Initial results of the phase 1 portion of an ongoing phase 1/2 study of RP1 as a single agent and in combination with nivolumab in patients with solid tumors

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Overview

Background

- Oncolytic viruses preferentially replicate in tumors, promote immunogenic cell death & the induction of systemic anti-tumor immunity, & may provide the optimal means by which to generate patient-specific anti-tumor immune responses
- RP1 is an enhanced-potency oncolytic HSV-1 expressing a fusogenic glycoprotein (GALV-GP R-) and GM-CSF which is being tested in a Phase 1/2 clinical trial in ~150 patients with a range of solid tumors (NCT03767348)
- The objectives of the clinical trial were to define the safety of RP1 alone and with nivolumab, determine the recommended phase 2 dose (RP2D), and in 30 patient phase 2 cohorts, assess efficacy in melanoma, non-melanoma skin cancer, urothelial carcinoma and MSI-H tumors; Initial Phase 1 data is reported here

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

Key objectives:

- Demonstrate safety of RP1, alone & combined with nivolumab by both superficial and deep injection routes
- Determine the recommended phase 2 dose (RP2D) for RP1, 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

Phase 1 data summary

- Heavily pre treated patients with extensive disease were enrolled

Dose rising monotherapy

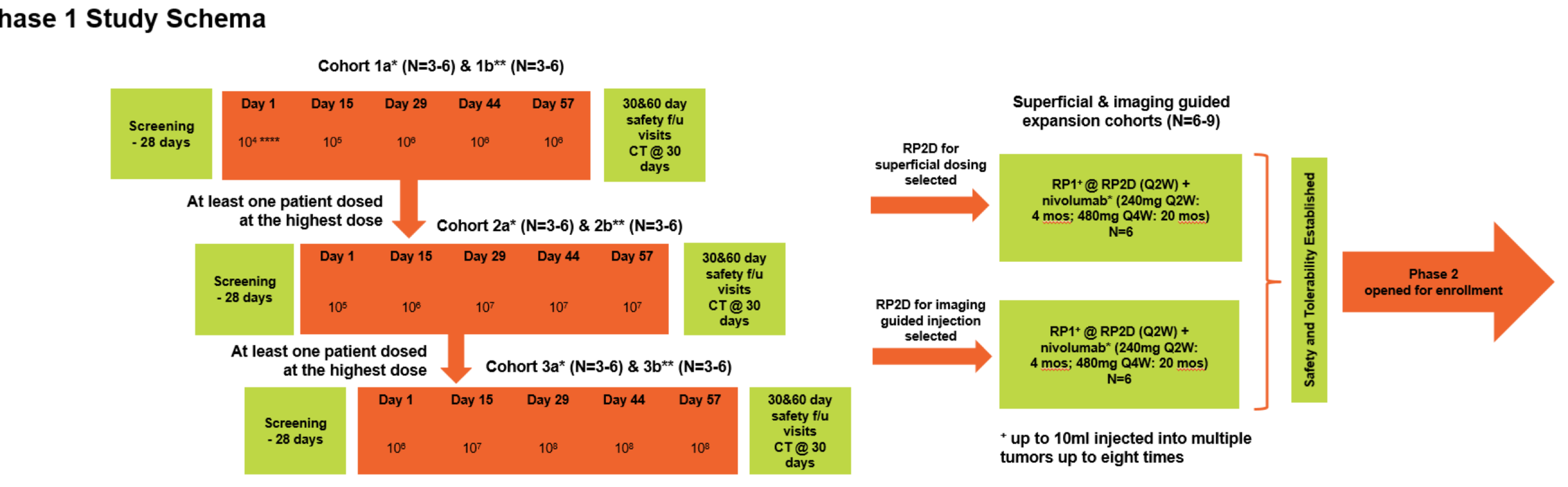
- The side effect profile was as expected
- The RP2D was established ($1x10^6$ pfu/ml followed by $1x10^7$ pfu/ml Q2W)
- Destruction of injected and un-injected tumors demonstrated, including delayed systemic post study tumor reductions without further therapy
- Kinetics of detection of RP1 suggest robust virus replication

Combination with nivolumab

- Clinical activity seen in multiple patients with various tumor types
  - Anti-CTLA-4 + anti-PD-1 refractory cutaneous melanoma – two out of three patients enrolled responding – as is the first ipilimumab/nivolumab refractory cutaneous melanoma patient in phase 2 (only such patient with follow up scans)
  - Clear clinical activity also seen in CSCC, including CR
  - Rapid tumor reduction seen before the first nivolumab dose, which is given from the second dose of RP1
  - Abscopal effects were observed
- Increases in CD8 & PDL1 staining seen across tumor types, including reversal of T cell exclusion
- Increases in expression of genes associated with immune activation by Nanostring analysis & increases in autoimmune B cell responses were observed

Clinical trial design

Phase 1 Study Schema



Phase 1 trial design – Dose rising cohorts

- Up to 5 doses of RP1 injected into a single tumor in three dose level cohorts by direct or ultrasound guided injection into superficial tumors & lymph nodes or CT or ultrasound guided injection into deep tumors including visceral
- Three patients/cohort, expand to 6 if DLTs
- CT scan at baseline and 30 days after last dose

Phase 1 trial design – Combination with nivolumab

- Up to 8 doses of RP1 Q2W at the RP2D combined with nivolumab (240mg Q2W for 4 months from the second RP1 dose, then 480 mg Q4W for 20 months)
- Unlike the dose rising phase, multiple tumors can be dosed
- Six patients by direct injection, six patients by imaging guided injection into deep lesions
- CT scans at baseline and every 8 weeks
- Biopsies taken from injected lesion taken at baseline & 6 weeks.
- Nanostring gene expression panel
- IHC (PD-L1, CD8)
- Oncimmune B cell response

Patient demographics

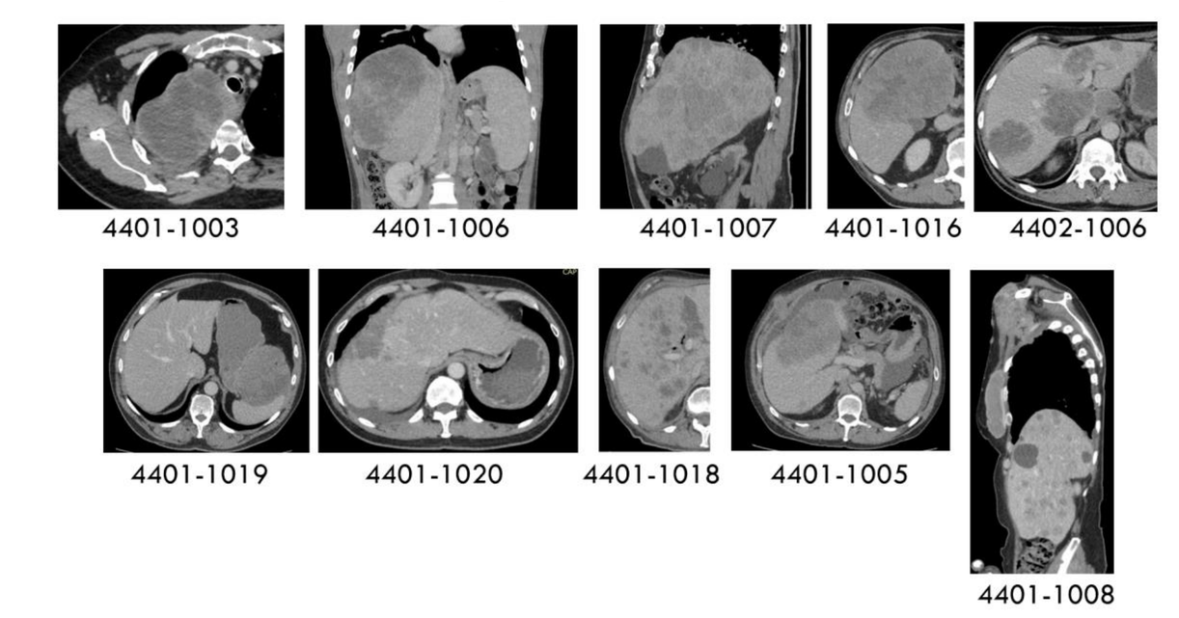
Dose rising cohorts

	Total	Melanoma	Colorectal	Head and neck	Breast	Oesophageal	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

Combination with nivolumab

	Total	Cutaneous melanoma	Uveal melanoma	Mucosal melanoma	CRC	CSCC	BCC	Breast	Bladder	Adeno. of cecum	MSI-H (Colon)	Esephageal
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

Advanced patients were enrolled



Heavily pre-treated patients were enrolled

Patient	Prior therapies (direct injection cohorts)
4401/1001	Dacarbazine, ipilimumab, vemurafenib, dabrafenib, pembrolizumab, Imcgp100, tremelimumab
4401/1002	Ipilimumab, pembrolizumab, dabrafenib, trametinib
4401/1004	Ipilimumab, pembrolizumab, RGT100-pei
4401/1011	Capecitabine/oxaliplatin, capecitabine/irinotecan
4402/1001	Cisplatin, fluorouricil
4402/1004	Carboplatin, epirubicin, capcitibine, bicalutamide, zoladex
4401/1013	Tamoxifen/cyclophosphamide/epirubicin/fluorouracil, docetaxel, Arimidex/Zoladex/pamidronate, ibandronate/capecitabine, carboplatin/gemcitabine, exemestane, paclitaxel, Tamoxifen, eribulin, vinorelbine, Syd985, Megace Ct7001
4401/1005	Capecitabine/oxaliplatin, fluorouracil/calcium levofolinate/irinotecan/cetuximab, capecitabine/cetuximab, oxaliplatin/calcium levofolinate/cetuximab/fluorouracil, calcium levofolinate/cetuximab/fluorouracil/irinotecan/
4401/1008	Cyclophosphamide/epirubicin/fluorouracil/methotrexate, anastrozole/cyclophosphamide/docetaxel/exemestane, exemestane, denosumab/fulvestrant, eribulin, capecitabine, palbociclib/tamoxifen, vinorelbine

Patient	Prior therapies (imaging guided injection cohorts)
4401/1003	Ipilimumab/nivolumab
4401/1006	Cetuximab, fluorouracil/irinotecan/leucovorin, bevacizumab/fluorouracil/folinic Acid/oxaliplatin, irinotecan/fluorouracil/leucovorin, capecitabine
4401/1007	Delcath hepatic chemoperfusion (melphalan), Imcgp100, Pqr309-003 pan-class I Pi3k Inhibitor
4401/1014	Oxaliplatin/capecitabine
4402/1015	Ipilimumab/nivolumab
4402/1016	Cisplatin/capecitabine, paclitaxel/ramucirumab
4401/1012	Ipilimumab/nivolumab
4401/1019	Ipilimumab/nivolumab
4401/1020	Transarterial Chemoembolization (tace), gemcitabine/nab-paclitaxel, oxaliplatin/fluorouracil/irinotecan/leucovorin, fluorouracil/irinotecan/leucovorin/oxaliplatin, gemcitabine
4401/1017	Fluorouracil/folinic acid/oxaliplatin, fluorouracil/folinic acid/irinotecan
4401/1018	Cisplatin/gemcitabine
4401/1021	Capecitabine/oxaliplatin, fluorouracil/irinotecan/leucovorin, Cxd101 HDAC inhibitor

Safety & tolerability

Treatment-related adverse events

Dose rising cohorts

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			

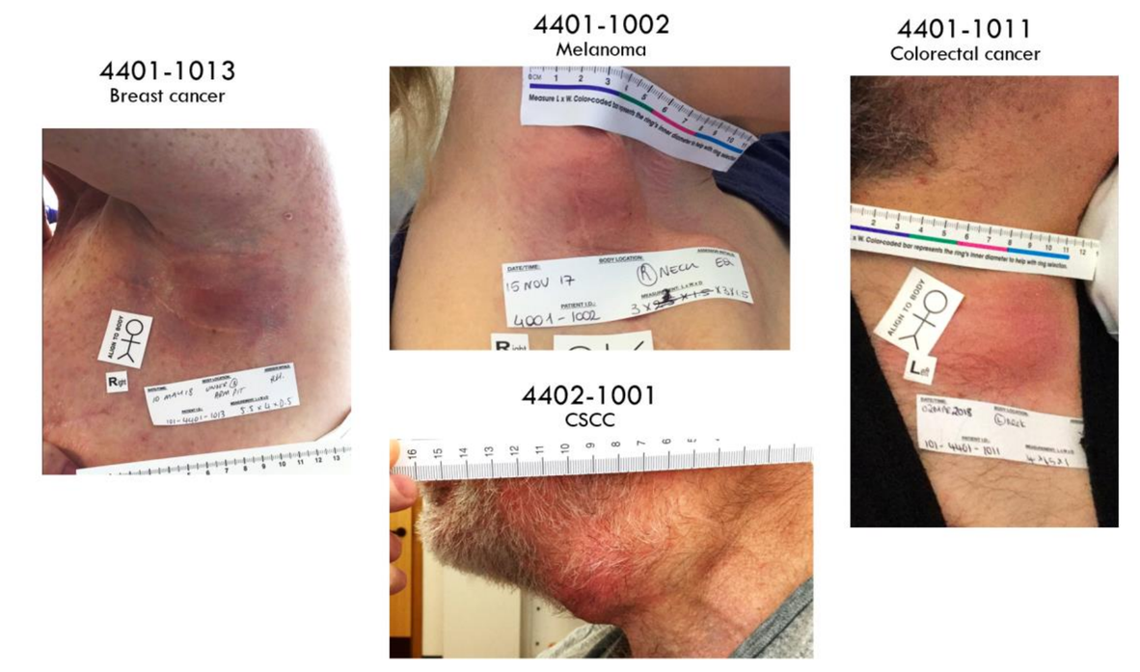
- Side effects were as expected for an oncolytic immunotherapy
- 'Flu-like constitutional symptoms, chills & rigors anecdotally more marked than with T-VEC; self resolving within 72hrs of injection
- No obvious differences between deep & superficial dosing
- Modest increase in Grade 1-2 events with dose
- 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
- RP2D by both dosing routes:
  - 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

Combination 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
- No immune related adverse events seen (20-25% would be expected with nivolumab alone)

Inflammation seen in patients with subcutaneous tumors at 24-72hrs

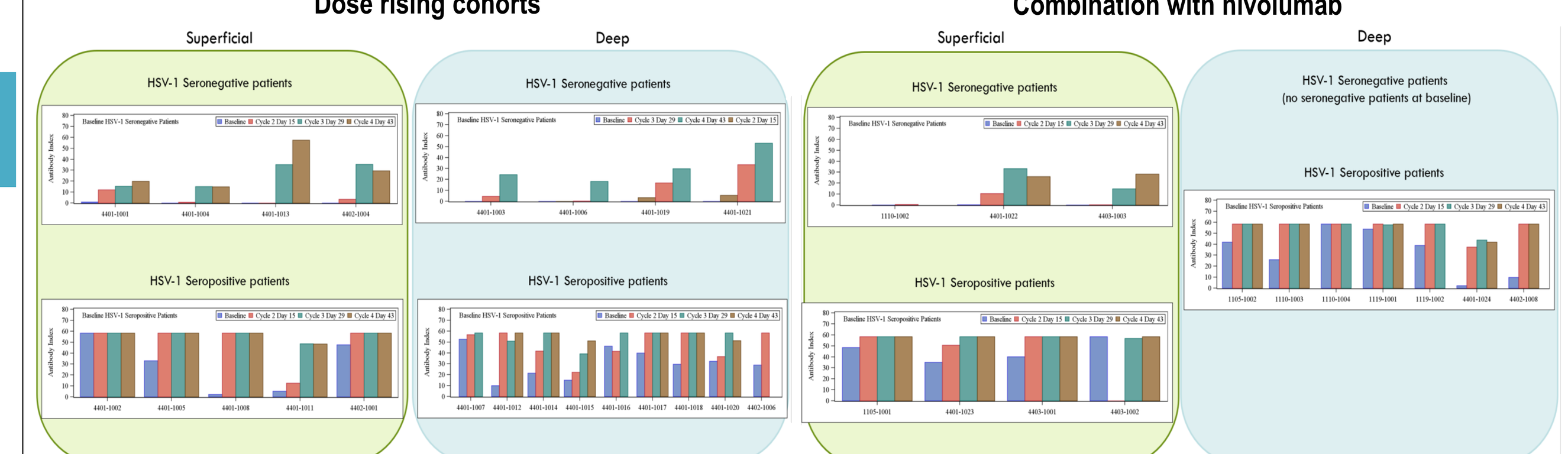


Safety & tolerability conclusions

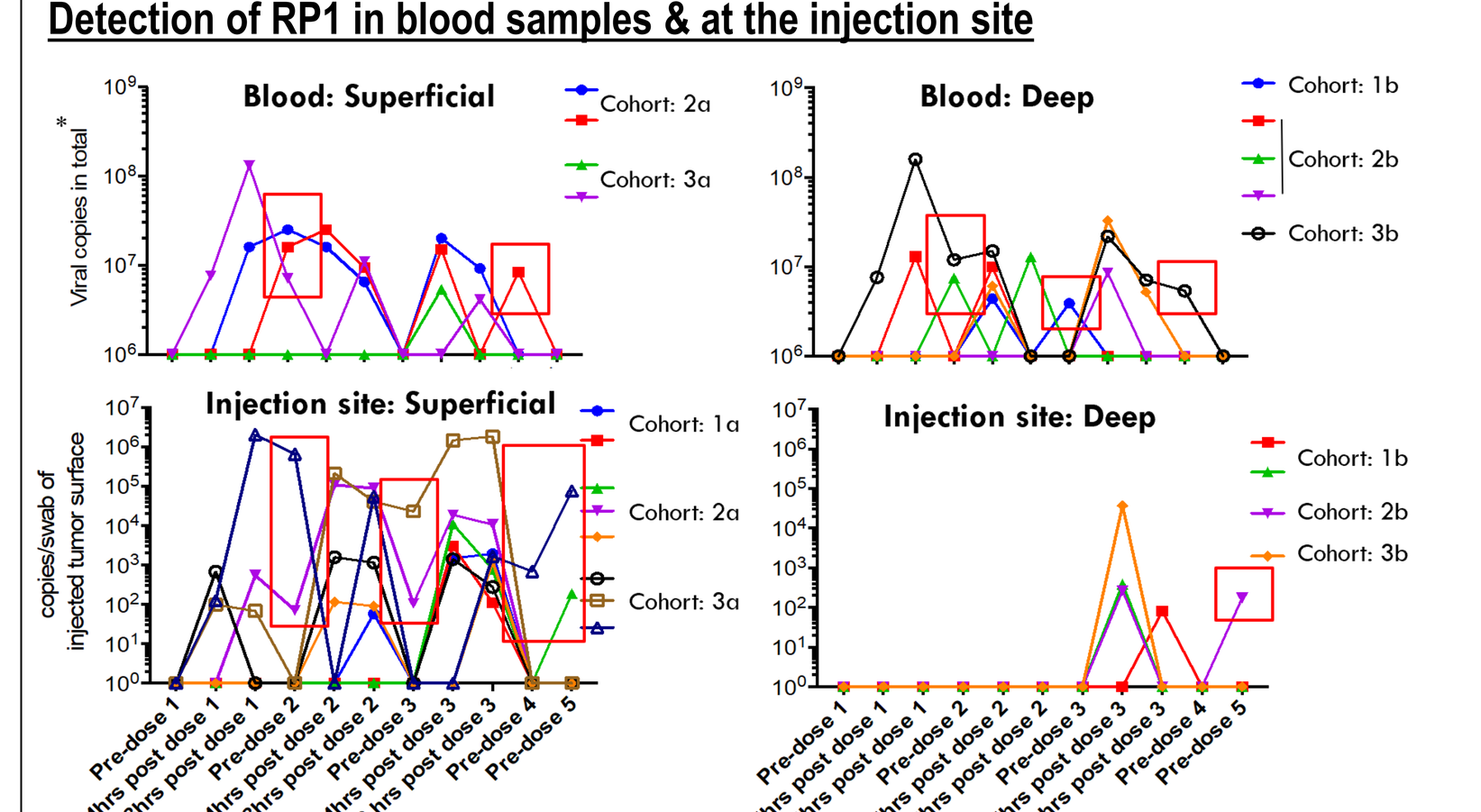
- RP1 is well tolerated alone and combined with nivolumab, with side effects as expected for each agent alone
- Both direct injection of superficial & nodal tumors, & imaging guided injection of deep/visceral tumors were well tolerated and practical

RP1 seroconversion & replication

Seroconversion



Detection of RP1 in blood samples & at the injection site



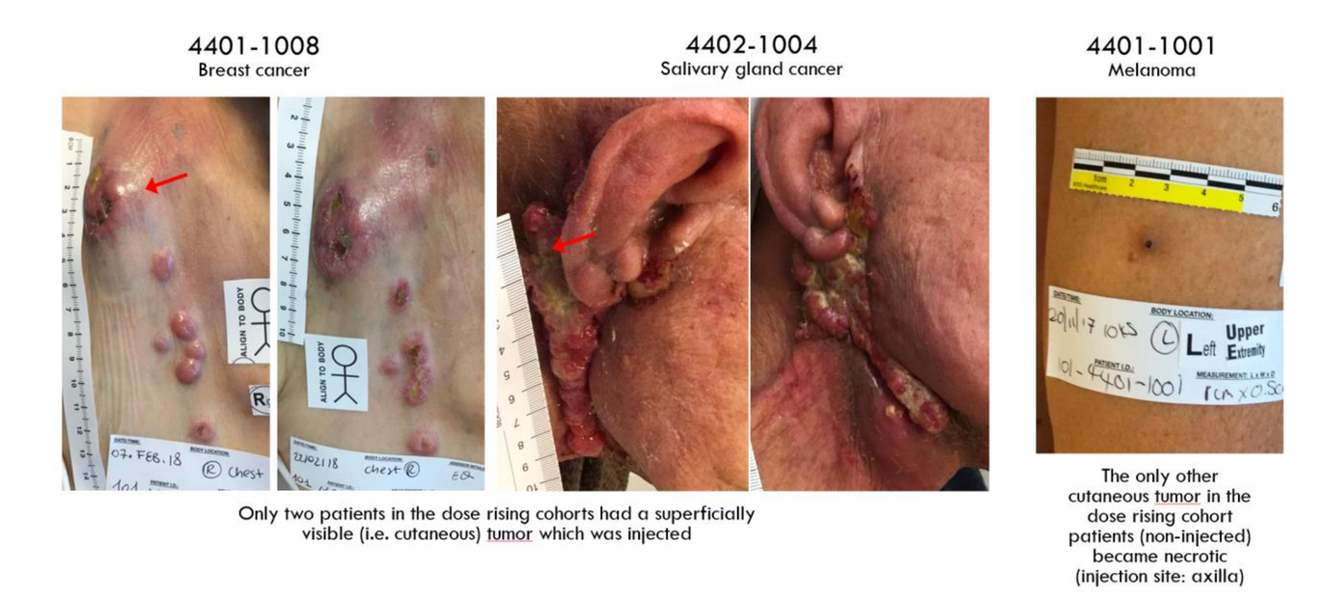
* assumes 15ug DNA/ml, 5L blood volume

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

Anti-tumor activity

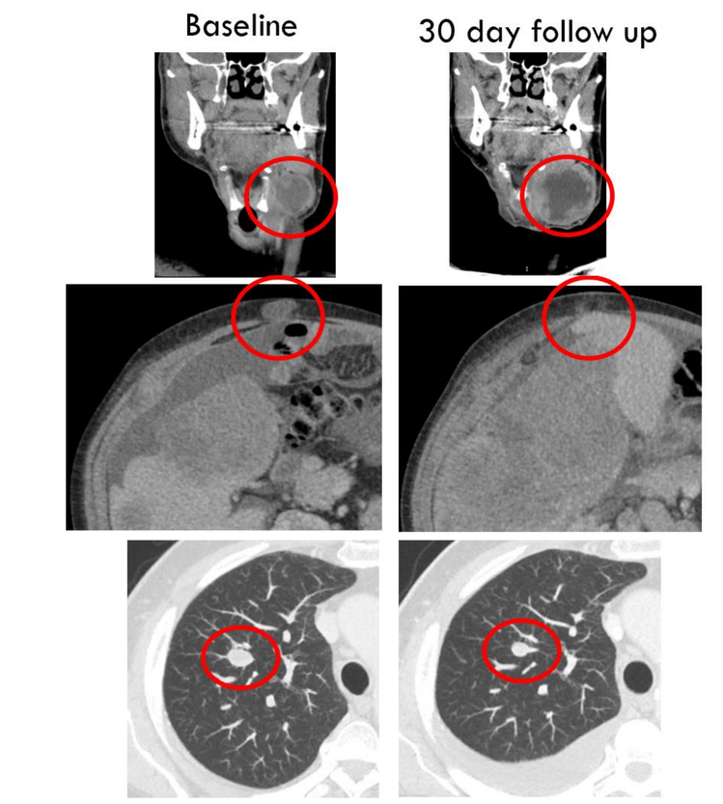
Dose rising cohorts

Shrinkage & necrosis of injected tumors



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

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



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

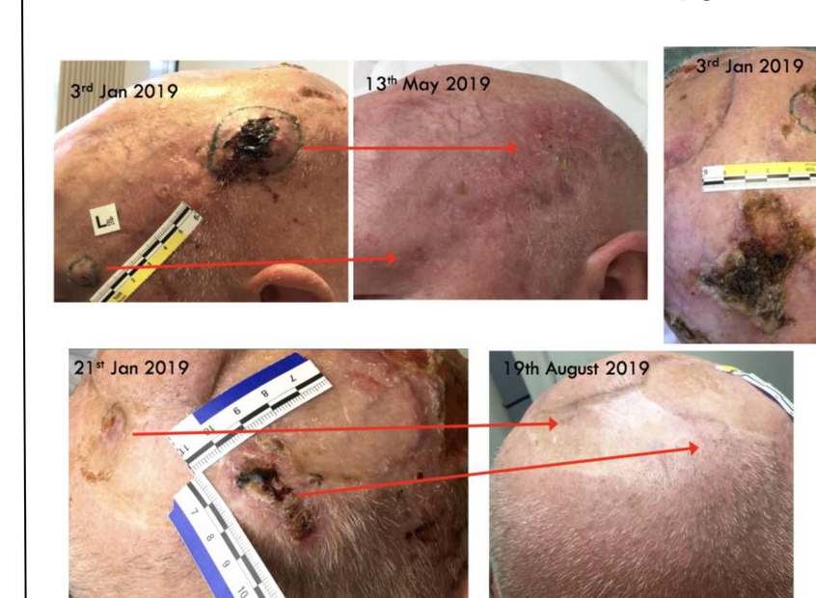
- Patients were followed per protocol in the dose rising for 30 days post the last RP1 dose to collect safety data, followed by a CT scan
- Delayed anti-tumor effects (systemic disease reduction) were seen in 2 patients following RP1 injected into a single tumor & a previously pembrolizumab refractory melanoma patient responded to subsequent nivolumab:

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

- Melanoma (4401-1003), prior ipilimumab & nivolumab. Baseline disease: lung, pleura, lymph node & sc. Injections into lung mass. Progression at 30 days, then with no further therapy reductions in the apical mass & hilar nodes, maintained for 8 months
- Cholangiocarcinoma (4401-1018). Baseline disease: liver & lung metastases. Injections into liver lesion. Progression at 30 days, then with no further therapy reductions in liver lesions, bone metastases & lymph nodes
- Melanoma (4401-1004), prior ipilumumab, pembrolizumab. 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

Combination with nivolumab

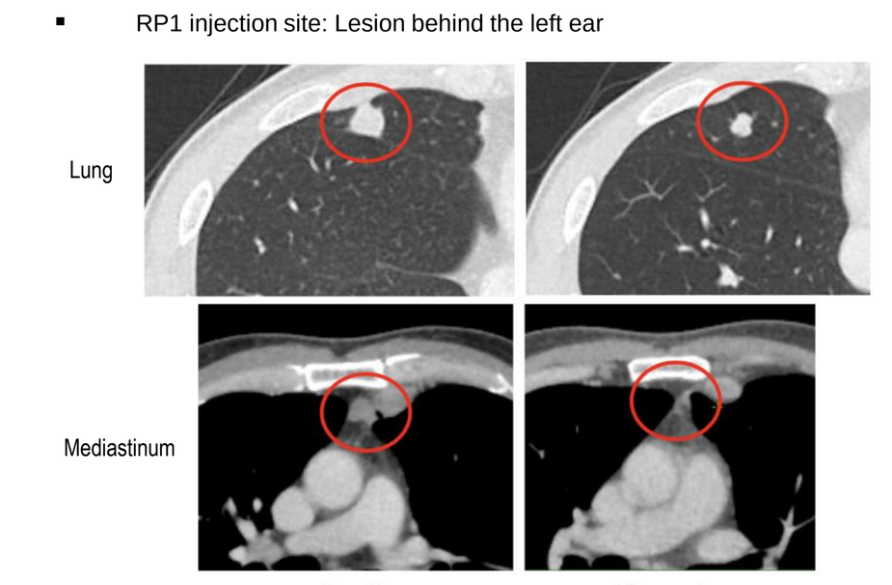
Patient 4403-1002 – chemotherapy refractory CSCC (CR)



- Extensive recurrent CSCC previously treated with surgery, radiotherapy, cisplatin/5FU & electrochemotherapy
- CR with residual areas tumor free by multiple biopsy & continuing to heal
- In addition to the ongoing complete response, the patients' quality of life has been dramatically improved

Patient 4401-1022 – ipi/pembro refractory cutaneous melanoma (PR)

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

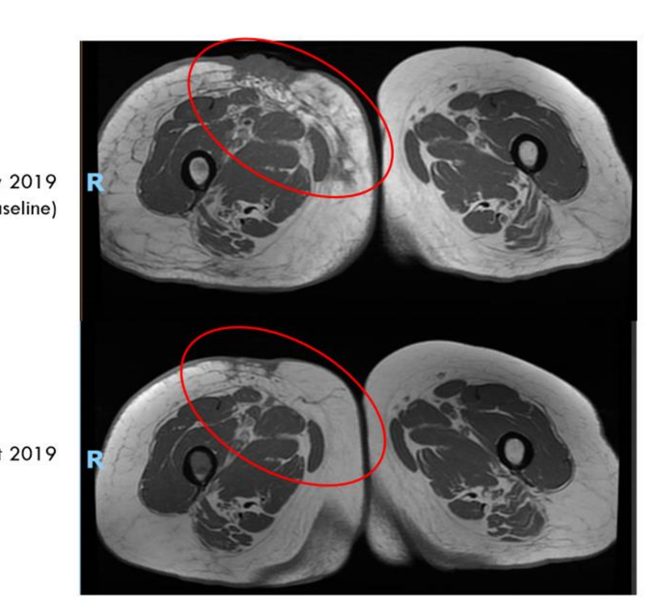


- Confirmed progression on prior ipi & pembro, where sequential PET scans demonstrated new lesions while also concurrently being treated with local therapy for the lesion behind the ear, then entry into the RP1 clinical trial
- Ongoing PR
- Patient remains on treatment at 11 months

Patient 4403-1003 – ipilimumab/nivolumab refractory cutaneous melanoma

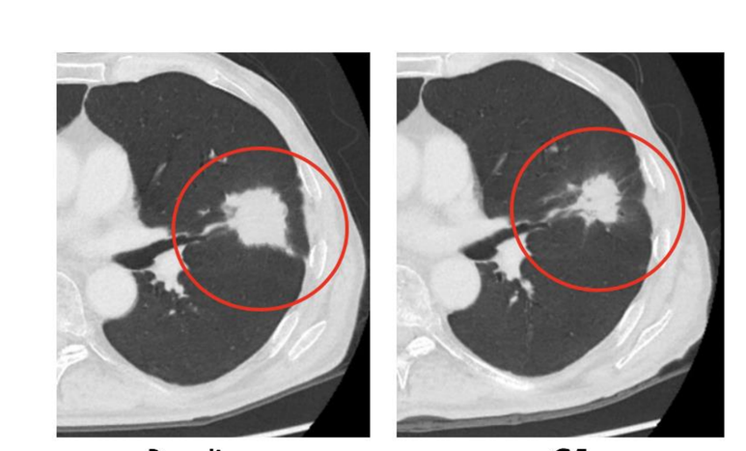
- All tumors flattened after the first dose of RP1 & extensive oedema rapidly reduced

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



- 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 5 months

Patient 4401-1024 - chemotherapy refractory esophageal cancer



- Lung lesions and lesions around the esophagus.
- Largest lung lesion injected 6 times after which too soft for further injections.
- Cycle 11 CT scans showed overall disease reduction of 23%
- Patient continues on nivolumab at C12

Tumor reduction after a single RP1 dose

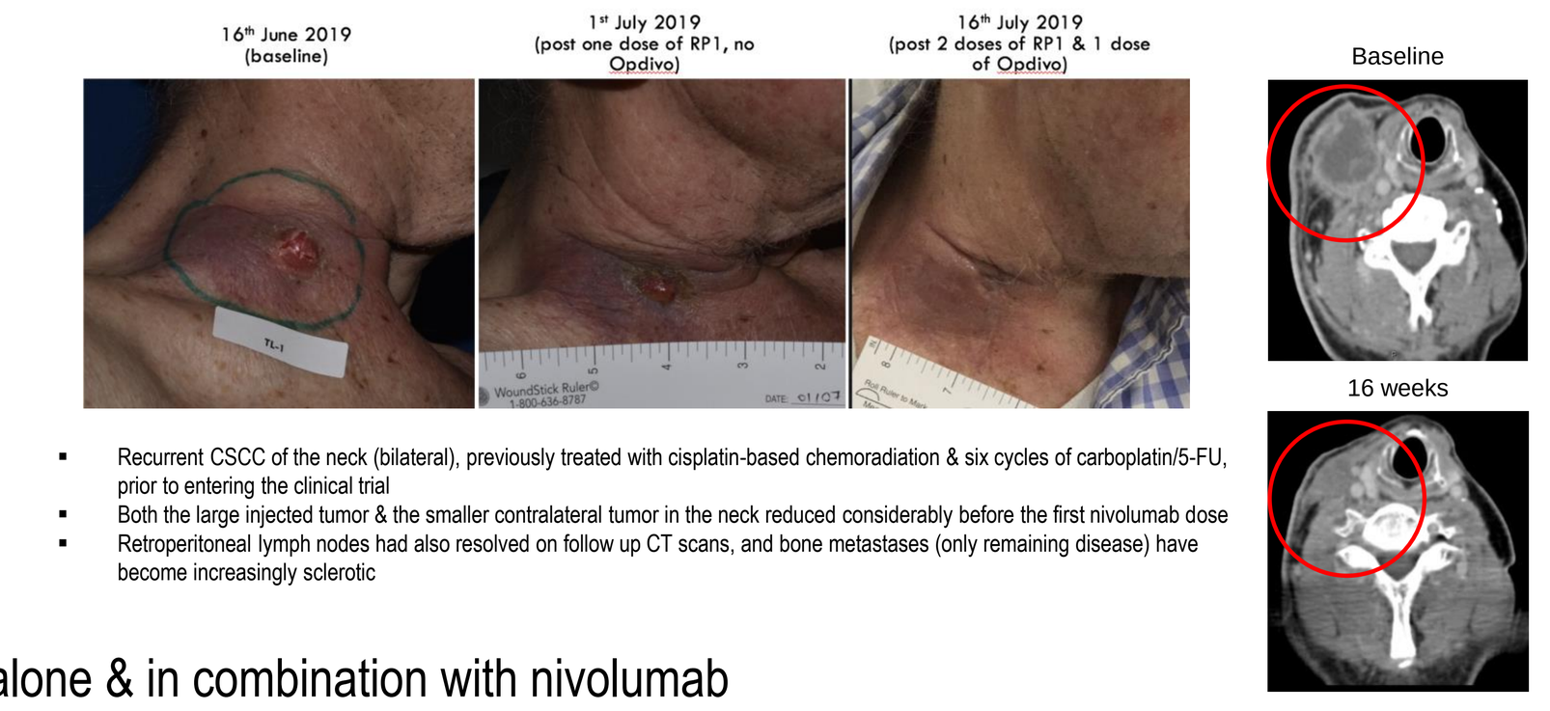
Patient 4403-1003 – pembrolizumab refractory melanoma (phase 2 patient)

- Increased drainage by D6 prior to tumor reduction by D13 (pre-nivolumab)
- Patient on treatment at 2-3 weeks

Patient 4403-1001 – ipi/nivo refractory uveal melanoma

- Patient has numerous additional subcutaneous lesions many of which reduced and/or were tumor free by biopsy
- Remains on nivolumab at >10 months

Patient 4401-2001 – chemotherapy refractory CSCC (phase 2 patient)



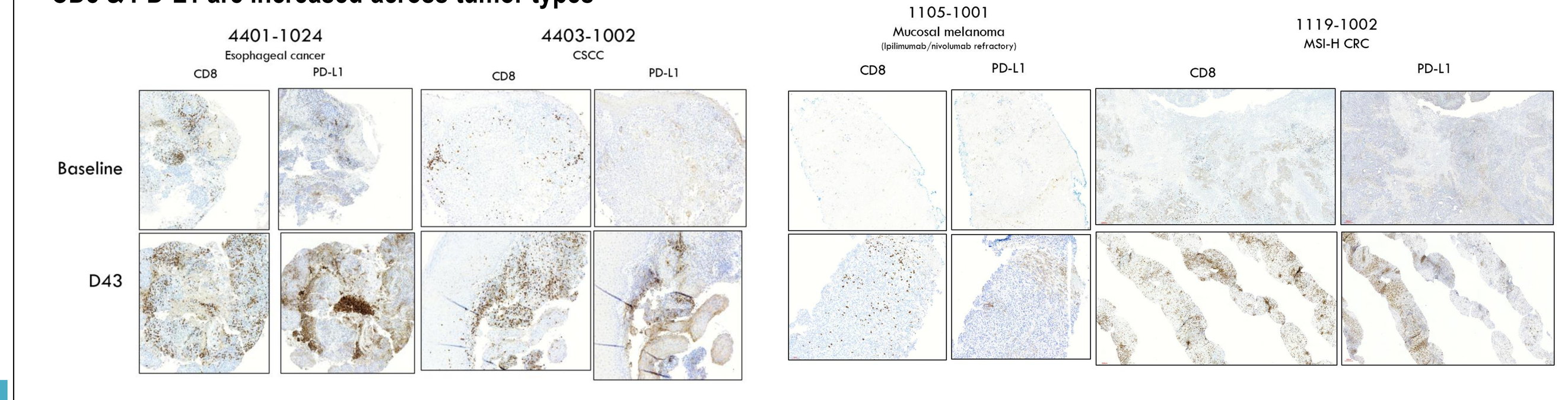
- Recurrent CSCC of the neck (bilateral), previously treated with cisplatin-based chemoradiation & six cycles of carboplatin/5-FU, prior to entering the clinical trial
- Both the large injected tumor & the smaller contralateral tumor in the neck reduced considerably before the first nivolumab dose
- Retroperitoneal lymph nodes had also resolved on follow up CT scans, and bone metastases (only remaining disease) have become increasingly sclerotic

Anti-tumor activity conclusions

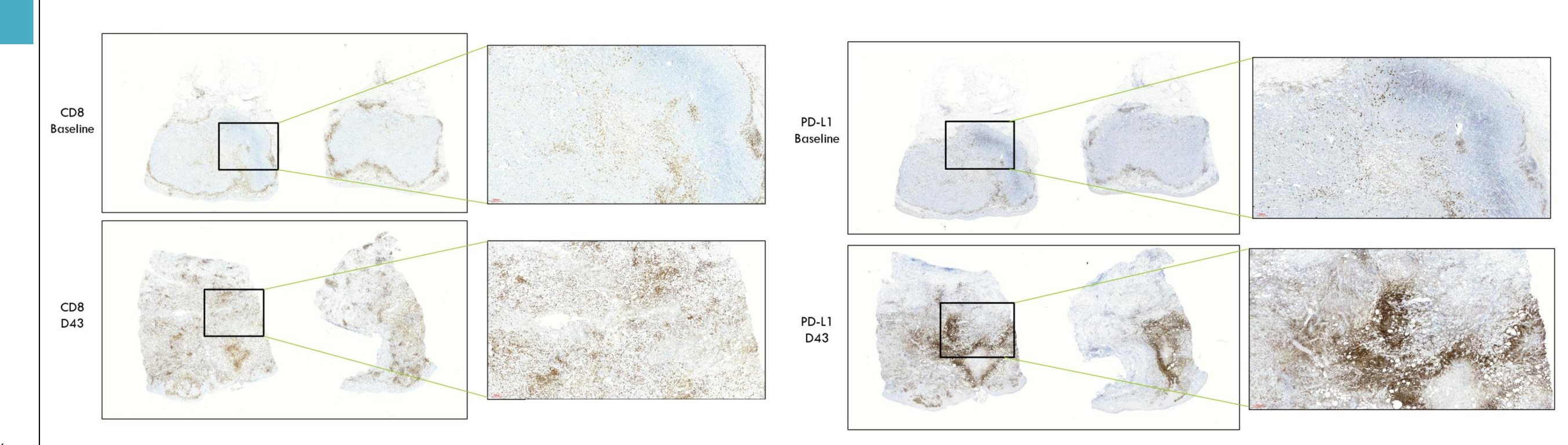
- Anti-tumor activity was seen with both RP1 alone & in combination with nivolumab
- Clear clinical activity was seen in CSCC (further supported by data from phase 2 patients)
- Clear clinical activity seen in anti-PD1 refractory cutaneous melanoma, with two of the three patients enrolled responding to combined treatment with RP1 & nivolumab (also further supported by data from phase 2 patients)
- Further details of these & further patients, including Phase 2 CSCC & melanoma, can be found at www.replimune.com

Biomarkers

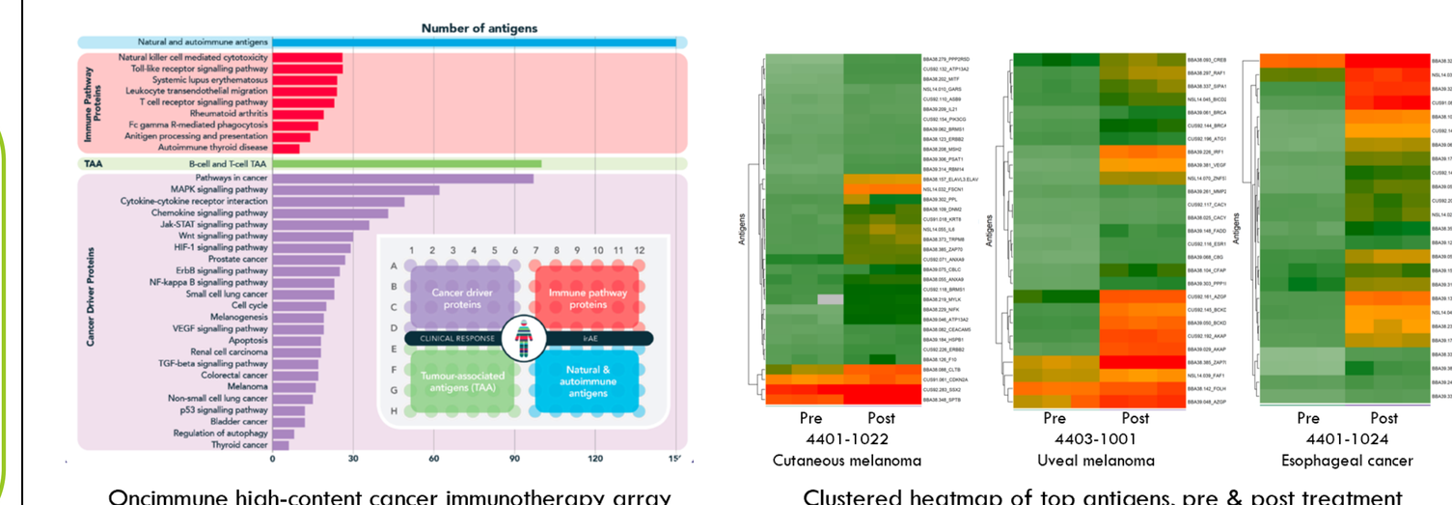
CD8 & PD-L1 are increased across tumor types



T cell exclusion is reversed (Patient 4403-1003) – ipi/nivo refractory melanoma

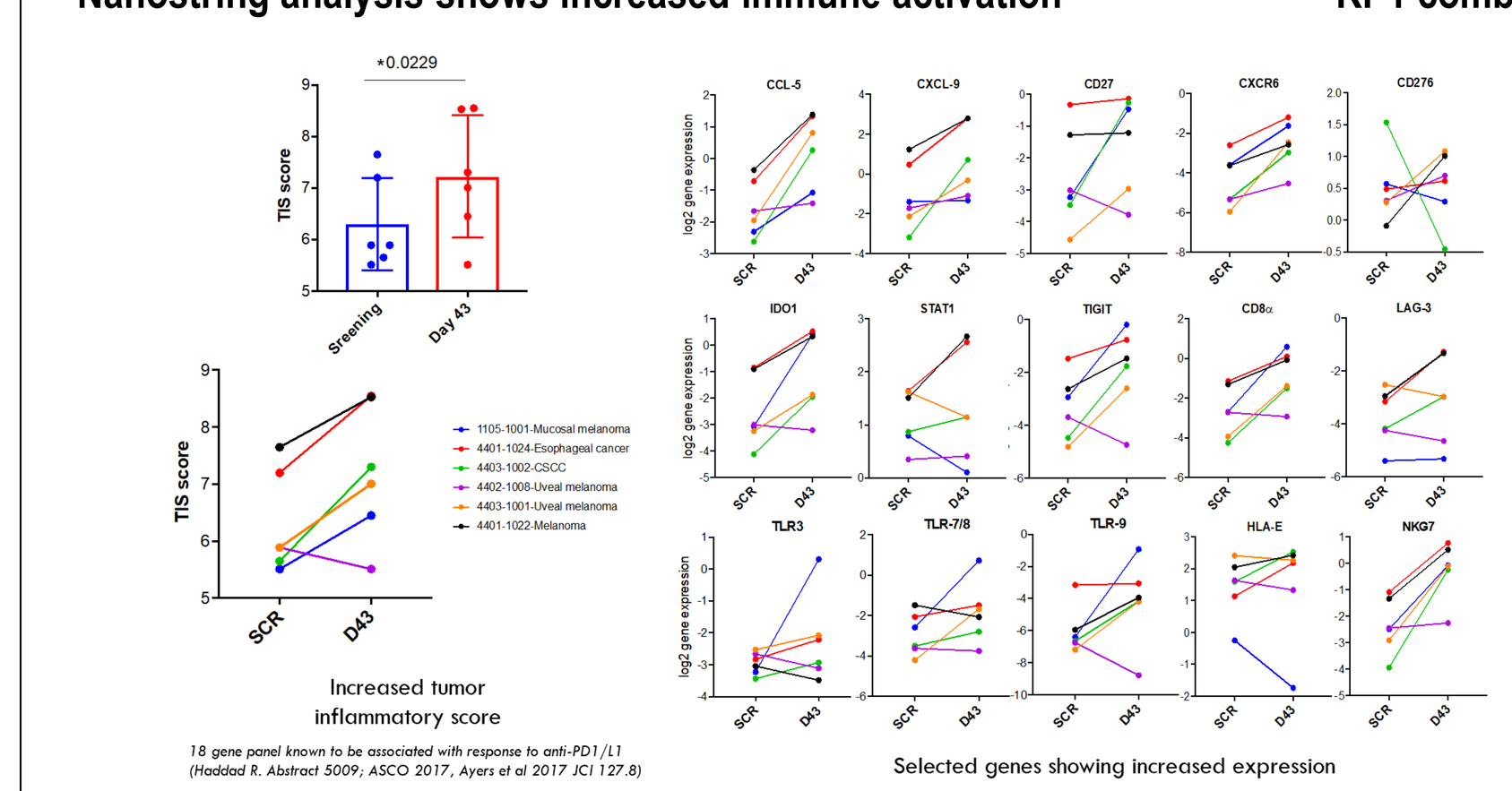


RP1+nivolumab increases autoimmune B cell responses

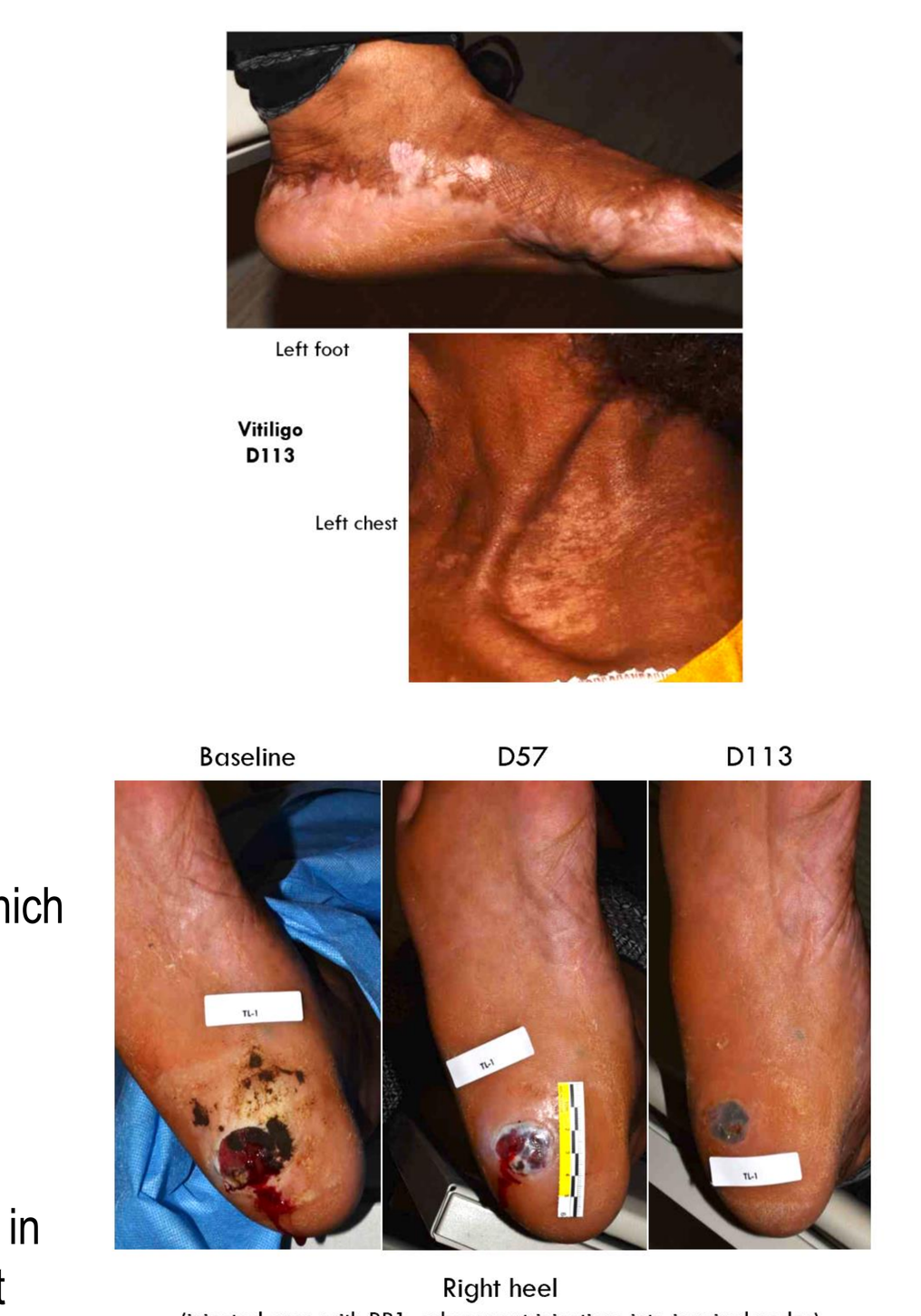


- Oncimmune have developed a high throughput approach to detecting autoimmune B cell responses which may be useful biomarkers for immuno-oncology
- This platform was used to assess pre- and post- blood samples (29 days) from four RP1+nivolumab treated patients
- Increased reactivity was seen to 72 proteins: 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

Nanostring analysis shows increased immune activation



RP1 combined with nivolumab induces vitiligo (phase 2 patient)



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

Biomarker conclusions

- The majority of biopsies were tumor free and/or heavily necrotic by day 43 which hindered quantification by IHC
- Increases in CD8 T cells & PD-L1 were seen across tumor types
- Reversal of T cell exclusion was observed
- Increases in autoimmune B cell responses were seen
- Increases in the tumor inflammatory score & changes in expression of genes in the bespoke oncolytic virus gene panel by Nanostring analysis indicated potent activation of both innate & adaptive immunity
- Overall, the data suggested broad immune activation by RP1

Overall conclusions

- RP1 is well tolerated alone & combined with nivolumab
- Both direct injection of superficial & nodal tumors, & imaging guided injection of deep/visceral tumors were well tolerated and practical
- RP1 provides potent oncolytic activity & abscopal effects
- Clinical activity was seen for RP1 alone & combined with nivolumab
- CD8 T cell levels and PD-L1 were increased across tumor types
- The kinetics of detection of RP1 suggests robust virus replication
- The clinical activity observed in CSCC and anti-PD1 refractory melanoma provides strong support for expanding the clinical programs with RP1 in these tumor types
  - New study as single agent in solid organ transplant recipients with CSCC
  - New study combined with anti-PD1 therapy in anti-PD1 refractory melanoma