Initial results of a phase 1 trial of RP2, a first in class, enhanced potency, anti-CTLA-4 antibody expressing, oncolytic HSV as single agent and combined with nivolumab in patients with solid tumors

Francesca Aroldi[1], Joseph J. Sacco[2], Kevin Harrington[3], Anna Olsson-Brown[2], Pablo Nanclares[3], Lavita Menezes[4], Praveen K. Bommareddy[4], Suzanne Thomas[4], Howard Kaufman[5], Selda Samakoglu[4], Robert S. Coffin[4], Mark R. Middleton[1]

[1]Churchill Hospital, Oxford, UK; [2]Clatterbridge Cancer Centre, Wirral, UK; [3]Royal Marsden Hospital, UK; [4]Replimune Inc, Woburn, MA; [5]Massachusetts General Hospital, MA.

Overview

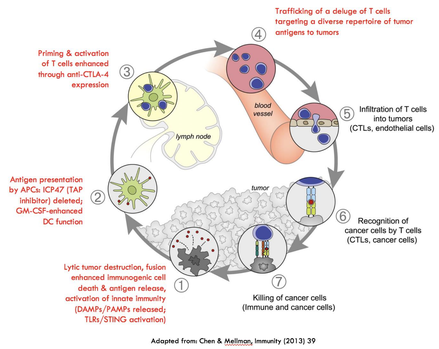
Rationale for RP2

- Administration of systemic anti-CTLA-4 (ipilimumab) is clinically active & FDA approved alone & when combined with PD1 blockade
- However, the efficacy of single agent anti-CTLA-4 is modest, and while improved in combination with anti-PD1 is associated with frequent toxicities, including dose related G≥3 irAEs of approximately 5%–25% & only a limited number of 'immunologically hot' tumor types respond
- We hypothesized that the likely lack of ongoing antigen presentation in most cancer patients (Signal 1), limits the efficacy of anti-CTLA-4, as the B7/CTLA-4 negative feedback loop interaction is only activated following engagement of T cells with antigen presenting cells
  - In most patients, anti-CTLA-4 alone would therefore not be expected to be clinically effective
- We further hypothesized that providing potent antigen release and inflammation through oncolytic tumor destruction, combined with expression of an anti-CTLA-4 antibody directly in the tumor would provide potent 'Signal 1' and APC/T cell engagement, and that the expressed anti-CTLA-4 would then block the B7/CTLA-4 negative feedback which would otherwise dampen the anti-tumor immune response which was generated
  - This would be expected to augment the systemic efficacy of oncolytic immunotherapy, provide enhanced clinical activity as compared to the use of systemic anti-CTLA-4, & also reduce anti-CTLA-4-mediated toxicity, when given as single agent and when combined with PD1 blockade

Description of RP2

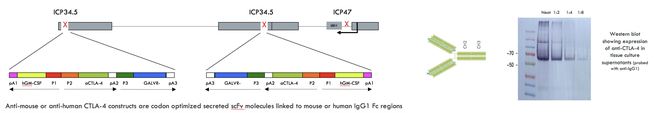
- RP2 is an oncolytic immuno-gene therapy based on herpes simplex virus (HSV) with the following properties:
  - Derived from a new clinical isolate of HSV resulting from a comprehensive screen of clinical strains for their ability to infect & kill human tumor cells
  - Deleted for the HSV gene encoding ICP34.5 to provide tumor selectivity
  - Has the HSV US11 gene upregulated to overcome the reduction in replication in tumors otherwise resulting from deletion of ICP34.5
  - Has ICP47 deleted to prevent inhibitions of antigen presentation (ICP47 blocks TAP)
  - Expresses GM-CSF – promotes dendritic cell expansion & maturation
  - Expresses a potent fusogenic protein (GALV-GP R-) which substantially increases tumor killing & immunogenic cell death, thereby intended to maximize Signal 1
  - Expresses an anti-CTLA-4 antibody-like molecule to block the B7/CTLA-4 negative feedback interaction, enhancing both Signal 1 & Signal 2
- The parental virus, RP1, which is identical to RP2 other than for the expression of anti-CTLA-4, has shown compelling clinical activity in combination with nivolumab, and is currently being evaluated in multiple clinical trials including registration-directed development in anti-PD1 relapsed/refractory cutaneous melanoma (in combination with nivolumab) & cutaneous squamous cell carcinoma (in combination with cemiplimab)

RP viruses are designed to maximize systemic immune activation: RP2 intended MOA



Adapted from: Chen & Mellman, Immunity (2013) 39

RP2 – A fusion-enhanced oncolytic HSV expressing anti-CTLA-4

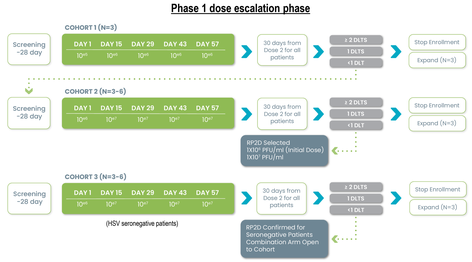


Anti-mouse or anti-human CTLA-4 constructs are codon optimized secreted scFv molecules linked to mouse or human IgG1 Fc regions

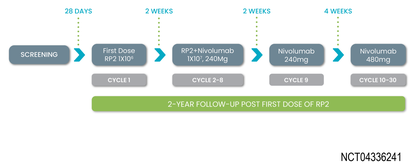
Western blot showing expression of anti-CTLA-4 in tissue culture supernatants (probed with anti-IgG1)

Trial design, key inclusion criteria & objectives

Phase 1 dose escalation phase



Phase 1 combination phase



NCT04336241

Key inclusion & exclusion criteria

- Histologically or cytologically confirmed advanced or metastatic non neurological solid tumors, who 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 tumor of ≥ 1 cm in longest diameter
- Adequate hematologic function
- ECOG performance status 0 – 1
- No prior treatment with an oncolytic therapy
- No active CNS metastases and/or carcinomatous meningitis

Key objectives:

- To determine the recommended Phase 2 dose (RP2D) of RP2
- To assess safety and tolerability
- To assess the objective response rate (ORR) and clinical benefit rate

Current trial status & data presented

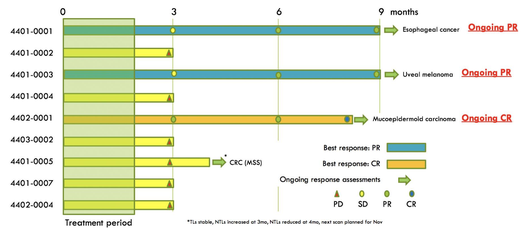
- The dose escalation portion of the trial s fully enrolled, with no dose level expansion, no DLTs having been observed (N=9)
- 10 patients have been enrolled into the combination with nivolumab portion, with initial safety data having shown the combination to be well tolerated so far – no follow up for efficacy is currently available
- The data presented is from the 9 patients enrolled into the dose escalation phase & treated with single agent RP2
- Biomarker data is pending

Detailed patient information

Subject Number	HSV sero status	Tumor type	Prior therapies	Disease sites	Injection site(s)		RP2 doses given/Volume	RECIST v1.1 best response	Other comments
					Superficial/ SC/Nodal	Visceral/ Deep			
4401-0001	+	Esophageal adenocarcinoma	Duvalumab, M6620_ATR Kinase Inhibitor, Capecitabine, Oxaliplatin, Tremelimumab, Radiotherapy	Abdominal lymph nodes, liver		Liver	(10^9PFU)/ 1 ml 4 x (10^8PFU)/ 0.5 ml	**Ongoing confirmed PR @ 12 months from treatment start**	SD at FU1*, PR at FU2** & 9 month scan. No remaining tumor in D43 biopsy.
4401-0002	+	Uveal melanoma	Ipilimumab, Nivolumab, Temozolomide Selumetinib/ Vistusertib, Cabaplatin, Paclitaxel	Axillary, cervical, thoracic supratrochlear LN, liver, lung, omentum, rib, skin, peritoneum	Lesion on chest wall, left axillary skin lesion		(10^9PFU)/ 10 ml 4 x (10^8PFU)/ 10 ml	PD	Died 60 days after last dose
4401-0003	+	Uveal melanoma	Ipilimumab/Nivolumab, Surgery	Liver		Liver	(10^9PFU)/ 3 ml 4 x (10^8PFU)/ 3 ml	**Ongoing confirmed PR @ 11 months from treatment start**	SD at FU1*, PR at FU2** & 9 month scan. Infarcted tumor cells (no viable) in D43 biopsy.
4401-0004	+	Cutaneous melanoma	Interferon, ipilimumab/nivolumab, anti-lag3	lung & vertebrae		Lung	(10^8PFU)/ 10 ml 4 x (10^7PFU)/10 ml	PD	
4402-0001	+	Mucoepidemoid carcinoma	Carboplatin/paclitaxel, bicalutamide, ceralasertib, radiotherapy,	cervical lymph nodes	Lesion on left neck/SCF		(10^8PFU)/ 4 ml (10^7PFU)/ 4 ml 2 x (10^8PFU)/5 ml (10^7PFU)/ 7 ml	**CR, ongoing @ 8 months from treatment start**	PR at both FU1* & FU2**, CR confirmed by PET scan 16th Oct
4403-0002	+	SCC	Carboplatin , cetuximab, 5-FU, nivolumab, P13K delta inhibitor	Cervical lymph nodes	Supraclavicular node		(10^8PFU)/ 0.5 ml 4 x (10^7PFU)/0.5 ml	PD	
4401-0005	_	MSS colon adenocarcinoma	Capecitabine, oxaliplatin, fluorouracil, irinotecan, Lonsurf, mitomycin, AGI-134	Liver, Lung, Peritoneum, Spleen, Stomach		Liver	(10^8PFU)/ 4 ml 4 x (10^7PFU)/4 ml	FU1* (Aug): TLs stable, NTLs increased. Unscheduled scan Sept: NTLs reduced. FU2** planned Nov	
4401-0007	_	Uveal melanoma	Ipilimumab/nivolumab; AGI-134	Skin lesions, liver	Skin lesions		(10^8PFU)/ 10 ml 2 x (10^7PFU)/6 ml	PD	Died due to PD @ 3 months
4402-0004	_	Cutaneous melanoma	Dabrafenib/trametinib, nivolumab	Pelvic Lymph Nodes	Left groin Left thigh		(10^8PFU)/ 10 ml 4 x (10^7PFU)/10ml	PD	PD at 3 months

* 30 days post last RP2 dose ** 4 months post last RP2 dose

Anti-tumor activity & kinetics of response



*TLs stable, NTLs increased at 3mo, NTLs reduced at 4mo, next scan planned for Nov

Patient demographics & safety

Patient demographics and disease characteristics

	RP2 (N=9)
Median age, years (range)	55 (36 - 76)
Female, n (%)	1 (11.1)
Male, n (%)	8 (88.9)
ECOG Performance	
0	6 (66.7)
1	3 (33.3)
Number of prior therapies (Median, Range)	
Prior anti-PD1 (#/%)	6 (66.7)
Prior chemotherapy (#/%)	4 (44.4)
Prior radiotherapy (#/%)	3 (33.3)
Prior other therapy (#/%)	9 (100.0)
Seronegative Patients, n(%)	3 (33.3)
Seropositive Patients, n(%)	6 (66.7)
Tumor Types, n (%)	
Cutaneous melanoma	1 (11.1)
Uveal melanoma	3 (33.3)
Mucosal melanoma	1 (11.1)
Colorectal adenocarcinoma (MSS)	1 (11.1)
Mucoepidemoid carcinoma	1 (11.1)
Squamous cell carcinoma	1 (11.1)
Oesophageal adenocarcinoma	1 (11.1)

Treatment related AEs

	RP2 (N=9)	
	Grades 1-2 N (%)	Grade = 3 N (%)
Any event	6 (66.7)	1 (11.1)
Pyrexia	6 (66.7)	
Fatigue	3 (33.3)	
Hypotension	3 (33.3)	
Chills	2 (22.2)	
Cytokine release syndrome		1 (11.1)*
Hyperhidrosis	1 (11.1)	
Hypocalcemia		1 (11.1)
Influenza like symptoms	1 (11.1)	
Nausea	1 (11.1)	
Rash	1 (11.1)	
Vomiting	1 (11.1)	
Uncoded (Left groin/thigh pain)	1 (11.1)	

*G3 CRS reported in 76 yo male with metastatic melanoma (HSV-1 seronegative) with onset on Day 2 after 1st injection with RP1 and fully recovered with standard medication by Day 5; not recurring upon rechallenge (4 repeat injections).

The patients enrolled

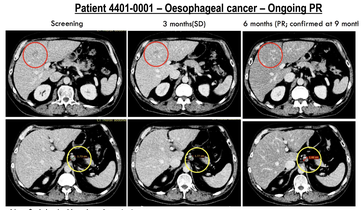
- Patients with heavily pre-treated, advanced solid tumors were enrolled, with a range of tumor types represented

Safety & tolerability conclusions

- Do DLTs were observed, with no dose level expansions being required
- RP2 demonstrated 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

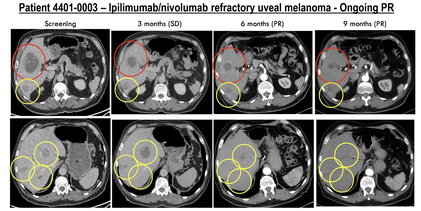
Individual responding patients

Patient 4401-0001 – Oesophageal cancer – Ongoing PR



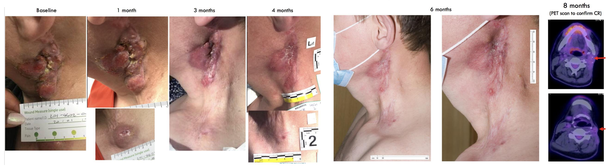
- Liver & abdominal lymph node metastases
- Prior therapies: Durvalumab (anti-PD-L1), M6620, capecitabine, oxaliplatin, cisplatin, chemoradiation
- Liver lesion injected with 1ml $1x10^8$ pfu/ml, then 0.5mL $1x10^8$ pfu/ml x4 RP2 Q2W

Patient 4401-0003 – Ipilimumab/nivolumab refractory uveal melanoma - Ongoing PR



- Extensive liver metastases (others not shown)
- Prior therapies: Ipilimumab/nivolumab
- Largest liver lesion injected with 3ml $1x10^8$ pfu/ml, then 3mL $1x10^7$ pfu/ml x4 RP2 Q2W

Injected Not Injected



Patient 4402-0001 – Mucoepidermoid cancer – Ongoing CR

- Cervical lymph node & 7 SCF metastases
- Prior therapies: Carboplatin/paclitaxel, bicalutamide, ceralasertib
- Cervical lymph node & SCF injected with 10ml $1x10^8$ pfu/ml, then 10mL $1x10^7$ pfu/ml x4 RP2 Q2W
- Dramatic tumor response confirmed as CR by PET/CT

Summary & conclusions

- Single agent RP2 has been generally well tolerated with side effects consistent with those previously seen with RP1
- Compelling clinical activity has been seen in heavily pre-treated advanced cancer patients, with immune insensitive tumor types, including two confirmed partial responses, in uveal melanoma and esophageal cancer, and a complete response in a patient with mucoepidermoid carcinoma
- Responses have been seen in both injected & uninjected tumors and following direct injection into superficial/nodal tumors & and by imaging guided injection to liver lesions
- Initial tumor inflammation appears to precede response; responses in two cases not being observed until the second scan four months after completing the course of 5 RP2 doses
  - A similar pattern may be developing in a third patient (MSS CRC)
- Responses have been durable to date at currently 8-11 months following treatment initiation
- Treatment of patients with RP2 combined with nivolumab is currently underway
- *Overall the data supports the hypothesis that oncolytic immuno-gene therapy-mediated expression of anti-CTLA-4 from RP2 provides potent & systemic anti-tumor effects, without substantial additional toxicity as compared to the oncolytic backbone (RP1), including without evidence of the side effects associated with systemic ipilimumab*