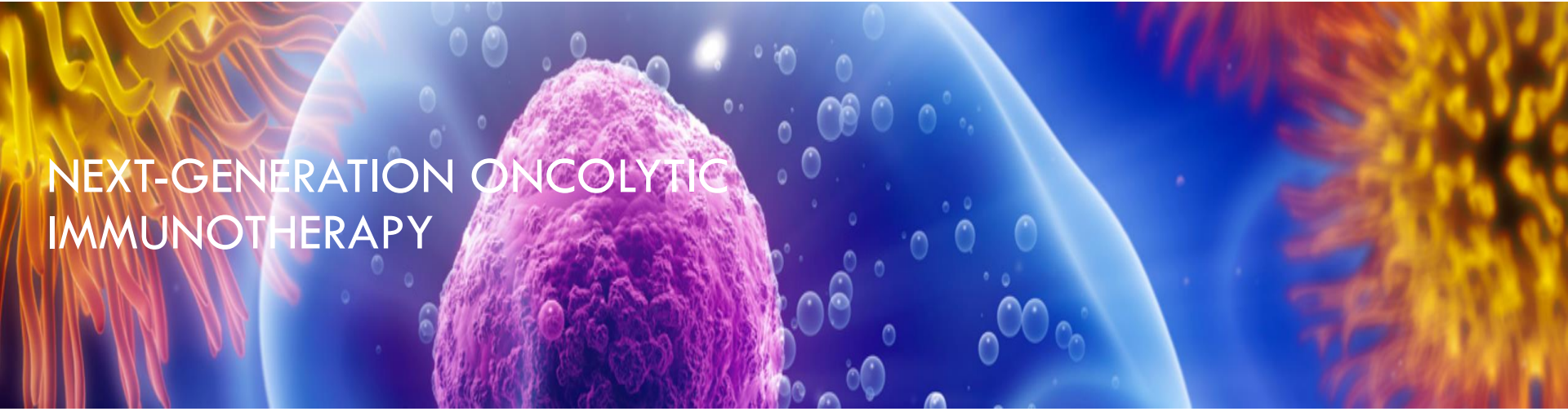
Replimune



SITC Data Summary

November 8th 2019 (updated Jan 2020)

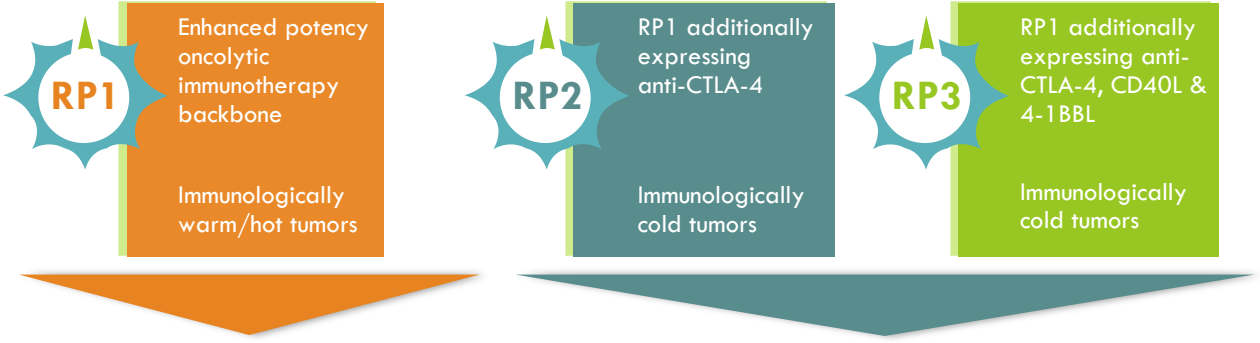
Replimune's Immulytic platform

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*

Intended for immune responsive tumor types

3. Delivery of potent immune stimulatory proteins

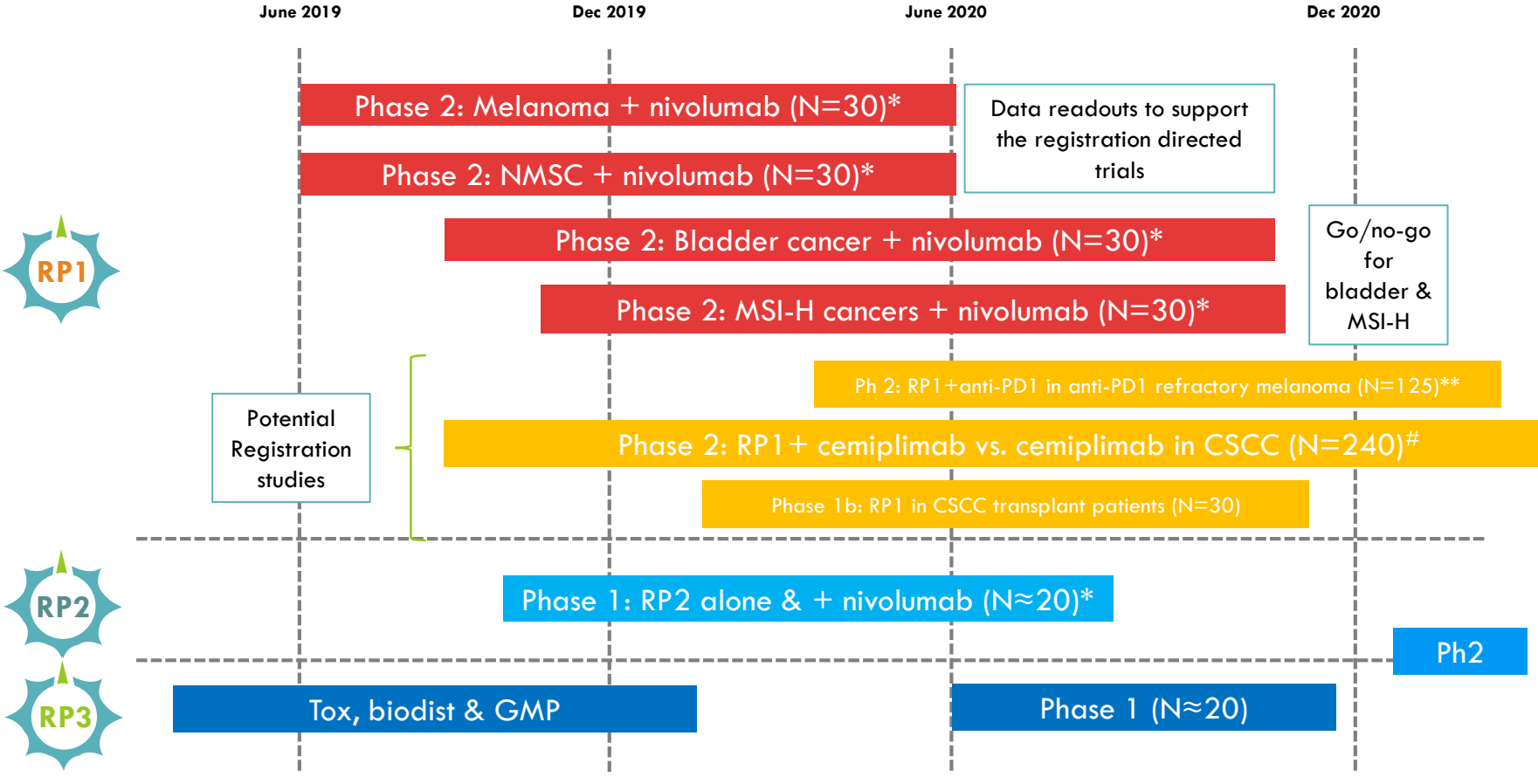
Focus on *clinically validated* pathways which function at the time & place of immune response initiation, but where systemic engagement is sub-optimal

- Anti-CTLA-4
- Immune-costimulatory pathway activators
- Aims to *increase efficacy* while *reducing toxicity*

Intended for less & non-immune responsive tumor types

* Replimune pre-clinical data published in Thomas et at JITC 2019

Replimune's development plan



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

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

** Intended additional 125 pt cohort in the Phase 1/2 clinical trial in combination with nivolumab

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*

Replimune

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
  - Four of five CSCC patients responding, with two ongoing PRs and two ongoing CRs
    - Indications of activity in other tumor types also seen, including an ongoing PR in esophageal cancer
  - 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

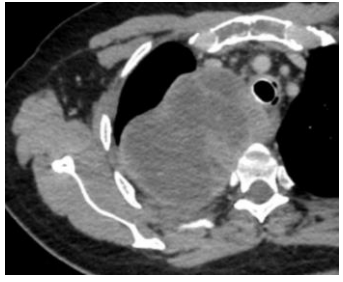
	Total	Cutaneous melanoma	Uveal melanoma	Mucosal melanoma	CRC	CSCC	BCC	Breast	Bladder	Adeno. of cecum	MSI-H (Colon)	Esepha geal
Number	14	3	2	1	1	1	1	1	1	1	1	1
Age: Range	28-74	28-67	53-64	74	70	61	56	59	51	41	50	70
ECOG performance status: 0, 1 (#)	0: 8 1: 6	0: 2 1: 1	0: 1 1: 1	0: 1	0: 1	1: 1	0: 1	0: 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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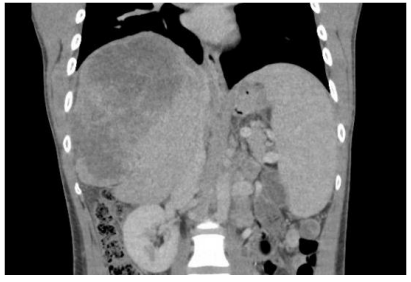
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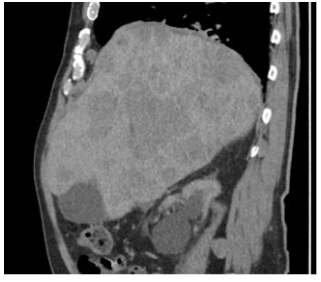
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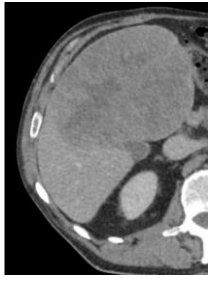
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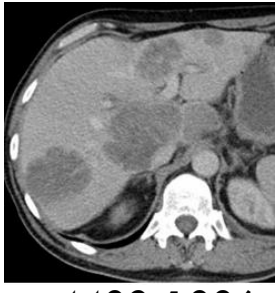
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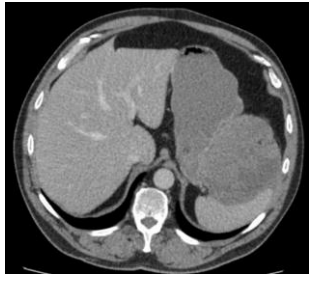
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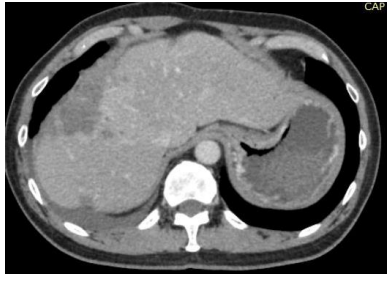

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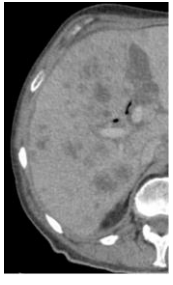
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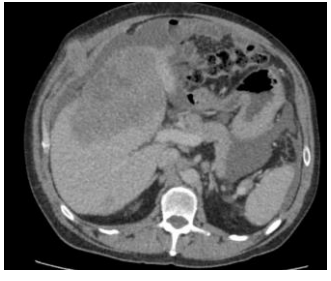
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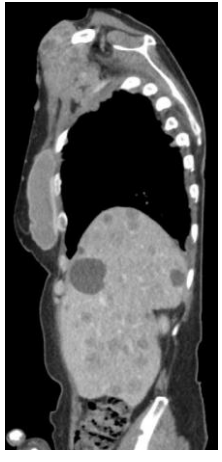

4401-1008

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

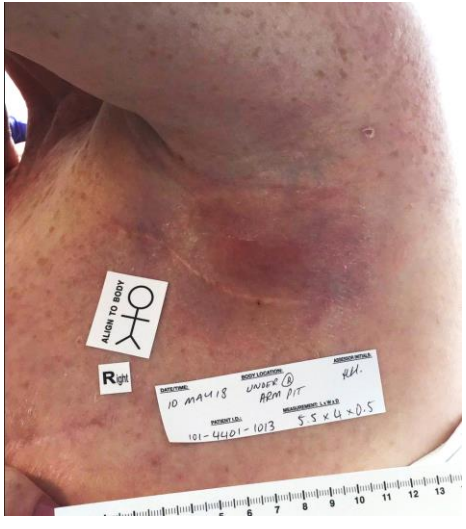
Treatment-related adverse events – with nivolumab

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			

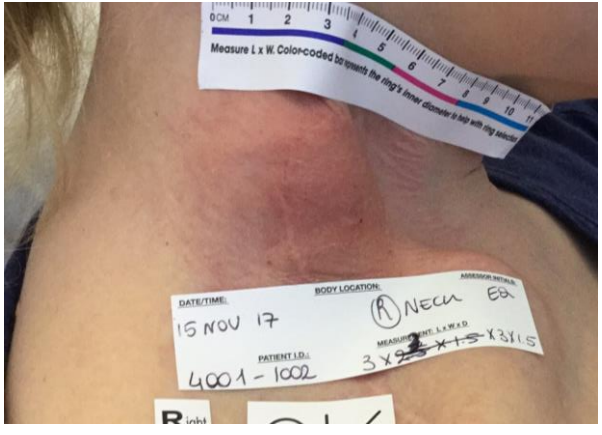
- No evidence of increased side effects as compared to that expected for either drug alone
- Two procedure-related AEs were seen (pneumothorax, n=2, self resolved)
- 10 SAEs seen, 0 related to RP1 or nivolumab
  - Procedure-related SAE: Pneumothorax
  - PD-related SAEs: 6
  - Co-morbid SAEs: 3
- <u>If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

Injection site erythema (24-48hrs post injection)

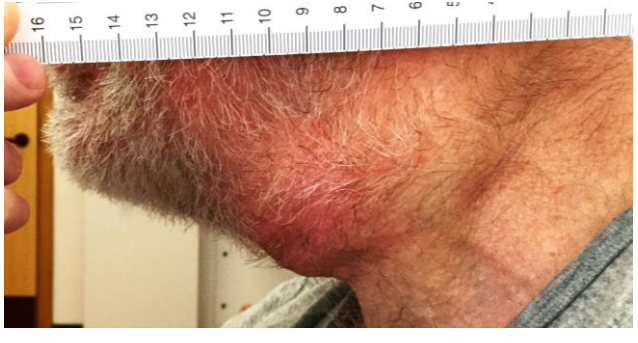
4401-1013
Breast cancer



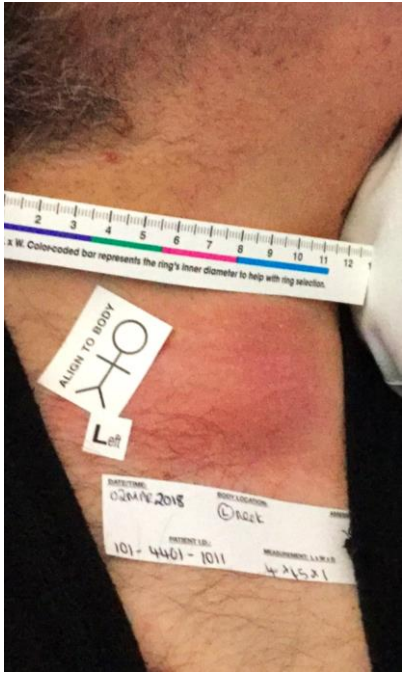
4401-1002
Melanoma



4402-1001
CSCC



4401-1011
Colorectal cancer

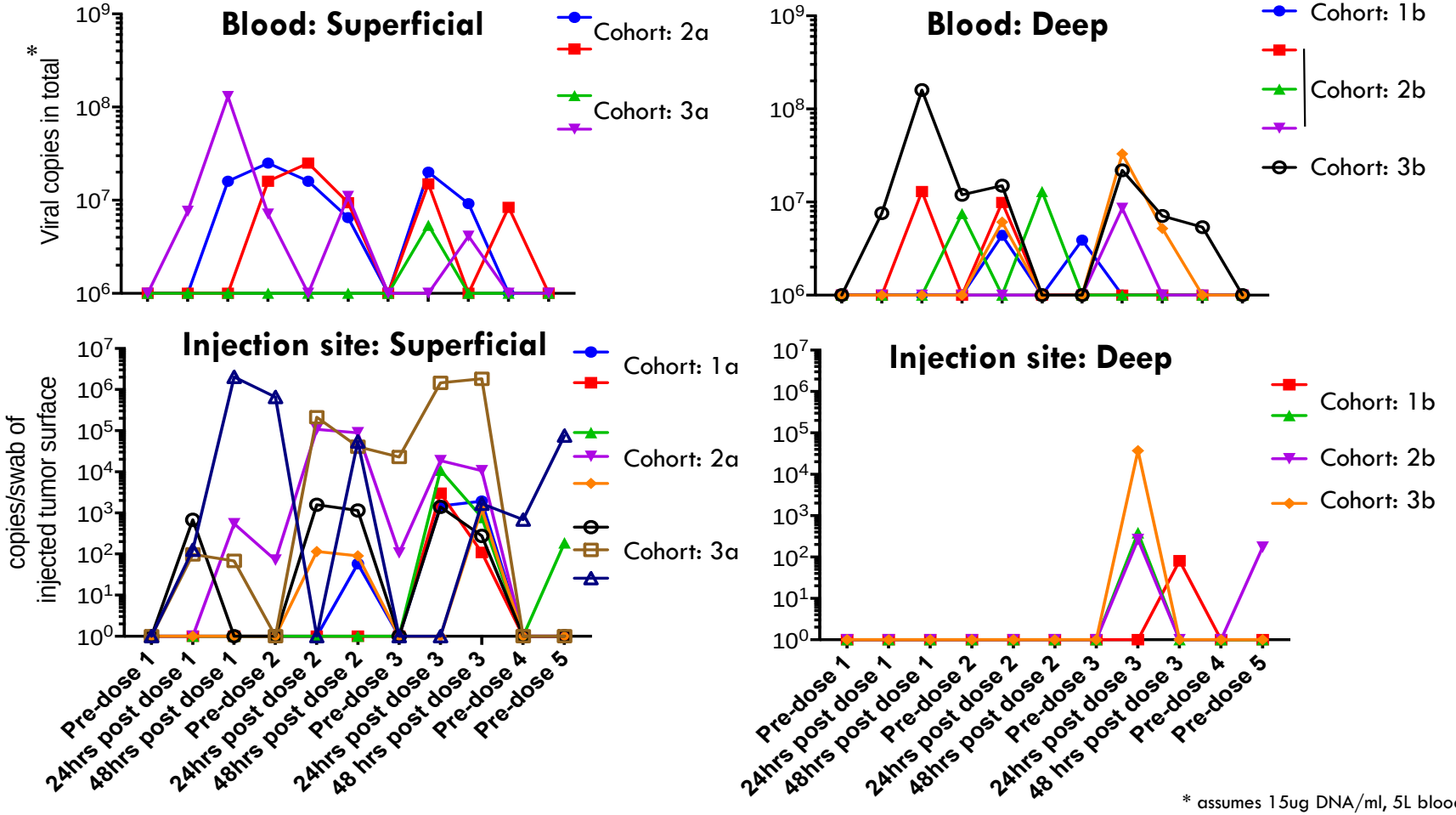


Safety & tolerability conclusions

- 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

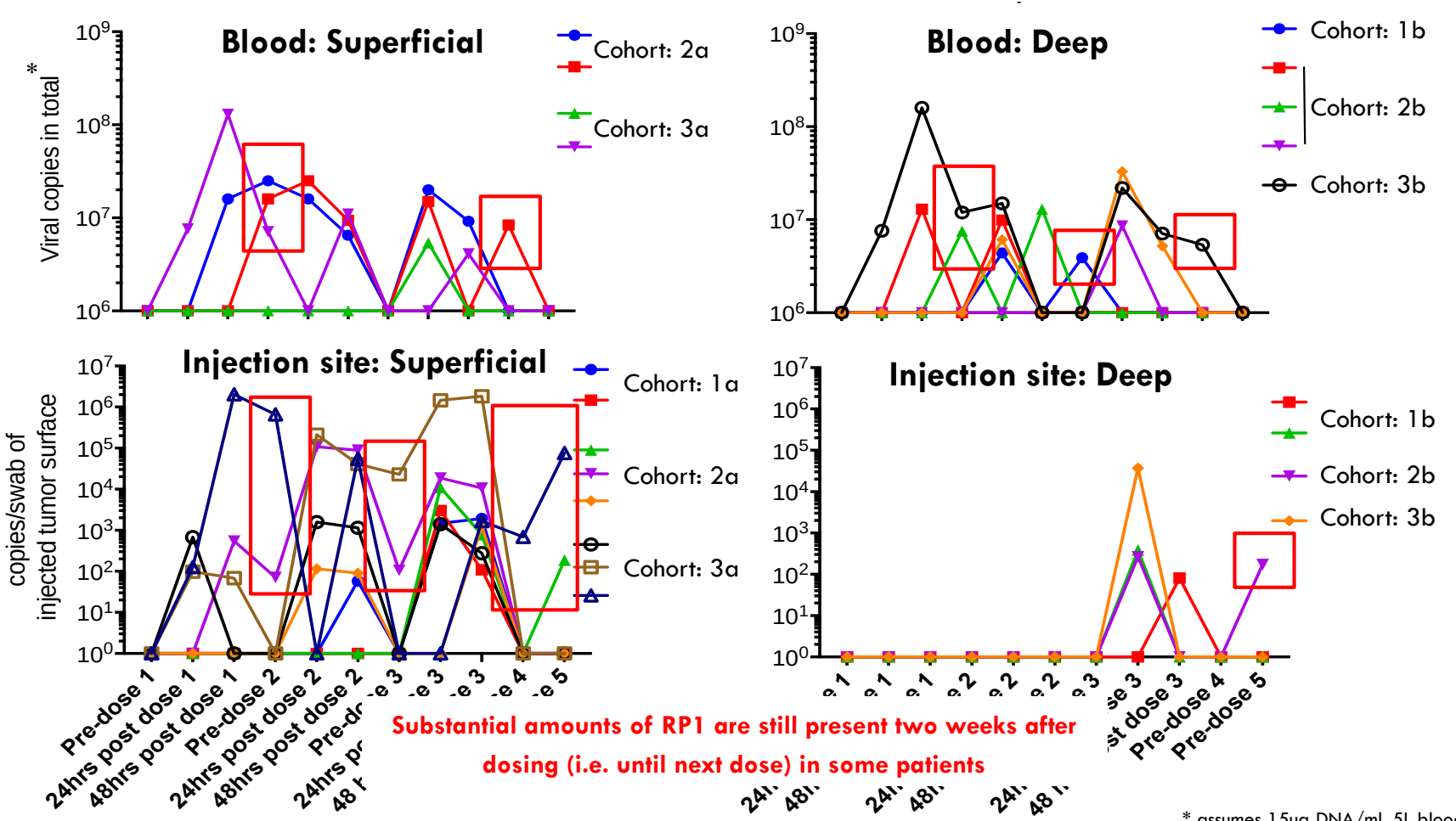
RP1 replication & seroconversion

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

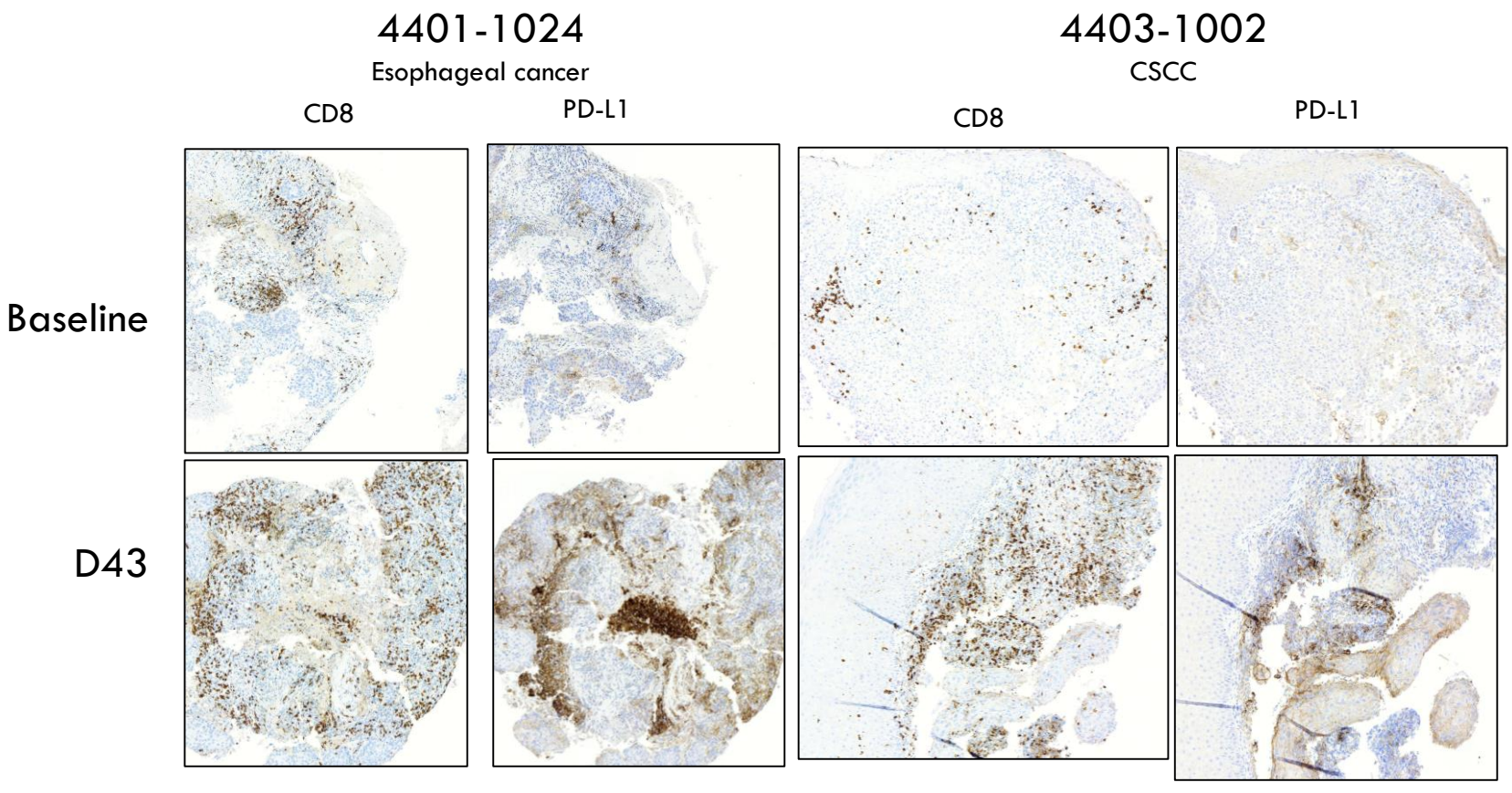
Biomarkers

- 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



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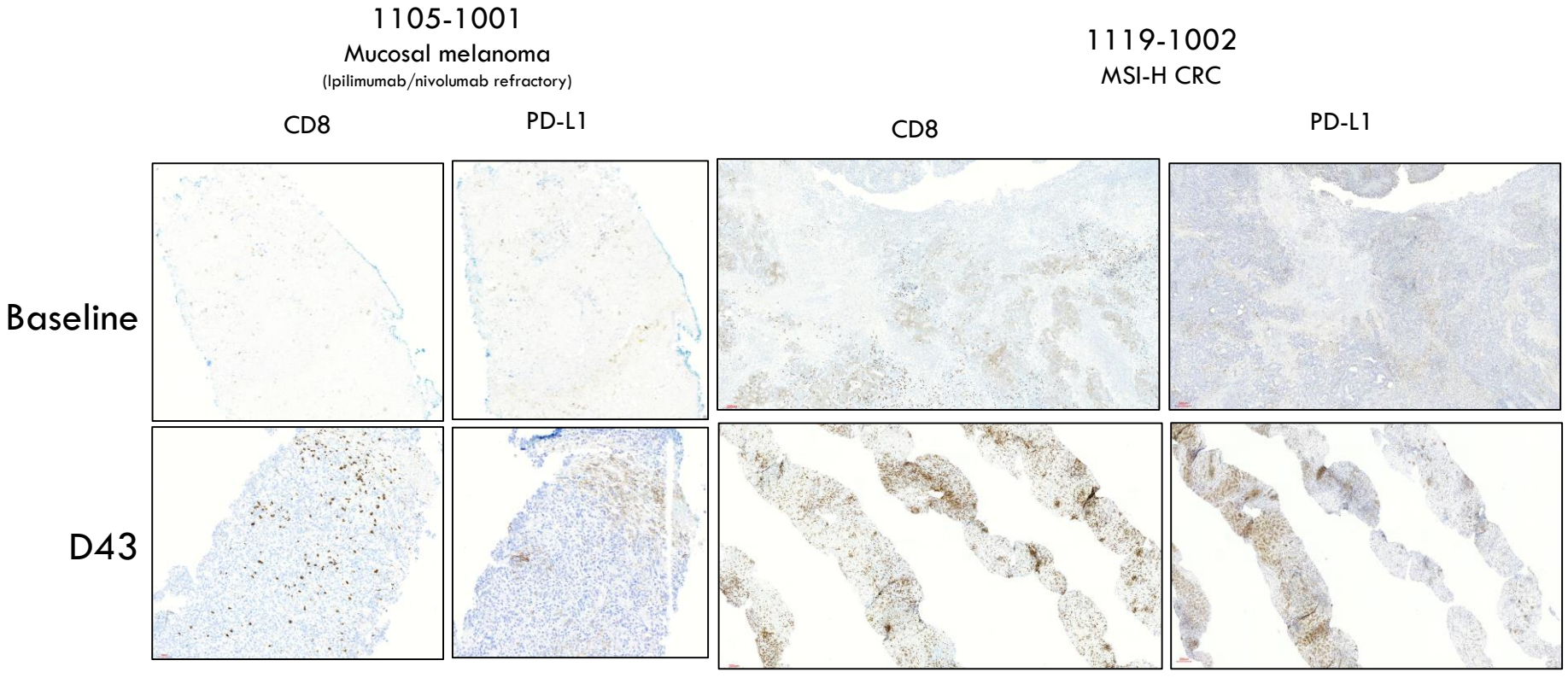
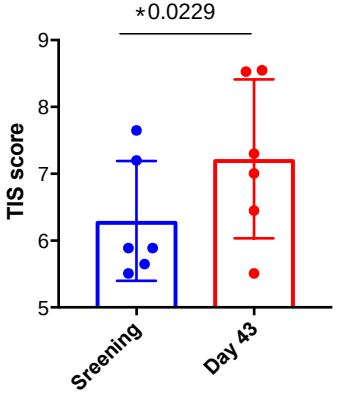
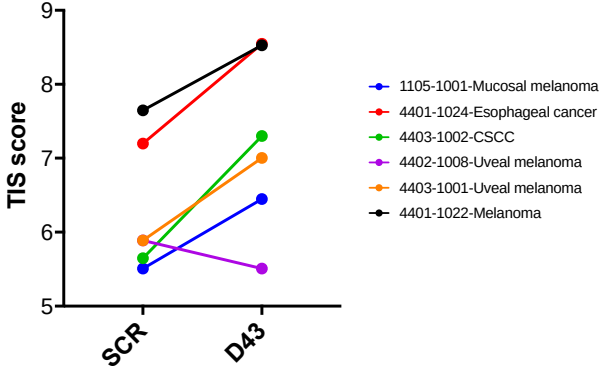
CD8 T cell & PD-L1 staining is increased across tumor types



Replimune

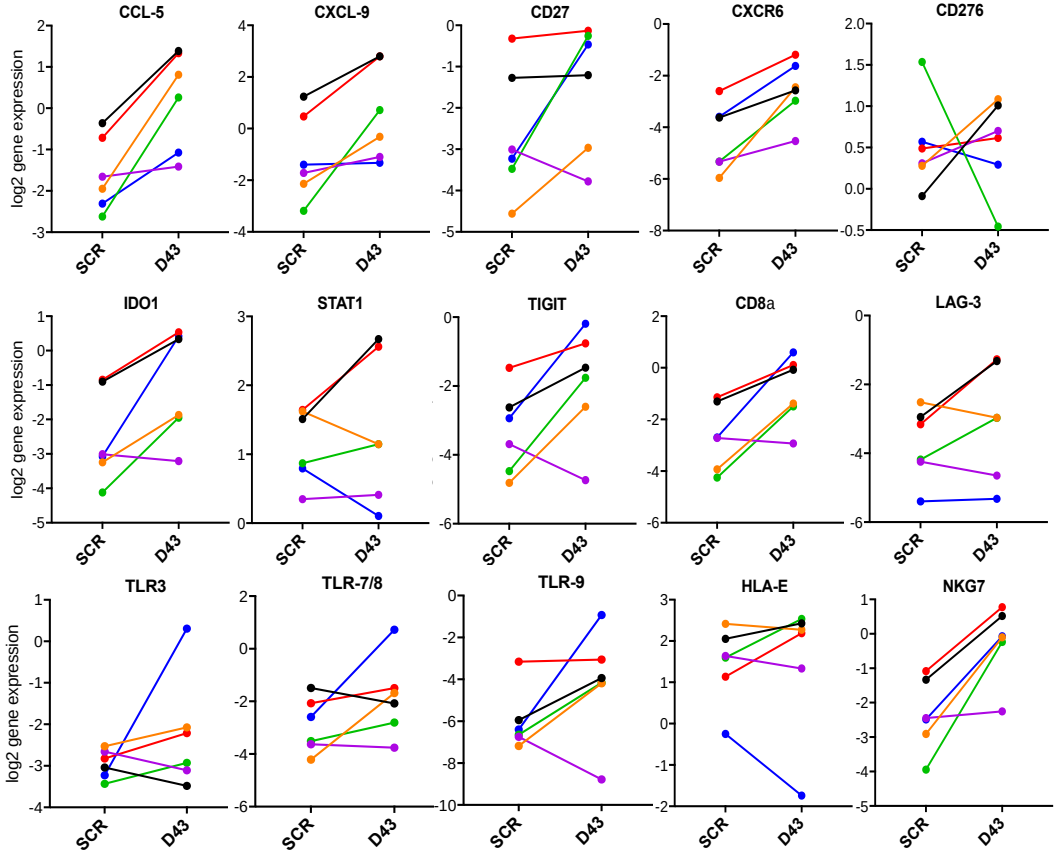
Nanostring analysis shows increased immune activation





Increased tumor inflammatory score

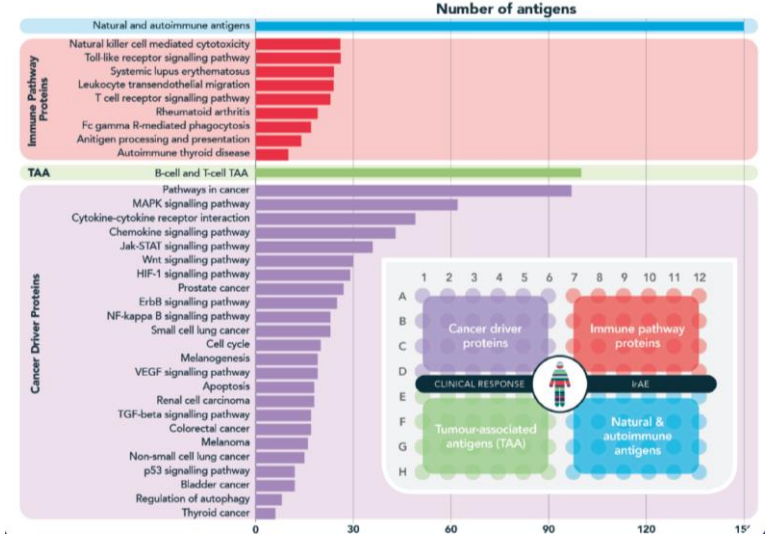
18 gene panel known to be associated with response to anti-PD1/L1 (Haddad R. Abstract 5009; ASCO 2017, Ayers et al 2017 JCI 127.8)



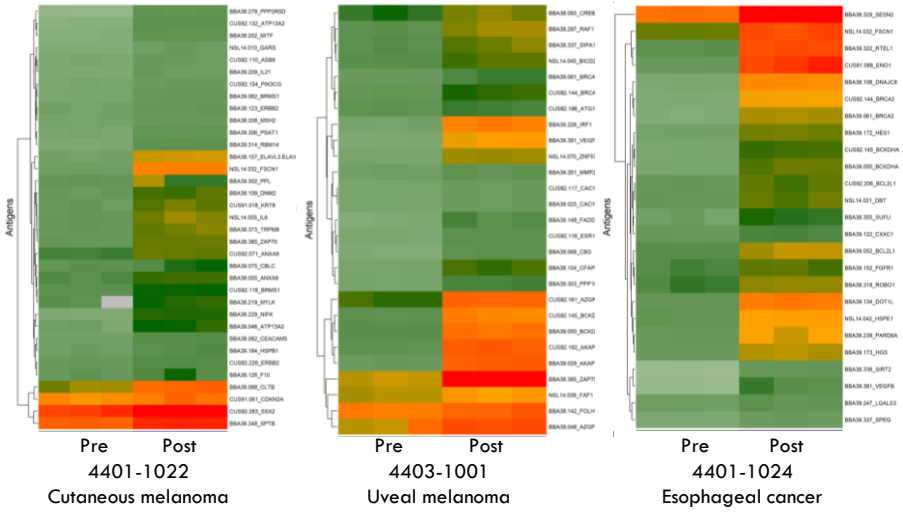
Selected genes showing increased expression

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

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

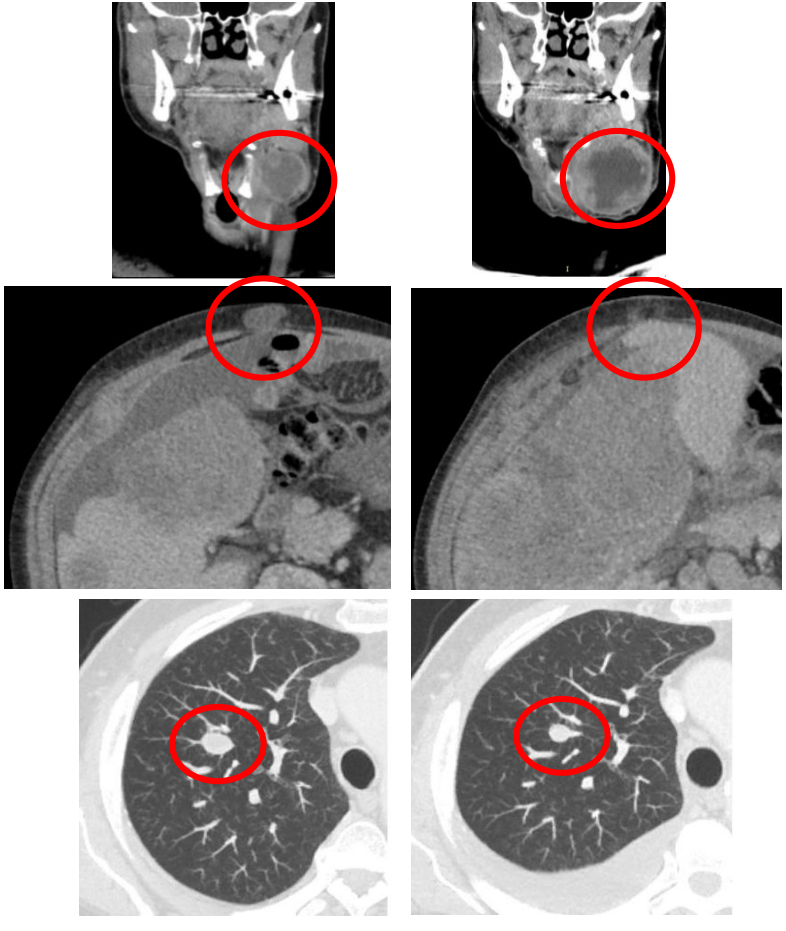
Anti-tumor activity - dose rising cohorts (single agent RP1)

- 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

Shrinkage/central necrosis of injected tumors

Baseline

30 day follow up



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 – patient still responding nearly two years later

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

RP1 combined with nivolumab

Lead indication: CSCC

- 700,000 new cases/year in the US; 10% have 'high risk' disease (recurs following initial surgery)
- Approximately 7,000 US deaths annually (most conservative addressable population)
- Anti-PD-1 therapy active: Cemiplimab (Regeneron) gave 46% response rate, but low CR rate
- 80% of patients die from locoregional progression, not metastatic disease
- Registration-directed randomized controlled Phase 2 trial in collaboration with Regeneron
  - 240 patients randomized 2:1 (RP1+ cemiplimab vs cemiplimab alone)
  - Primary endpoint ORR, secondary endpoints including CR rate, duration of response, PFS, OS
- 30 patient clinical trial of single agent RP1 in solid organ transplant recipients with CSCC*
  - Organ transplant recipients are at increased risk of malignancy, with CSCC most prevalent
  - 70% of patients develop CSCC within 20 years
  - Anti-PD1 therapy contra-indicated due to the risk of organ rejection
  - Clinical data indicates that RP1 has single agent activity in CSCC
- Intend expansion of the CSCC program to also include testing for neoadjuvant use

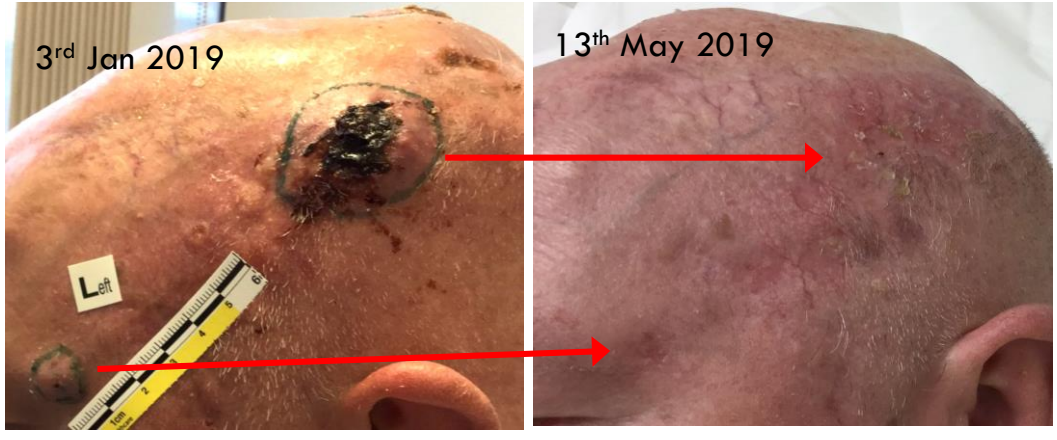
* see additional data in the Appendix

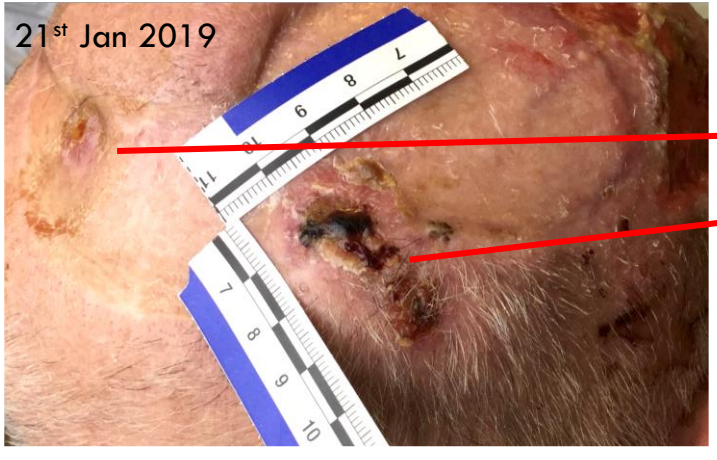
Lead indication: CSCC

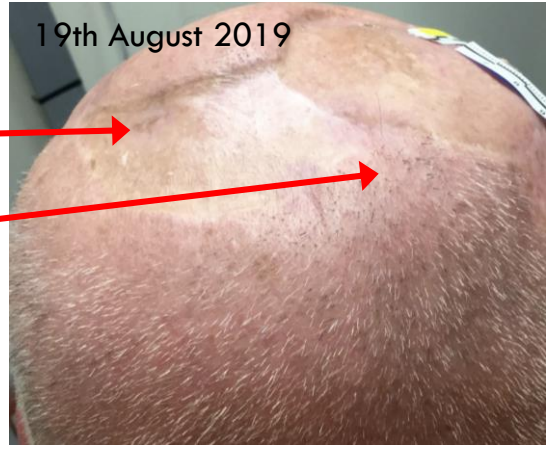
- Five CSCC patients had been dosed at the time of SITC
- The current response status of these patients is
  - Ongoing CR of extensive disease of the scalp
  - Ongoing PR of disease of the head and neck, retroperitoneal lymph nodes and bone metastases
  - PD
  - Ongoing PR of disease of the head and neck and lung metastases (improved from SD at SITC)
  - Ongoing CR of loco-regional disease of the head and neck (improve from SD at SITC)

* see additional data in the Appendix

Patient 1(4403-1002): Ongoing CR





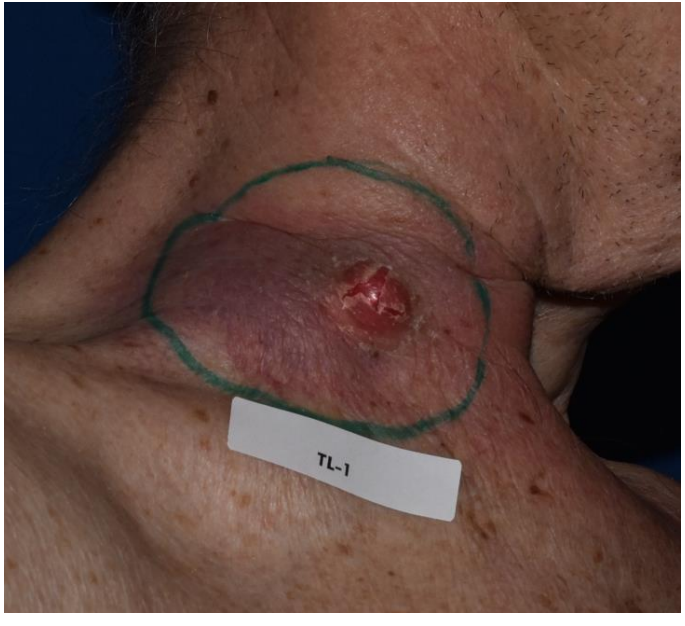


- Patient with extensive recurrent CSCC previously treated with surgery (including skin grafts), radiotherapy, cisplatin/5FU, then electrochemotherapy
- Ongoing CR with residual areas tumor free by multiple biopsy & continuing to heal
- In addition to the complete tumor response, the patients' quality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

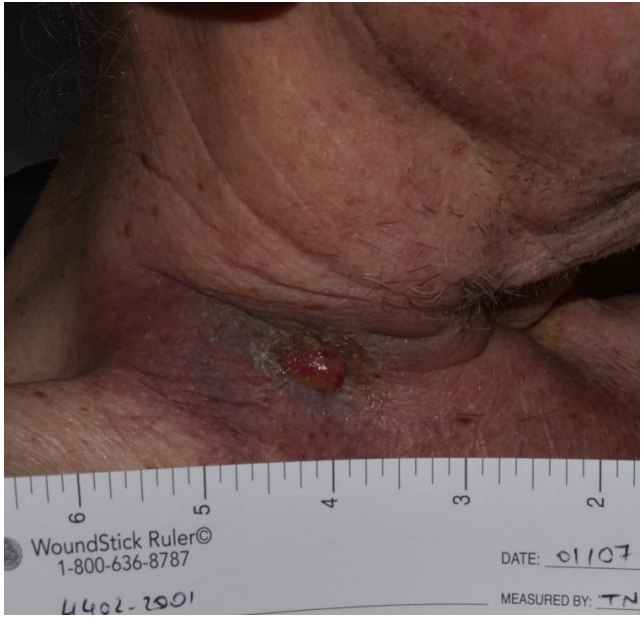
Patient 2 (4402-2001): PR

Patient close to CR – the only remaining lesions are a number of non-measurable bone metastases which are increasingly sclerotic

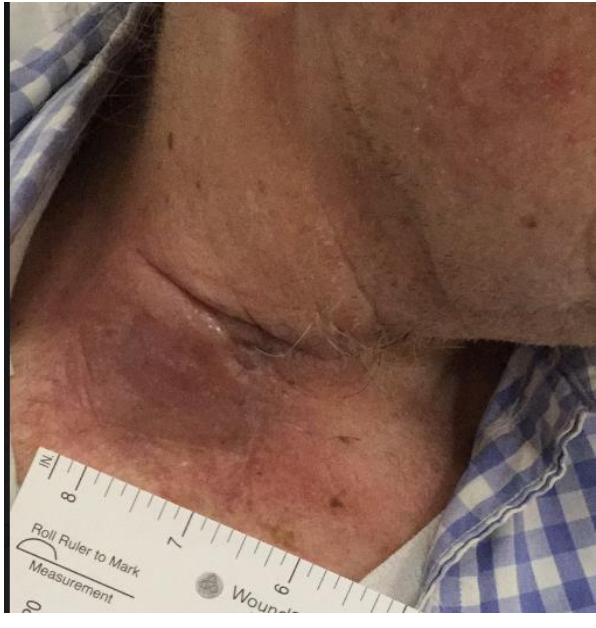
16th June 2019 (baseline)



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



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

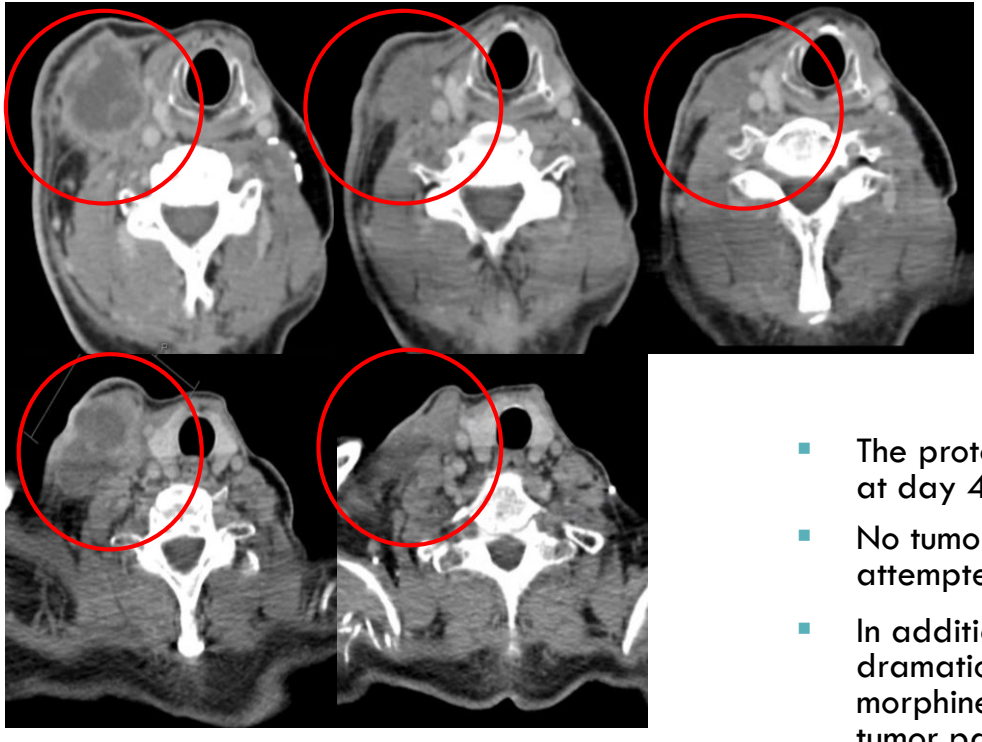


- Patient with recurrent CSCC of the neck (bilateral), previously treated with cisplatin-based chemoradiation & six cycles of carboplatin/5-FU, prior to entering the clinical trial
- Both the large injected tumor & the smaller contralateral uninjected tumor in the neck reduced considerably before the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

Patient 2 (4402-2001): Ongoing PR

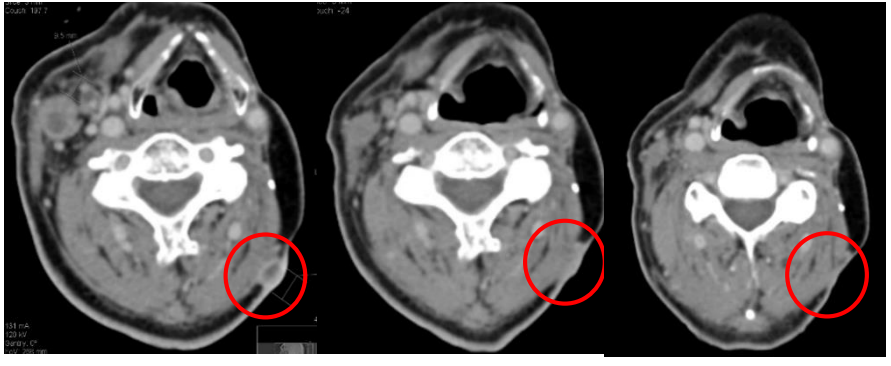
Right neck (injected)

Baseline 8 weeks 16 weeks



Left neck (not injected)

Baseline 8 weeks 16 weeks

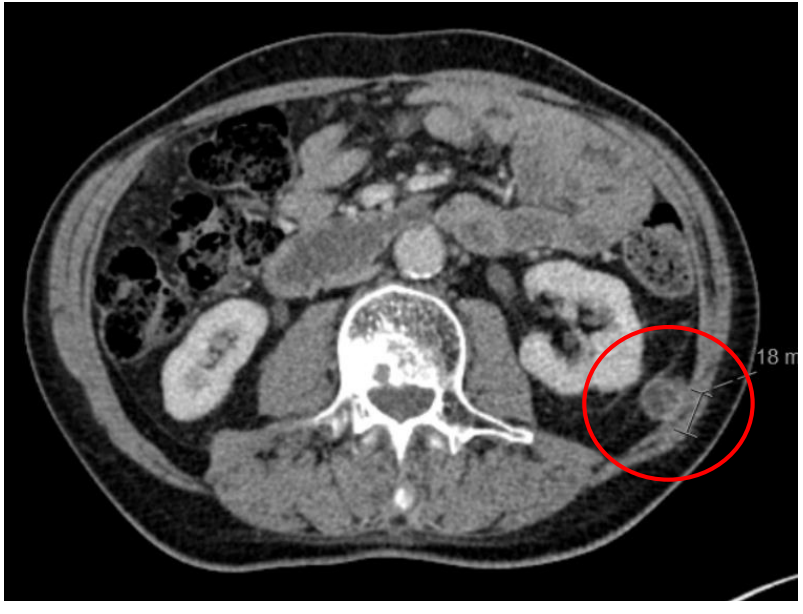


- The protocol mandated biopsy of the injected tumor taken at day 43 was tumor free
- No tumor was found to remain when a biopsy was attempted from the left neck
- In addition to the tumor response, this patient has had a dramatic improvement in quality of life & is now off morphine which was previously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

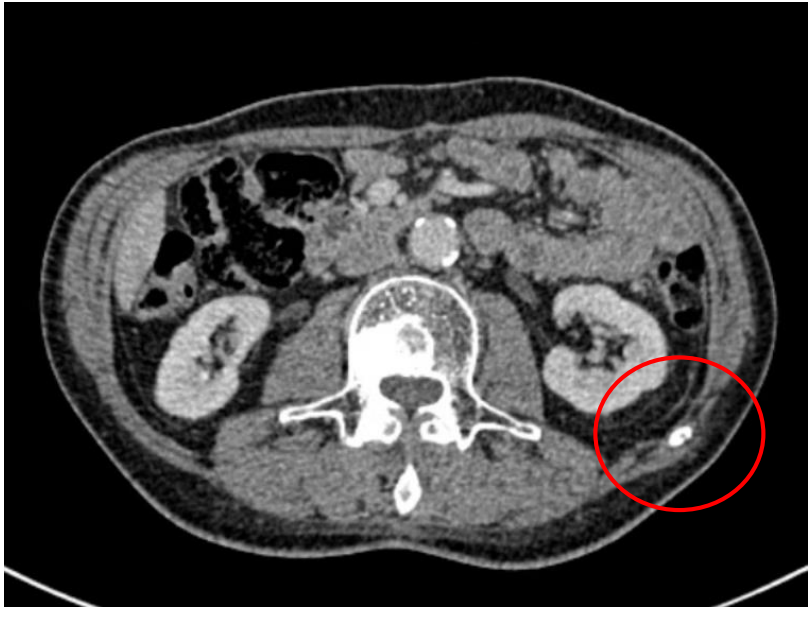
Replimune

Patient 2 (4402-2001): Ongoing PR

Baseline



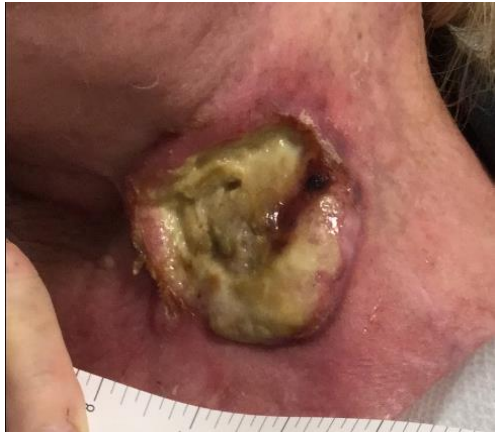
16 weeks



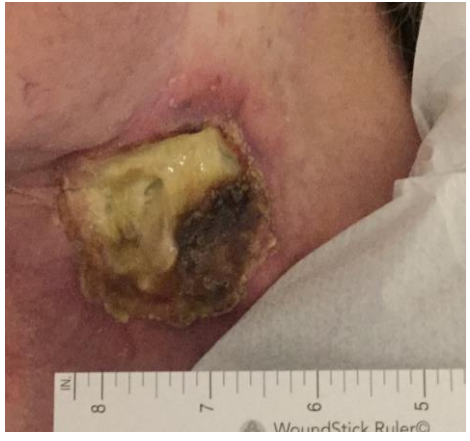
- The patient also had baseline retroperitoneal tumors (uninjected) which have completely resolved
- The only remaining disease are a number of non-measurable bone metastases, which were the main source of the cancer pain which has now resolved
- The bone lesions are increasingly sclerotic by CT scan, also indicative of a treatment response, with Zometa (stimulates bone formation) also now having been withdrawn

Patient 4 (4402-2004): Ongoing PR

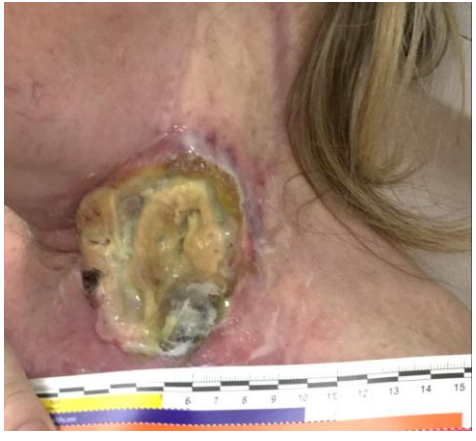
2nd Sept 2019, pre-dosing



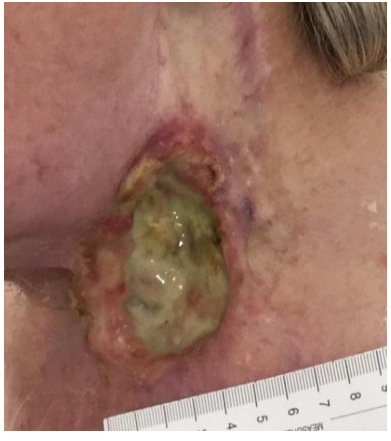
16th Sept (post single RP1 dose)



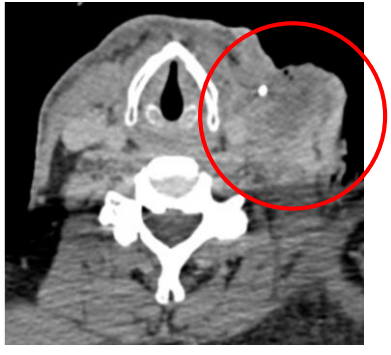
15th Oct



2nd Dec



Baseline scan

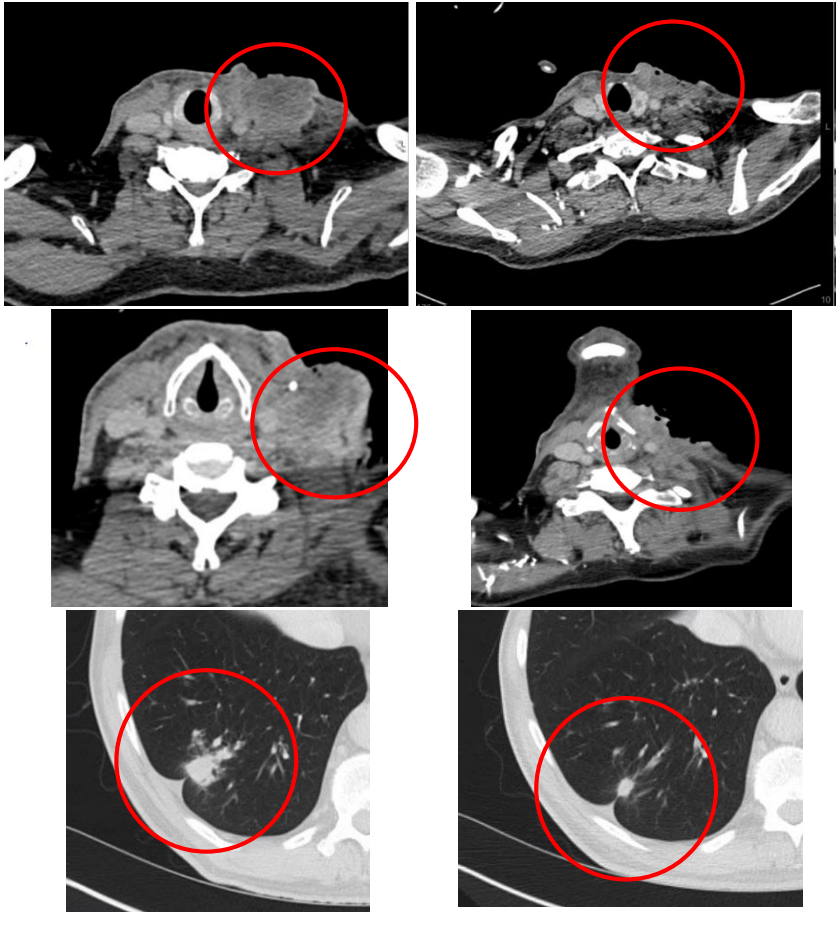


- Recurrent CSCC of the neck, previously treated with radiotherapy with immediate relapse after which the patient entered the clinical trial
- The large injected tumor in the neck flattened considerably after the first dose of RP1 (i.e. before the first Opdivo dose), & continued to reduce thereafter
- Follow up scan 25th October confirmed substantial reduction (next slide)

Patient 4 (4402-2004): Ongoing PR

28th August 2019

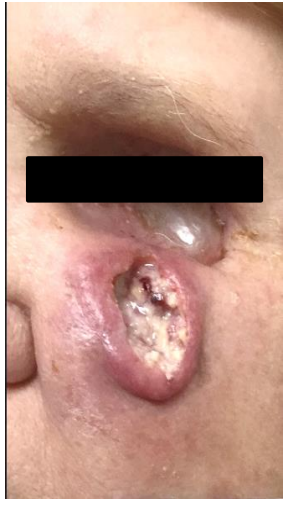
25th October 2019



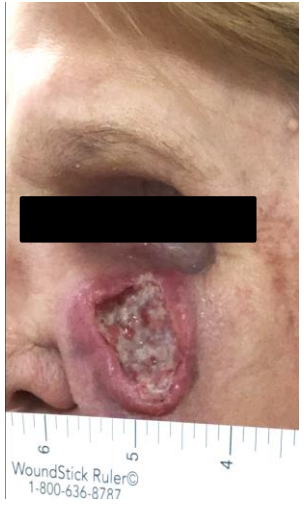
Replimune

Patient 5 (4402-2005): Ongoing CR

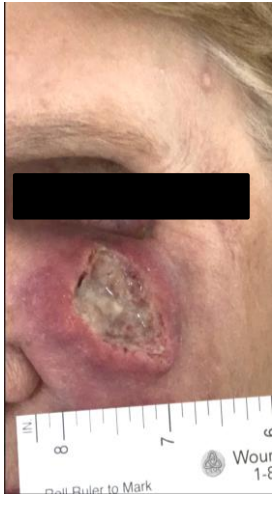
25th September 2019 (Baseline)



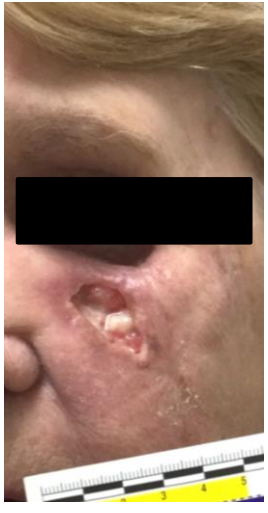
9th October 2019 (pre nivolumab)



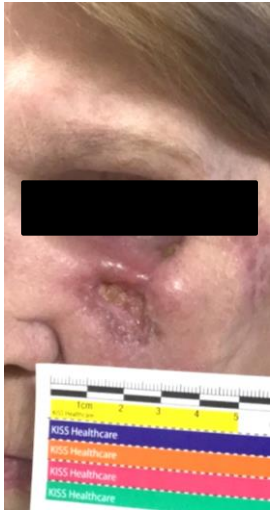
23rd Oct 2019



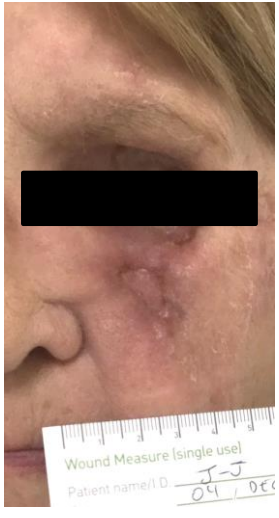
6th Nov 2019



20th Nov 2019



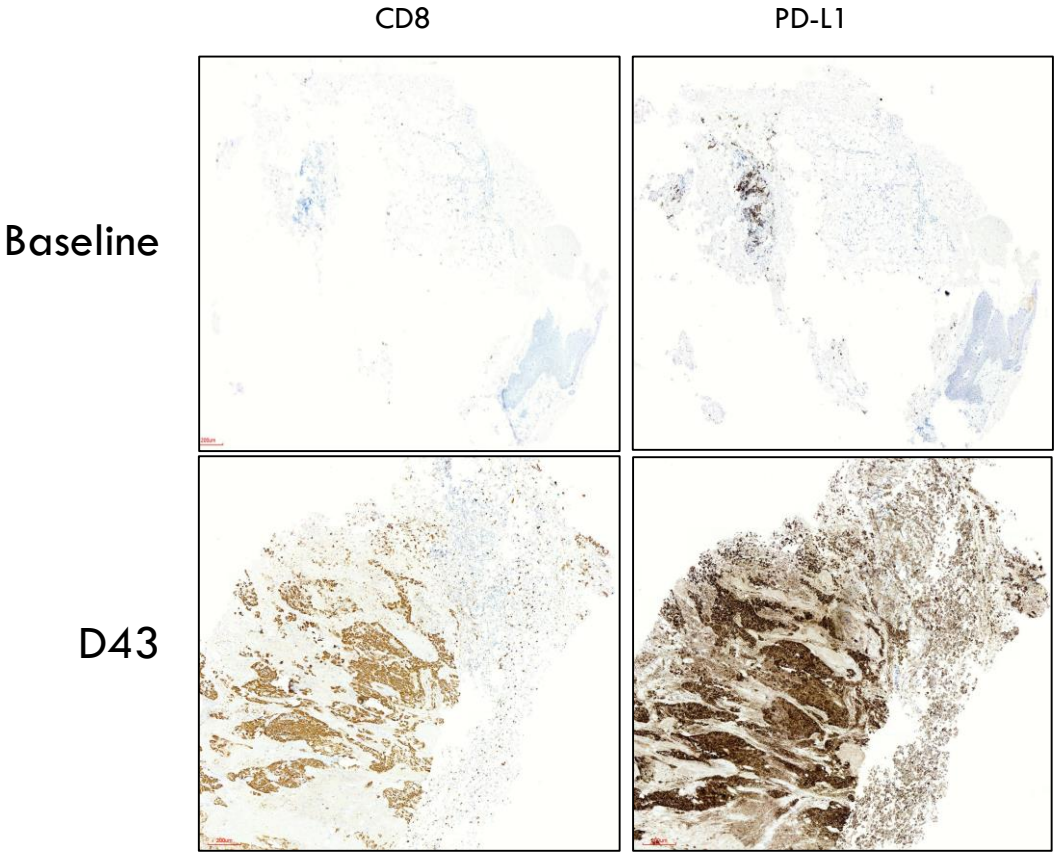
4th Dec 2019



- Recurrent, rapidly progressing CSCC of the left cheek with bone invasion through the maxillary region, previously treated with surgery & radiation before trial entry
- The lesion flattened considerably after the first dose of RP1, and continued to reduce & resolve thereafter – recent biopsy (December) demonstrates tumor free
- In addition to the ongoing CR, quality of life has dramatically improved

Replimune

Patient 2 (4402-2001): CD8 T cell & PD-L1 staining



Replimune

Second indication: anti-PD1 refractory melanoma

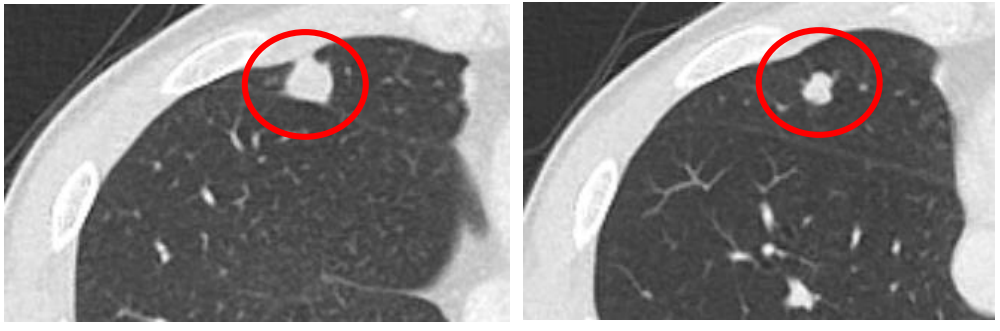
- Approximately half of advanced melanoma patients still die of their disease, despite multiple approved therapies now being available
  - anti-PD1, anti-CTLA-4, combined anti-CTLA-4/anti-PD1, BRAF targeted agents
- Approximately 8,000 US deaths annually (most conservative addressable population)
- Targeting patients with primary resistance to anti-PD1 therapy
  - No response following ≥12 weeks of therapy & with confirmed progression
  - Includes patients failing anti-PD1 adjuvant therapy
  - Very unlikely to respond to further treatment with single agent anti-PD1
  - Significant un-met medical need

- At the time of SITC, four anti-PD1 refractory patients had been enrolled, with three of the four responding to treatment

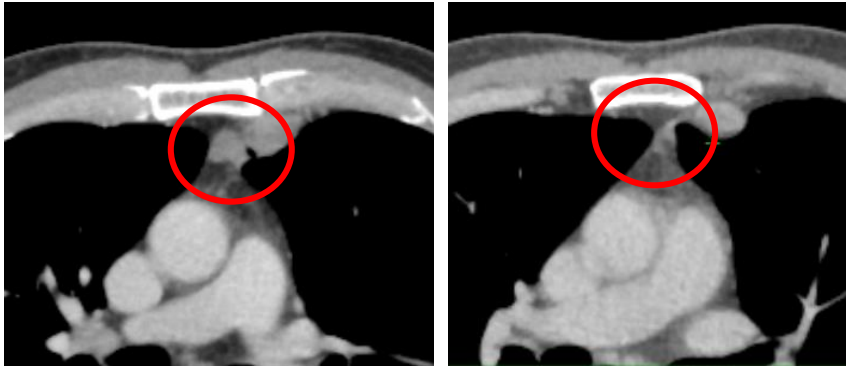
Patient #: 4401-1022 (ipilimumab/pembrolizumab refractory melanoma)

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

Lung



Anterior mediastinum

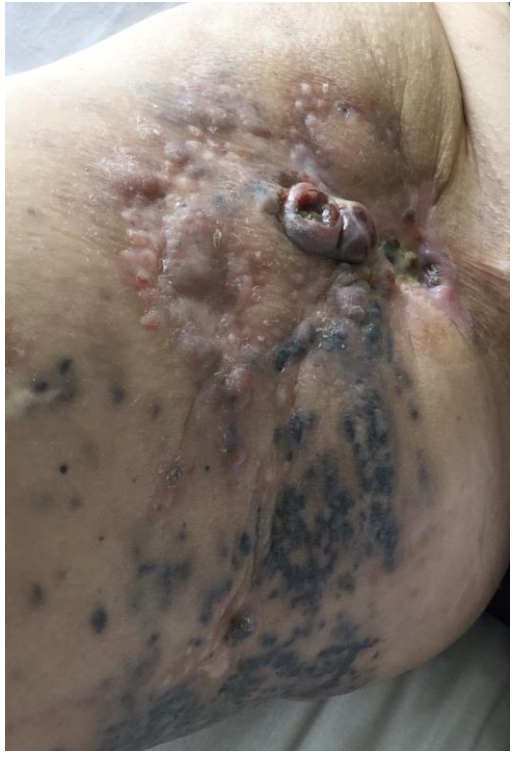


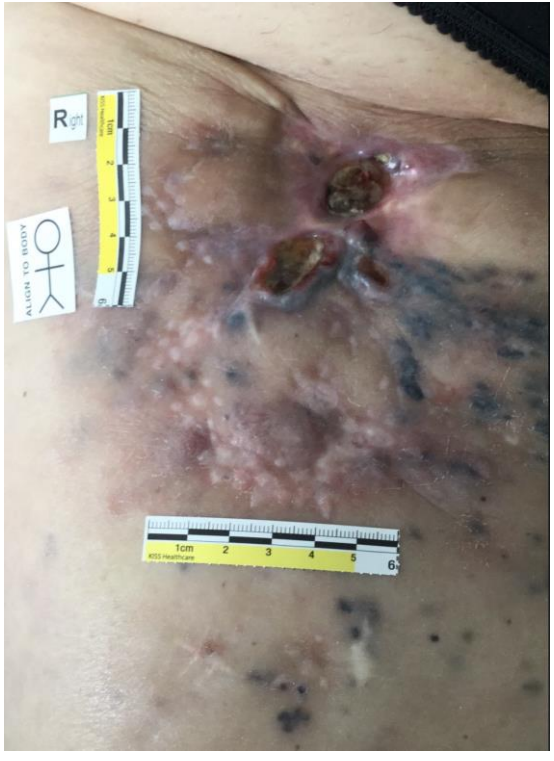
Baseline 10 months

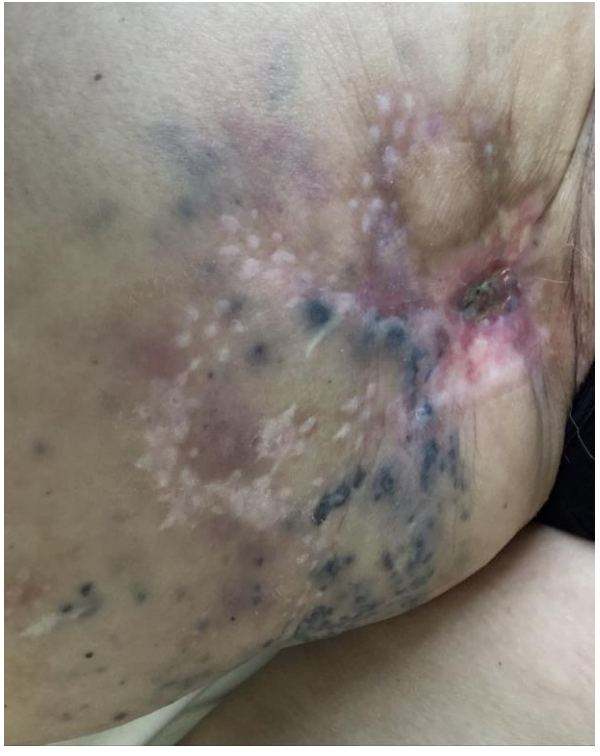
- Confirmed progression on prior immune checkpoint blockade, where two sequential PET scans demonstrated new lesions while also concurrently being treated with local therapy for the lesion behind the ear, then entry into the RP1 clinical trial
- PR with reduction in the breast, lung, mediastinum & anterior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







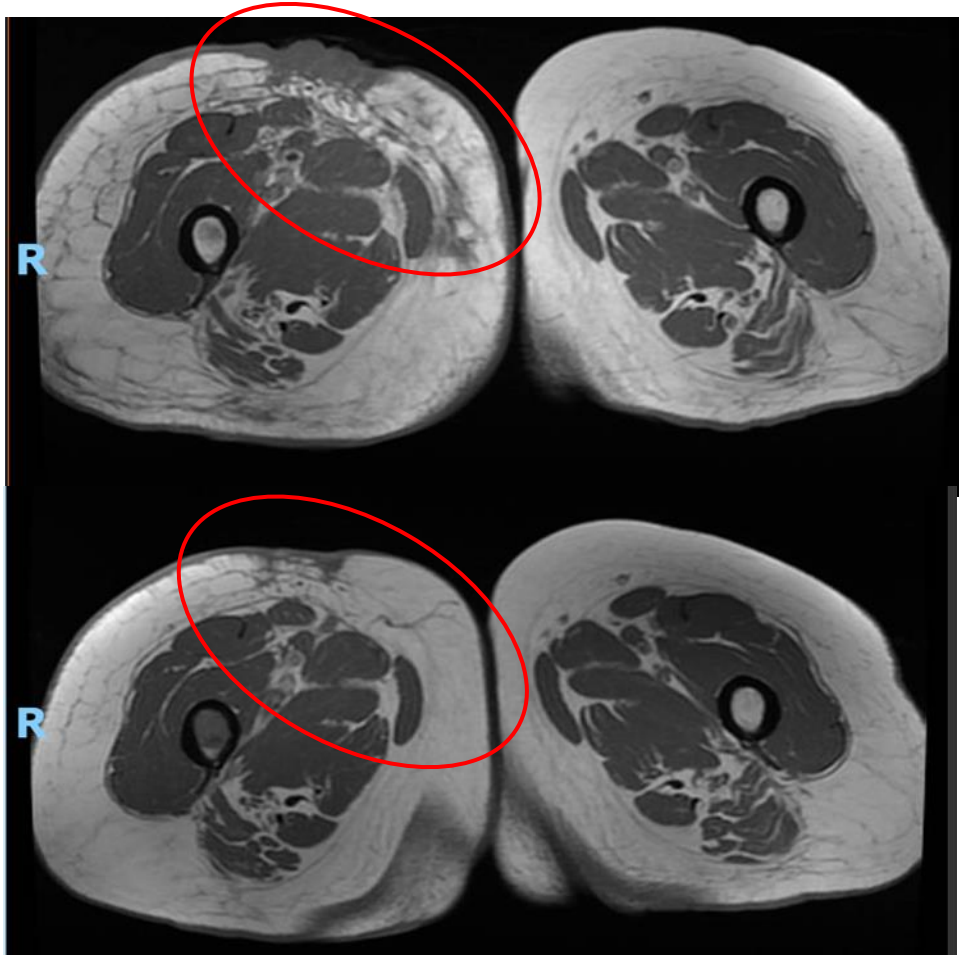
Patient history: Metastatic disease initially treated with ipili/nivo with best response of SD, then clear progression in the groin & thigh when radiotherapy followed by electrochemotherapy was added to continued nivolumab; following further clear progression, enrolled into the current trial

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

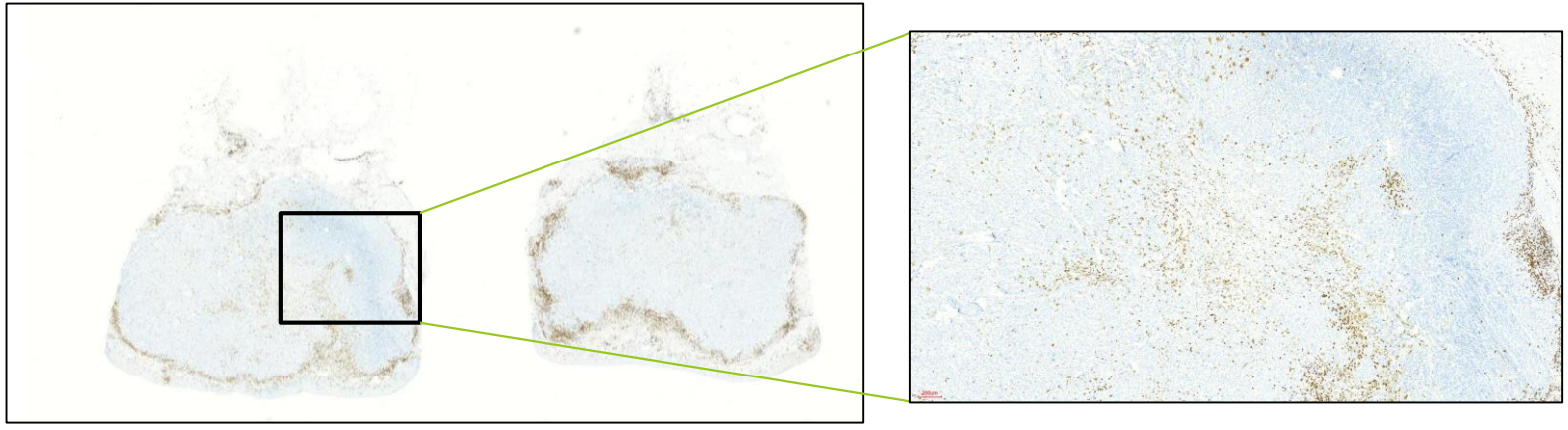


- Patient also had nodes in the groin which increased and are now reducing and lung metastases which following no change for prior 18 months are now reducing
- Patient quality of life has also greatly improved, from being essentially immobile at baseline to now able to go on long country walks
- Patient remains on treatment at 8 months

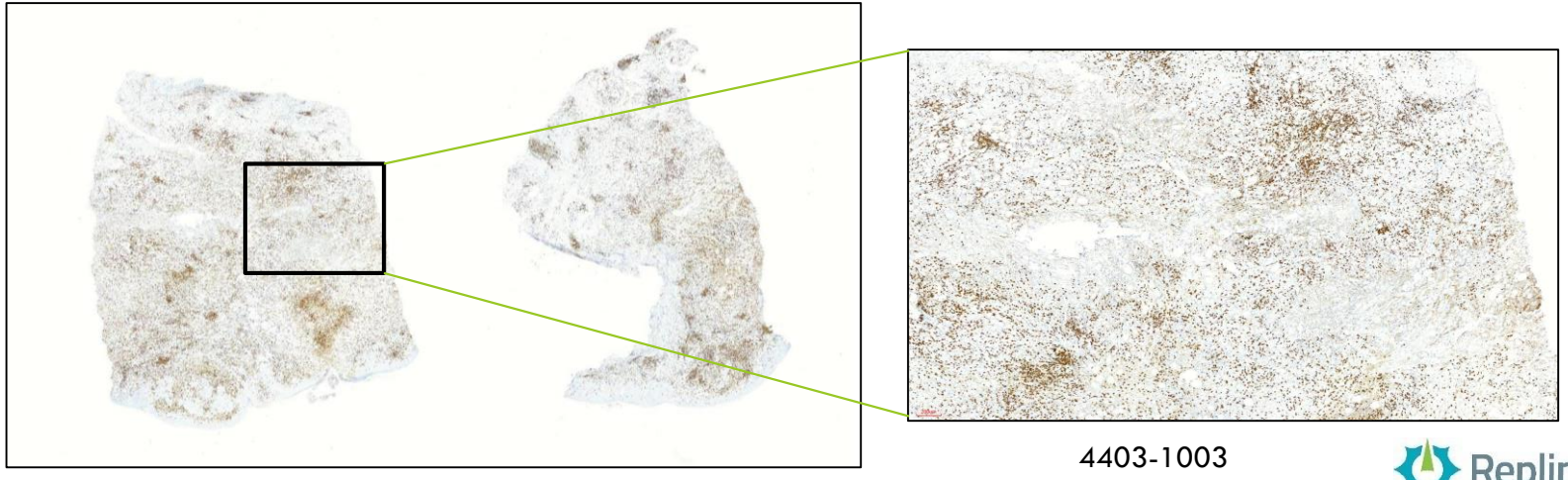
Replimune

Reversal of T cell exclusion with RP1 combined with nivolumab

CD8
Baseline



CD8
D43

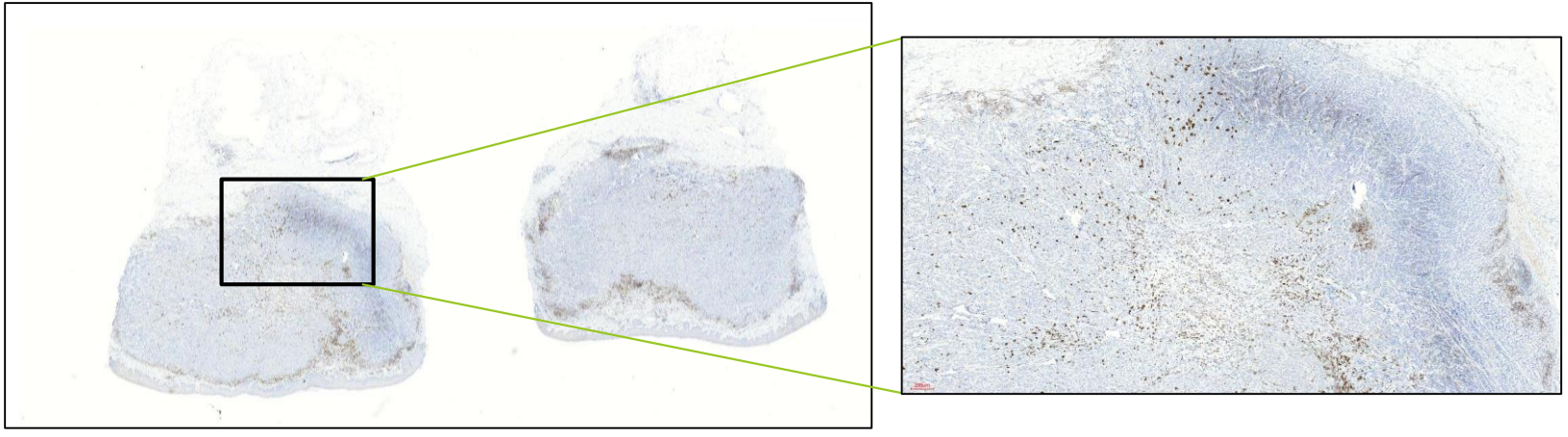


4403-1003
Cutaneous melanoma
(ipilimumab/nivolumab refractory)

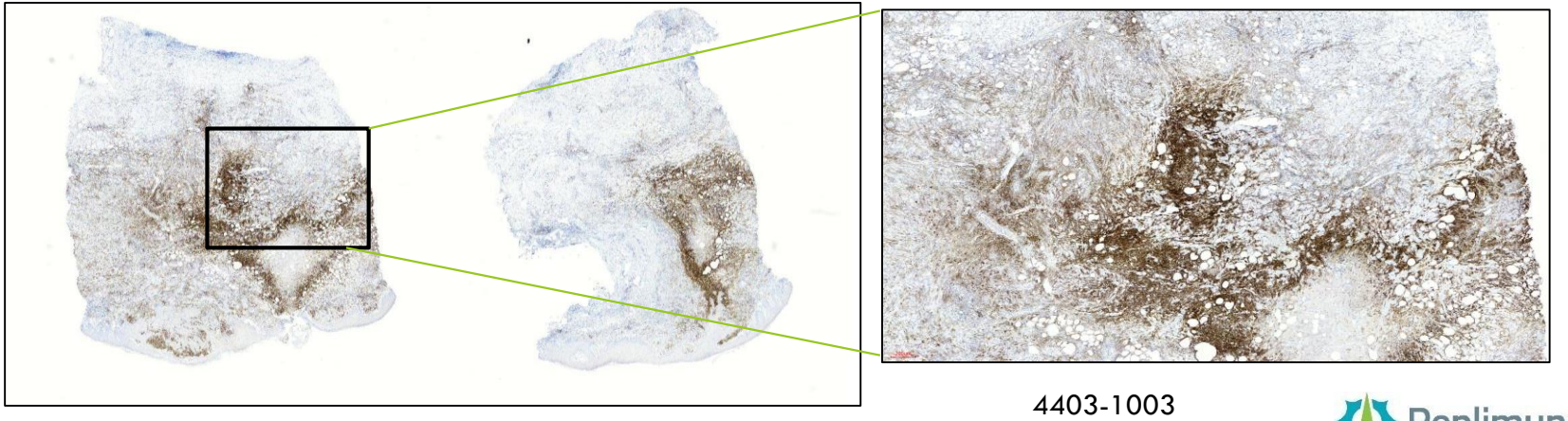
Replimune

Reversal of T cell exclusion with RP1 combined with nivolumab

PD-L1
Baseline



PD-L1
D43



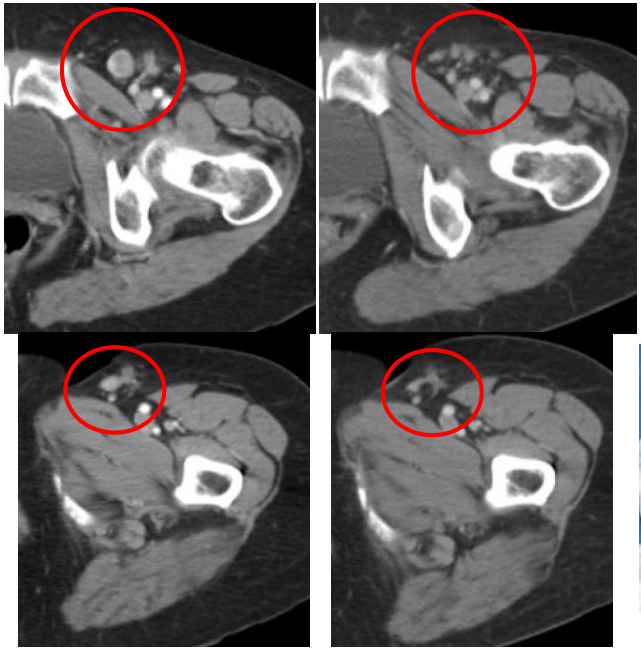
4403-1003
Cutaneous melanoma
(ipilimumab/nivolumab refractory)

Replimune

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

2nd July 2019 (screening)

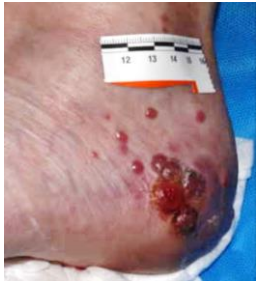
17th Sept 2019

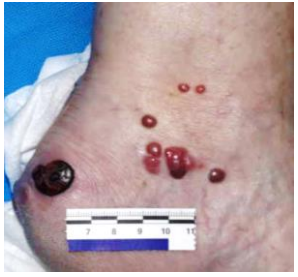


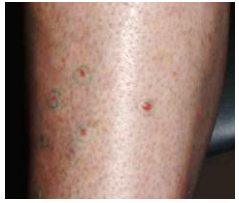
The first ipilimumab/nivolumab refractory melanoma patient enrolled into the Phase 2 part of the study. Other such patients do not have follow up scans.

Current status: Ongoing partial response

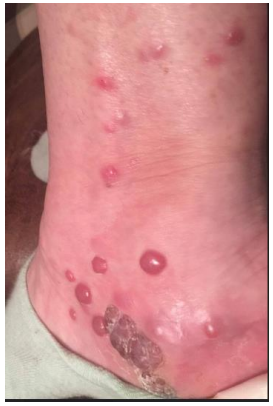
1st July 2019 (screening)

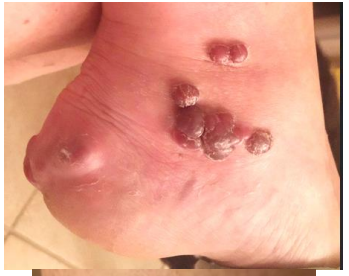


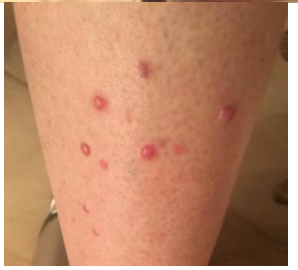




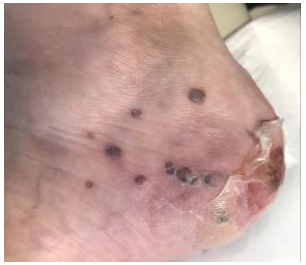
26th August 2019

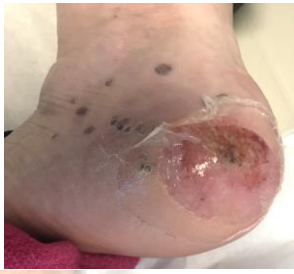


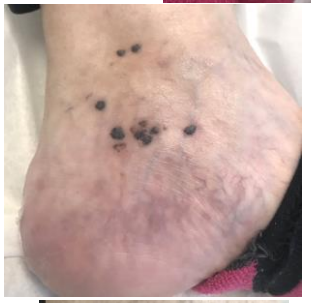


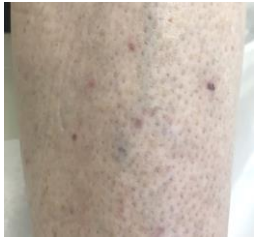


24th October 2019





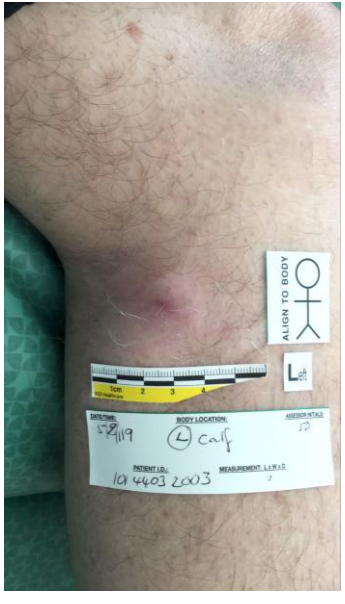




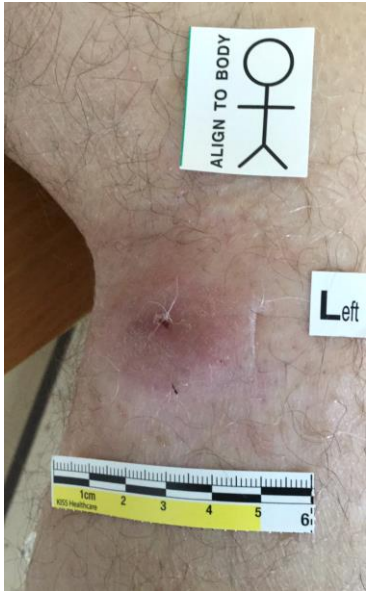
Other indications

Patient #: 4403-2003 (anti-PD1 naïve melanoma) – Ongoing PR

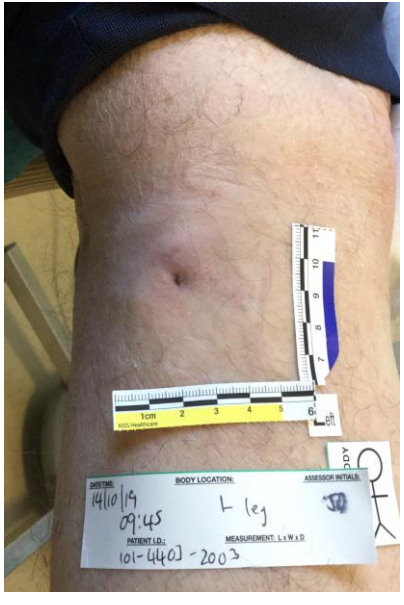
5th August 2019 (D1C1)



19th August 2019

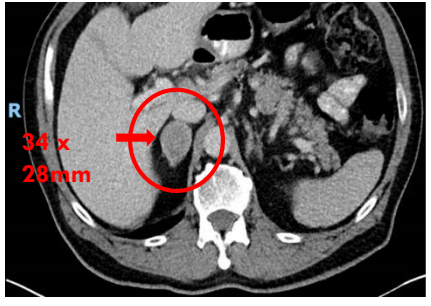


14th October2019

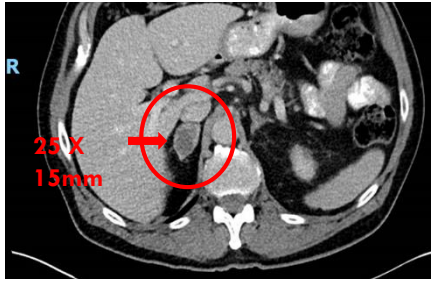


- D43 biopsy of the injected popliteal lesion tumor free
- Adrenal mass (uninjected) reduced from 34x28mm to 25x15mm at C5
- Patient remains on treatment 3 months
- Current status: Ongoing partial response

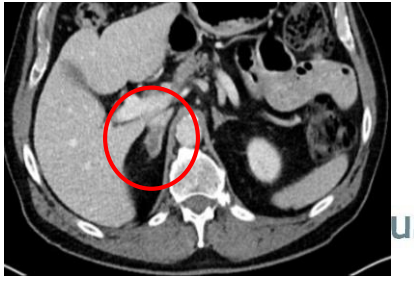
16th July 2019 (screening)



30th September 2019



25th November 2019

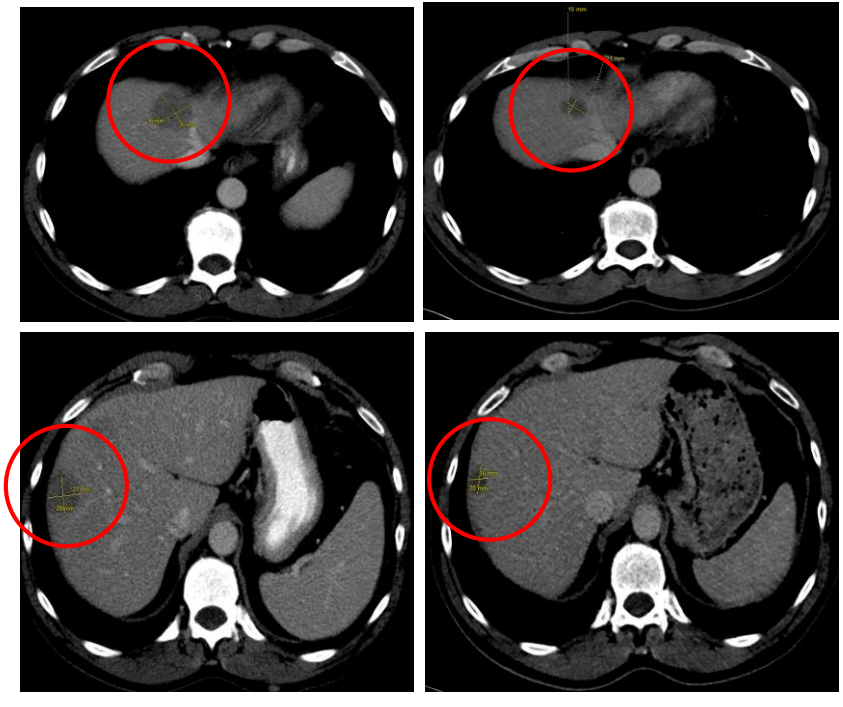


une

Patient #: 1103-2001 (anti-PD1 naïve melanoma) – Ongoing PR

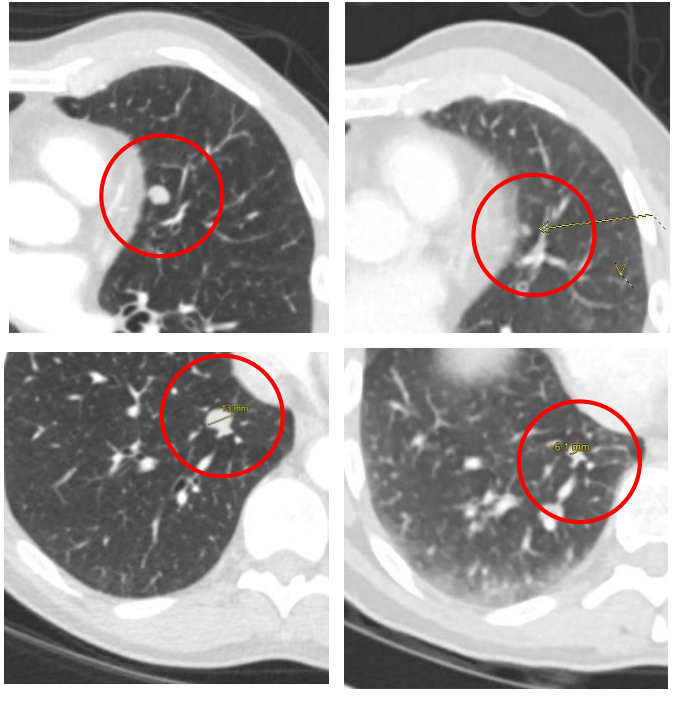
12th Aug 2019 (screening)

20th October 2019



12th Aug 2019 (screening)

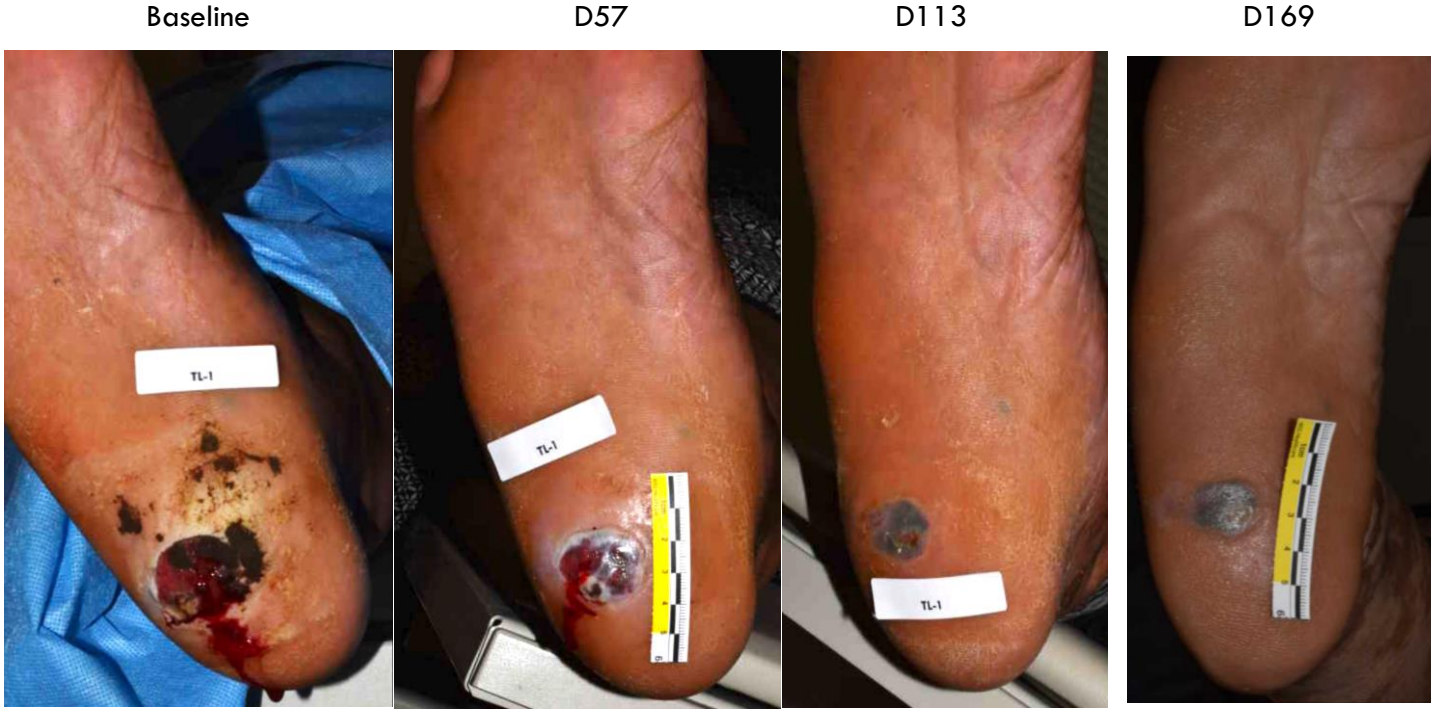
20th October 2019



- 5x3ml injections into medial right thigh
- Current status: Ongoing PR with marked reduction of multiple uninjected lesions including liver, lungs, resolved soft tissue lesion of right gluteus & injected lesion with necrotic center
- Remains on treatment at 3 months

Replimune

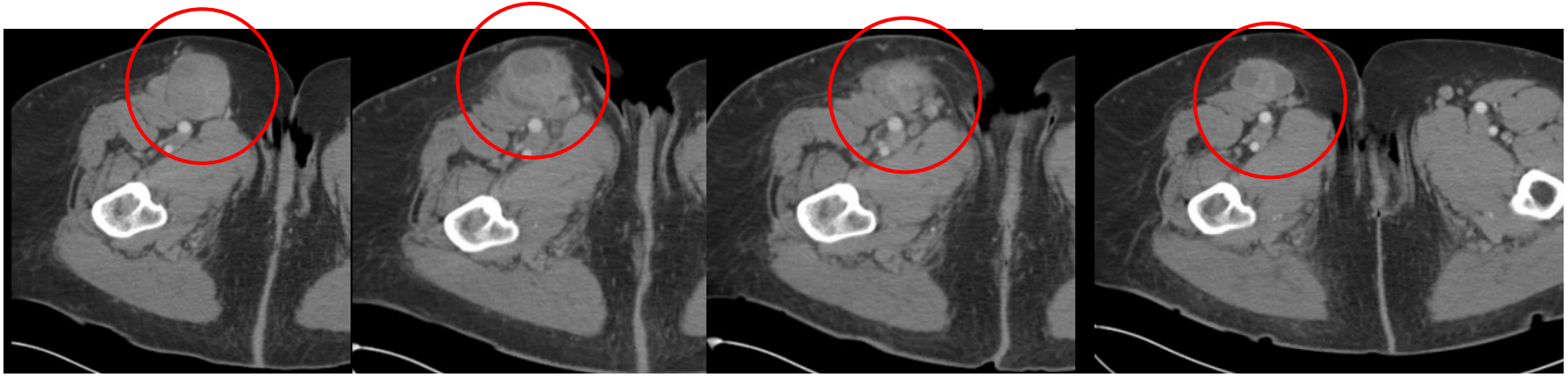
Patient #: 1119-2001 (anti-PD1 naïve melanoma)



- Baseline disease in the foot, inguinal nodes and liver
- Heel injected once, subsequent injections into inguinal nodes only
- Initial increase seen in inguinal nodes and liver, followed by reduction (see next slides)
- Patient remains on treatment at 8 months

Patient #: 1119-2001 (anti-PD1 naïve melanoma)

23rd May 2019 | 30th July 2019 | 10th September 2019 | 19th November 2019



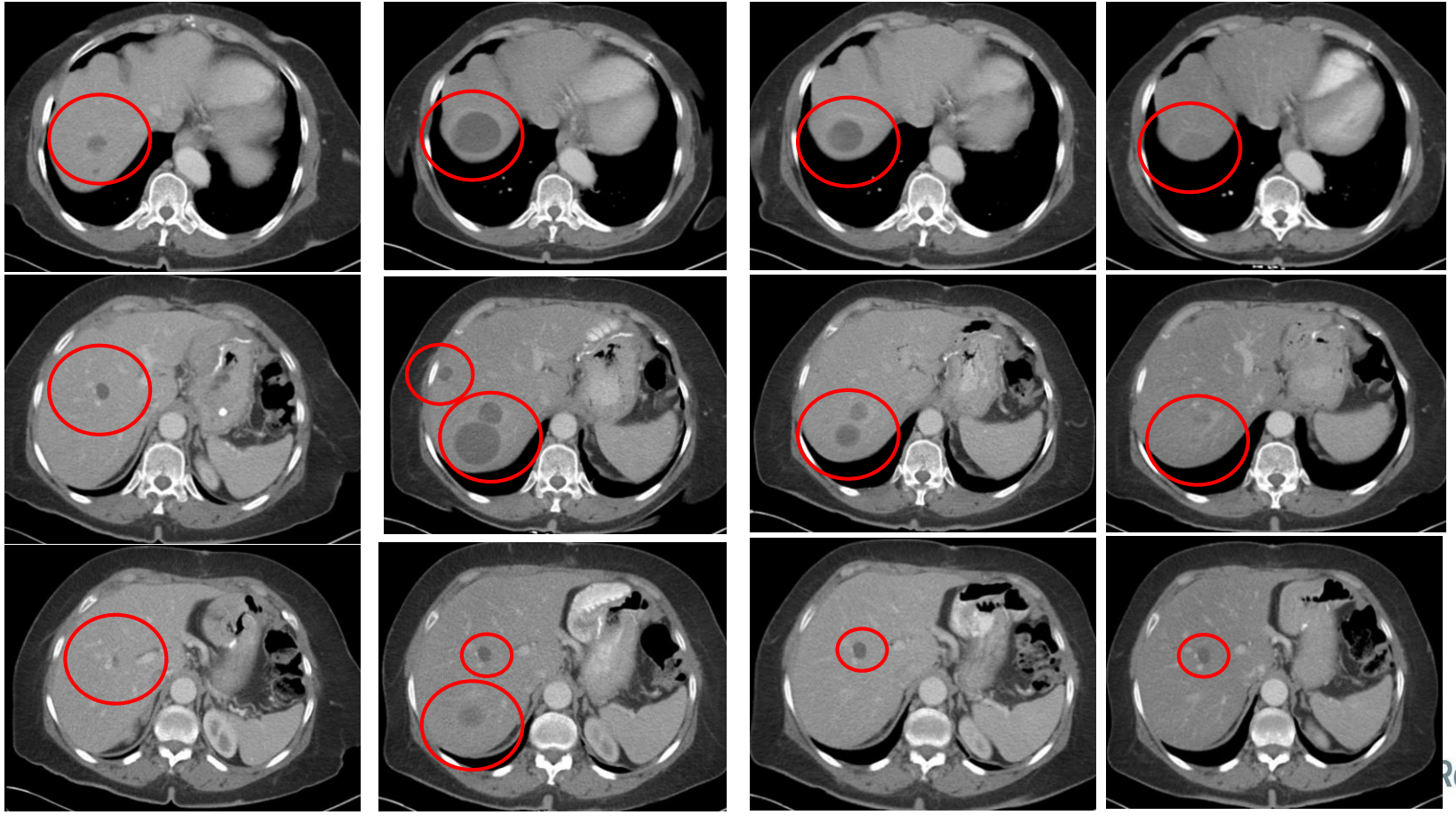
- Progression of inguinal nodes determined at C5 scan, reducing by 6 weeks later

Replimune

Patient #: 1119-2001 (anti-PD1 naïve melanoma)

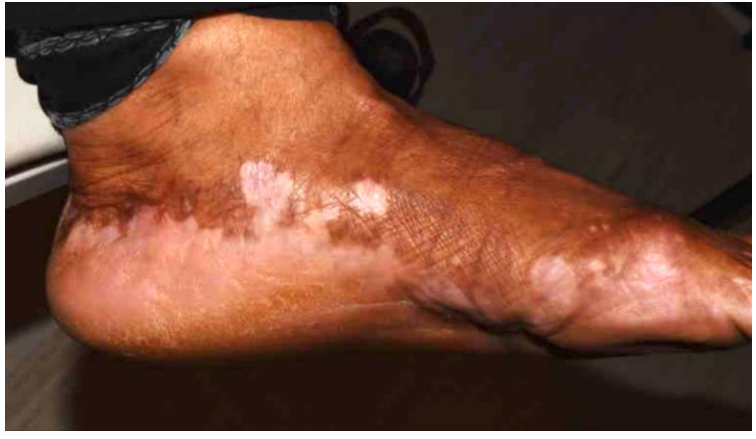
- Progression in the liver (uninjected) determined at C5 scan, reducing by 6 weeks later.

23rd May 2019 | 30th July 2019 | 10th September 2019 | 19th November 2019

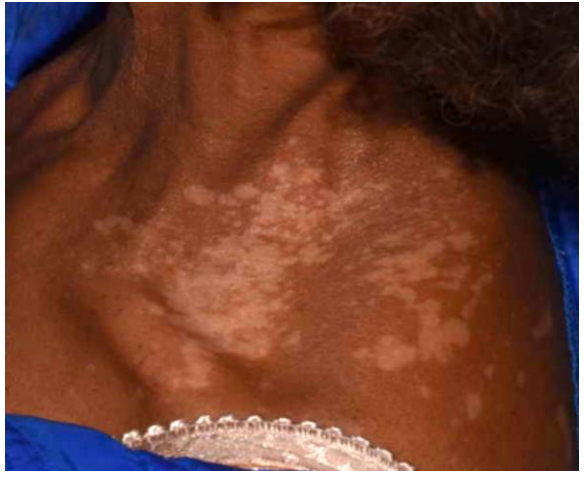


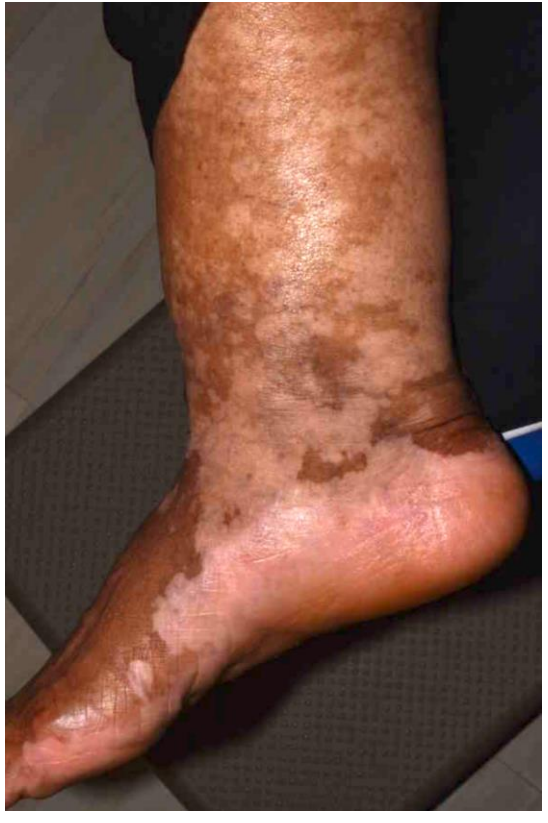
Patient #: 1119-2001 - Vitiligo

Left foot
(D113)



Left chest
(D169)

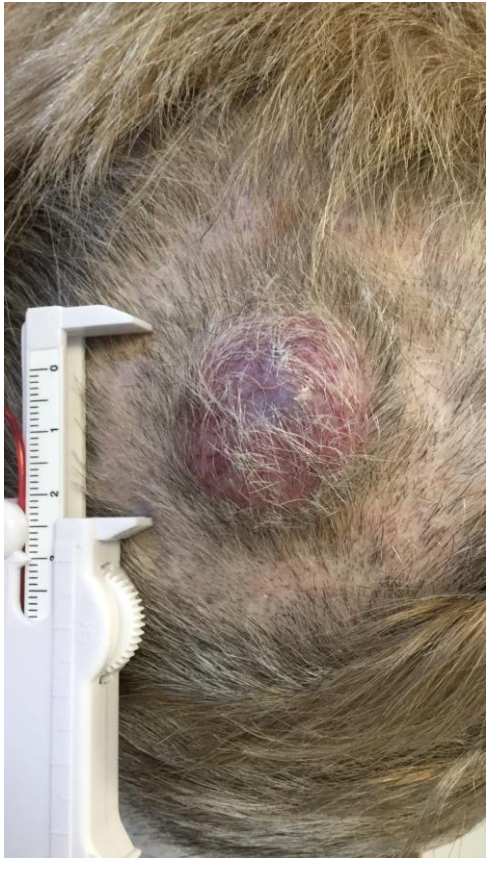




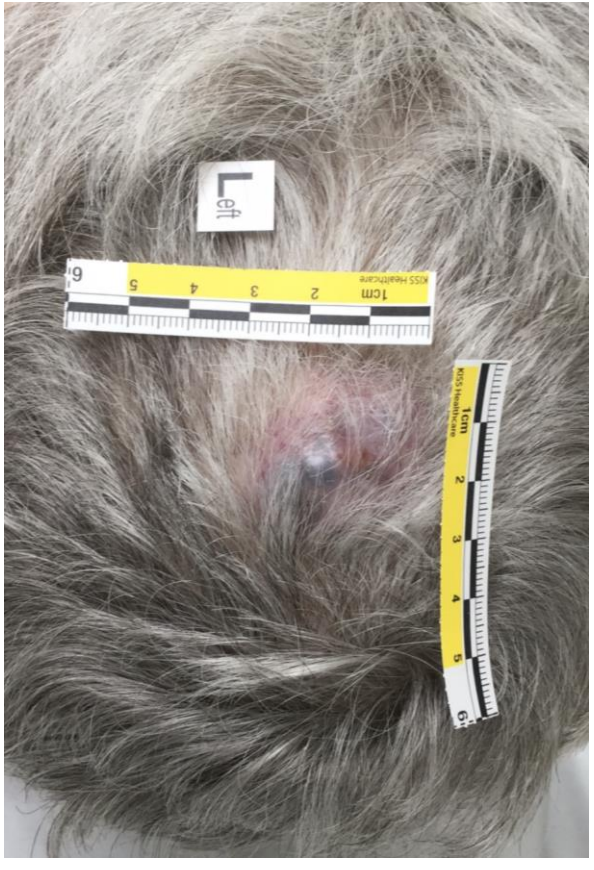
Right foot
(D169)

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

Baseline (2nd Jan 2019)



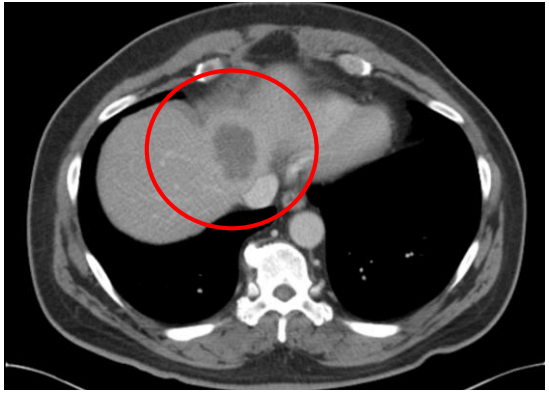
24th April 2019



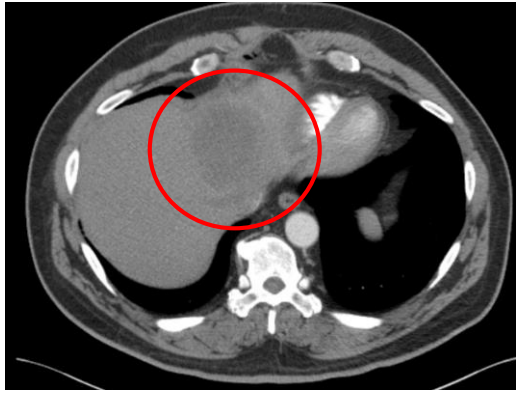
Patient has numerous additional subcutaneous lesions - remains on nivolumab at >9 months

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

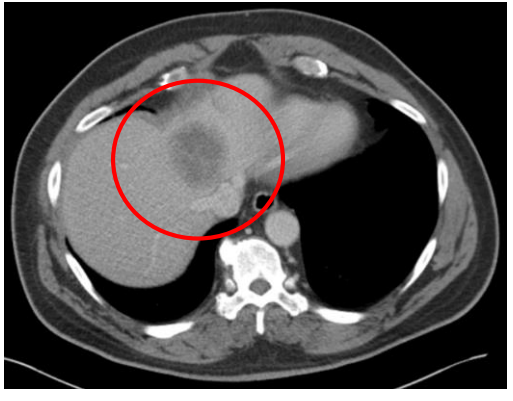
- Chemotherapy refractory MSI-H colorectal cancer
- 5cm liver metastasis and other liver metastases of around 1cm
- The liver lesions showed initial substantial increase (presumed inflammation), then reduction
- A biopsy taken at C4 demonstrated "A few viable glands of adenocarcinoma with extensive necrosis, 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)



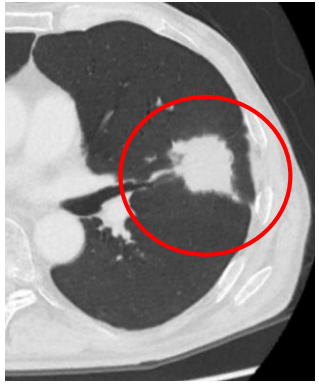
26th August 2019 (8x6cm)



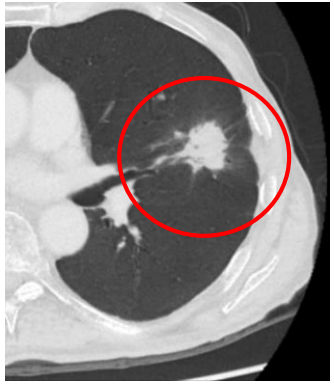
23rd September 2019 (5x5cm)
(Biopsy taken 9th Sept showed extensive necrosis & inflammation)

Patient #: 4401-1024 (esophageal cancer) – Ongoing PR

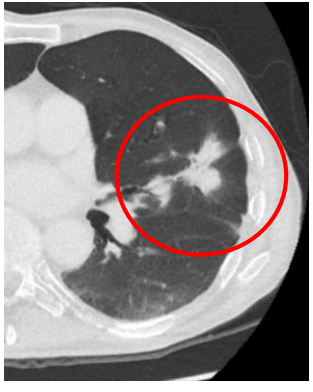
- Heavily pre-treated esophageal cancer (8 prior therapies)
- Lung lesions & lesions around the esophagus.
- Patient continues on treatment at 10 months
- Current status: Ongoing PR



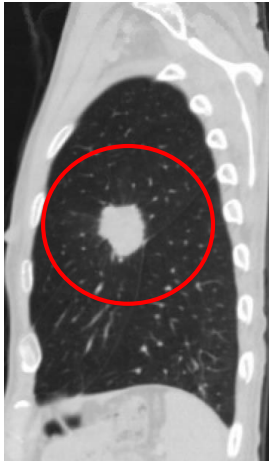
Baseline



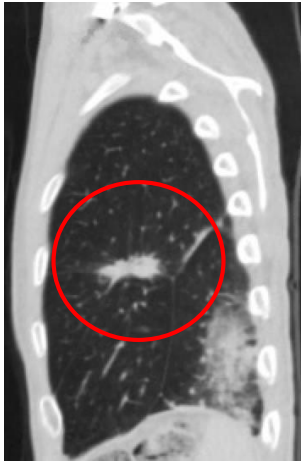
C5



C11



Baseline



C11

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

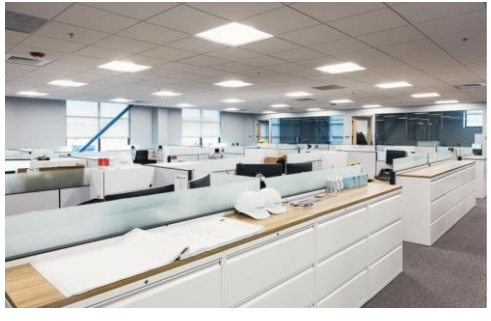
Overall conclusions from the clinical data so far

- 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

Critical focus on manufacturing

- RP1-RP3 currently manufactured by a CMO for ongoing clinical development
- For later stage development & commercialization, in-house manufacturing is prefered
- The team has extensive manufacturing experience
- 63,000 ft^2 manufacturing facility leased in July 2018 in Framingham, MA, appropriate for multi-product production
  - State of the art facility
  - Fully fitted out; first tech transfer run successfully completed
  - Scale sufficient to cover full global commercialization of Replimune's products at full capacity
- Expected to be on-line to produce clinical product in H1 2020





Framingham manufacturing facility



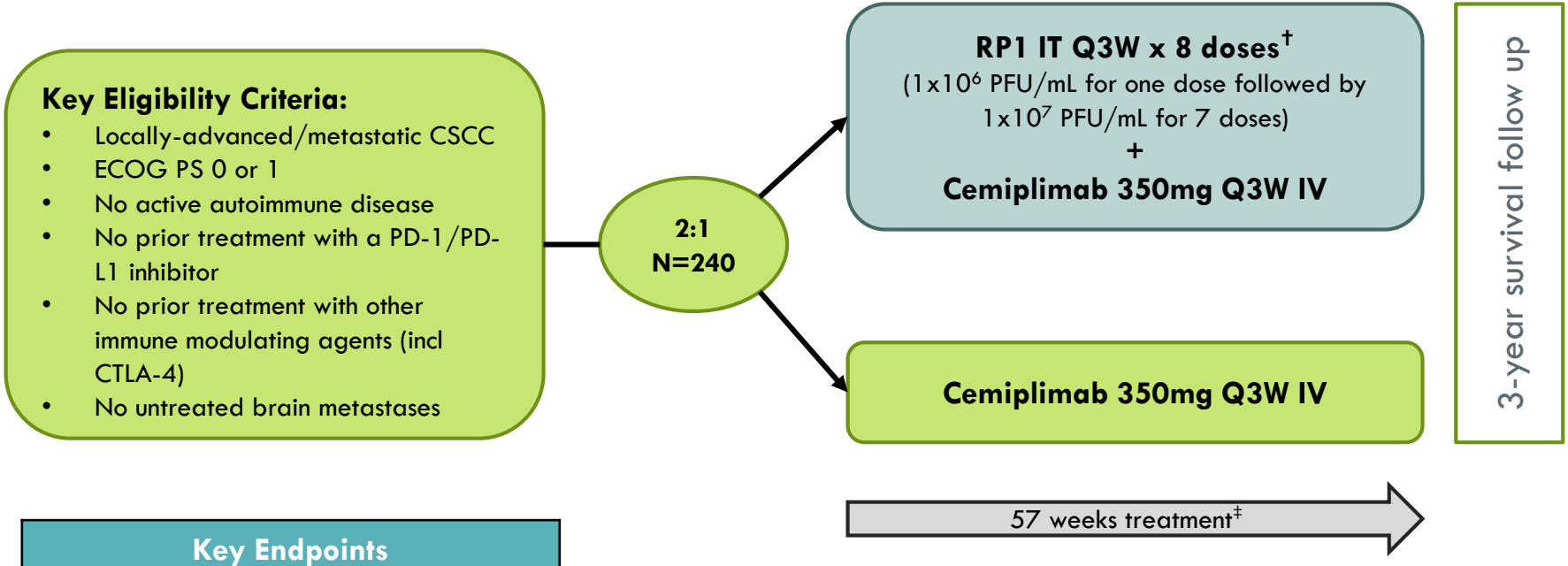






Appendix

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

CSCC in patients with sold organ transplants

- Approximately 30,000 lung & kidney transplants are conducted in the US each year
- Solid organ transplant recipients are at a 2-4 fold increased risk of cancer compared to the general population
- There is a particularly high risk of developing skin cancers
  - 2-8 fold increased risk of developing melanoma
  - 65-250 fold increased risk of developing CSCC
    - Up to 70% of patients develop CSCC within 20 years
- Clinical trials with immune checkpoint blockade drugs have excluded transplant patients due to the risk of transplanted organ rejection (41% kidney, 35% liver, 20% heart)
- However, response rates to immune checkpoint blockade seem to be similar to the general population
- There is therefore a substantial unmet need in solid organ transplant recipients with CSCC
- Single agent RP1 may be an attractive option for these patients