Mythos Biotechnology Fund

$REPL case study

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with helpful discussion from Vandon Duong

October 2020

Disclaimers

- The sole purpose of this case study is to serve as a training material for our fund's investment analysts and others who are new to biotech investing.
  - This case study is not an investment recommendation and the information presented may be inaccurate or out-of-date.
  - We do not offer professional investment advice. We recommend that readers conduct independent due diligence on the stock.
- Mythos is currently holding a long position in $REPL, but the fund may exit the position at any given time for either gain or loss.
  - Our fund operates as a general partnership and do not have limited partners. Our activities are centered around education in biotech investing.
  - Past performance is not indicative of future results. Any investment involves considerable risk. Individual partners are not liable for capital losses incurred by the Mythos Biotechnology Fund.

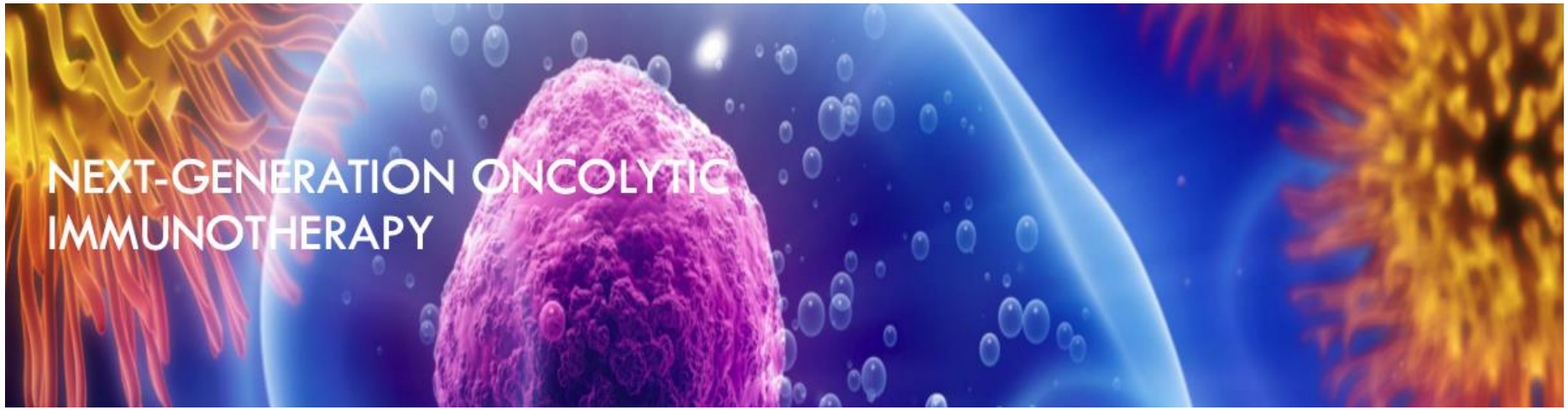
Outline of case study

- Diligence resources
- Company profile and investment thesis
- Biological and technology background
- Preclinical and clinical results
- Management team
- Upcoming catalysts, risks, and recommendation
- Post-diligence, post-decision information
- Update on stock performance since investment (10/17/20)
- Additional slides
  - Landscape analysis
  - Additional scientific information

Diligence resources

- SEC filings
  - 10-K: annual report on company business and detailed analyses
  - 10-Q: quarterly report with unaudited financial statements
  - 8-K: unscheduled report of material events
- Company presentations
  - Replimune corporate slide decks
- Scientific literature (not exhaustive)
  - Guo, S.Z., et al. Vaccinia virus-mediated cancer immunotherapy: cancer vaccines and oncolytics. J. ImmunoTherapy of Cancer. 2019
  - Peters, C., et al. Updates on oncolytic virus immunotherapy for cancers. Mol. Thera. Onco. 2019
- Analyst Reports
  - Wedbush

$REPL company profile



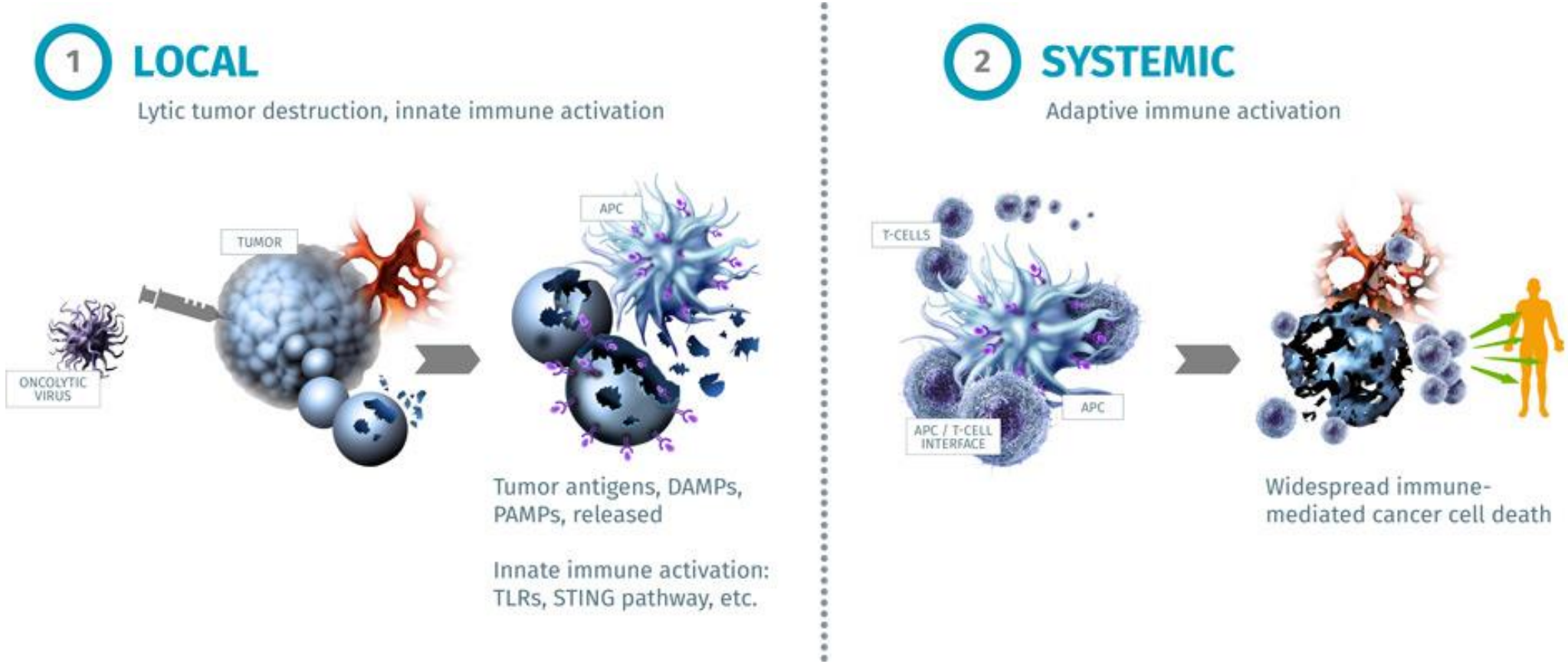
- Market cap: $502.47M
- Cash: $200M (11/29/2019)
- Cash burn: ~$11M (enough cash until late 2021)

Investment thesis

Pitched at the Mythos meeting in December 2019

"At present, we believe Replimune to be undervalued. The scientific and clinical risk of Replimune's asset is significantly de-risked with BioVex's development of the FDA approved therapy Talimogene laherparepvec (T-VEC/Imlygic). BioVex was purchased by Amgen for $1B in 2015, and we believe this to reflect the minimal valuation of Replimune. In addition, a significant component of Replimune's management team consists of previous members of BioVex's management team, and we believe their knowledge and experience with developing T-VEC will translate into developing Replimune's assets effectively."

Mechanism of Action: OV killing of tumors



Source: Company Website

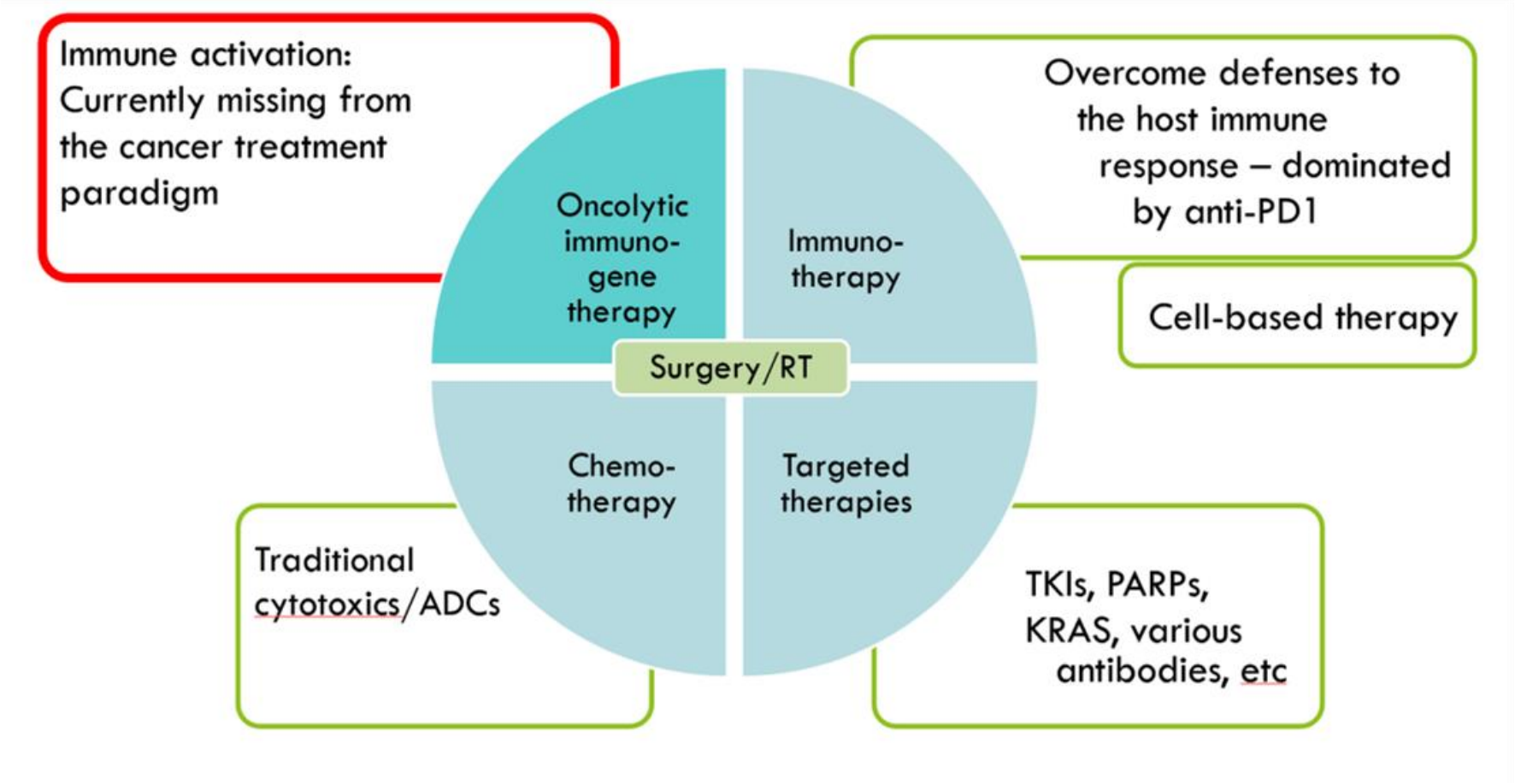
Mechanism of Action: OV killing of tumors

- OVs trigger cell death
  - Initiated by endoplasmic reticulum stress
  - Results in a highly immunogenic cell death (ICD)
  - ICD results in the release of damage-associated molecular patterns (DAMPs), such as ATP, uric acid and high mobility group protein B1 (HMGB1), translocation of calreticulin to the tumor cell surface, and the release of cytokines such as type I IFNs, TNF-α, IFN-γ, and IL-12 .
- Immune response to OV has antitumor activity
  - Viral PAMPs (pathogen-associated molecular pattern molecules) such as TLRs, RIG-1, PKR and cyclic GMP-AMP synthase (cGAS) are recognized by receptors on innate immune cells called pattern recognition receptors (PRRs), resulting in a proinflammatory response that culminates in the release of cytokines.

- Initiates response against tumor-associated antigens (TAAs)
  - Cell death releases TAA that were otherwise inaccessible.
  - DCs present the processed antigens to CD4+ and CD8+ T cells in the context of immunostimulatory cytokines, resulting in their expansion and trafficking to the sites of the tumor.

Source: Wedbush Reports

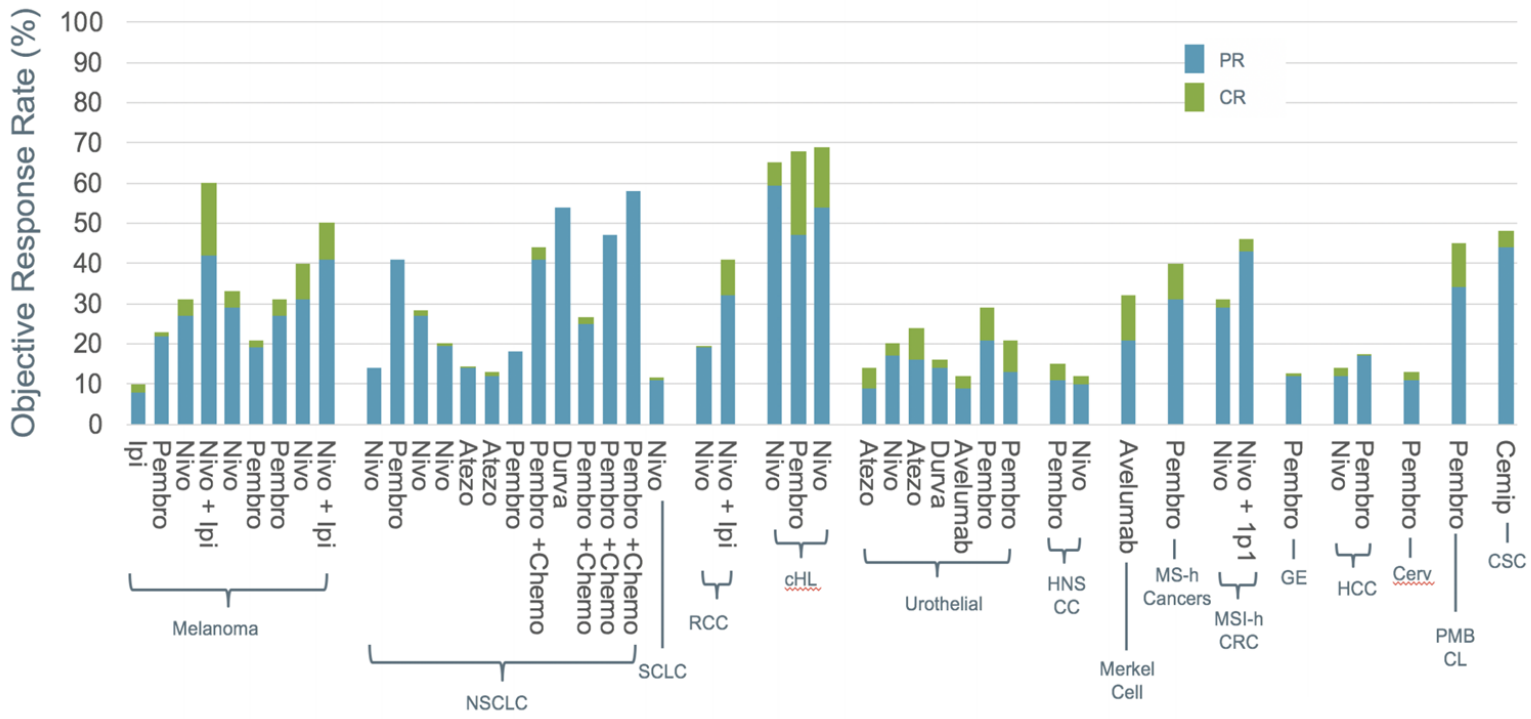
Oncolytic viral therapy as the fourth cornerstone of cancer treatment



Source: Corporate Presentation

Oncolytic viral therapy addresses a missing need in checkpoint blockade therapy for solid tumors

- Checkpoint blockade effective if patient has pre-existing immune response to their cancer and tumor is inflamed
- Turns “cold” tumors “hot”



Source: re-drawn from FDA presentation at AAADV Workshop, 5/8/2019. Data as of 11/2018.

Source: Corporate Presentation

Benefits of oncolytic viral therapy

- Includes neoantigens as well as defined antigens
- Off the shelf approach
- Potently activates innate and adaptive immunity
- Potentially applicable to all solid tumor patients in combination with checkpoint blockade therapy

Oncolytic viral therapy details

Characteristics of a successful oncolytic virus:

- Be non-pathogenic (low seroprevalence)
- Can be engineered to express genes (immunomodulators)
- Tumor-selective through cell entry mechanisms (receptor recognition) and/or transcription mechanisms
- Often engineered to have reduced viral gene expression and replication (kinase deletions to limit replication ability in non-dividing cells)

The selectivity of oncolytic virus can be improved by:

- Using cancer-specific promoters or microRNAs to regulate expression
- Confine to infecting tumor cells overexpressing a specific target (ex. Targeting HER2)

Commercially available oncolytic viral therapy

OV	Approved in	Indications
Rigvir (enterovirus)	Latvia/Georgia/ Armenia	Melanoma: Rigvir + resection v. resection alone, improved survival in stage I-II, questionable efficacy in advanced melanoma
Oncorine (adenovirus)	China	Squamous cell carcinoma of head and neck AND esophageal cancer: Oncorine w/ chemo v. chemo alone, 78.8% v 39.6% ORR (approved as combo therapy)
T-Vec/IMLYGIC (HSV)	USA	Non-resectable metastatic melanoma: approved as monotherapy, Ph2 T-VEC + anti-PD-1, Ph1 T-VEC + anti-CTLA4. Currently in trial: liver, pancreatic, and advanced non-central nervous system solid tumors - alone or in combination with checkpoint inhibitors, chemotherapy, or radiation therapy

Characteristics of REPL's virus choice (HSV) as a viable oncolytic viral therapy platform

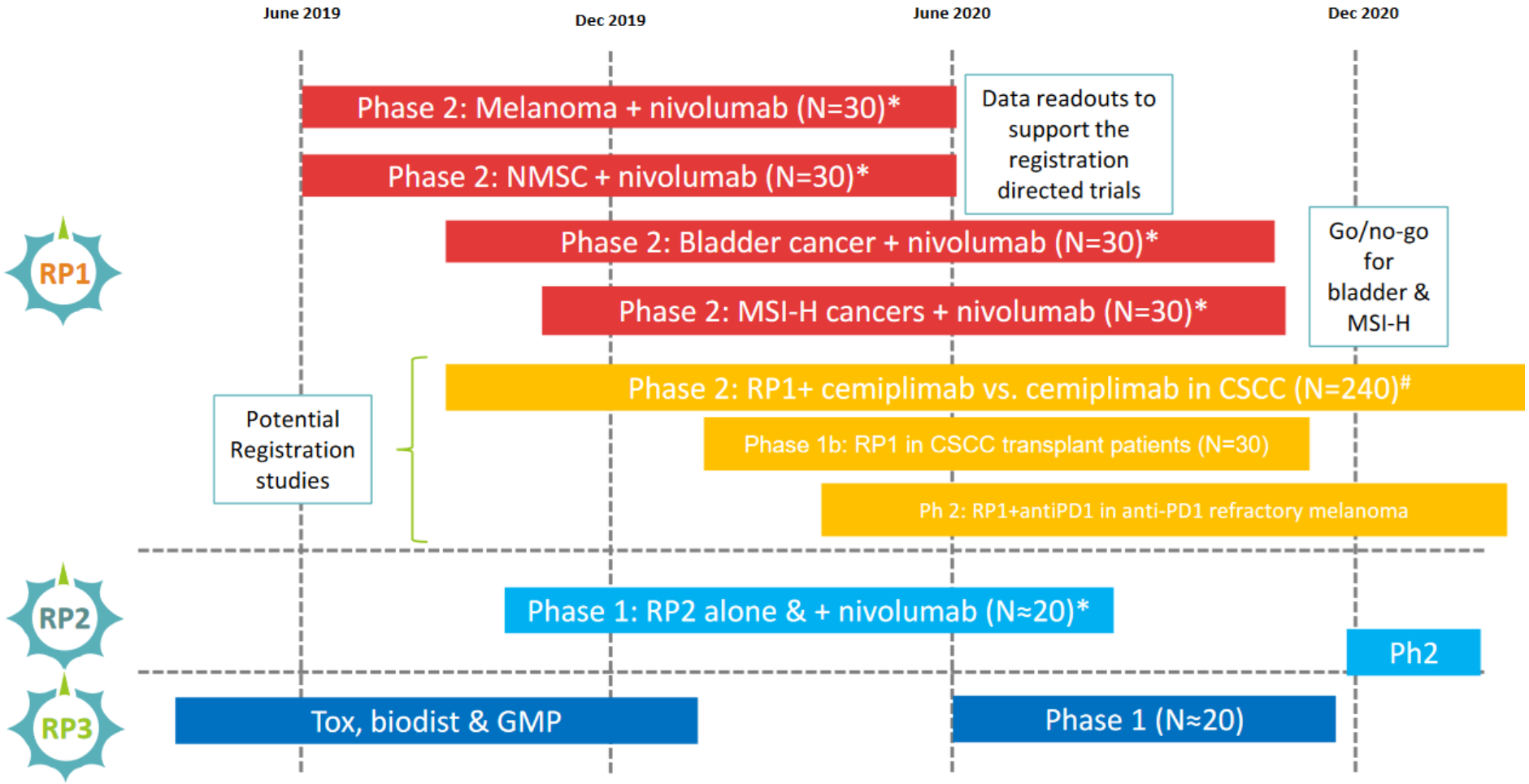
Advantages

1. Large, well-characterized genome that allows for easy insertion of genes
2. Has the ability to remain as a viral episode, reducing concerns for insertional mutagenesis
3. Minimal risk for secondary transmission
    - Lipid bilayer is susceptible to lipid solvents and/or disinfectants
4. Modified vectors still vulnerable to anti-HSV agents (acyclovir)
    - Good safety profile - rarely causes serious illnesses
5. Can infect many different tumor types and can destroy tumor cells through highly lytic viral replication
6. Deletion of genes encoding HSV-1 ICP34.5 protein provides tumor-selective virus replication and a well-characterized non-pathogenic phenotype

Concerns

1. High seroprevalence of HSV-1 neutralizing antibodies in US population remains a barrier to systemic delivery of oncolytic HSV vectors
2. delivered locoregionally or intratumorally

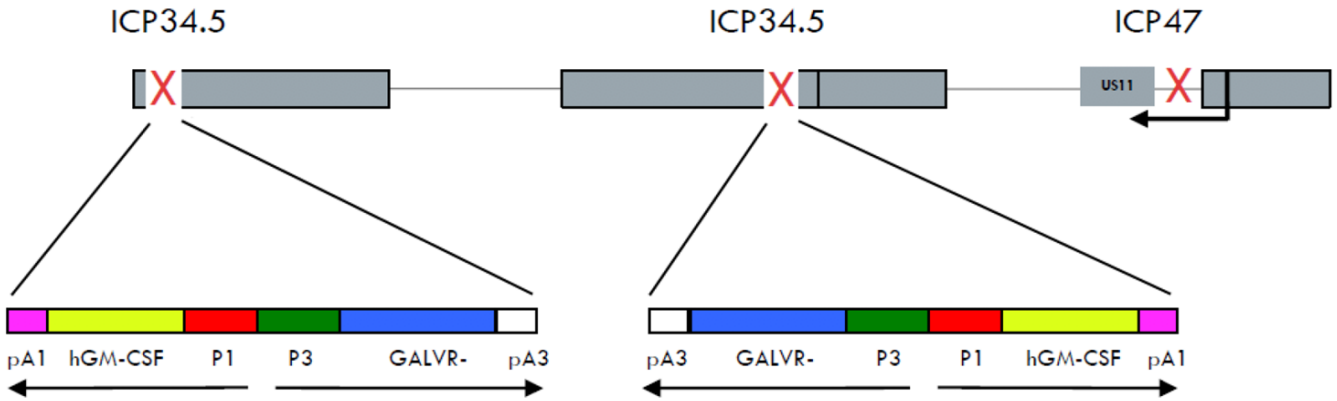
Clinical Development Platform



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

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

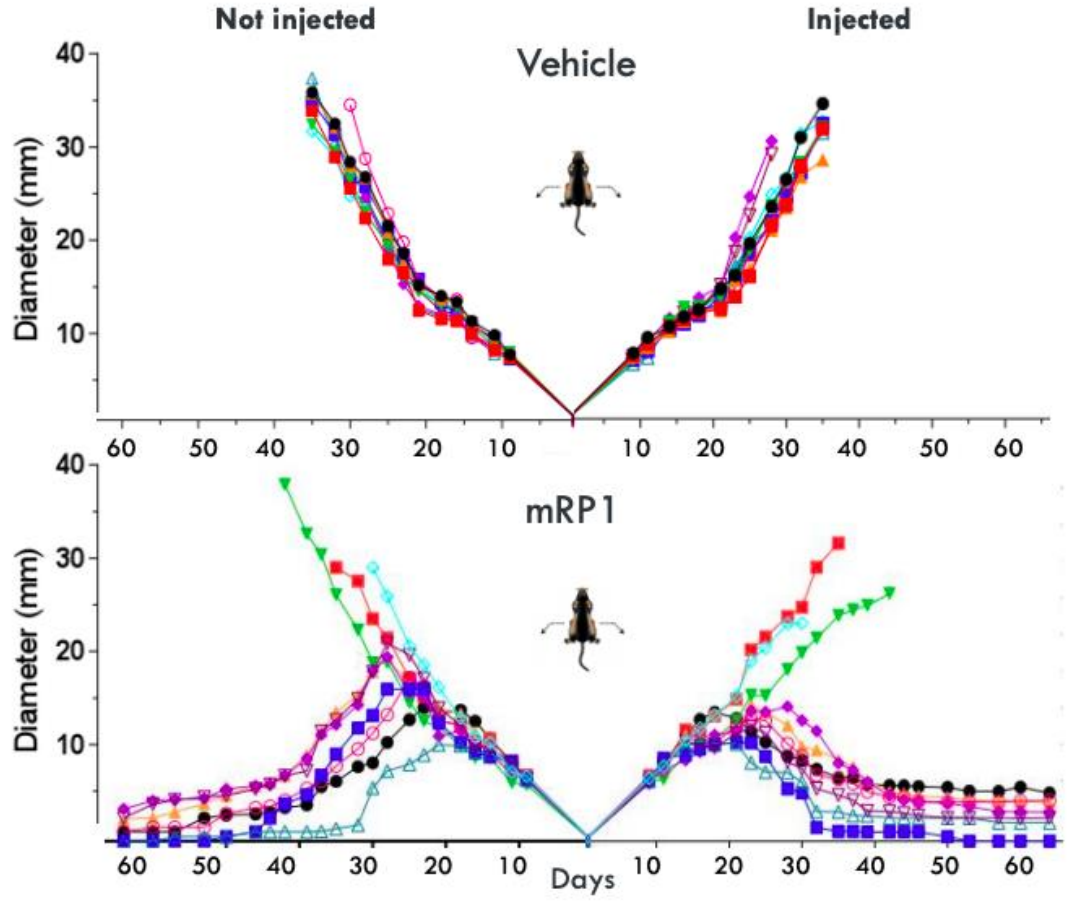
RP1 components contain T-VEC elements combined with two insertions of GALVR-



1. ICP34.5 (neurovirulence factor) deletion (ICP = infected cell protein)
   - Promotes selective replication in tumors
2. ICP47 deletion
   - Prevents rapid viral clearance; prolongs viral life cycle = more potent cytolytic effects
3. GM-CSF insertion
   - Increases potency of immune response
4. GALVR- insertion
   - Increases tumor cell death (by membrane fusion)

Source: Wedbush Reports

Preclinical: RP1 decreases tumor size in both injected and non-injected tumors



Immune competent rat model (dual flank)

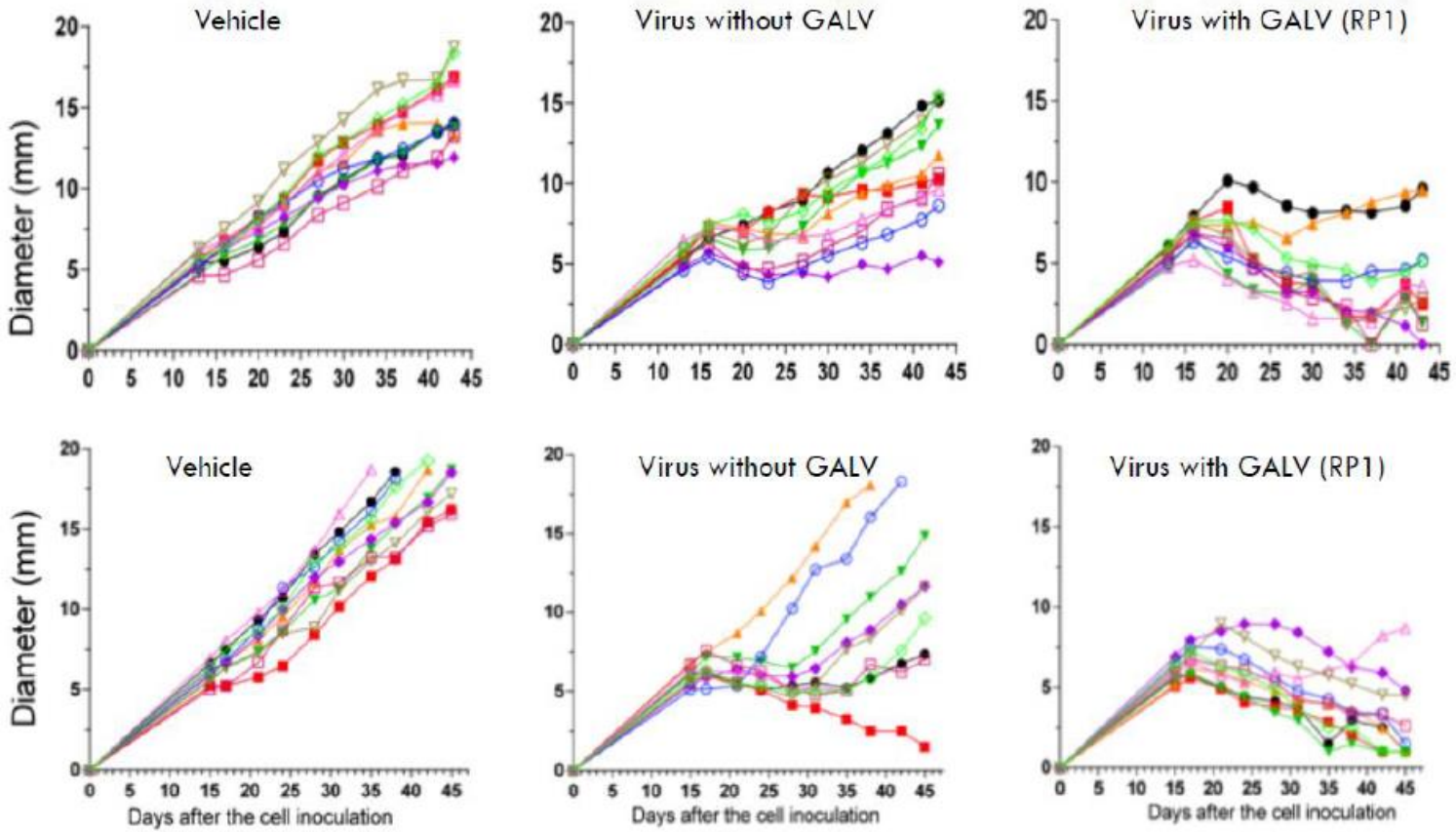
Right flank tumors injected 5x with $5x10^6$ pfu

Source: Company Filings

Preclinical: RP1 + GALVR- increases anti-tumor efficacy

A549
lung cancer

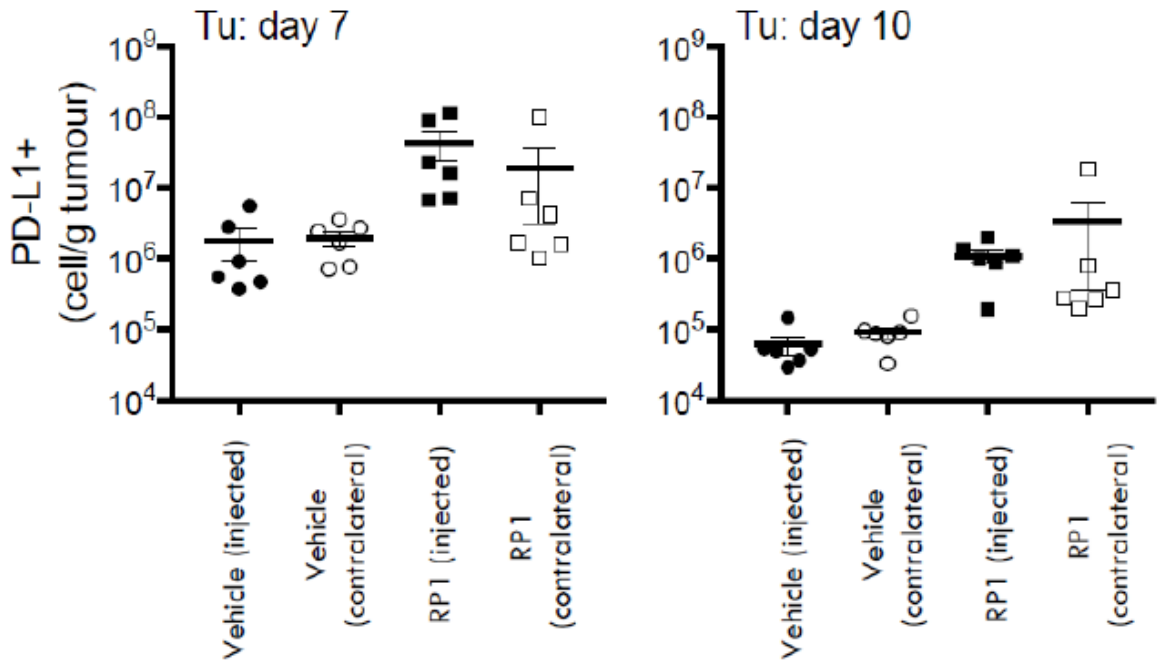
MDA-MB-231
breast cancer



3 injections over 1 week; virus dose 5x10³ pfu

Source: Company Filings

Preclinical: RP1 increased PD-L1 in tumors



Mouse 4434 melanoma tumors (dual flank)

50ul ($1x10^8$ pfu/ml) of RP1 injected 3x into the right tumor only (Days 1, 3, 5)

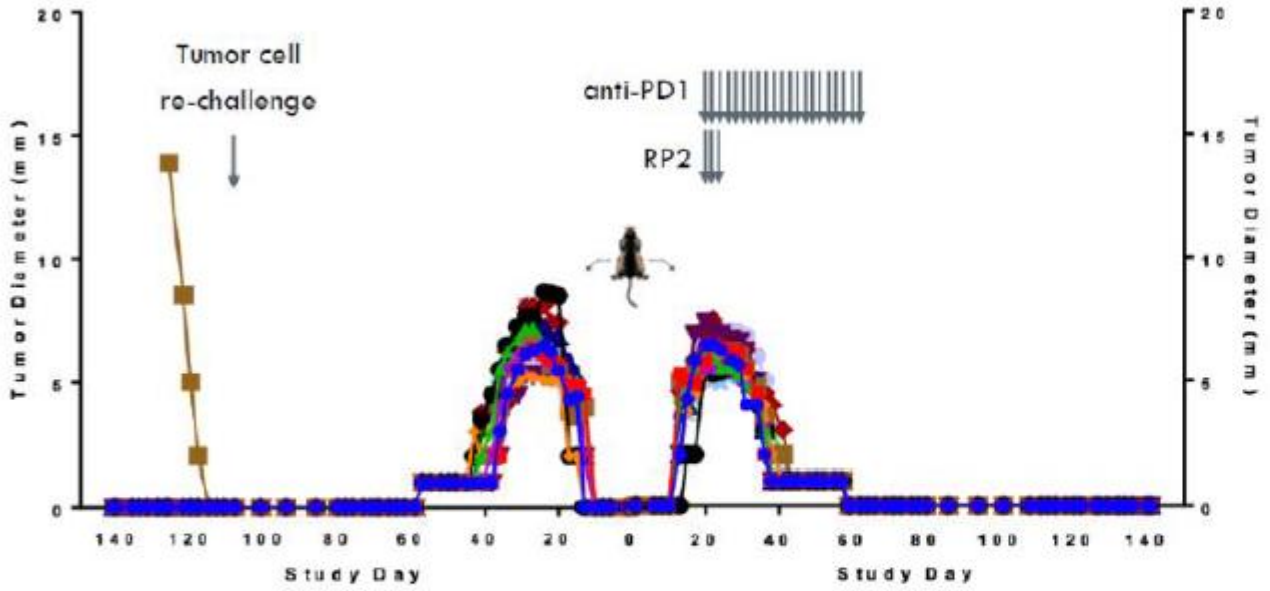
Tumors were harvested on the indicated days after treatment initiation

PD-L1 expression is indicative of a cellular response to innate immune stimuli induced by the virus, as well as an adaptive immune resistance mechanism due to T-cell infiltration.

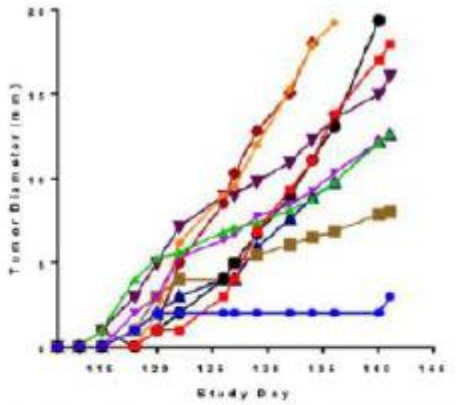
These data support the rational use of PD-(L)1 blockade as a combination strategy with RP1.

Source: Company Filings

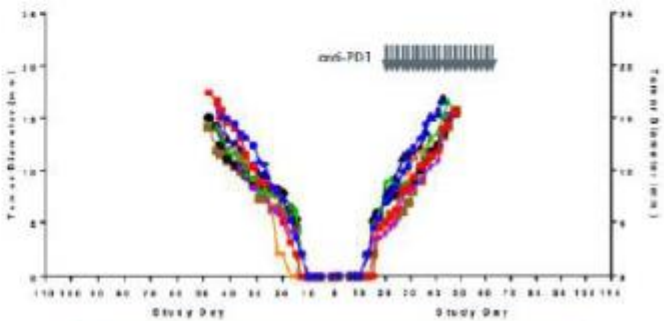
Preclinical: RP2 (GM-CSF, GALVR-, anti-CTLA4) prevents tumor return upon re-challenging



15 mice previously cured of bilateral tumors by treatment with RP2 + anti-PD1 were re-challenged with tumor cells on the uninjected flank on Day 108 and followed for a further 32 days. Fourteen of the fifteen mice were completely protected from re-challenge.



10 tumor & virus naïve mice challenged with tumor cells on the same day all grew tumors

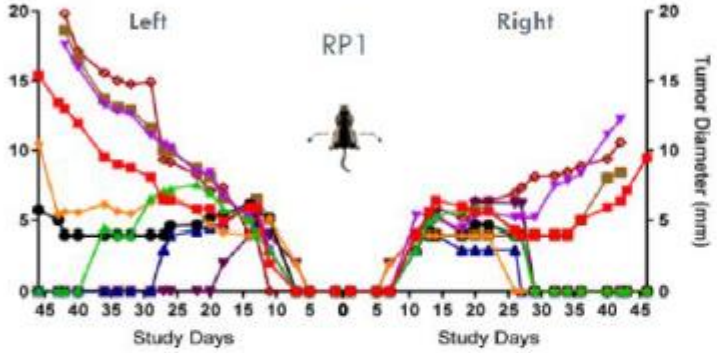


Mice treated with anti-PD1 alone do not respond

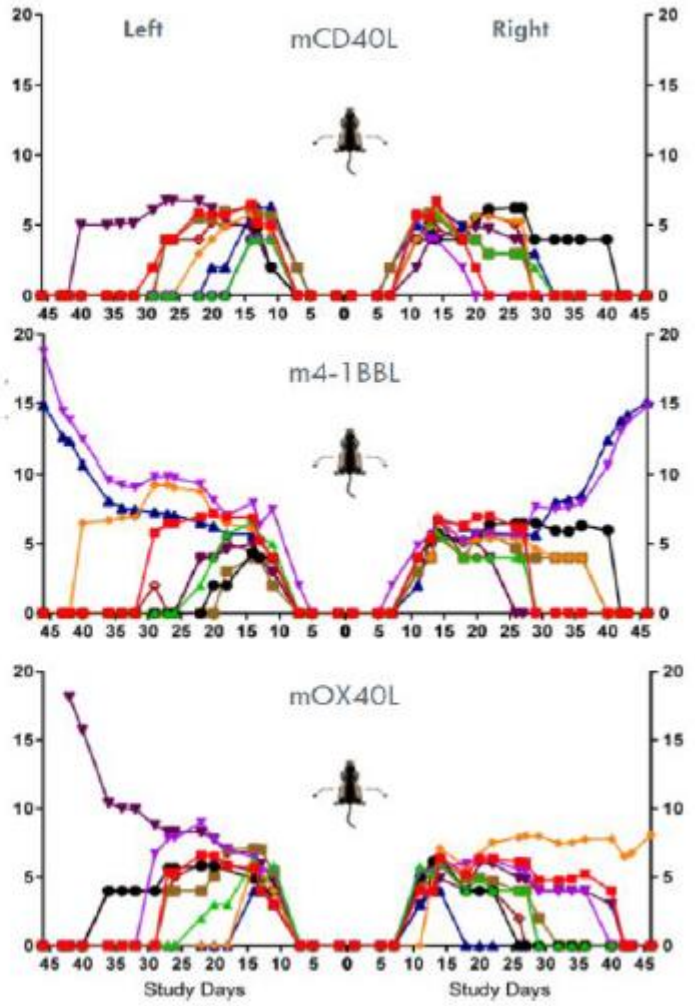
Increasing local anti-CTLA4 expression via a virus may reduce global toxicity

Source: Company Filings

Preclinical: RP3 (GALVR-, co-stimulatory factors) improves tumor regression



Immune competent A20 mouse tumor model
Subtherapeutic dose for RP1 ($5x10^4$ pfu) injected 3x into the right tumor only



Source: Company Filings

Melanoma Benchmark: T-VEC Monotherapy

Bucket 1: T-Vec Monotherapy (Melanoma, All Lines of Tx)	
	W/A*
ORR (irRC)	26%
CR (irRC)	11%
Stable Disease (irRC)	24%
Disease Control Rate (PR+CR+SD for >3 months)	46%
12 month OS	72%
24 month OS	50%
mPFS (months)	2.1
mOS (months)	23.3

W/A = weighted average of all trial phases

T-VEC efficacy by Lines of Therapy

T-VEC in front line setting had better response rates

Bucket 1: T-Vec Monotherapy (Melanoma)	
	W/A*
ORR (irRC) – 1L	37%
CR (irRC) – 1L	23%
mOS (months) – 1L	33.1
ORR (irRC) – 2L	18%
CR (irRC) – 2L	14%
mOS (months) – 2L	14.3

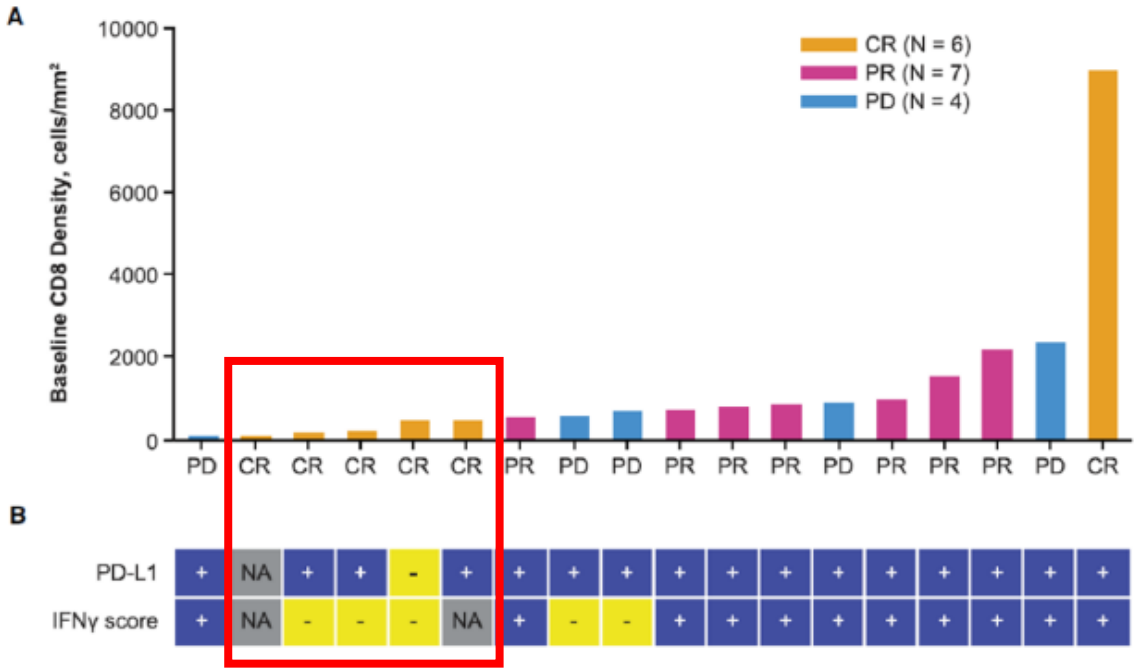
<u>T-VEC is commercially unsuccessful:</u>
AMGN's FY2018 sales of "other" products was $275M. T-VEC and three other drugs was in these "other" products.

Source: SVB Leerink Research

Melanoma Benchmark: T-VEC + anti-PD1

Combination therapy was better than anti-PD1 monotherapy (ORR 35% - 40%) in naïve melanoma patients

Bucket 3: T-Vec + Anti-PD-1 (Keytruda) (Previously-Untreated Melanoma)	MASTERKEY-265 (Phase Ib)
	T-Vec + Keytruda
ORR (irRC)	61.9%
CR (irRC)	33.3%
Injected Lesions (≥50% decrease)	88%
Injected Lesions (Complete Res.)	81%
Uninjected Lesions (≥50% decrease)	60%
Uninjected Lesions (Complete Res.)	60%



BUT trial consisted of patients with favorable prognostic factors:

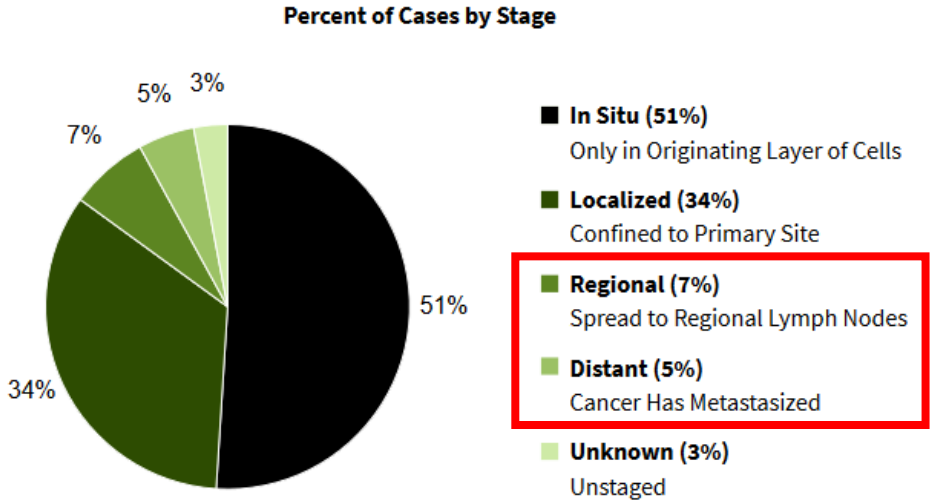
These were anti-PD1 naïve patients with advanced melanoma (n=21). 81% were PD-L1+ and 76% had low baseline levels of LDH.

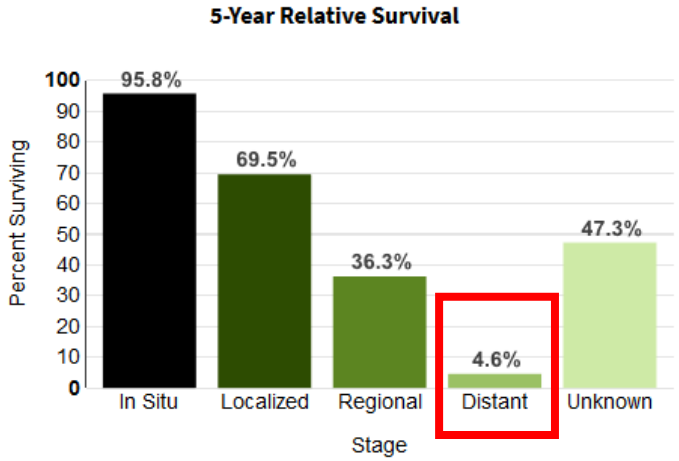
Sources: SVB Leerink Research and Ribas *et al.* Cell 2017

Tough Lessons from Amgen's T-VEC

- T-VEC brings in ~$100M/year in sales
- Slow sales primary due to advent of checkpoint inhibitors
  - Trials did not include comparison with these new class of drugs
- OV field has since shifted to combination of therapies
  - The field largely agrees that OV has significant value through checkpoint inhibitors

Phase 1/2: RP1 in *Metastatic* Bladder Cancer





- **Prevalence (2016):** ~700K in US
- **Incidence (2019):** ~80.5K/yr (stable trend)
- RP1 is targeting 12% of these patients

Standard of Care:
1.) Chemo + Surgery
2.) Immunotherapy (anti-PD1/L1)
3.) *RP1 + anti-PD1 or RP1 alone?*

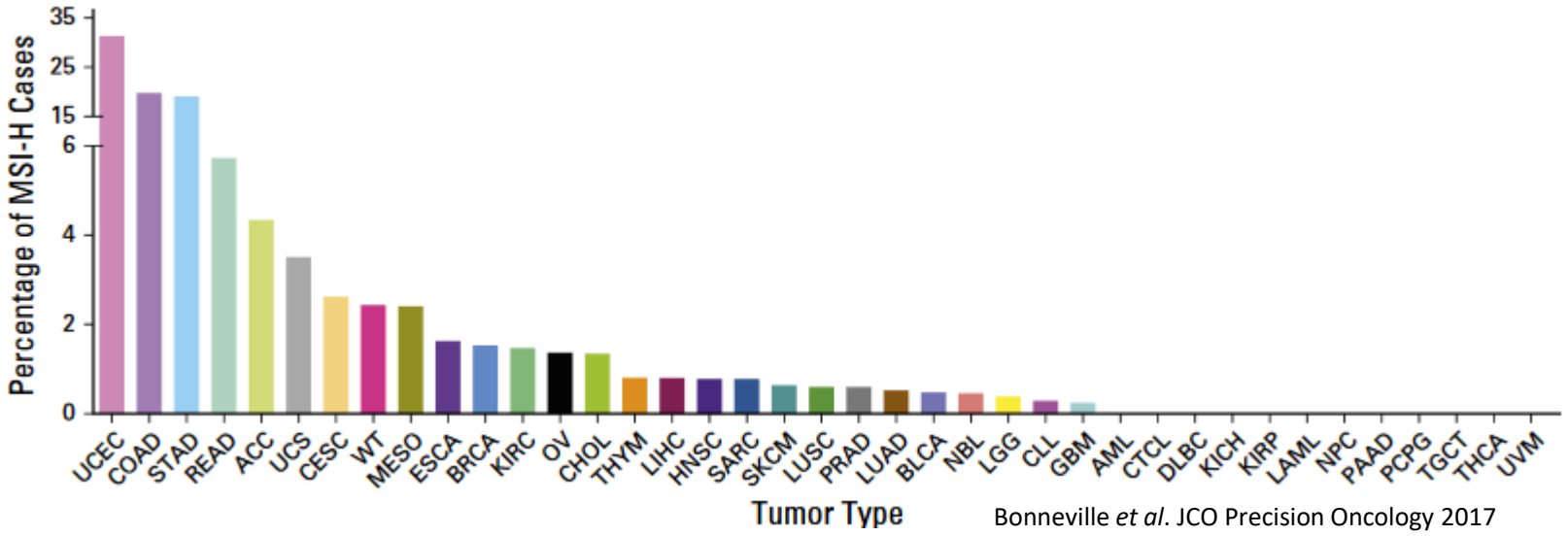
Assuming 20% market penetration & $70K price, estimated annual peak sales of $135M

Direct Competitor:
Merck/Viralytic's Cavatak + anti-PD1

Sources: seer.cancer.gov

Phase 1/2: RP1 in MSI-H & dMMR Cancers

- Targeting any cancer with MSI-H/dMMR biomarkers, most frequent in colorectal , gastric, and esophageal cancers (see below)
- Mutations in >30% microsatellites with inability to repair mistakes
- The immune system can easily recognize these tumors meaning immunotherapy drugs work well



Bonneville *et al*. JCO Precision Oncology 2017

Why are they not targeting MSS+ (microsatellite stable) tumors? These are "cold" tumors that do not respond to immunotherapies. 80% colorectal cancer pts are MSS+.

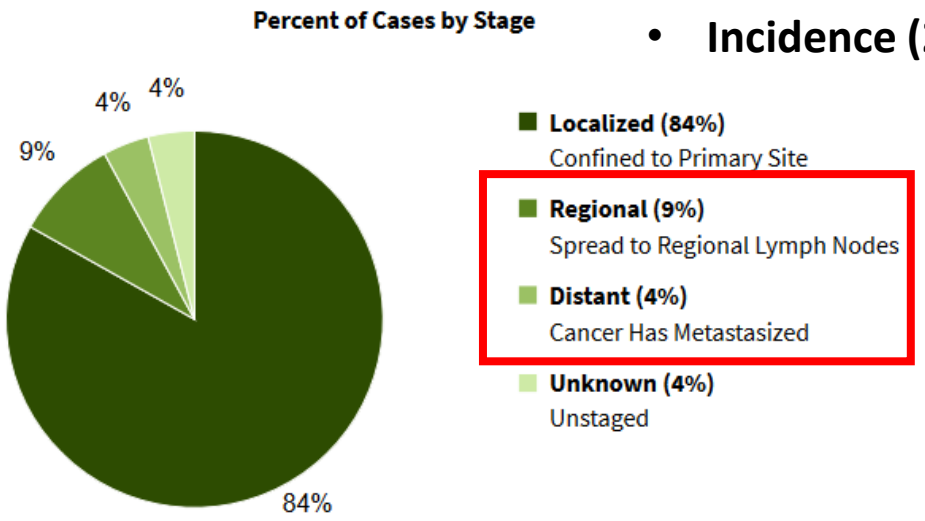
Standard of Care:
1.) Chemo
2.) anti-PD1/L1 Treatment

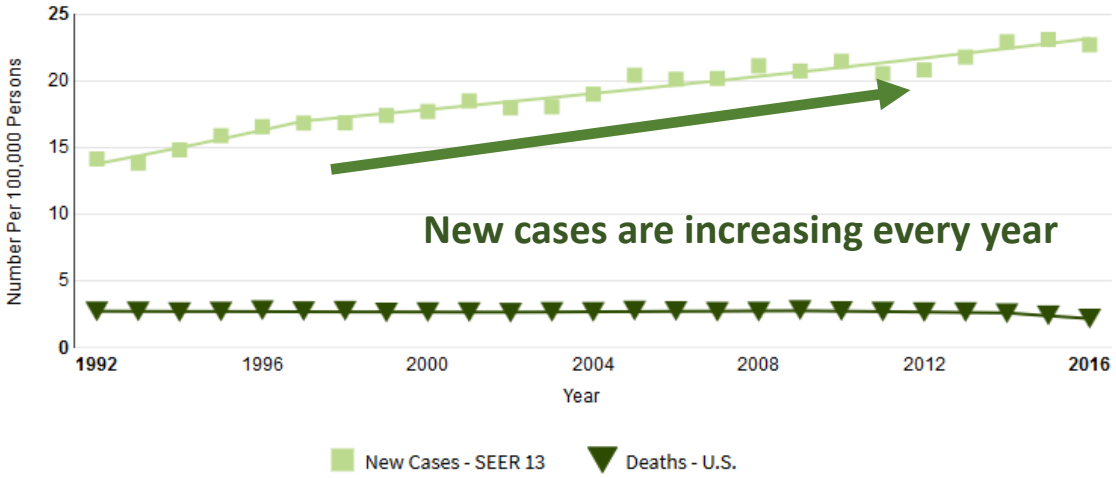
MSI-H/dMMR (incidence)	% Stage 4	Peak Market Potential
Gastric (22K)	7%	~$108M
Colorectal (145K)	5%	~$508M
Esophageal (17K)	4%	~$48M

(Incidence and % stage 4 from Amonkar et al. 2019)
Est. annual price of RP1 at $70K

Phase 1/2: RP1 in Checkpoint Failed Melanoma

- **Prevalence (2016):** 1.2M in US
- **Incidence (2019):** 97K/yr





Standard of Care:

1.) Radiation, Chemo, and/or Surgery
2.) BRAF mutation: BRAF or MEK inhibitors
3.) C-KIT mutation: imatinib, nilotinib
4.) Immunotherapy: anti-PD1/L1 or anti-CTLA4 + anti-PD1 or IL-2 injections
5.) T-VEC (direct competitor)

Due to very competitive space:

Assuming 5% market penetration & $70K price, estimated annual peak sales of $44M

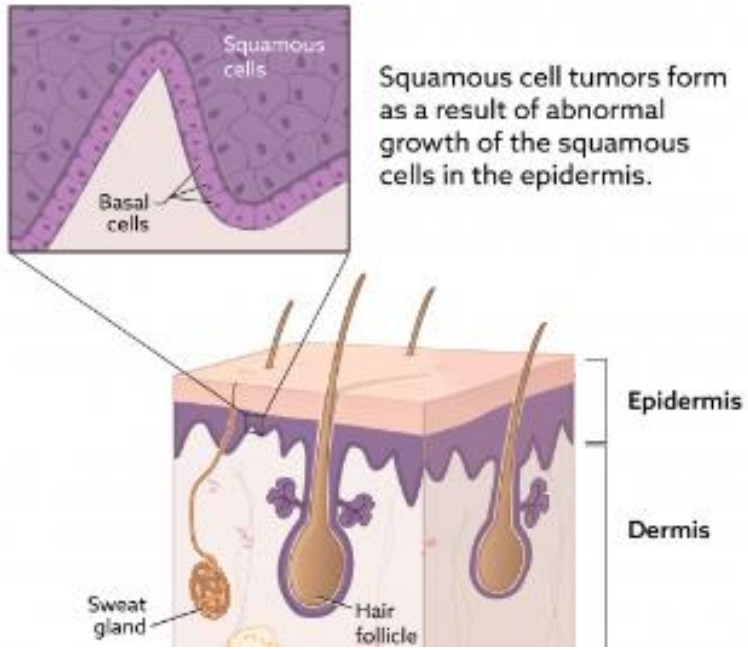
Direct Competitors:

- Merck/Viralytic's Cavatak + anti-CTLA4: Ph1 ORR of 60% and 38% for checkpoint naïve and experienced pts, respectively (n=18). Pretty safe.
- Many others: Iovance's TIL, Dynavax,….

Sources: seer.cancer.gov

Phase 2: RP1 in cutaneous squamous-cell carcinoma

700K cases/year in the US



- 2nd most common form of skin cancer in the US
- 5x more prevalent than melanoma
- Advanced/metastatic CSSC poses most risk (10% pts)
- Highly immunogenic form of cancer with huge mutational burden

Standard of Care:
1.) Radiation + surgical removal
2.) anti-PD1/L1 + RP1?

Huge potential with no good treatments:
Assuming 20% market penetration & $70K price, estimated annual peak sales of $980M

Direct Competitor:
Amgen's T-VEC (Ph2 ongoing)

SITC 2019: Promising activity in chemo refractory CSCC pts

Only 5 patients treated with RP1 + anti-PD1 so far. All patients were anti-PD1 & CTLA4 naïve. This activity supports the continuation to Ph2.

Patient #	# Prior Treatments	Response	Increase in PD-L1 & CD8 T Cells @ D43?	Notes
4403-1002	4	**CR**	**Yes**	Had relatively high baseline levels of PD-L1 and CD8+ T cells.
4402-2001	2	PR	**Yes**	Still has bone lesions but these lesions are responding.
4402-2004	1	SD —> PR	Pending	Reduction in lung lesions as well.
4402-2005	2	PD	Pending	
???	??	Passed Away		Died from PD <6 weeks from starting therapy.

Source: Replimune SITC 2019 Presentation

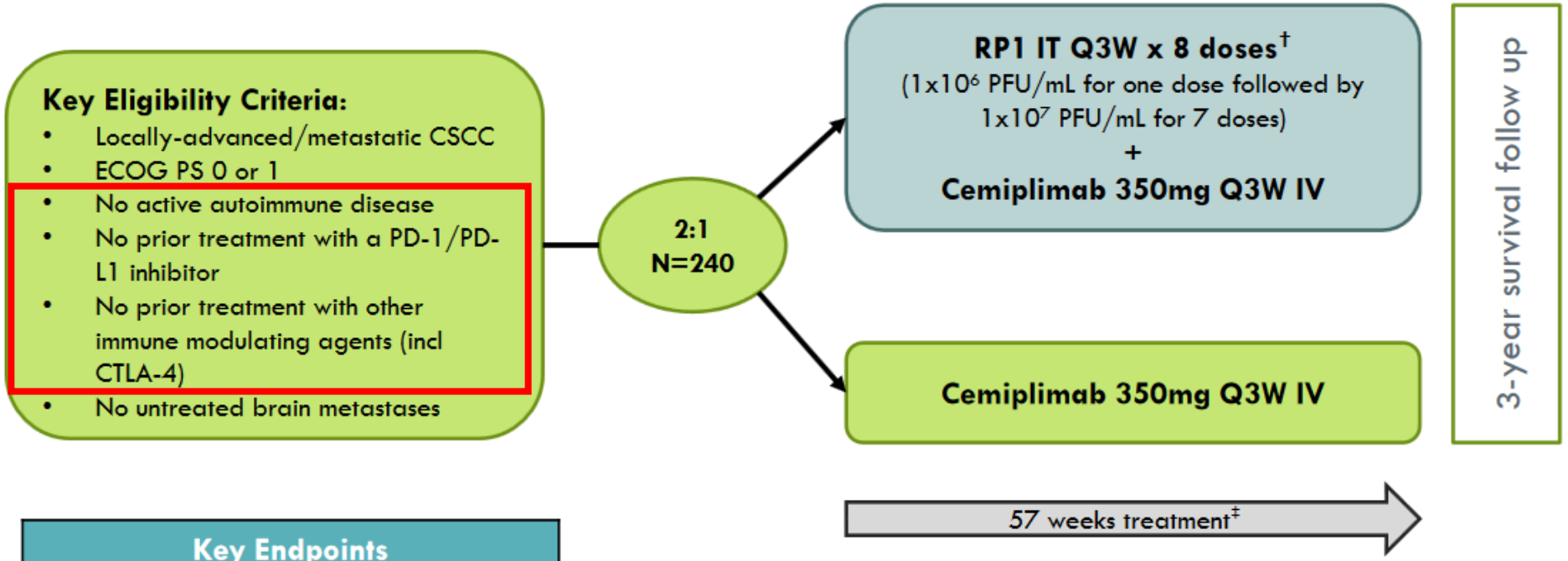
SITC 2019: Ph1 data checks all the boxes

- **Did anti-PD1 refractory patients respond to RP1?**
  - YES. Three melanoma patients are now responding.
- **Did CD8+ T cells increase (immune cell activation)?**
  - YES. Increases in CD8+ T cells and PD-L1 were seen across all tumor types. There was also autoimmune B cell response signatures. 50% of patients could not be assessed by histology due lack of tumor
- **Was there abscopal effects?**
  - YES. Reductions in lesions in other areas were seen at lung, liver, and bone in multiple patients.
- **Any safety issues?**
  - Mostly grade 1-2 flu-like symptoms and one grade 4 elevated lipase
  - RP1 combined with nivolumab (anti-PD1) induced vitiligo (likely caused by nivolumab)
  - Up to 10mL injection/day. T-VEC was 4mL.

Source: Replimune SITC 2019 Presentation

RP1 Ph2 trial design in CSCC

They are focusing on anti-PD1 and anti-CTLA4 naïve patients. This will increase success of trial.



Key Endpoints

Primary: ORR (RECIST v1.1)
Secondary: DOR, PFS, OS, Disease-Specific Survival, safety/tolerability

†First dose of RP1 to be given as monotherapy with cemiplimab to be given with second dose of RP1
‡57 weeks treatment for the combination arm; treatment duration for cemiplimab-only arm is 54 weeks

Source: Replimune SITC 2019 Presentation

REPL management, comprised of former BioVex team, inspires confidence in guiding company

ROB COFFIN
Chief Executive Officer
Founder & CTO of BioVex, VP at Amgen

PHILIP ASTLEY-SPARKE
Executive Chairman
CEO BioVex, Chairman of UniQure

COLIN LOVE
Chief Operating Officer
CDO BioVex; VP at Amgen through T-VEC BLA filing

PAMELA ESPOSITO
Chief Business Officer
VP BD at BioVex; CBO of Ra Pharmaceuticals

HOWARD KAUFMAN
Chief Medical Officer
World leading clinical immuno-oncologist; ex-SITC President

SUSAN DOLEMAN
VP Clinical Development
Director of Clinical Operations, BioVex/Amgen for T-VEC

ANNE WOODLAND
SVP Regulatory & Quality
VP Regulatory at BioVex; led T-VEC BLA filing for Amgen post acquisition

TIM HANKE
VP Medical Affairs
VP Commercial at BioVex; led T-VEC trial recruitment for Amgen post acquisition

Potential Milestones in 2020

- Initiate & complete single agent RP1 registrational clinical trial in organ transplant recipients with CSCC
  - Initial data read out in H2 2020
  - Additional CSCC data from Ph2 in combination with nivolumab expected in mid-2020
- Initiate registrational-directed trial in anti-PD1 refractory melanoma
  - Additional melanoma data from Ph2 in combination with nivolumab expected in mid-2020
- Complete Ph2 MSI-H and bladder cancer cohorts (RP1 + anti-PD1)
- RP2 Phase 1 data
- RP3 to enter the clinic

Bull and Bear Case & Our Recommendation

Firm	PT
BMO Capital	$31.00
JP Morgan	$26.00
Leerink	$25.00
Wedbush	$24.00

Recommendation:

Buy 5% and evaluate in 2H2020

- RP1 Ph2 data in CSCC registration cohort
- RP1 Ph2 data in MSI-H & bladder cancer go/no-go decision
- RP2 Ph1 data

Bull case: Next gen HSV oncolytic virus platform becomes a universal combination partner for checkpoint inhibitors & is applicable to all injectable solid tumors.

- Experienced management team with game plan
- Platform updates leads to improved potency over T-VEC
- Improved potency over T-VEC allows REPL to pursue multiple indications
- Proven monotherapy activity & robust combination therapy
- I.T. has advantages over I.V.

Bear case: Crowed competitive landscape for OV platforms and lack of efficacy and/or adoption with next gen HSV

- Platform updates will not provide significant clinical benefit
- Crowded landscape: >20 OV companies
- I.V. administration is untenable which prohibits blood cancer treatment
- Production & purification of OV can be challenging and costly leading to delays

Post-diligence, post-decision information

Stop here! What is your assessment of the diligence and recommendation?

- How thorough was the diligence? What was the most useful material?
- What lingering questions do you have? How can you answer these?
- What is your risk assessment on the investment opportunity?
- Do you agree with the recommendation? Were exit opportunities clear?

Make a rational and calculated decision on whether to invest…

- How will you keep an eye on the stock price?
- What could happen between now and your exit points?
- What is your expected return? What is your stop loss?

Update since Mythos entered position

SITC 2020 Meeting Update:

- **RP2**: Of the six patients treated with single agent RP2, three had ongoing PRs. Only grade 1-2 AEs were observed. This trial is currently testing RP2 with nivolumab as well.
- **RP1 + nivolumab combo:** CSCC patients have 87.5% ORR & 62.5% CR!!!!

REPL announces presentation at the 2020 Society for Immunotherapy of Cancer (SITC) Annual Meeting

See 10/14/20 press release

Mythos entered position

Additional Slides

Comparison of common oncolytic viruses

	Adenovirus[a]	Herpes simplex virusb	Pox virus	Coxsackie virus	Maraba virus	Poliovirus	Measles virus	Newcastle Disease virus
Genome	dsDNA	dsDNA	dsDNA	ssRNA	ss (–) RNA	ss (+) RNA	ss (–) RNA	ss (–) RNA
Genome size	Moderate (32 kb)	Large (152 kb)	Large (130–375 kb)	Small (~8 kb)	Small (11–15 kb)	Small (7.5 kb)	Small (~16 kb)	Small (~15 Kb)
Cell entry mechanism	Endocytosis	Endocytosis; penetration	Membrane penetration and fusion	Micropinocytosis via epithelial tight junctions	Endocytosis; pH-dependent fusion activation	Receptor-mediated endocytosis	Membrane fusion	Endocytosis; pH-independent direct fusion
Cell entry receptors	hCAR; VCAM1; CD46	HVEM; nectin 1; nectin 2	GAGs; EFC	CAR; DAF	Unknown	CD155	CD46; SLAM	Neuraminidase receptor; sialoglyco-conjugates
Transgene capacity	Moderate	High	High	Low	Very low	Low	Low	Low
Viral immunogenicity	Low	Low	High	Low	Low	Moderate	Low	Low
Pathogenicity of native virus	Respiratory and GI tract infections; pharyngitis; pneumonia; meningitis; follicular conjunctivitis	Cold sore and/or fever blister; latent infection in CNS possible	Fever, myalgia, lymphadenopathy; progressive vaccinia; eczema vaccinarum; encephalitis; generalized vaccinia	Common cold; HFM disease; pleurodynia; myocarditis	Flu-like syndrome; rabies (Maraba virus; not extensively studied)	Poliomyelitis; paralysis	Measles; pneumonia	Transitory conjunctivitis

Other oncolytic viruses in clinical development

OV	Why are they considered	Drug Candidates/Indications (not comprehensive)
Measles	**Pro**: highly fusogenic, extensive cytopathic effects such as large multinucleated cells, preferentially targets CD46-expressing cells (overexpressed on tumor), naturally expresses sodium iodine symporter - allows for non-invasive virus imaging \ **Con**: intratumorally or intravesically (not IV)	**Vyriad's MV-NIS** Ph1-2 MV-NIS complete remission in bladder cancer. Other: glioma.
Rhabdoviruses (VSV)	**Pro**: rapid ~12-hour lytic replication cycles, highly potent, highly sensitive to type I IFN - leverage to selectively target virus replication to tumors only, encodes NIS transporter for non-invasive virus imaging, low seroprevelance (not very immunogenic) so amenable to IV or IT **Con**: uses the low-density lipoprotein (LDL) receptor for cell entry, allowing VSV to infect nearly all cell types (not selective unless engineered)	**Vyriad's Voyager V-1** relapsed or recurrent cancers including multiple myeloma, lymphoma, leukemia, endometrial cancer, breast cancer. Ph2 w/ anti-PDL1: metastatic colorectal cancer; w/ anti-PD1: NSCLC, head and neck cancer.
Adenovirus	**Pro**: low pathogenic risk, high genome stability, 70 serotypes (5 common), tumor selectivity variable by strain, high viral titer, highly efficient transduction, well proven safety **Con**: necessary to further reduce pathogenicity, DNA loading limited (4kb), high seroprevalence (highly immunogenic) limits IV use	**Targovax's ONCOS-102**. ONCOS-102 + Ph2 Pemetrexed/cisplatin (SoC) - Rare MPM lung cancer (50% disease control rate at 6mo), orphan drug approval. Ph1 ONCOS-102 + anti-PD1 - melanoma (33% ORR).

Other oncolytic viruses in clinical development (cont.)

Vaccinia	**Pro**: 25kb of identified non-essential regions removed in genome, unprecedented amount of space for future transgene arming, well demonstrated safety **Con**: highly inflammatory so limited to intratumoral administration	**SillaJen's PEXA-VEC**. Ph2 PEXA-VEC + anti-PD1 - Renal Cell Carcinoma - 47% ORR in Ph1. Ph1 PEXA-VEC + anti-CTLA-4 - solid tumors. Ph3 PEXA-VEC + sorafenib v. sorafenib alone - terminated early (9/19), futility - advanced liver cancer (HCC).
Coxsackievirus (common cold)	**Pro**: smaller (25nm) than larger OVs, good safety, low toxicity, amenable to intratumoural, intravenous, and intravesicular (into bladder) administration **Con**: small genome (7kb) for expressing genes	**Merck/Viralytics' CVA21/Cavatak** - advanced melanoma, lung and bladder cancers. Monotherapy: Ph2 CALM (late-stage melanoma) - i.t. - improved survival, primary endpoint 38.6%, well-tolerated, local and distant tumor responses. Combo: anti-CTLA (Ph1 MITCI - late-stage melanoma), anti-PD1 (Ph1 CAPRA - advanced melanoma, Ph1 - NSCLC), other combo (Ph1 CANON - bladder cancer)
Reovirus	**Pro**: suitable for intratumoral or intravenous administration, highly non-pathogenic (widely hosted in the gut), selective replication in cells with Ras pathway activation (tumor)	**Oncolytics Biotech's Pelareorep/Reolysin -** metastatic breast cancer, early stage breast cancer, multiple myeloma and pancreatic cancer. Ph2 Pelareorep + chemo - pancreatic cancer, breast cancer - combo therapy improves survival. Ph1 Pelareorep + chemo/anti-PD1 - breast cancer - combo therapy improves survival.

Other oncolytic viruses in clinical development (cont.)

Retrovirus	**Pro**: expresses yeast cytosine deaminase (CD) gene that converts prodrug 5-FC to anticancer drug, 5-FU (decreases systemic toxicity due to increases local drug concentration), selective dividing in cells with defective innate immunity pathways (tumor) **Con**: nonlytic (all other OVs are lytic)	**Tocagen's TOCA-511** Phase 2/3 v. SoC - i.t., high grade glioma (HGG) - 9/19 did not meet primary endpoint of OS. Others: colorectal, pancreatic, bladder, lung cancers.

What is GALVR-?

GALVR- is a fusogenic membrane glycoprotein (FMG) from the gibbon ape leukemia virus (GALV) with its R protein removed (Fu et al., 2003, Sakuma et al., 2010, Fielding et al., 2000). FMGs are envelope proteins on viruses that facilitate the death of its host cells. Specifically, FMGs cause multiple host cells to fuse together to form into one large multi-nucleated cell, impairing cell function and ultimately causing cell death in a highly immune-stimulatory manner (immunogenic cell death) (Bateman et al., 2000). Expression of GALV leads to an increase in tumor cell killing of >30x more in vitro and tumor shrinkage of ~5-10x in vivo (Simpson et al., 2006). Importantly, GALV does not impair the virus's ability to replicate.

Oncolytic virus delivery method comparison

- Unclear if intravenous vs. intratumoral will be the best technology
- Due to high seroprevalence of HSV1, REPL can only do intratumoral

Intravenous (IV)	Intratumoral (IT)
- Useful because can target solid and liquid tumors - Prone to higher toxicity due to greater systemic immune response, and therefore can only be used with viruses with low seroprevalence (i.e. HSV1 not possible) - For solid tumors, may be useful for increasing response to visceral and/or highly metastatic tumors	- Can only target solid tumors (not liquid tumors) - Useful because IT injection in solid tumors initiates tumor cell destruction + release of neoantigens - IT has been shown to elicit both local and systemic immune responses