A phase 1 clinical trial of RP2, an enhanced potency oncolytic HSV expressing an anti-CTLA-4 antibody, as a single agent and combined with nivolumab in patients with advanced solid tumors

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Overview

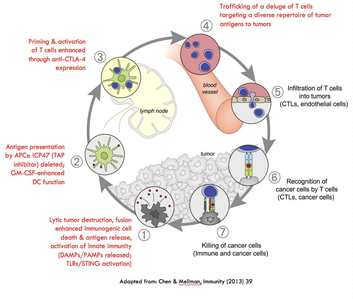
RP2 is an oncolytic immuno-gene therapy based on herpes simplex virus (HSV) with the following properties:

- 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 to promote dendritic cell expansion & maturation
- Expresses a potent fusogenic protein (GALV-GP R-) which substantially increases tumor killing & immunogenic cell death, thereby intended to maximize immunogenic 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 failed cutaneous melanoma (in combination with nivolumab) & cutaneous squamous cell carcinoma (in combination with cemiplimab)
- Data from the dose rising RP2 monotherapy cohorts has previously been presented (SITC 2020)
- This poster presents further follow up from the monotherapy patients and data from the ongoing combination with nivolumab portion of the clinical trial.

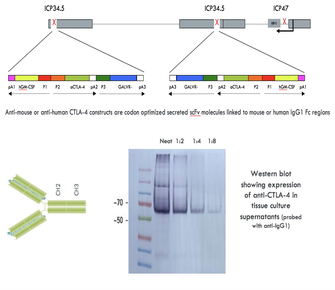
Rationale for RP2

- Administration of systemic anti-CTLA-4 (ipilimumab) is clinically active & FDA approved alone & when combined with nivolumab
- 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) may limit 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
- 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

Intended MOA of RP2



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



Patient demographics & safety

Patient demographics

	RP2 (N=9)	RP2 + Nivo (N=30)
Median age, years (range)	55 (36-76)	57 (36-82)
Female, n (%)	1 (11.1)	13 (43.3)
Male, n (%)	8 (88.9)	17 (56.7)
ECOG Performance		
0	6 (66.7)	16 (53.3)
1	3 (33.3)	14 (46.7)
Prior Therapies, n (%)		
Chemotherapy	4 (44.4)	12 (40)
Other therapy	9 (100)	20 (66.7)
Anti-PD1	7 (77.8)	15 (50)
Radiotherapy	3 (33.3)	23 (76.7)
HSV serostatus, n(%)		
Seronegative	3 (33.3)	8 (26.7)
Seropositive	6 (66.7)	20 (66.7)
Tumor Types, n (%)		
Cutaneous Melanoma	2 (22.2)	9 (30.0)
Uveal Melanoma	3 (33.3)	8 (26.7)
SCCHN	1 (11.1)	3 (10.0)
NPC	0	1 (3.3)
Salivary Gland	0	2 (6.7)
Sarcoma	0	4 (13.3)
Carcinoma	1 (11.1)	1 (3.3)
Chordoma	0	2 (6.7)
Colon Adenocarcinoma	1 (11.1)	0
Oesophageal Adenocarcinoma	1 (11.1)	0

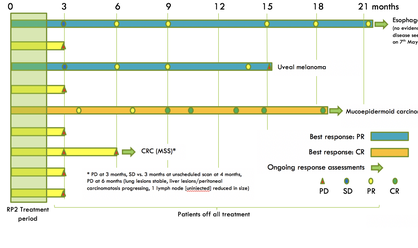
Treatment related adverse events

Preferred Term	Treatment Related AE RP2 Monotherapy (N=9)		Treatment Related AE RP2 + Nivo (N=30)	
	Grade 1 – 2 (All) N (%)	Grade 3 (All) N (%)	Grade 1 – 2 (>10%) N (%)	Grade 3 (All) N (%)
Pyrexia	5 (55.6)	0	17(56.7)	2 (6.7)
Chills	2 (22.2)	0	13 (43.3)	0
Influenza like illness	1 (11.1)	0	11 (36.7)	0
Fatigue	3 (33.3)	0	8 (26.7)	0
Pruritus			6 (20.0)	0
Hypotension	3 (33.3)	0		1 (3.3)
Nausea	1 (11.1)	0		
Vomiting	1 (11.1)	0		
Arthralgia				2 (6.7)
Dysphagia				1 (3.3)
Abdominal pain upper				1 (3.3)
Abscess limb				1 (3.3)
Haemorrhage				1 (3.3)
Hyponatremia				1 (3.3)
Immune-mediated hepatitis				2 (6.7)
Infusion related reaction				1 (3.3)
Myalgia				1 (3.3)
Confusional state	1 (11.1)	0		
Cytokine release syndrome	0	1 (11.1)		1 (3.3)
Hyperhidrosis	1 (11.1)	0		
Hypocalcaemia	0	1 (11.1)		
Injection site pain	1 (11.1)	0		
Rash	1 (11.1)	0		

- RP2 combined with nivolumab has been generally well tolerated, with no new safety signals
- As for RP1, injection into visceral organs has also been well tolerated, with in general only procedure related AEs seen, which are of similar severity & frequency as seen for imaging-guided biopsy

Anti-tumor activity & kinetics of response

RP2 monotherapy response & duration of response (N=9)

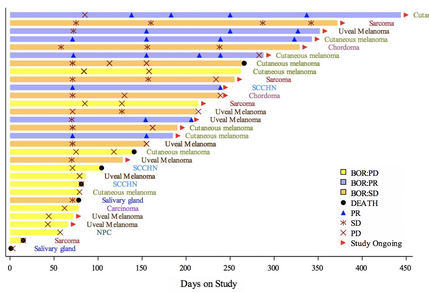


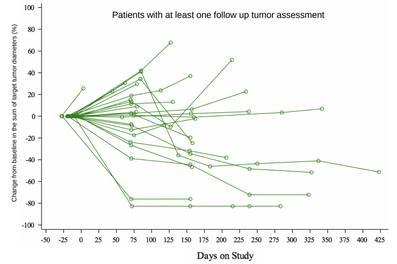
Best response by tumor type for RP2 + nivolumab (N=30)

Tumor type (Prior therapies)	All	Cutaneous melanoma (Anti-PD1 or anti-PD1/anti-CTLA-4 +/- additional prior therapies)	Uveal melanoma (IMCgp100 x1 & ipi/nivo x1; anti-PD1 or anti-PD1/anti-CTLA-4 x4, anti-PD1 naive x3; prior therapy unknown x1)	SCCHN (Chemo/anti-PD1 failed x2; RT failed x1)	Other (NPC, thyroid, salivary, sarcoma, sarcomatoid, chordoma)
# of patients	30	9	8	3	10
Best response					
PR	7	4	2*	1**	0
SD	10	2	3	0	5
PD	13	3	3	2	5
Current ORR	23.3%	44.4%	25%	33%	0%

*Nivolumab and ipilimumab/pembrolizumab failed
**Prior nivolumab, 5-FU/cisplatin, radiotherapy

RP2 + nivolumab duration & kinetics of response (N=30)



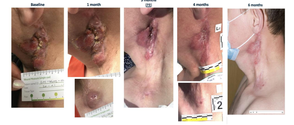


Data cut-off 12th Oct 2021

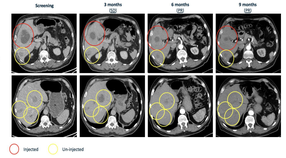
Example patient responses & biomarker data

RP2 monotherapy

Pt 4402-0001 - ongoing CR
- Mucoepidermoid carcinoma of the parotid
- Prior therapies: Carboplatin/ paclitaxel, bicalutamide, cerulasertib
- Cervical lymph node & supraclavicular fossa injected

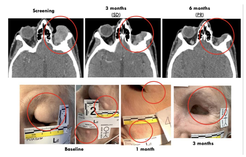


Pt 4401-0003 - PR
- Uveal melanoma
- Extensive liver metastases (others not shown)
- Prior therapies: Ipilimumab/ nivolumab
- Patient progressed at 15 months

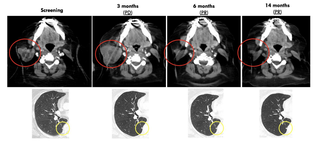


RP2 + nivolumab

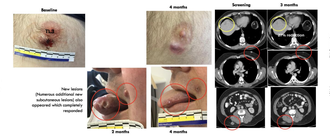
Pt 4402-0007 - PR
- Uveal melanoma
- Disease of the orbit, cheek & iliac bone metastases
- Prior therapies: Nivolumab, radiotherapy



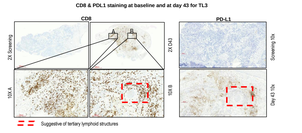
Pt 4403-0004 - PR
- Cutaneous melanoma
- Prior therapies Nivolumab, dabrafenib, trametinib
- Other small lung & brain lesions also stable since baseline
- Had been off work for 3yrs & in significant pain Now off all pain meds & back at work



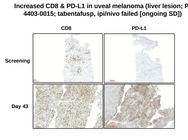
Pt 4401-0016 – Mixed response
- Cutaneous melanoma
- Prior therapies: Nivolumab, Ipilimumab
- Initial response, new lesions appeared which responded, followed by PD at 5 months



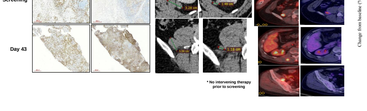
CD8 & PD-L1 staining at baseline and at day 43 for TL3



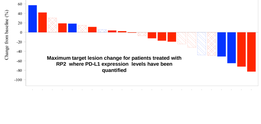
Increased CD8 & PD-L1 in uveal melanoma (liver lesion; Pt 4403-0015; tabentafusp, ipilimvo failed [ongoing SD])



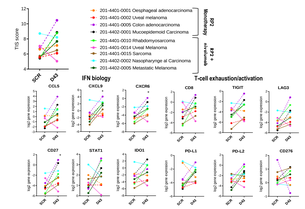
Discordant CD8 & PD-L1 staining at baseline changing to concordant staining at day 43 (deep nodal lesion; Pt 4402-0014; ipilpembro failed uveal melanoma [PR])



The degree of tumor response is not dependent on baseline PD-L1 levels

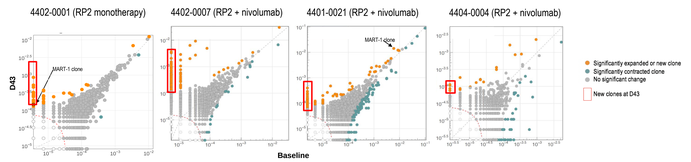


Gene expression data (Nanostring) demonstrates consistent increases in key genes implicated in immune activation and response to anti-PD1 therapy



Increase in peripheral T cell diversity and emergence of new T cell clones

- TCR sequencing of PBMCs revealed expansions of T cell clones post RP2 monotherapy and in combination with nivolumab in the samples subjected to TCR sequencing to date
- Many of the expanded clones are newly detected at Day 43, suggesting that treatment not only expanded existing T cell clones but generated new T cell clones
- Expansion of pre-existing and generation of new T cell clones and specific for MART-1 was observed in a patient treated with RP2 monotherapy and a patient in combination



Trial design

Dose Escalation

Phase 1 Combination

Key Objectives

- To determine the recommended Phase 2 dose (RP2D) of RP2
- To assess safety and tolerability of study treatment
- To assess the efficacy of study treatment

Key inclusion criteria

- Histologically confirmed advanced solid tumors, who have progressed on 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
- Adequate hematologic, hepatic and renal function
- ECOG performance status 0 – 1

Key exclusion criteria

- Prior treatment with an oncolytic therapy
- Known history of hepatitis B or known active hepatitis C virus or human immunodeficiency virus (HIV) infection
- A systemic infection requiring intravenous (IV) antibiotics or other serious infection within 14 days prior to dosing
- Active significant herpetic infections or prior complications of HSV-1 infection (e.g., herpetic keratitis or encephalitis)
- Requires intermittent or chronic use of systemic (oral or intravenous) antivirals with known antiherpetic activity
- Known active CNS metastases

Summary & conclusions

- RP2 monotherapy and RP2 combined with nivolumab have been generally well tolerated
- RP2 monotherapy continues to demonstrate deep & durable responses
  - Mucoepidermoid cancer: Ongoing CR at 19 months
  - Esophageal cancer: Ongoing PR at 22 months; PET scan showed no evidence of metabolic disease on 7th May 2021
  - Uveal melanoma with liver metastases; PR, progressed at 15 months
- As for RP2 monotherapy, RP2 combined with nivolumab has demonstrated durable activity in a Phase 1 patient population with hard-to-treat anti-PD1 failed cancers
  - *All seven responding patients had anti-PD1 failed disease, with durability maintained in all but one to date*
  - *Tumor responses are achieved independent of baseline PD-L1 status*
- Additional patients without formal RECIST responses have experienced extended and ongoing clinical benefit
- Biomarker data continues to support the mechanism of action of igniting an anti-tumor immune response and turning immunologically 'cold' tumors 'hot'
- A protocol amendment is currently being activated to enroll 24 further patients treated with RP2 combined with nivolumab with liver metastases derived from lung, GI, breast cancer & uveal melanoma
- *Overall the data, including the durability of the responses, supports the hypothesis that oncolytic immunotherapy-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*