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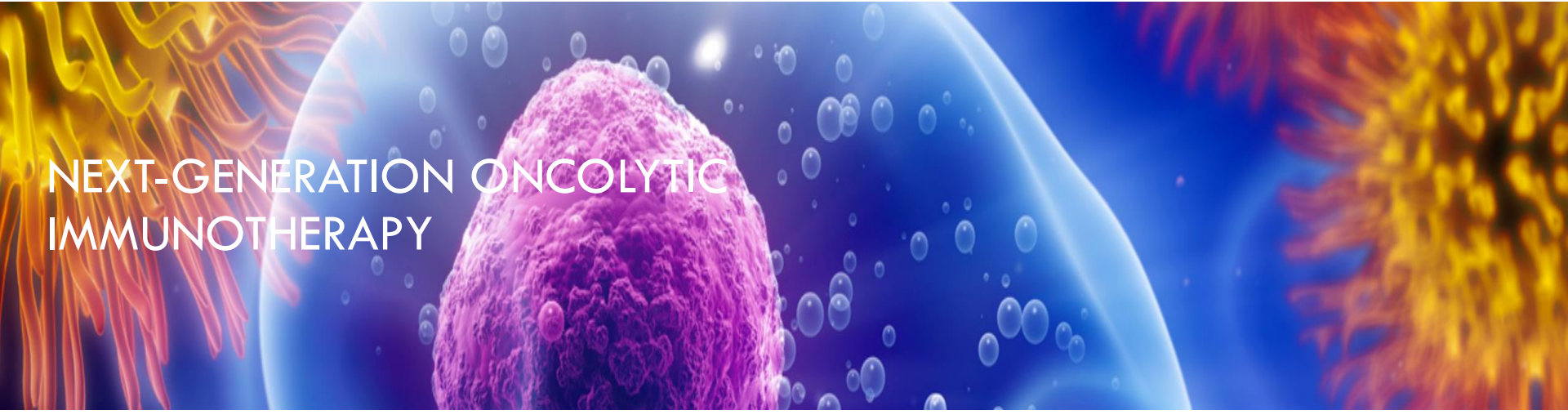

"Next Generation Oncolytic Immuno-Gene Therapy Based on HSV"

Robert Coffin; Replimune Inc

Immuno-Oncology Summit

October 2020

Safe Harbor

Any statements contained herein that are not statements of historical facts may be deemed to be forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including statements regarding the advancement of our clinical trials, patient enrollments in our existing and planned clinical trials and the timing thereof, the potential impact of COVID-19 on our milestones, the results of our clinical trials, the timing and release of our clinical data, our goals to develop and commercialize our product candidates, our expectations regarding the size of the patient populations for our product candidates if approved for commercial use and other statements identified by words such as "could," "expects," "intends," "may," "plans," "potential," "should," "will," "would," or similar expressions and the negatives of those terms. Forward-looking statements are not promises or guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, and which could cause actual results to differ materially from those contemplated in such forward-looking statements. These factors include risks related to our limited operating history, our ability to generate positive clinical trial results for our product candidates, the costs and timing of operating our in-house manufacturing facility, the timing and scope of regulatory approvals, changes in laws and regulations to which we are subject, competitive pressures, our ability to identify additional product candidates, political and global macro factors including the impact of the SARS-COV-2 coronavirus as a global pandemic and related public health issues, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, and other reports we file with the Securities and Exchange Commission. Our actual results could differ materially from the results described in or implied by such forward-looking statements. Forward-looking statements speak only as of the date hereof, and, except as required by law, we undertake no obligation to update or revise these forward-looking statements.

Fundamental issue in cancer treatment: Most cancers go un- or insufficiently recognized by the immune system

The Problem: Most patients don't have any or much of pre-existing immune response to their cancer

As a result

- Immune checkpoint blockade is ineffective in most patients and tumor types
- Depth and durability of response is limited and require other treatments

Our objective

- Develop a new generation of therapy to fully harness the power of the human immune system
- Initiate strong Signal 1 & Signal 2 to ignite the immune response to cancer
- Achieve transformational clinical outcomes in more patients and tumor types

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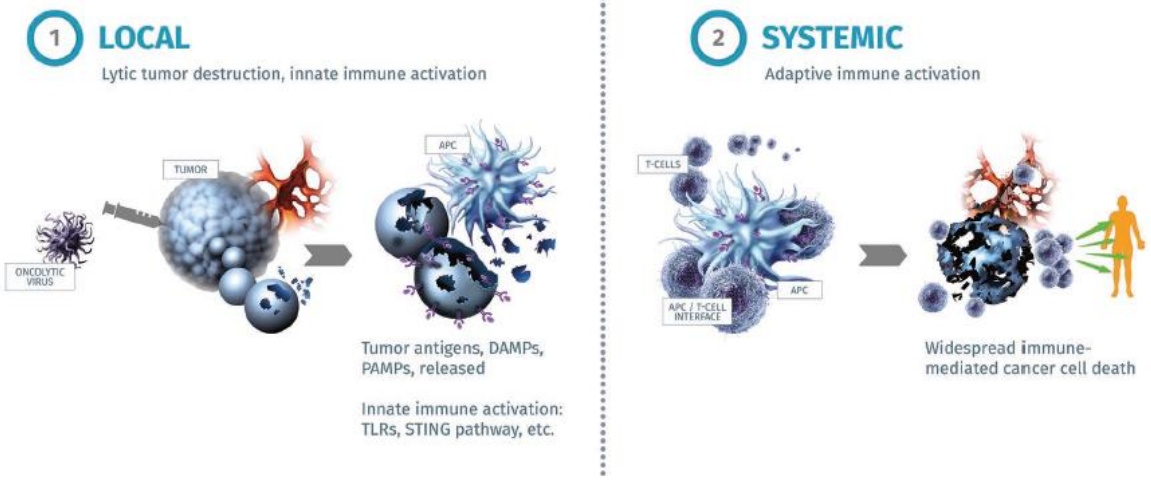
Oncolytic immunotherapy

- The use of viruses that selectively replicate in & kill tumors to treat cancer
  - Highly inflammatory: Activates both innate and adaptive immunity
  - Systemically activates the immune system against the tumor & neo-antigens released
  - Can be 'armed' with additional genes to augment the natural properties of the virus & provide additional MOAs
  - "Off the shelf"
- Single agent T-VEC is clinically validated & FDA approved



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Replimune's product design objectives & solutions

1. Maximize direct tumor destruction & immunogenic cell death through design and development of a virus with the best ability to infect, replicate in & kill tumor cells
   - *Based on a potent new clinical HSV strain resulting from a comprehensive screen**
   - *ICP34.5 deleted for selectivity, US11 upregulated to retain near wild type replication in tumors**
   - *Encodes a potent fusogenic protein, increasing killing & immunogenic cell death 10-100 fold**
   - ➢ Together providing maximal 'Signal 1'

2. Further arm with immune activating transgenes to maximize Signal 2 & thereby systemic immune activation (including through induction of inflammatory cytokines: Signal 3)
   - *GM-CSF – DC expansion & maturation*
   - *Anti-CTLA-4 – block APC/T-cell feedback loop*
   - *CD40L & 41-BBL – Activate co-stimulation; induce inflammatory cytokines (IL-2, IL-8, IL-12 etc)*

3. Focus on targeting pathways with human clinical validation

* Replimune's fusion-enhanced backbone virus is described in Thomas et al (2019) JITC 10; 214

Evolution of oncolytic HSV: Replication & direct tumor killing

Properties which will reduce or increase replication in & killing of tumors*

	1716	G207	G47A	HF10	ONCR-177	T-VEC	RP1	RP2	RP3
Based on a laboratory HSV strain, not selected for tumor killing potency	✓	✓	✓	✓	✓				
One or both copies of ICP34.5 deleted (two copies needed for full activity)	✓	✓	✓		✓	✓	✓	✓	✓
Other mutations which reduce replication & spread: ICP6 deletion, UL37 mutation, ICP0/ICP4 copy deletion, miRNA target sequence insertion		✓	✓	✓	✓				
Based on a clinical HSV strain – substantially increased infection & killing of human tumor cells compared to lab strains						✓	✓	✓	✓
US11 up-regulated – restores replication resulting from ICP34.5 deletion			✓			✓	✓	✓	✓
Fusion-enhanced to increase immunogenic tumor killing – insertion of GALV-GP-R- **(maximizes Signal 1)**							✓	✓	✓

'Historical' viruses largely tested in glioma

No single agent activity on melanoma

Current clinical viruses

1716	G207	G47A	HF10	ONCR-177	T-VEC (FDA approved)	RP1, RP2 & RP3
ICP34.5 only deletion reduces replication in tumors	ICP6 also delete, further reduces replication	US11 upregulated version of G207 (overcomes ICP34.5 deletion)	Multiple regions deleted rendering non-pathogenic	Uses microRNA targeting (including of the one remaining copy of ICP34.5) & other modifications (UL37 mutation, ICP0/4 copy deletion) expected to reduce replication & killing vs. wt HSV	Clinical strain chosen from two tested, ICP34.5 deleted, US11 upregulated	Clinical strain chosen from 29 tested, ICP34.5 deleted, US11 upregulated, fusion enhanced (expresses GALV-GP R-)

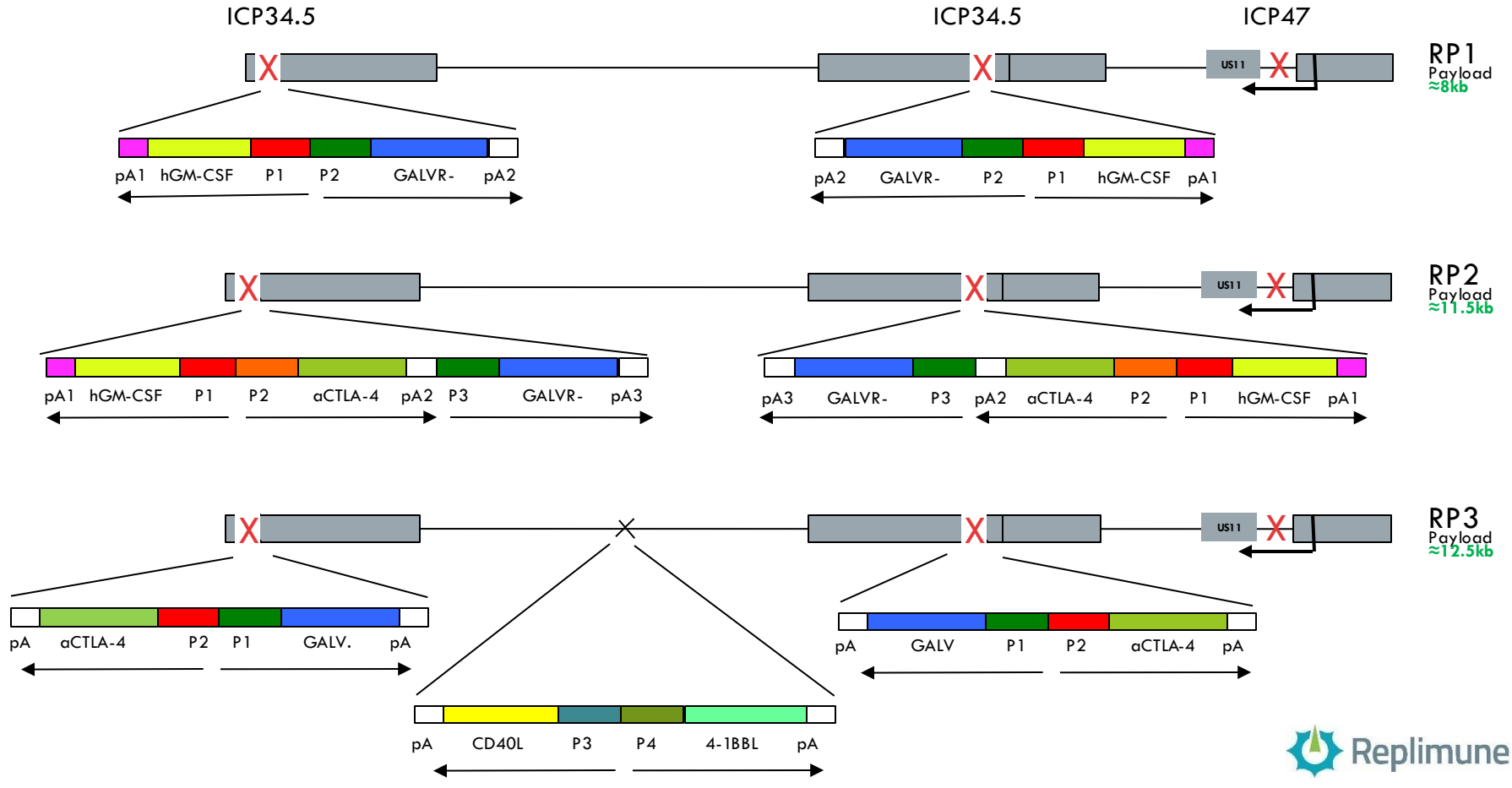
* all statements supported by published data – references can be provided upon request

Evolution of oncolytic HSV: Arming with therapeutic genes

General properties in relation to therapeutic transgene expression	1716 to HF10	ONCR-177	T-VEC	RP1	RP2	RP3
Armed with therapeutic transgenes		✓	✓	✓	✓	✓
Total inserted DNA		≈6.3kb	≈2.5kb	≈8kb	≈11.5kb	≈12.5kb
Transgenes chosen on the basis of human clinical validation, i.e. to best treat cancer in humans			✓	✓	✓	✓
Expression maximized through use of separate strong viral promoters; secreted protein-encoding genes inserted twice			✓	✓	✓	✓
Secreted proteins detected in mouse blood (expected if high level replication & expression in tumors achieved)			UNK	✓	✓	✓

The transgenes expressed	ONCR-177	T-VEC	RP1	RP2	RP3
GM-CSF/FLT3-L/CCL4 - improve DC expansion & maturation/immune cell chemoattractant	✓	✓	✓	✓	Induced by CD40L
GALV-GP R- - improves tumor killing & immunogenic cell death **(Signal 1)**			✓	✓	✓
IL-12 – aids T cell differentiation to Th1, activates NK cells **(Signal 3)**	✓				Induced by CD40L
Anti-CTLA-4 – Blocks negative APC/T cell feedback loop **(Signal 1/2)**	✓			✓	✓
Anti-PD1 – Blocks inhibitor of T cell effector function (local expression not expected to increase systemic activity)	✓	Used in combination with systemic anti-PD1			
CD40L/4-1BBL – Pleiotropic activation of co-stimulation **(Signal 2)** - also induces inflammatory cytokines, e.g. IL-12, IL-8, IL-2 etc **(Signal 3)**					✓

RP1, RP2 & RP3



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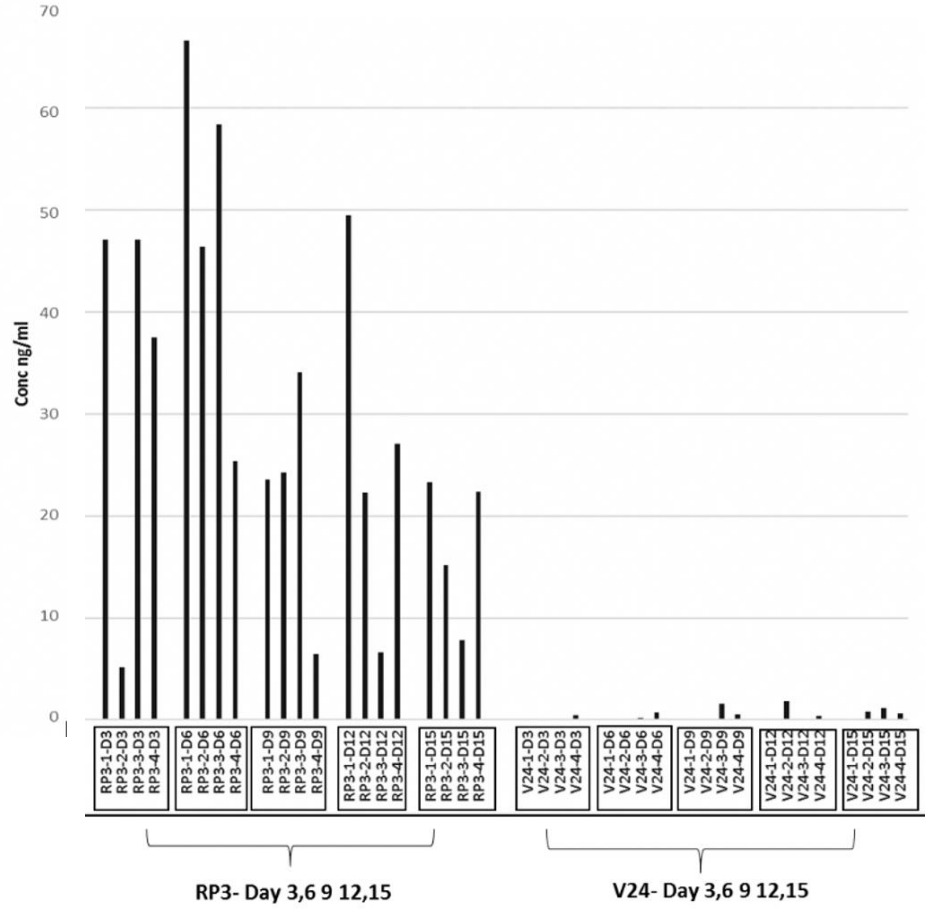
Anti-CTLA-4 detection in mouse blood following intra-tumoral injection



<u>Mouse 4434 melanoma tumors, immune competent mice</u>
$5x10^5$ pfu of the indicated virus injected twice Q3D

Abundant detection in mouse blood, as expected if robust replication & expression in tumors occurs

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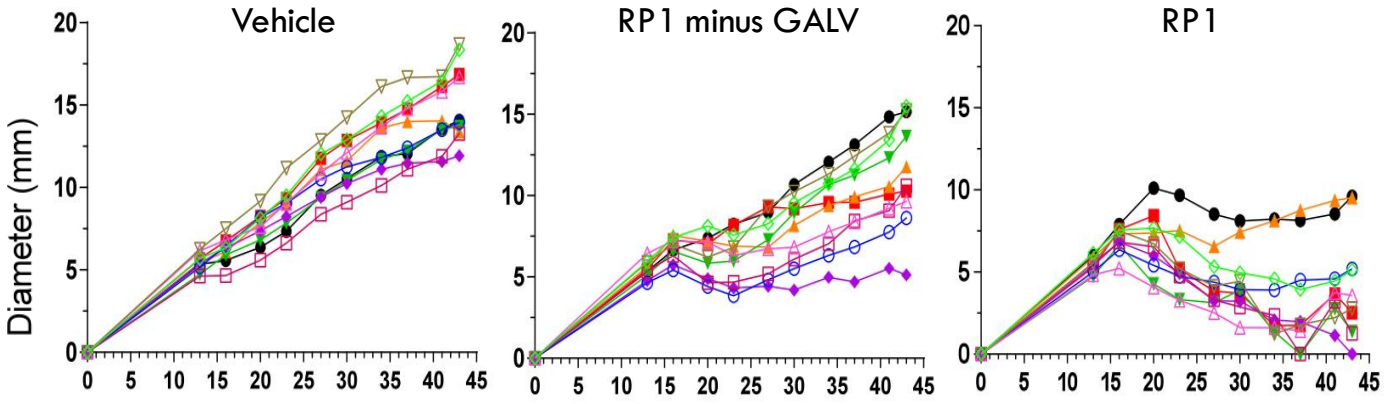
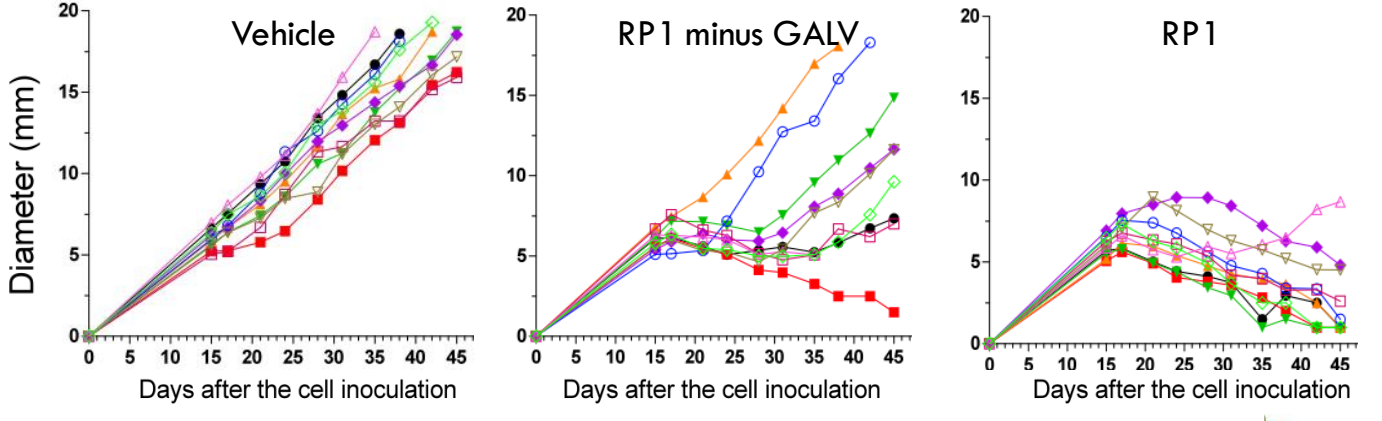
Fusion enhances efficacy

A549
lung cancer



MDA-MB-231
breast cancer



3 injections over 1wk. Virus dose **$5x10^3$ pfu**

Nude mice: No immune effect. GALV is not active in mice so immune competent mouse models can't be used

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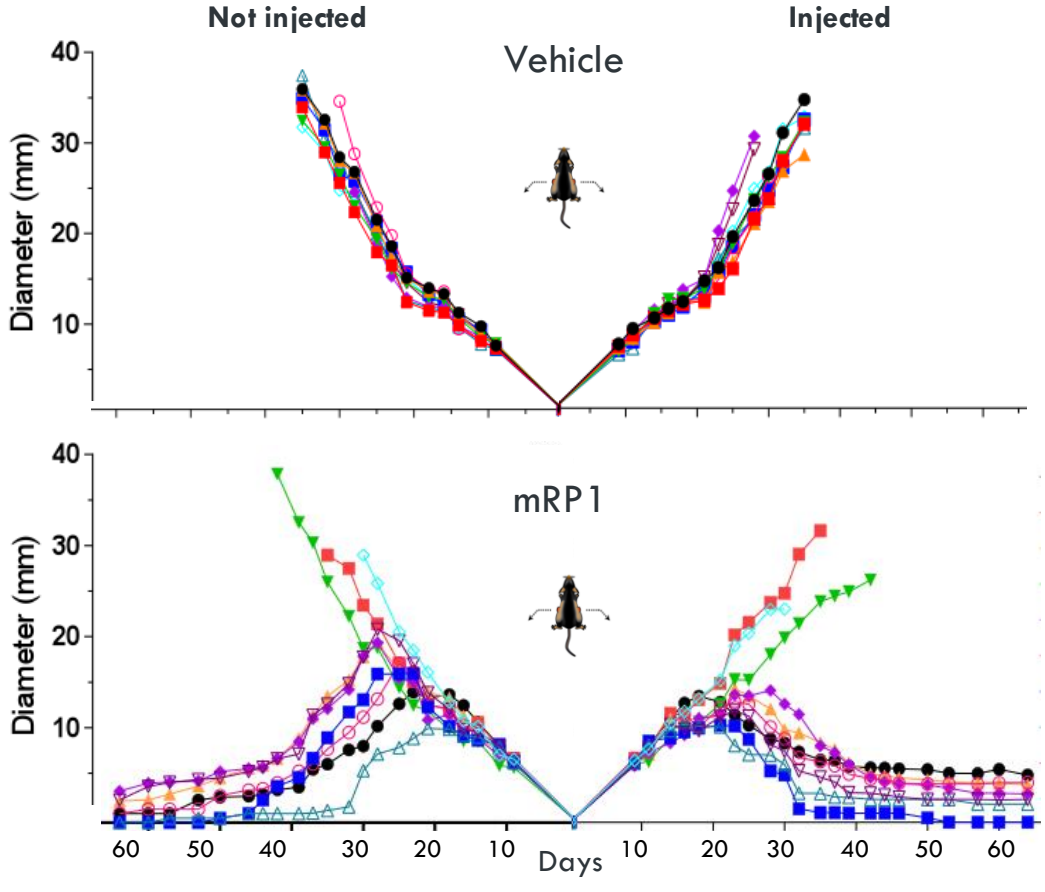
RP1 provides potent systemic efficacy in large tumors in rats



Rat 9L glioma tumors in immune competent rats (dual flank tumors)

Virus: $5x10^5$ pfu into the right tumor

Rat 9L cells are of limited susceptibility to HSV, but GALV is active in rats

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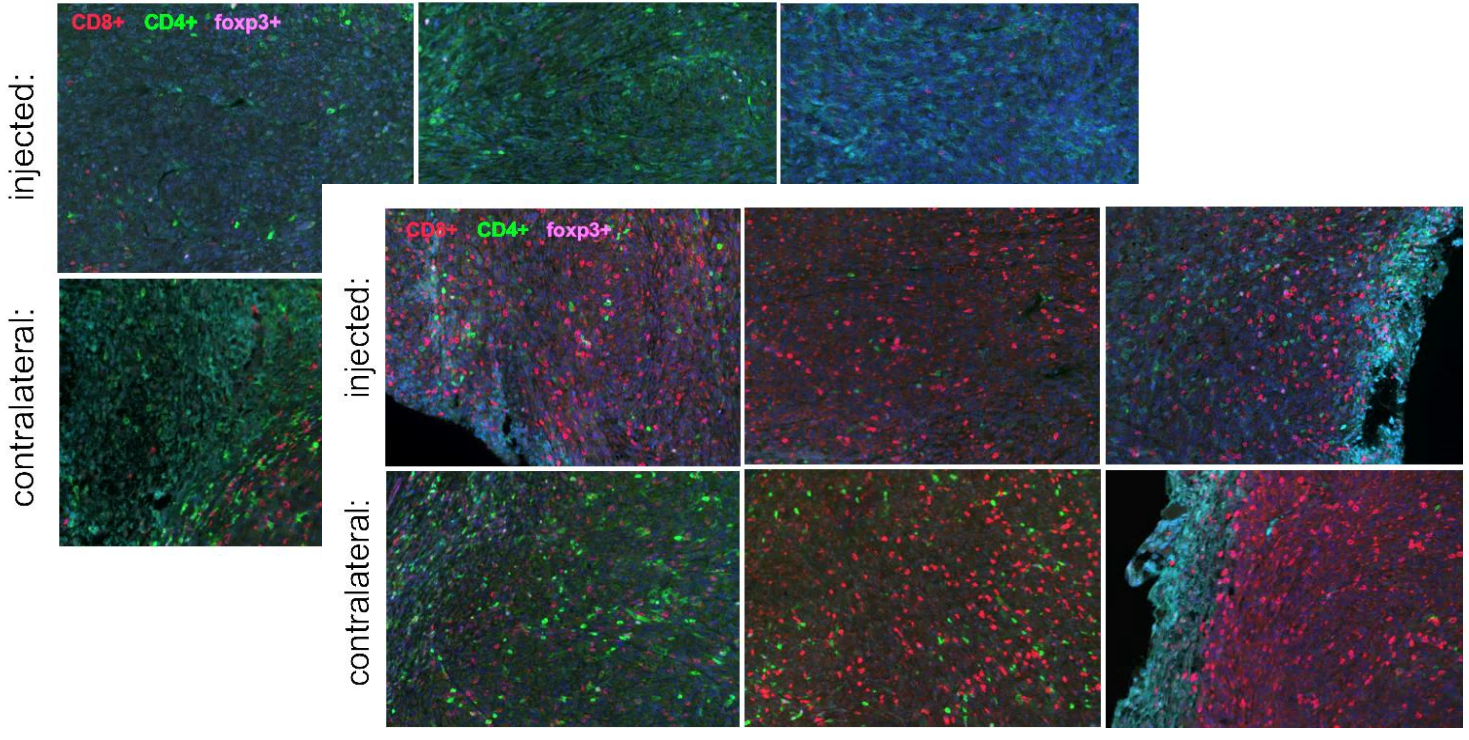
RP1 increases CD8 T cells in injected and uninjected tumors



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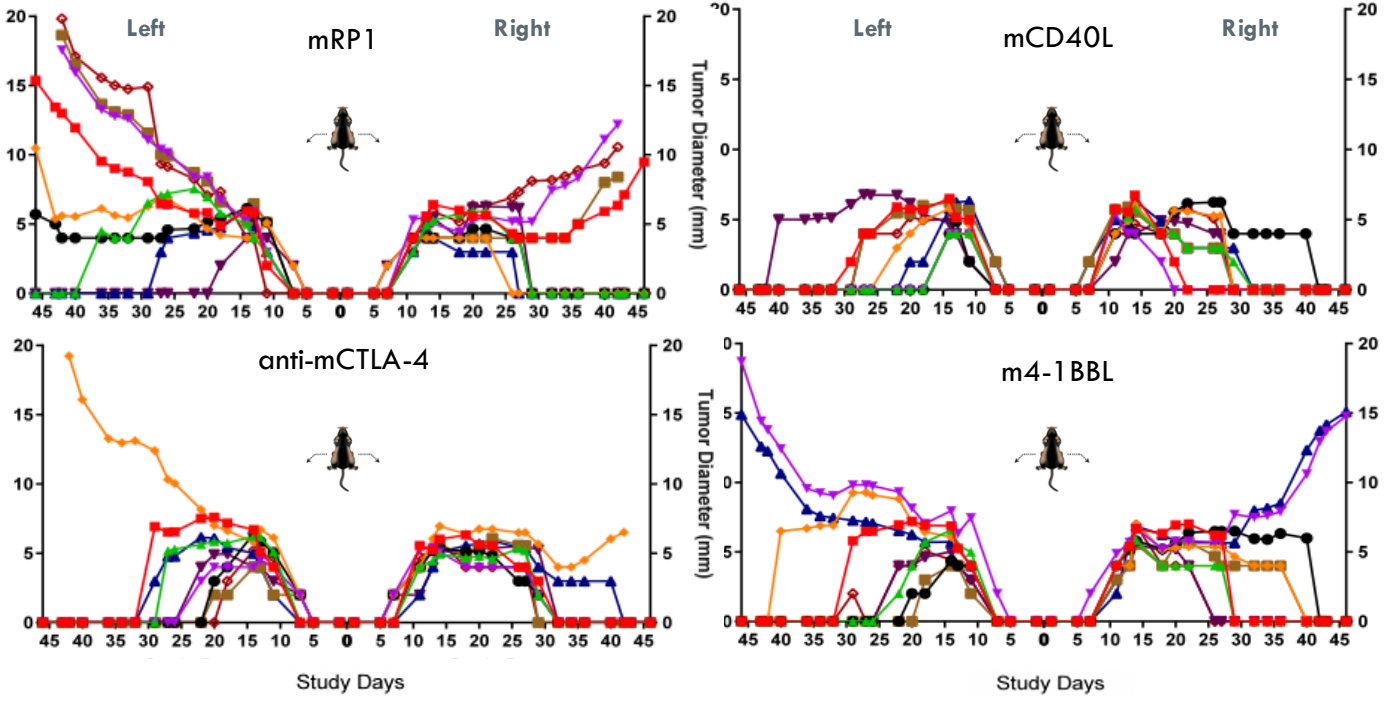
Expression of anti-CTLA-4 or co-stim ligands increases efficacy



Mouse A20, immune competent mice

$5x10^4$ pfu of the indicated virus 3x into the right tumor

Subtherapeutic dose for mRP1

No effect of GALV

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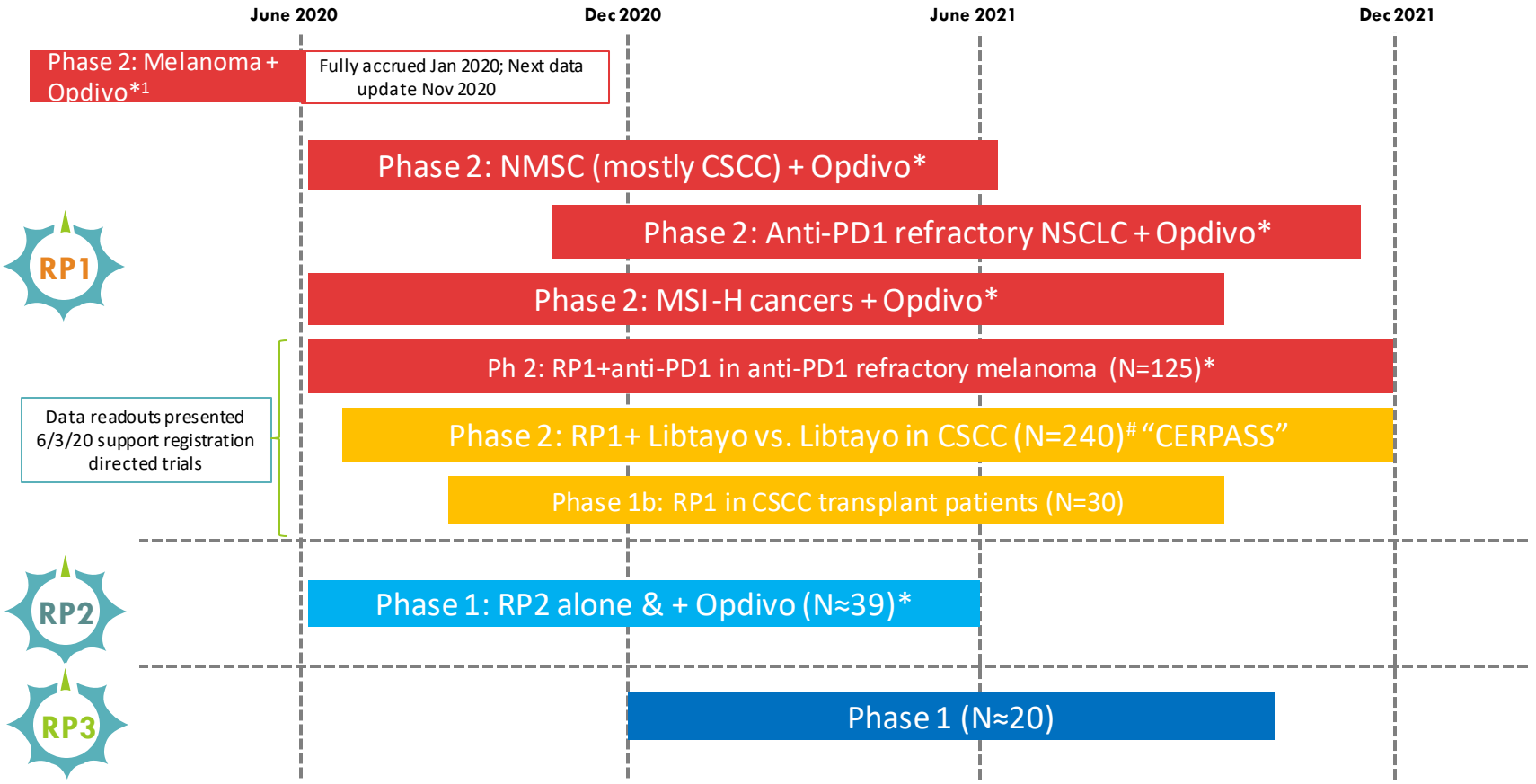
Replimune's development plan



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

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

[1] Completed enrollment January 2020

Data summary in lead indications (as of May 2nd)

CSCC

- Six of seven patients with follow in response (86%)
- Four of seven patients with ongoing CRs (57%)
  - Clear differentiation from anti-PD1 monotherapy
  - Supportive biomarker data

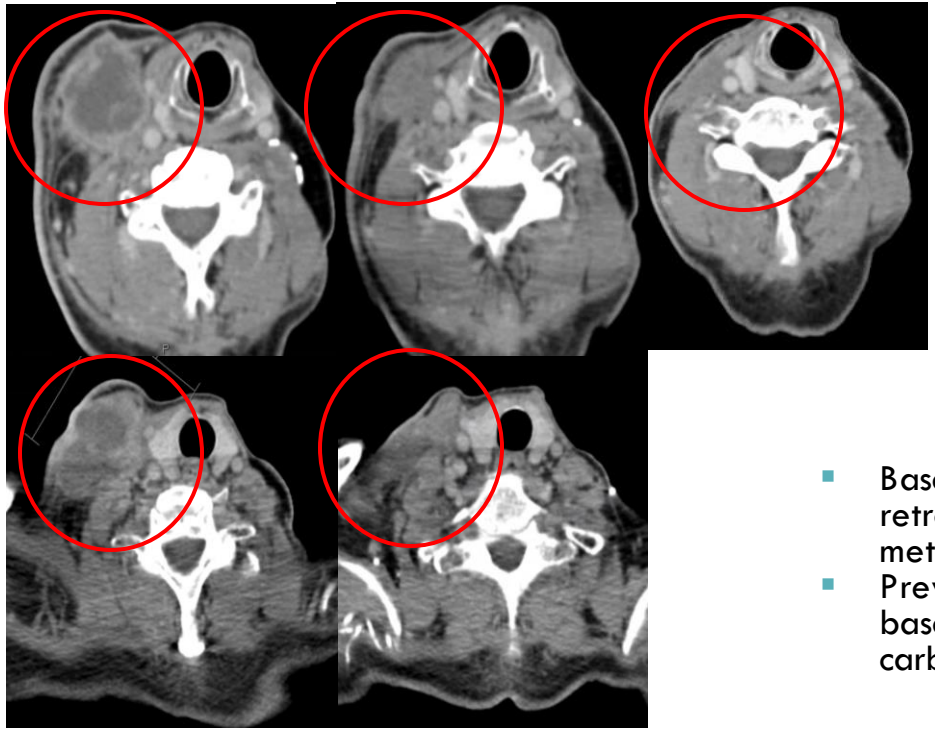
Anti-PD1 refractory cutaneous melanoma

- 16 patients treated
- Very late stage visceral disease population (87.5% Stage IVM1b/c)
- Nine patients showed initial clinical benefit (SD or better with evidence of anti-tumor activity)
- Five patients in response (31%): four failed both anti-PD1 and anti-CTLA 4 therapies
- Two further patients remain on treatment with the opportunity for response
- Clinical data supported by biomarker data including reversal of T cell exclusion
- Activity also seen in anti-PD1 refractory uveal and mucosal melanoma

Example CSCC patient with ongoing CR

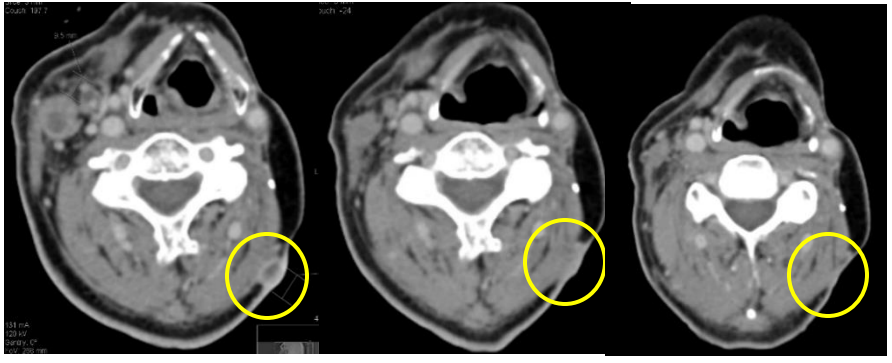
Right neck (injected)

Baseline 8 weeks 24 weeks



Left neck (not injected)

Baseline 8 weeks 16 weeks



- Baseline disease: Bilateral neck, retroperitoneal lymph nodes, bone metastases
- Previously treated with cisplatin-based chemoradiation & carboplatin/5-FU

Injected

Not injected

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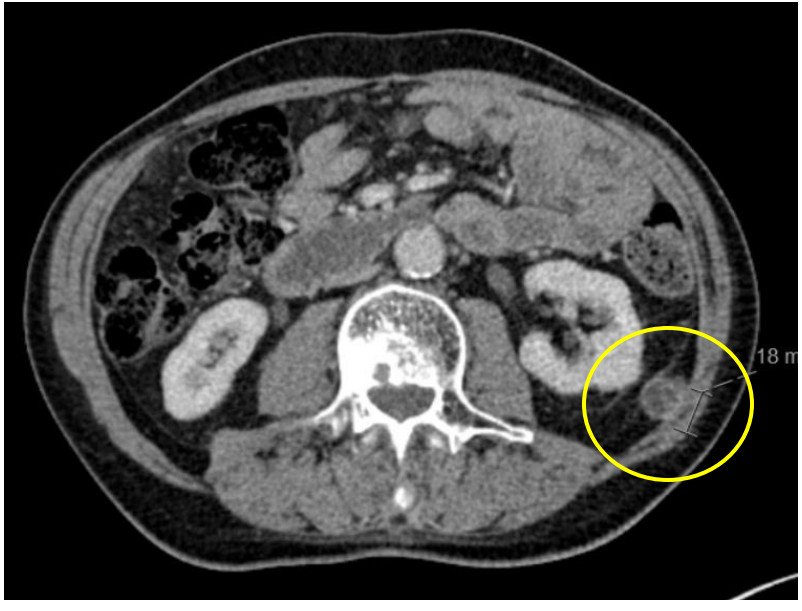
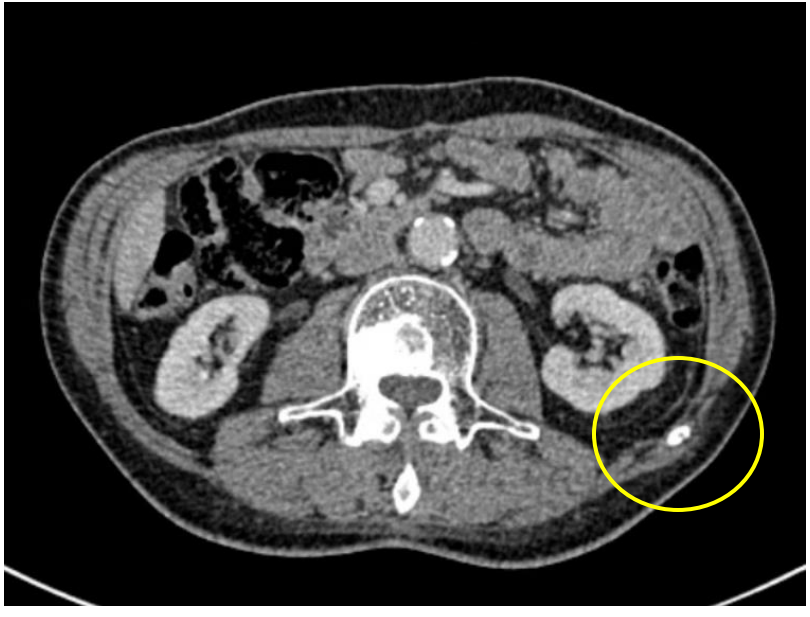
Example CSCC patient with ongoing CR

Baseline



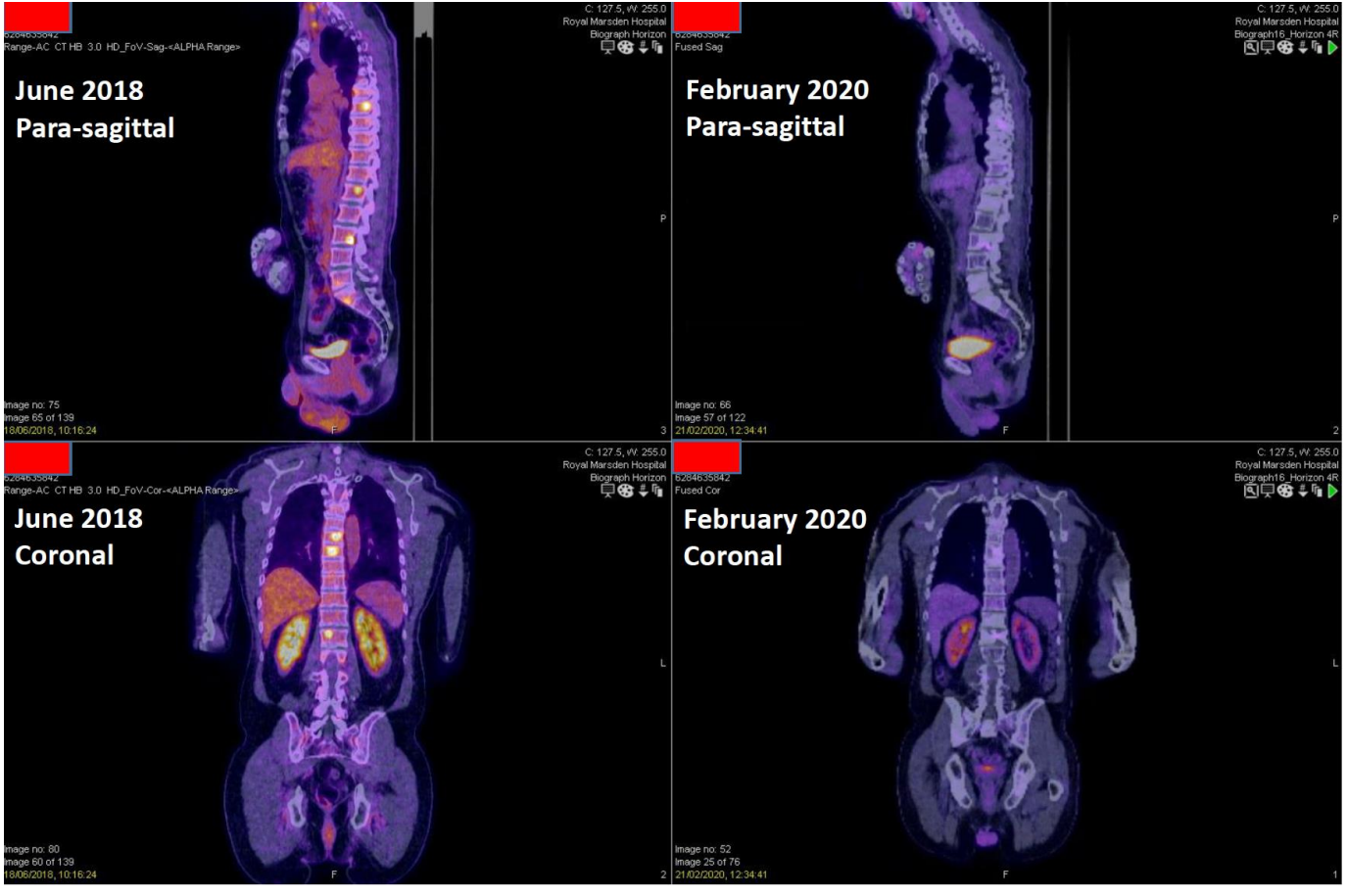
16 weeks



- The patient also had baseline retroperitoneal tumors which have completely resolved

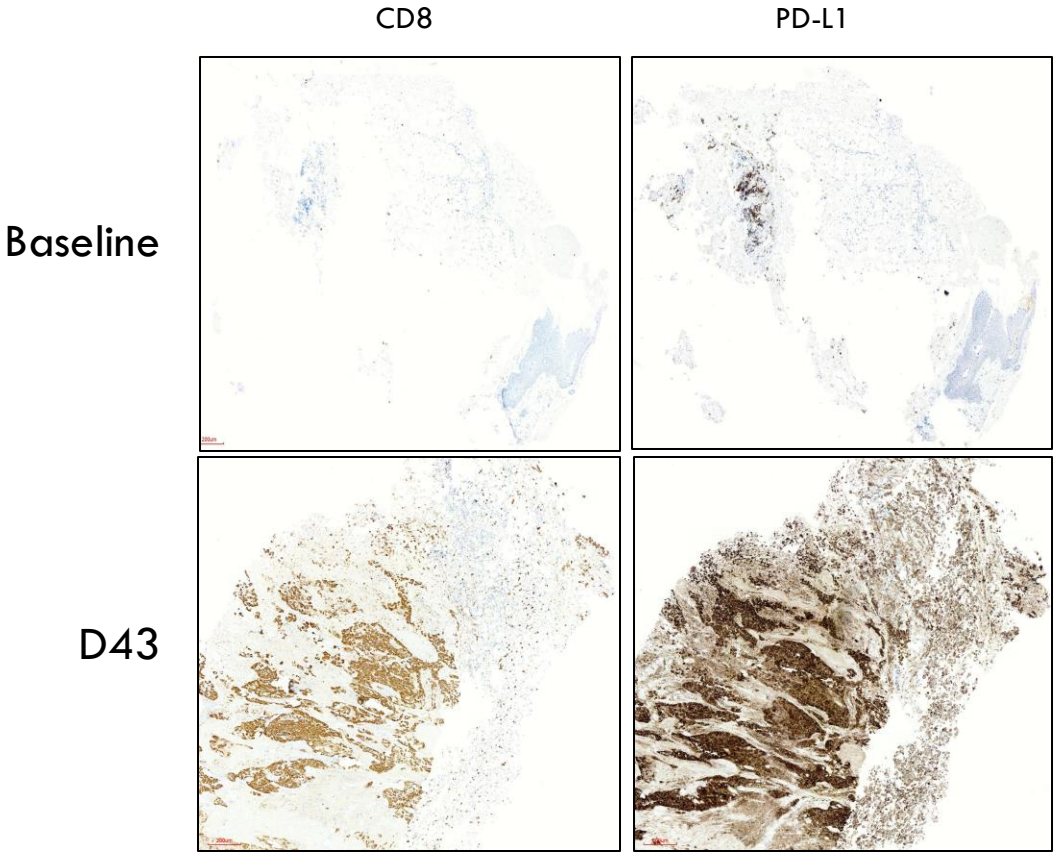
Not injected

Example CSCC patient with ongoing CR



Not injected

Example CSCC patient with ongoing CR



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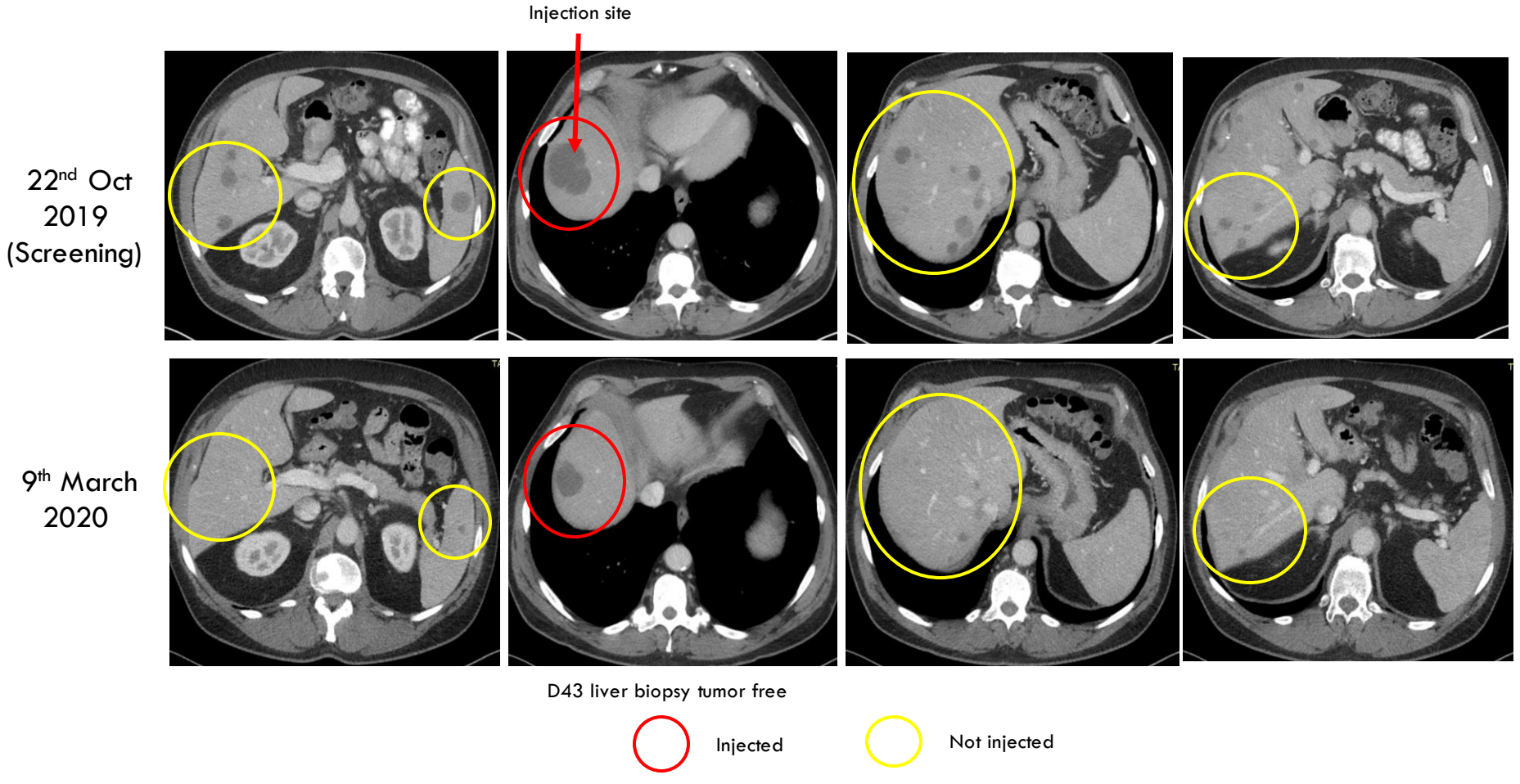
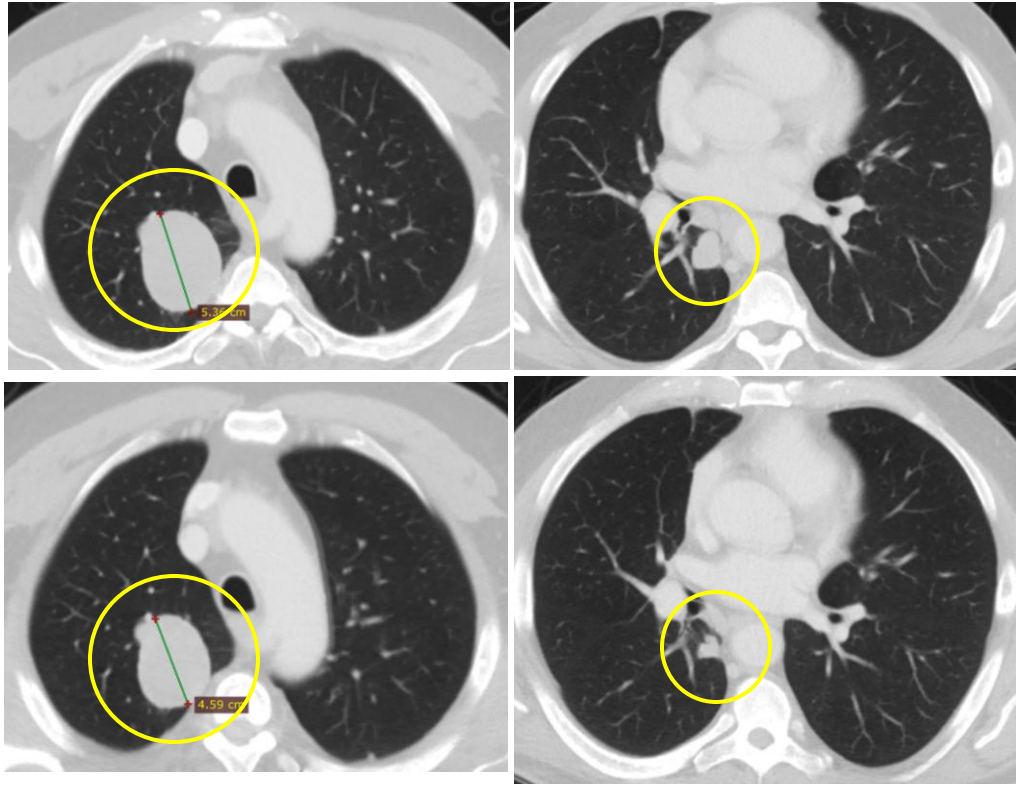
Example ipi/nivo refractory melanoma patient with ongoing PR



Example ipi/nivo refractory melanoma patient with ongoing PR

22nd Oct 2019 (Screening)

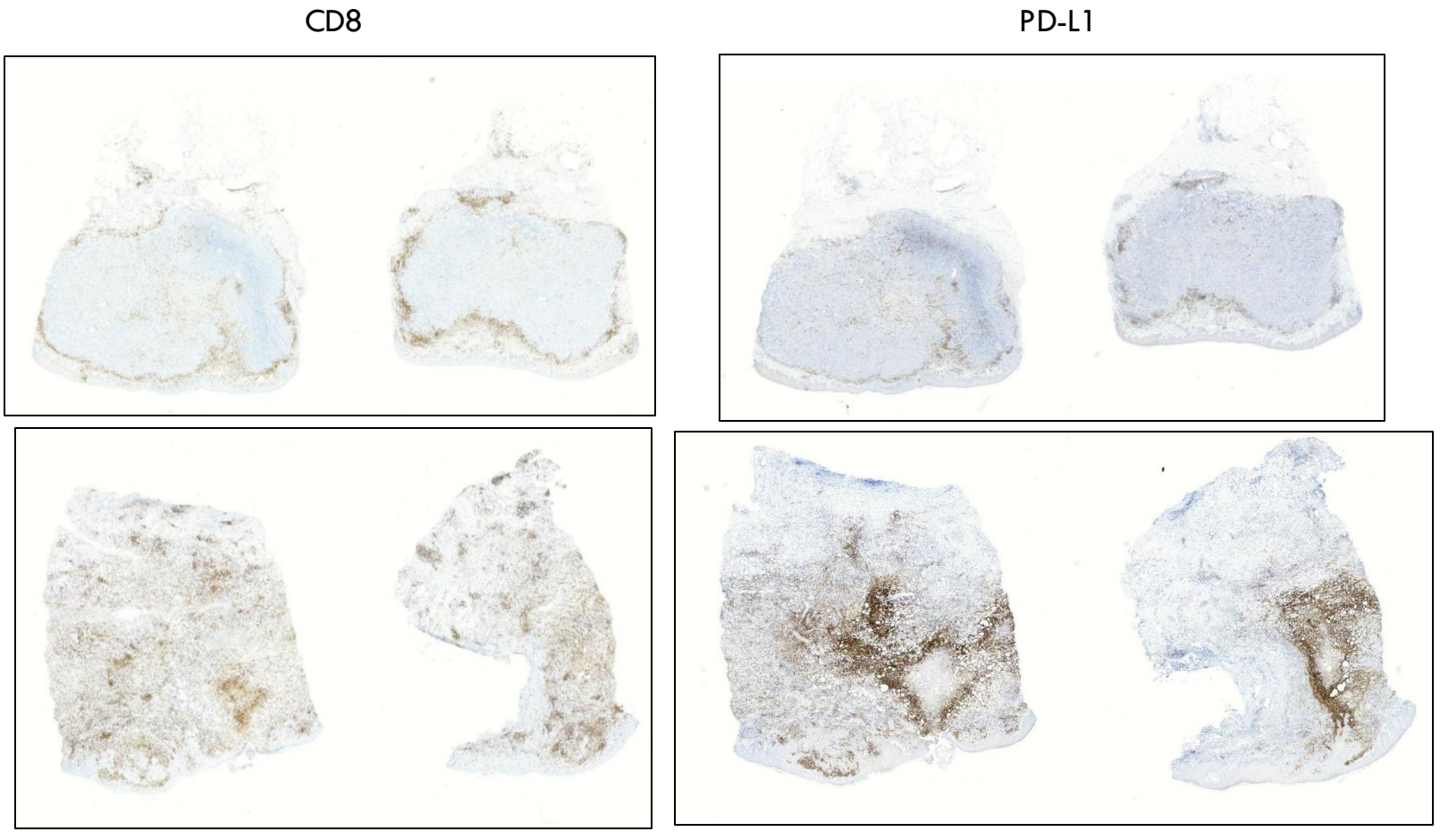
9th March 2020



Not injected

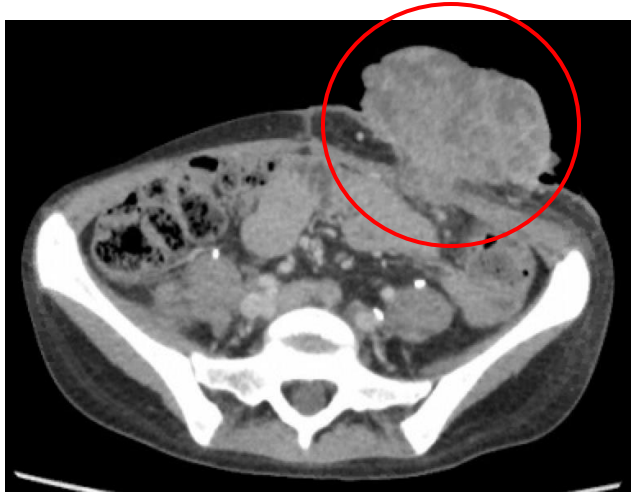
Reduction of uninjected lung lesions

Reversal of T cell exclusion with RP1 combined with nivolumab

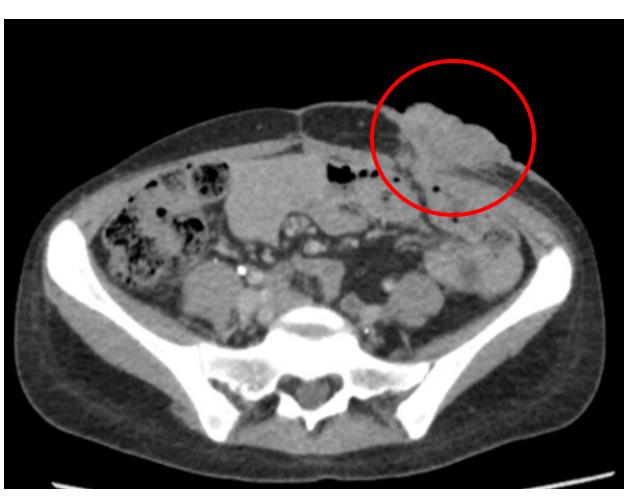


Ipi/nivo refractory cutaneous melanoma patient with ongoing PR

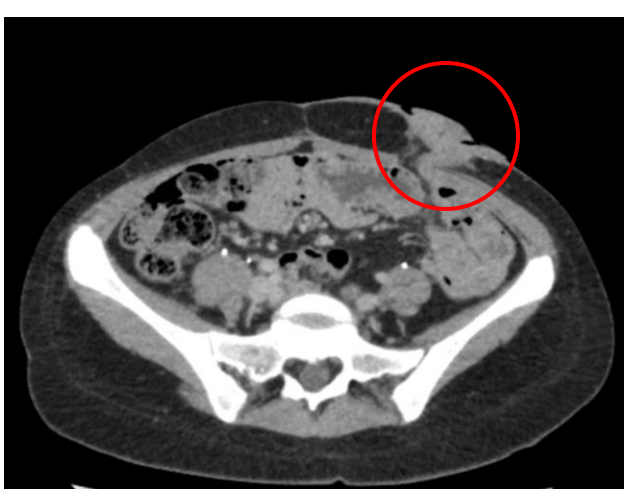
Example activity in other tumor types: MSI-H CRC



4th Dec 2019



29th Jan 2020



25th March 2020

- 93% reduction

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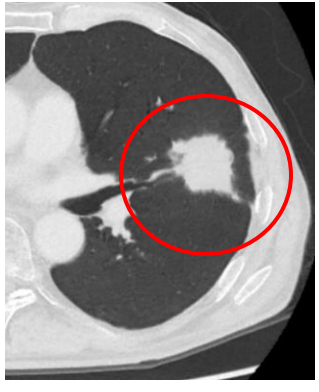
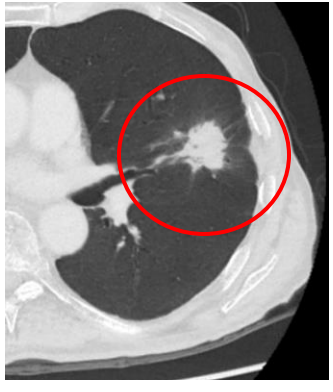
Example activity in other tumor types: Esophageal cancer

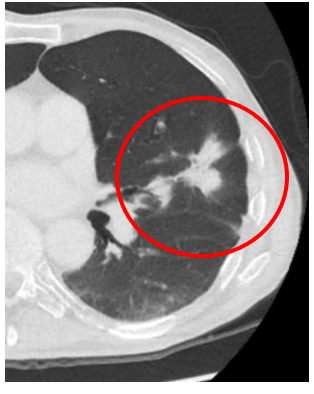
- Heavily pre-treated esophageal cancer (8 prior therapies)
- Lung lesions & lesions around the esophagus.



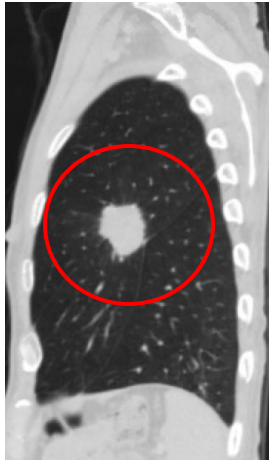
Baseline



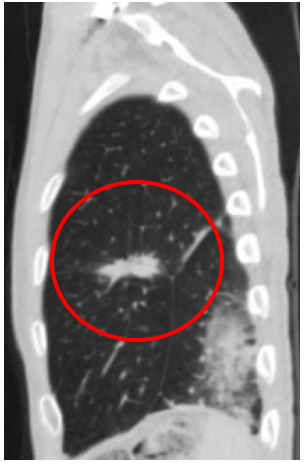
C5



C11



Baseline



C11

Summary/Conclusions

- An oncolytic immuno-gene therapy platform designed to maximize Signals 1-3 has been developed
- Intended to provide potent systemic immune activation against a patient's own cancer with a fully off the shelf approach
- Pre-clinical data shows robust enhancement of efficacy through each of the strategies employed
  - Use of a clinical strain of HSV identified through a comprehensive screen
  - Expression of a fusogenic protein to increase the extent & immunogenicity of tumor killing
  - Expression of further immune activating proteins targeting clinically validated pathways to activate Signals 2 & Signal 3
- Initial clinical data with RP1 alone & combined with nivolumab is promising, with registration directed development underway in CSCC and anti-PD1 refractory melanoma
- RP2 & RP3 are following rapidly behind, with initial safety & efficacy data with single agent RP2 to be presented later this year

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