A multicenter, Phase 1/2 clinical trial of RP1, an enhanced potency oncolytic HSV, combined with nivolumab: Updated results from the skin cancer cohorts

Mark R. Middleton[1], Francesca Aroldi[1], Joseph J. Sacco[2], Mohammed M. Milhem[3], Brendan D. Curti[4], Ari M. Vanderwalde[5], Scott Baum[5], Adel Samson[6], Anna C. Pavlick[7], Jason Alan Chesney[8], Jiaxin Niu[9], Terence Duane Rhodes[10], Tawnya Lynn Bowles[10], Robert Conry[11], Anna Olsson-Brown[2], Douglas Earl Laux[3], Howard Kaufman[12], Praveen K. Bommareddy[13], Alex Deterding[13], Selda Samakoglu[13], Robert S. Coffin[13], Kevin Harrington[14].
[1]Churchill Hospital, Oxford, UK; [2]Clatterbridge Cancer Centre, Wirral, UK, [3]University of Iowa, IA; [4]Providence Cancer Center, Portland, OR; [5]West Cancer Center, TN; [6]University of Leeds, UK, [7]NYU Langone Medical Center, NY; [8]Brown Cancer Center, University of Louisville, KY; [9]Banner MD Anderson Cancer Center, Gilbert, AZ; [10]Intermountain Med Ctr, UT;; [11]University of Alabama, AL; Jefferson City Medical Grp, Columbia, MO; [12]Massachusetts General Hospital, MA, [13]Replimune Inc, Woburn, MA, [14]Royal Marsden Hospital, UK.

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 based on a new clinical strain which expresses a fusogenic glycoprotein (GALV-GP R-) and GM-CSF which is being tested in combination with nivolumab in patients with a range of solid tumor types (NCT03767348)
- RP1 is administered by direct or imaging guided injection into tumors, including at visceral sites
- The objectives of the phase 2 portion of the clinical trial are to assess the safety and efficacy of RP1 combined with nivolumab in 30 patient cohorts of patients with melanoma, non-melanoma skin cancer (NMSC), and MSI-H tumors, with additional cohorts of anti-PD1 relapsed refractory NSCLC (N=30) and anti-PD1 relapsed refractory cutaneous melanoma (N=125) subsequently being added based on the initial data seen
- Phase 1 data was reported at SITC 2019, with initial Phase 2 data reported in June 2020
- Updated data from the patients with skin cancer is presented here
- This includes the 30 patient phase 2 melanoma cohort which completed enrollment in January 2020 and data from the still enrolling NMSC cohort together with melanoma & NMSC patients from the initial phase 1 expansion group of RP1 combined with nivolumab (N=57 for the safety evaluable population; N = 53 for the efficacy evaluable population; data cut-off October 15th 2020)

Key inclusion & exclusion criteria (melanoma & NMSC cohorts)

- At least 1 measurable & injectable tumor of ≥ 1 cm
- ECOG performance status 0-1
- Lactate dehydrogenase (LDH) < 1.5 × ULN (melanoma patients)
- PD1 directed therapy: Allowed for melanoma; not allowed for NMSC
- No prior treatment with an oncolytic therapy
- No known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are radiologically stable.

Key objectives:

- Primary: To assess the safety and tolerability of RP1 in combination with nivolumab
- Secondary: To assess the efficacy of RP1 in combination with nivolumab as determined by DOR, CR rate, disease control rate (DCR), PFS, and 1-year and 2-year OS

Data summary

Safety:

- Treatment with RP1 combined with nivolumab results in predominantly Grade 1/2 side effects with Grade 3 side effects being more rarely seen, with no treatment related Grade 4 or 5 side effects observed

Melanoma:

- In cutaneous melanoma patients who have failed prior anti-PD1 or combined ipilimumab/nivolumab, the current ORR is 31.3% in a particularly advanced population (87.5% Stage IV M1b/c)
- Responses are durable & systemic (abscopal effects seen), including following injections to visceral sites
- Evidence of activity has also been seen in anti-PD1 relapsed/refractory uveal & mucosal melanoma

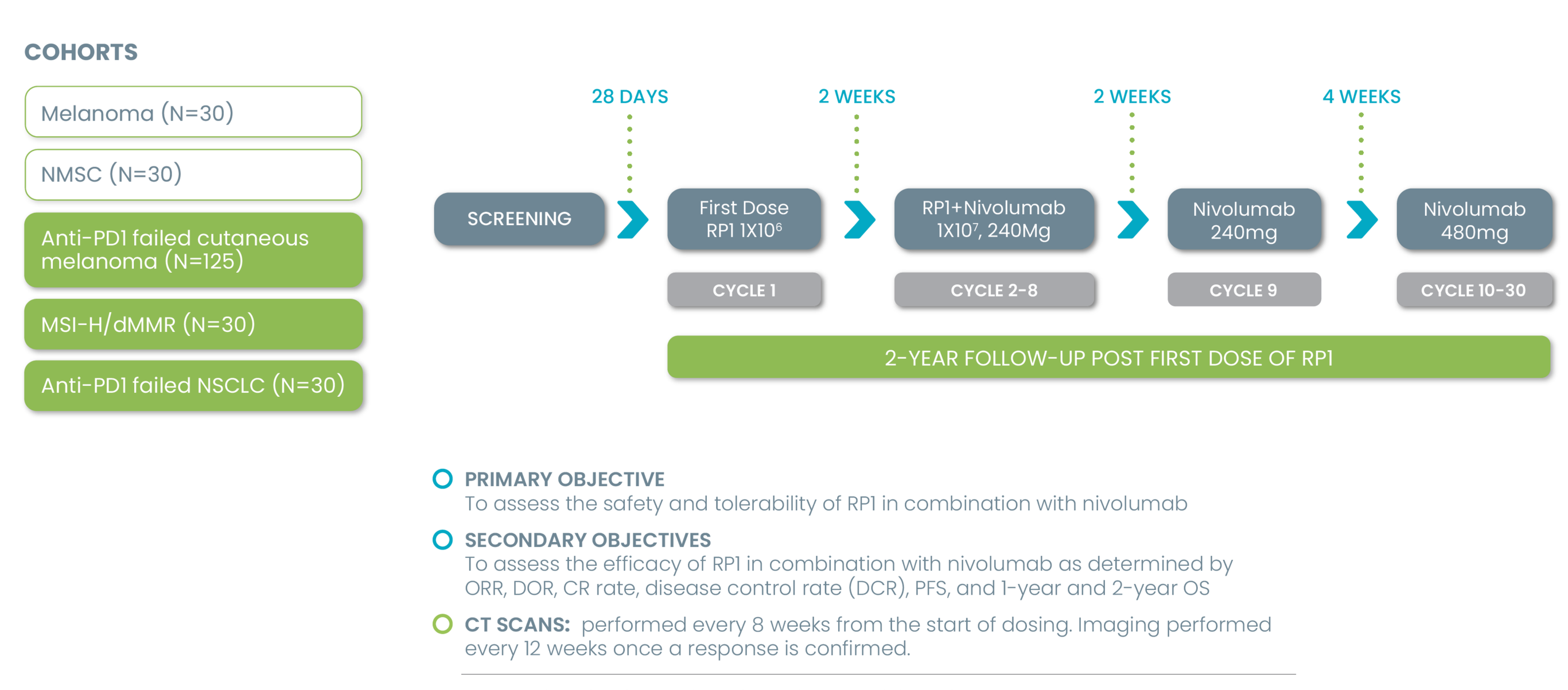
NMSC:

- Compelling, deep & durable activity continues to be seen in cutaneous squamous cell carcinoma (CSCC)
- Activity also seen in angiosarcoma

Biomarkers:

- Clear increases in PD-L1 and CD8 staining are seen in tumor biopsies, with Nanostring data also indicating broad activation of the immune system

Clinical trial design (Phase 2)



Patient demographics

All skin cancer patients

Patients with skin cancer	Expansion/Phase II (N=57)
Median age, years (range)	66 (28 - 97)
Female	23 (40.4%)
Male	34 (59.6%)
ECOG Performance 0 1	 33 (57.9%) 24 (42.1%)
Tumor Types Cutaneous melanoma (anti-pd1naive) Cutaneous melanoma (prior anti-pd1 therapy) Uveal melanoma Mucosal melanoma Cutaneous squamous cell carcinoma (CSCC) Basal cell carcinoma Merkel cell carcinoma Angiosarcoma	 8 (14.0%) 16 (28.1%) 6 (10.5%) 6 (10.5%) 13 (22.8%) 3 (5.3%) 2 (3.5%) 3 (5.3%)

Patients with melanoma

	Cutaneous melanoma	Mucosal melanoma	Uveal melanoma
Number	24	6	6
Age: Range	28-95	40-78	44-85
Prior anti-PD1	16*	5	4
Prior single agent anti-PD1	7	1	1
Prior anti-PD1/anti-CTLA-4	9	4	3
Stage IIIc	2	0	0
Stage IV M1a	3	4	0
Stage IV M1b	10	1	0
Stage IV M1c	9	1	6
Stage IV M1b/c %	79%	33%	100%

*87.5% with Stage IV M1b/c (visceral) disease

Patients with NMSC

	Cutaneous squamous cell carcinoma	Basal cell carcinoma	Merkel cell carcinoma	Angiosarcoma
Number	13	3	1*	3
Age: Range	47-80	56-83	60-60	43-97
Metastatic	8			
Locally advanced	5			
Prior radiation	7	2	1	1
Prior chemotherapy	3	1	0	1

*Data not entered for second MCC patient (first dose 13th Oct 2020)

Anti-tumor activity

Patients with melanoma

Intent to treat population

	Cutaneous: Anti-PD1 naive	Cutaneous: PD1-failed	Mucosal: Anti-PD1 naive	Mucosal: PD1 failed	Uveal: Anti-PD1 naive	Uveal: PD1 failed
Number of Patients	8	16	1	5	3	3
Best overall response n (%)						
CR	2 (25.0)	1 (6.3)	0	1 (20.0)	0	0
PR	2 (25.0)	4 (25.0)	1 (100.0)	0	0	0
SD	4 (50.0)	2* (12.5)	0	0	1 (33.3)	3 (100.0)
PD	0	8 (50.0)	0	4 (80.0)	2 (66.7)	0
ORR	4 (50.0)	5 (31.3)	1 (100.0)	1 (20.0)	0	0
CR+PR+SD	8 (100.0)	7 (43.8)	1 (100.0)	1 (20.0)	1 (33.3)	3 (100.0)
DOR (mos.) Median Range	>8.86 >6.18 - >11.8	>6.98 >4.66 - >12.3	>5.42 >5.42	>6.74 >6.74	NA	NA

* 1 patient classified as SD achieved surgical CR; the other SD patient remains on treatment at 10 months

Patients with NMSC

Efficacy evaluable population (Patients with at least one tumor assessment or PD)

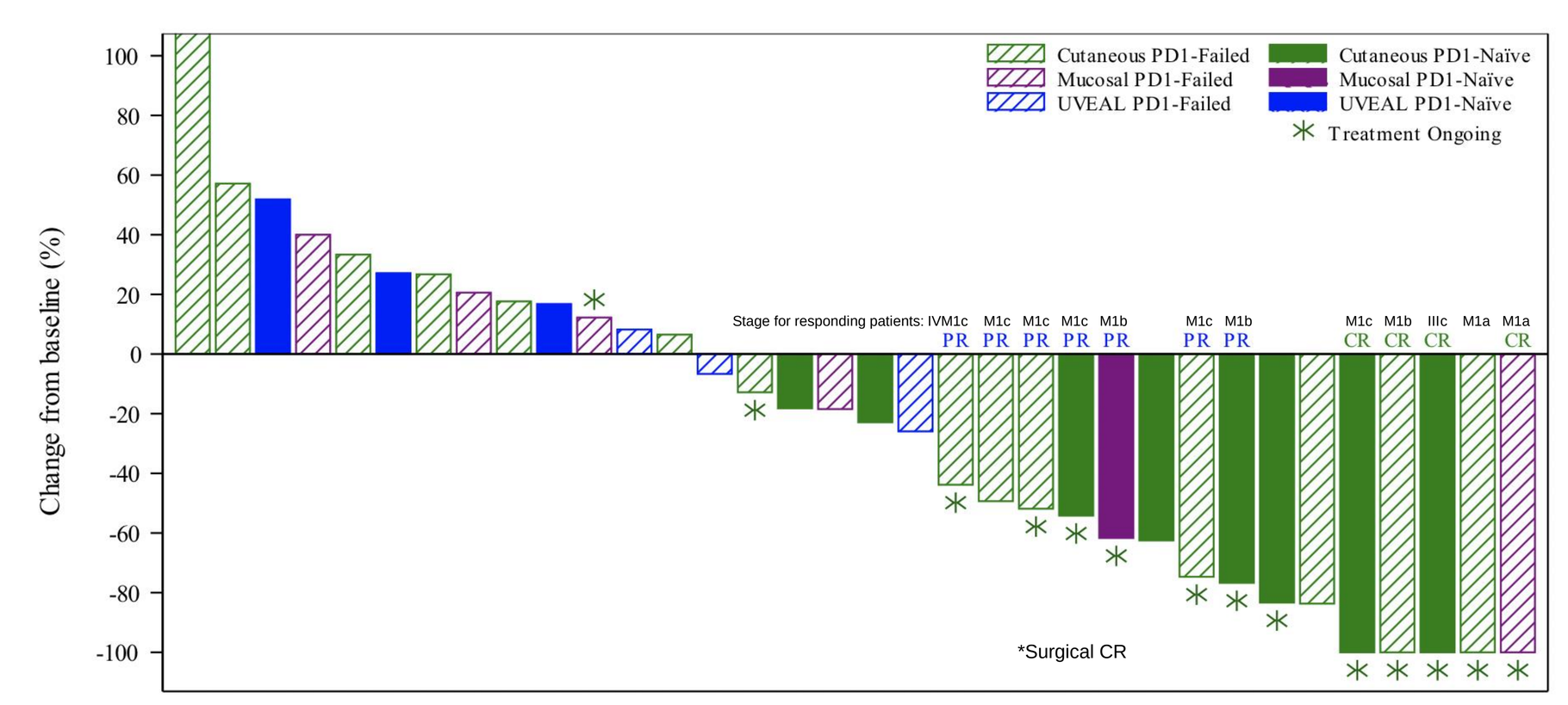
	CSCC	BCC	Merkel cell carcinoma	Angiosarcoma
Number of patients	11	3	1	3
Best overall response n (%)				
CR	5 (45.5)	0	0	0
PR	3* (27.3)	0	0	2 (66.7)
SD	1# (9.1)	2 (66.7)	0	1 (33.3)
PD	2 (18.2)	1 (33.3)	1 (100)	0
ORR	8 (72.7)	0	0	2 (66.7)
CR+PR+SD	9 (81.8)	2 (67.7)	0	3 (100)
DOR (mos.) Median Range	>4.66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

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

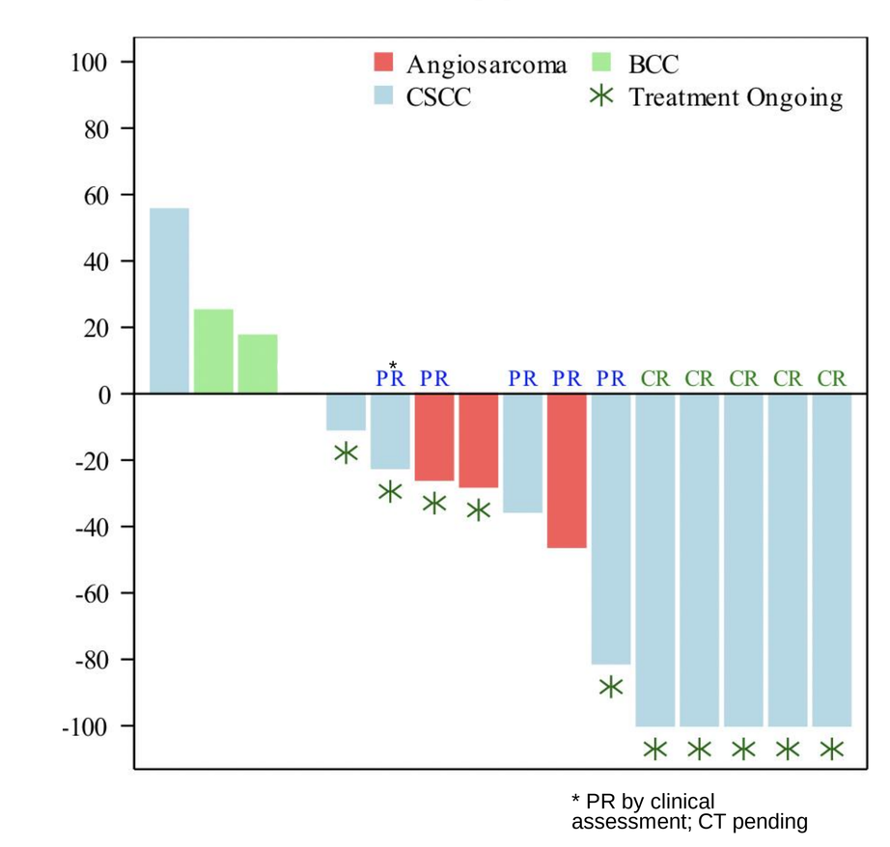
Maximum percent tumor reduction

Patients with follow up scans

Melanoma



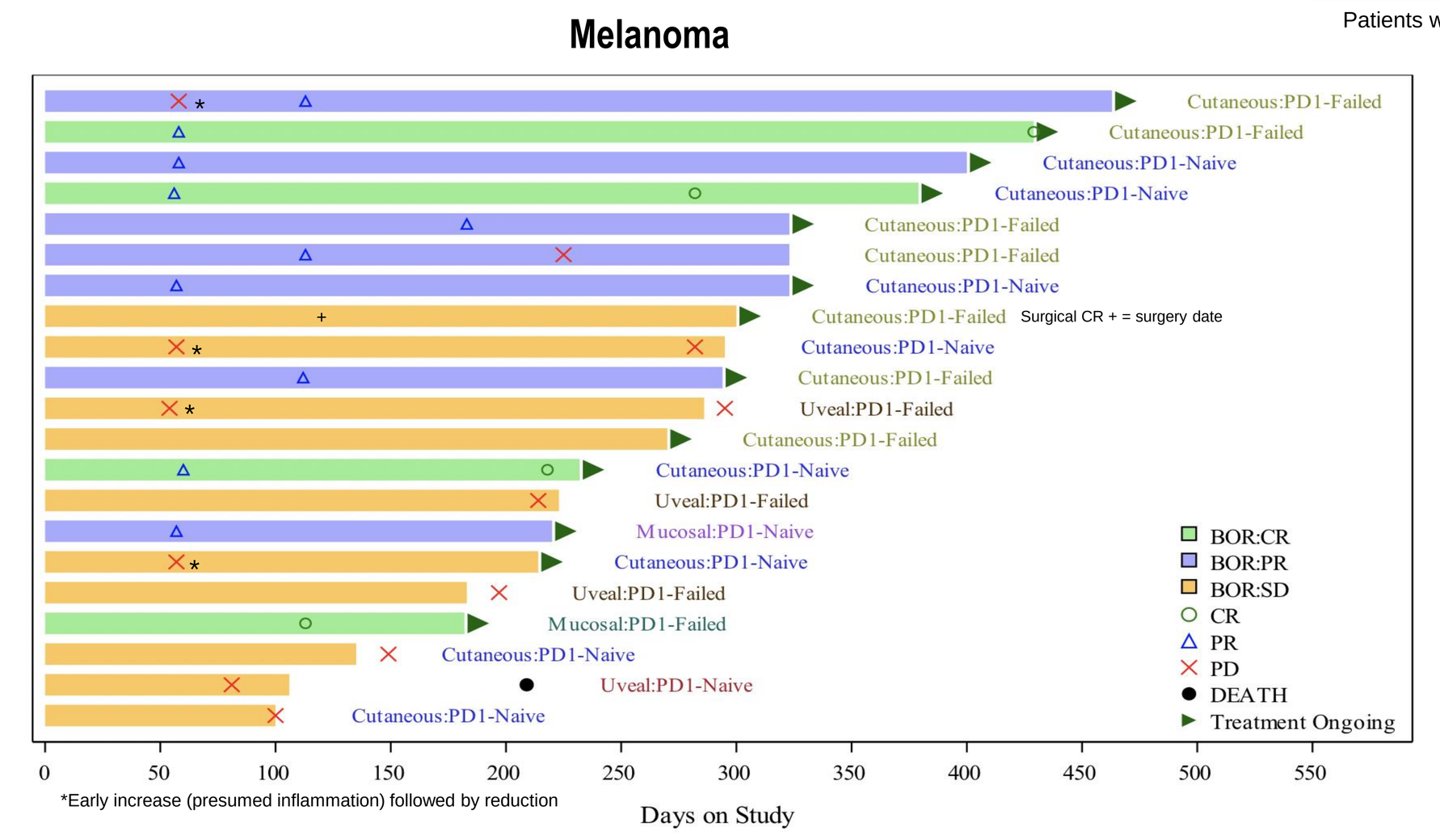
NMSC



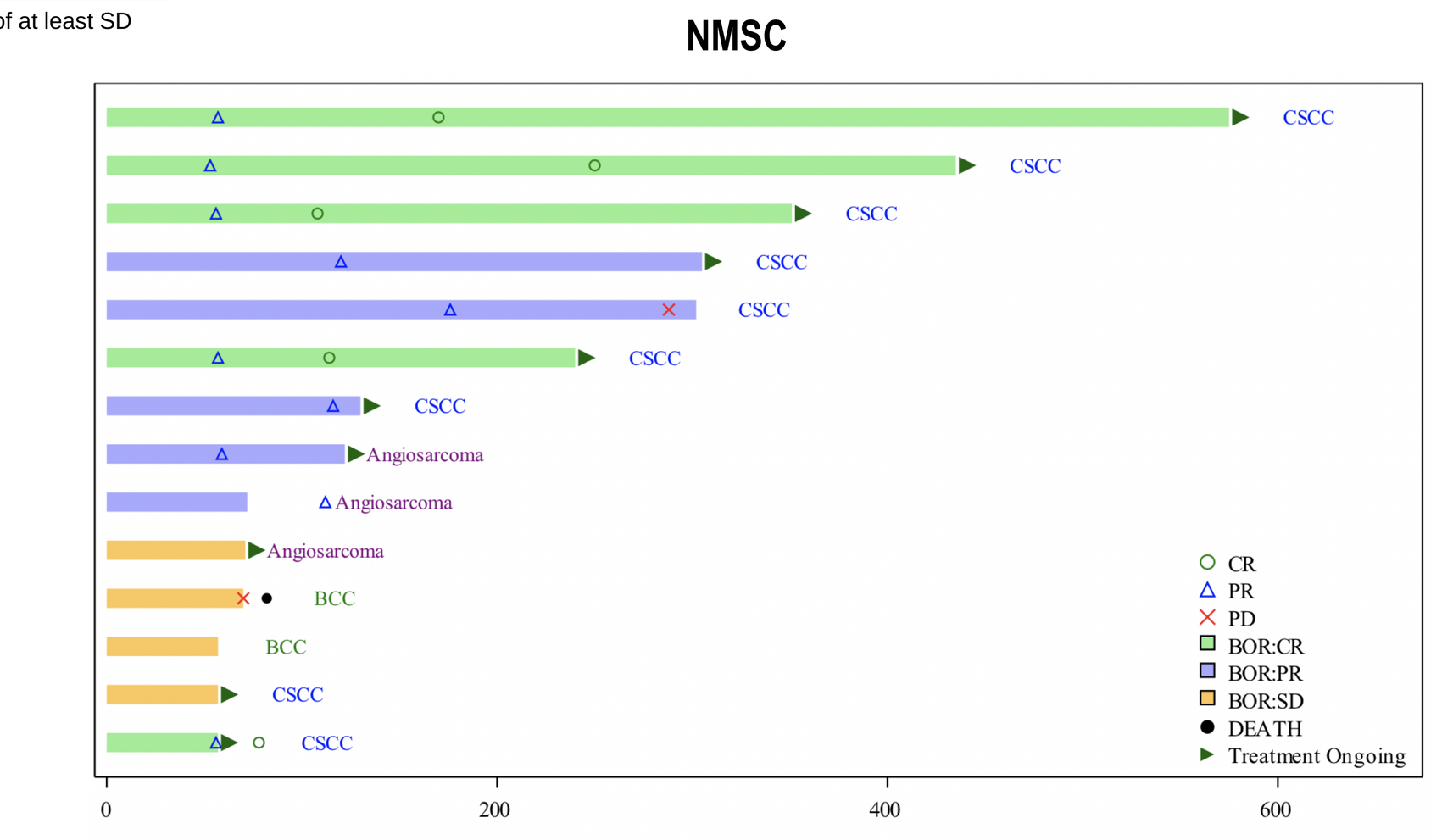
Duration of best response

Patients with a best response of at least SD

Melanoma



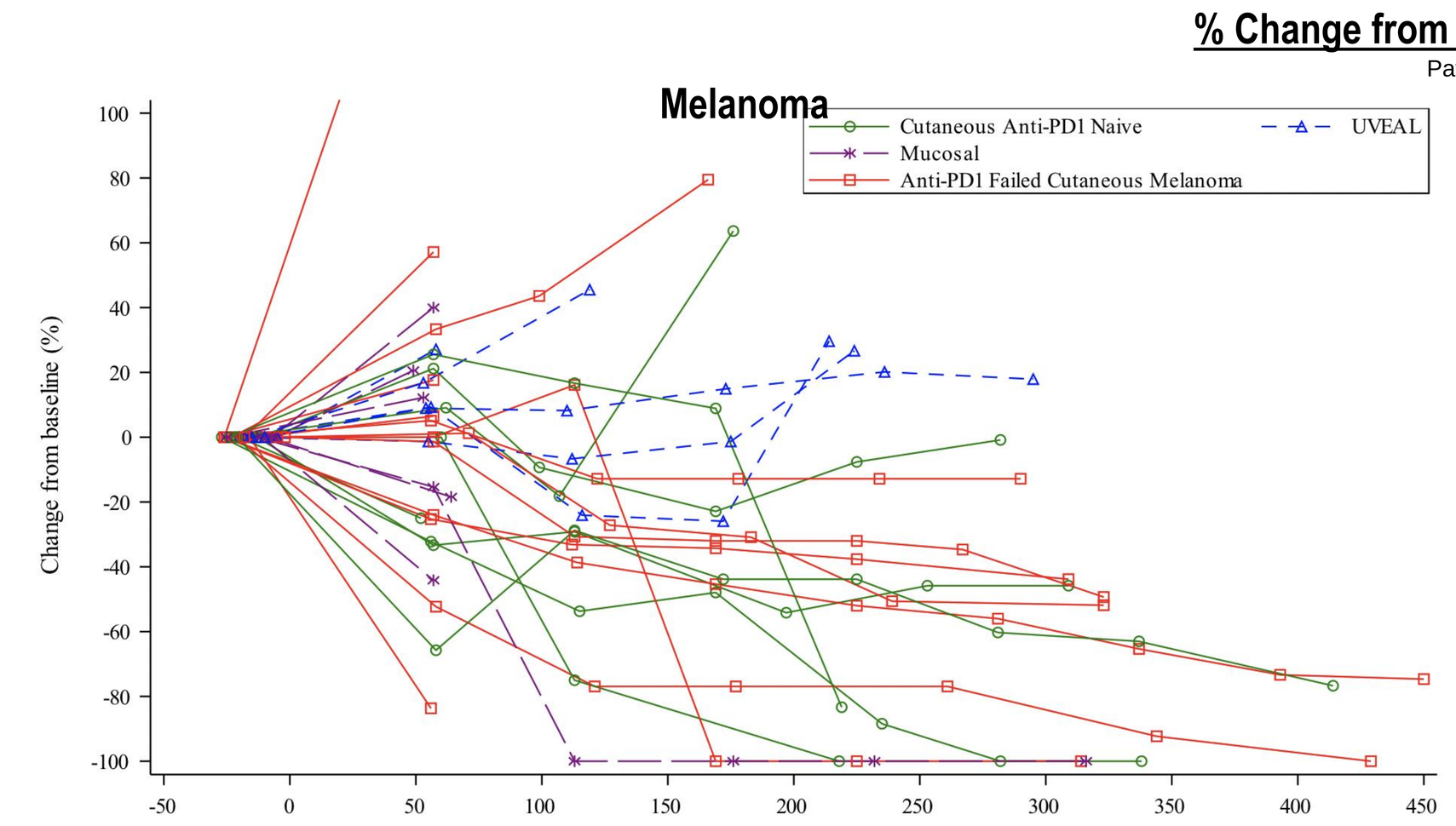
NMSC



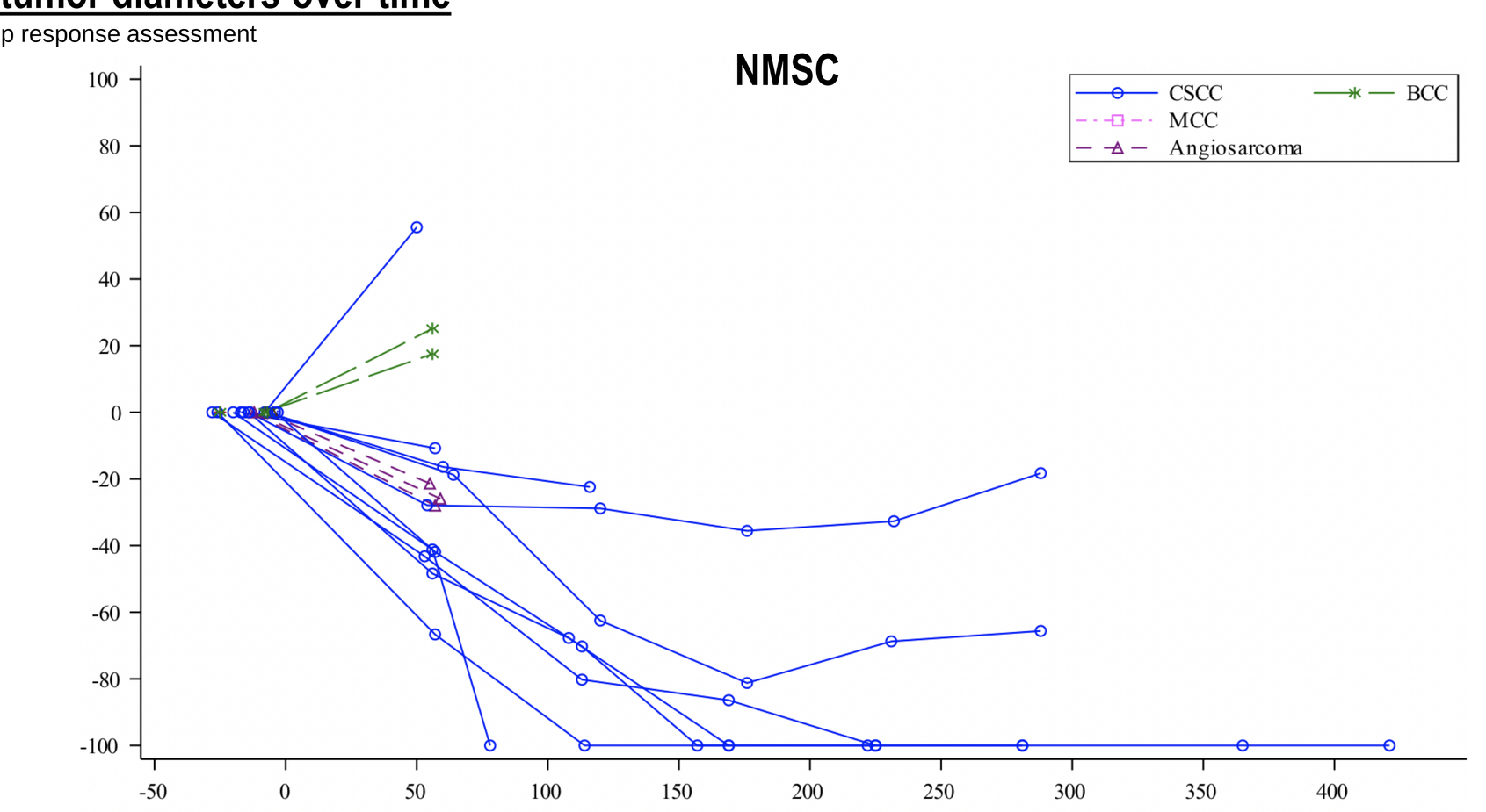
% Change from baseline in sum of tumor diameters over time

Patients with at least one follow up response assessment

Melanoma



NMSC



Safety & tolerability

Treatment related to either RP1 or nivolumab AEs in safety evaluable patients with melanoma and NMSC

Preferred Term	All Grades ≥10% of patients (N=57) n (%)	All Grade≥3 (N=57)
Pyrexia	21 (36.8)	1 (1.8)
Chills	20 (35.1)	
Fatigue	20 (35.1)	5 (8.8)
Influenza like illness	16 (28.1)	
Pruritis	14 (24.6)	
Nausea	13 (22.8)	
Rash	8 (14.0)	
Vomiting	7 (12.3)	
Diarrhoea, headache, myalgia, tumor pain	6 (10.5 each)	
Hypotension		2 (3.5)
Lipase increased		2 (3.5)
Rash maculo-papular		2 (3.5)
ALT increased, AST increased, decreased appetite, dehydration, eczema, injection site necrosis, localized oedema, lymph node pain, oedema, seroconversion test positive*, uveitis, vertigo		1 (1.8) for each

** AE term expected to change, query resolution pending*

No Grade 4/5 related events were reported

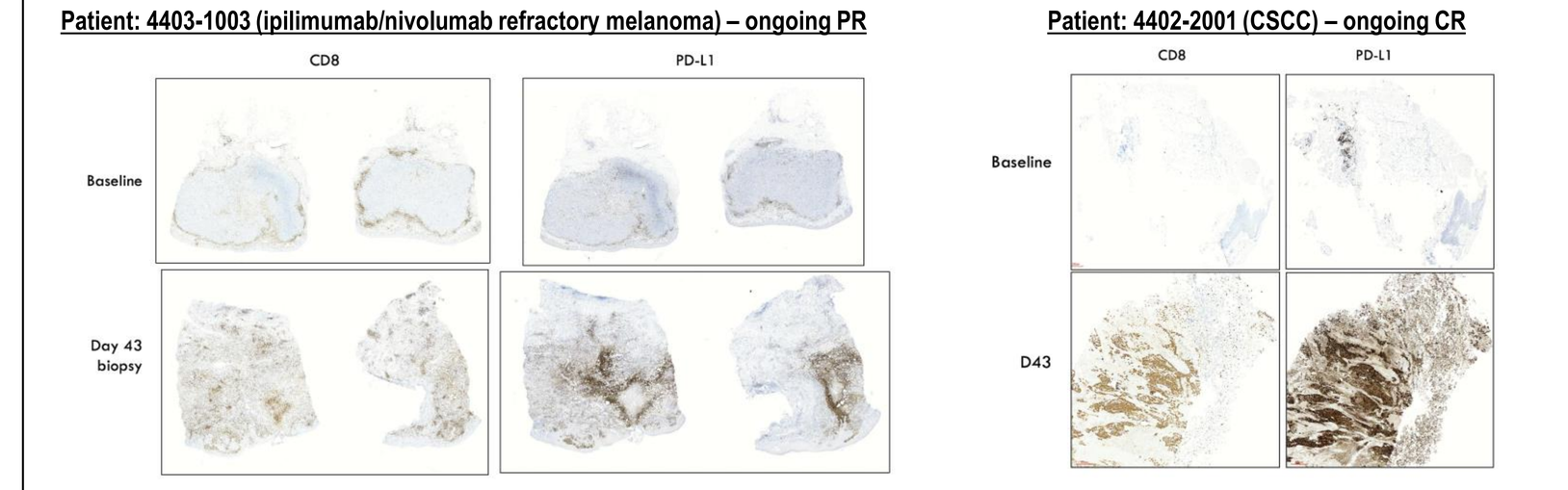
Safety & tolerability conclusions

- RP1 combined with nivolumab continues to demonstrate an acceptable safety profile, with most AE's being Grade 1/2
- Both direct injection of superficial & nodal tumors, & imaging guided injection of deep/visceral tumors were well tolerated and practical, with comparable safety between the two groups

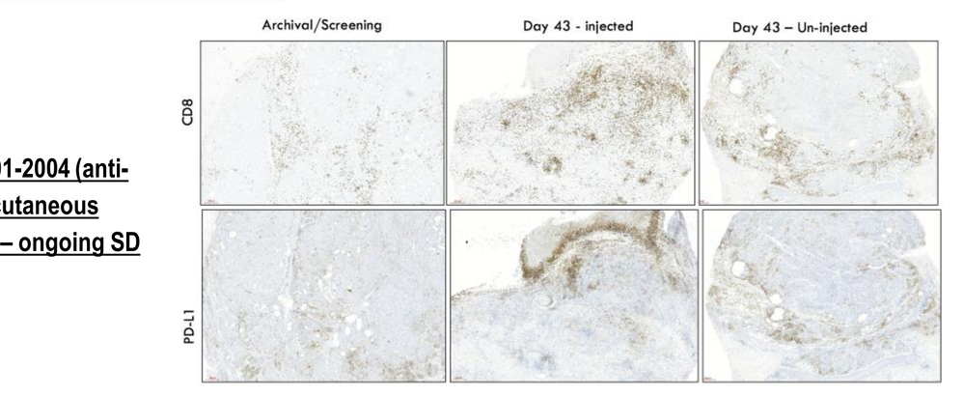
Biomarkers

Patient: 4403-1003 (ipilimumab/nivolumab refractory melanoma) – ongoing PR

Patient: 4402-2001 (CSCC) – ongoing CR



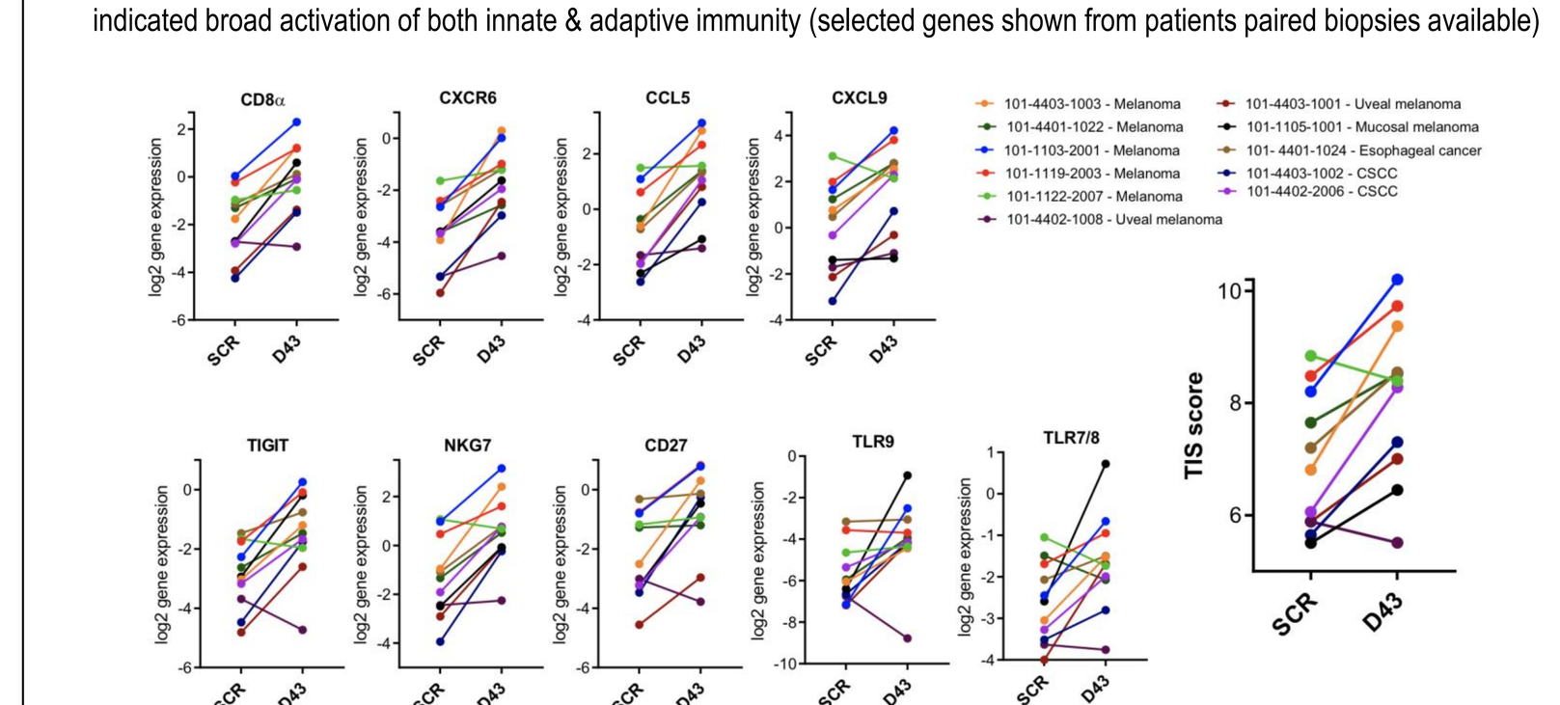
Patient: 4401-2004 (anti-PD1 naïve cutaneous melanoma) – ongoing SD



Biopsies were taken from an injected (& rarely uninjected) lesions at screening and D43 for immunohistochemistry & Nanostring analysis

Nanostring analysis indicates broad immune activation

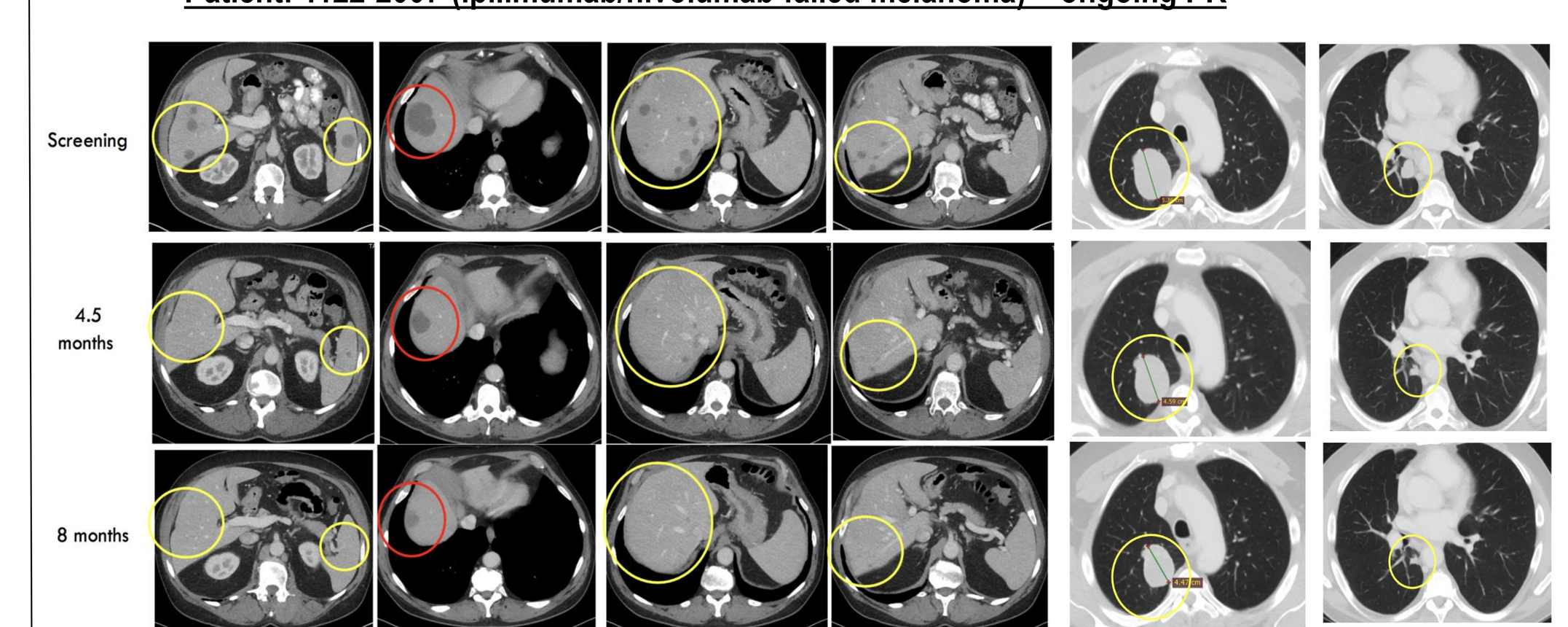
Tumor inflammatory score (TIS) was determined on the basis of an 18 gene signature previously identified as being associated with response to anti-PD1 therapy (Ayers M et al. JCI. 2017), included in a bespoke 40 gene panel. Both TIS & other genes indicated broad activation of both innate & adaptive immunity (selected genes shown from patients paired biopsies available)



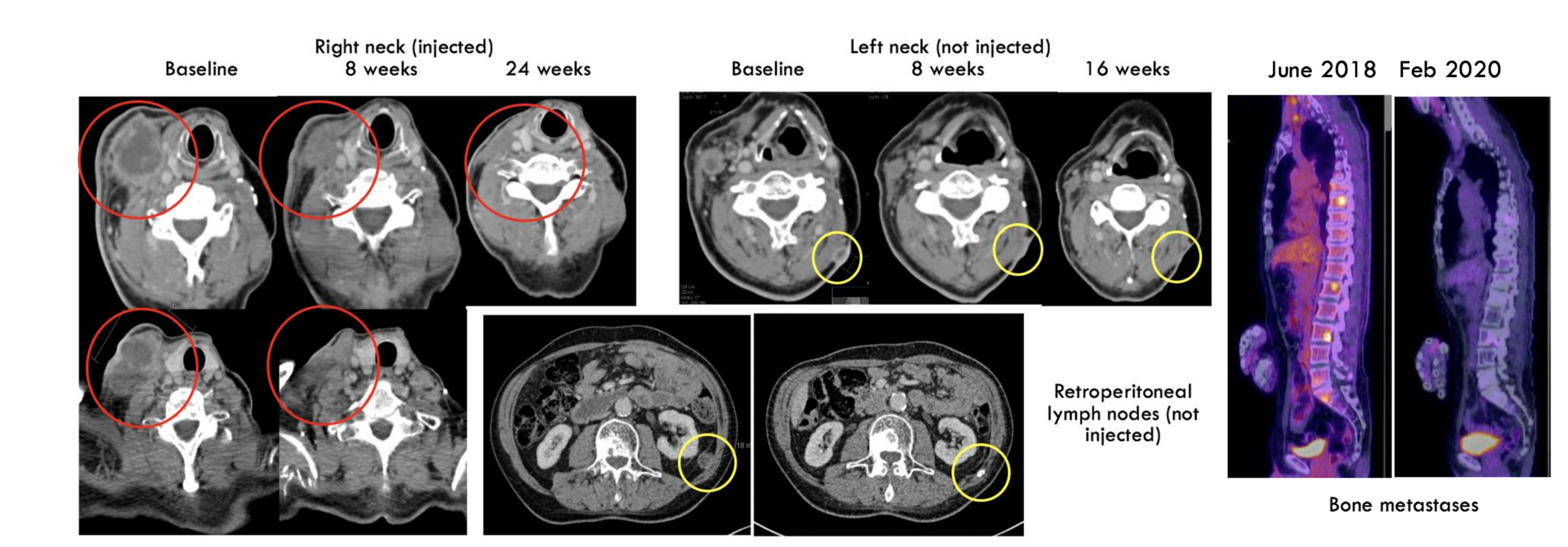
Example patients

(Further examples are at www.replimune.com)

Patient: 1122-2007 (ipilimumab/nivolumab failed melanoma) – ongoing PR



Patient 4402-2001 (Chemoradiation/carboplatin/5-FU failed CSCC) - ongoing CR



Overall conclusions

Safety

- RP1 combined with nivolumab continues to be well tolerated in patients with skin cancer
- RP1 can be safely injected into superficial & subcutaneous tumors & also into deep/visceral tumors using imaging guidance, including into tumors in e.g. the liver or lung
- Safety is comparable between the two routes of administration

Efficacy

- A compelling frequency of response is seen in patients with skin cancers
- This includes in anti-PD1 failed melanoma & in CSCC
- In CSCC a particularly high rate of complete responses has been observed, including in both injected and non-injected tumors
- Systemic overall responses are seen irrespective of sites of disease & of injection, including responses of tumors in visceral organs
- Responses are durable, with only one responding melanoma & and one responding CSCC patient having progressed
- Many patients not achieving RECIST response achieve disease control, which is often of clinically meaningful duration
- In addition to CSCC & melanoma, promising evidence of activity has also been seen in angiosarcoma

Biomarkers

- Increases in PD-L1 and CD8 staining in tumor biopsies are reproducibly seen, including in biopsies from uninjected tumor
- The tumor inflammatory score (TIS) was also increased, with Nanostring indicating broad activation of innate & adaptive immunity

Overall

- Dosing of RP1 into both superficial & deep tumors is both feasible & well tolerated
- RP1 combined with nivolumab is a promising approach to the treatment of patients with skin cancers, including those with widespread metastatic disease
- Systemic efficacy has been observed with responses in superficial & visceral tumors which have not been injected
- The data to date support the registration directed studies of RP1 combined with either cemiplimab or nivolumab in patients with CSCC (NCT04050436) & anti-PD1 failed cutaneous melanoma (NCT03767348) respectively