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Oncolytic Virus Clinical Data - The Turnstone Experience

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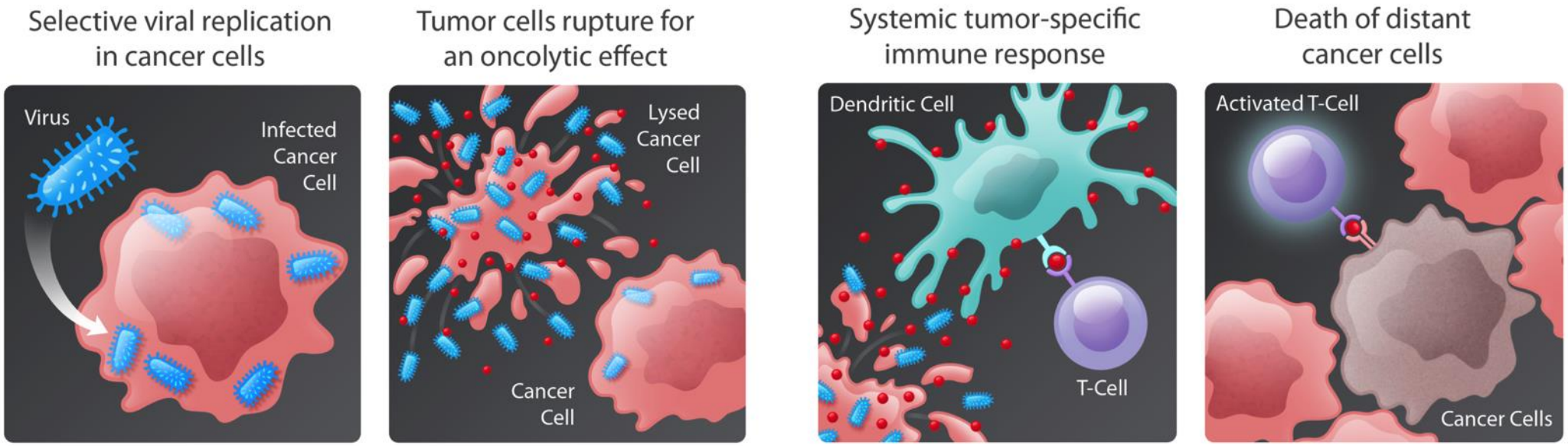
Presenter Disclosure Information

Brian Lichty

The following relationships exist related to this presentation:

Turnstone Biologics, Received, (co-founder, share holder, SVP Basic Research)

Traditional Oncolytic Viruses

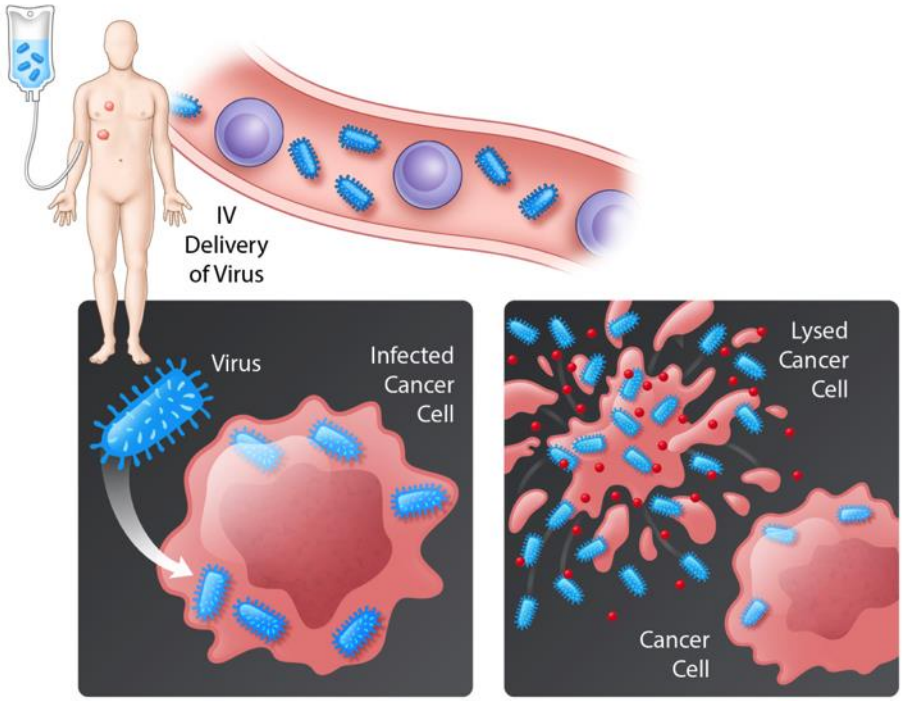


Local Effect:
Tumor Cell Lysis

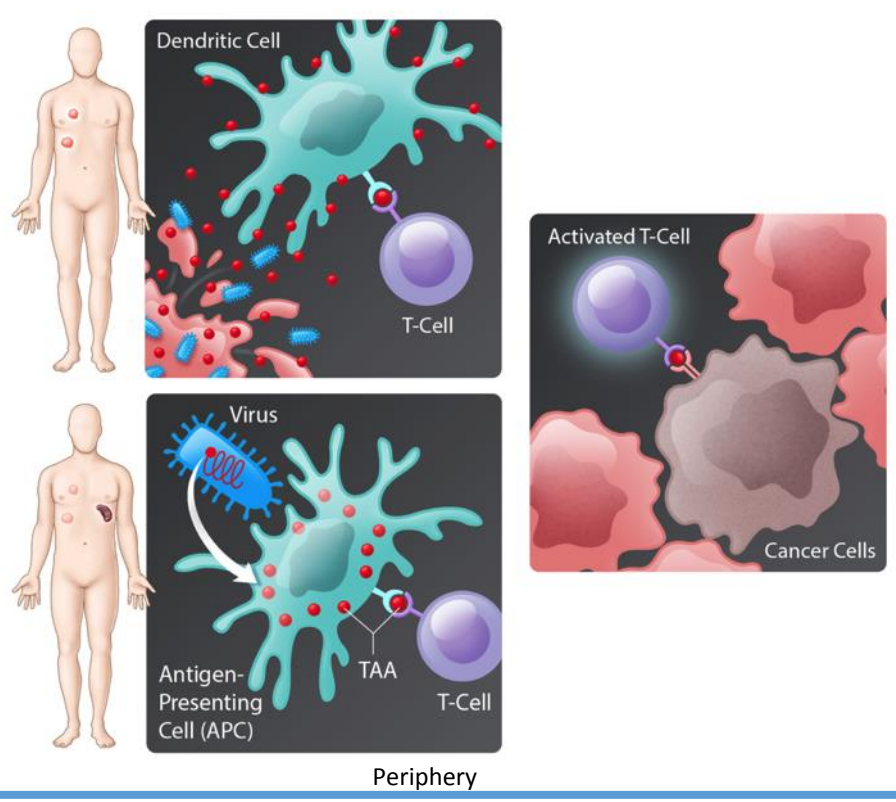
Systemic Effect:
Tumor-Specific Immune Response

Turnstone's Next-Gen Oncolytic Viral Immunotherapy

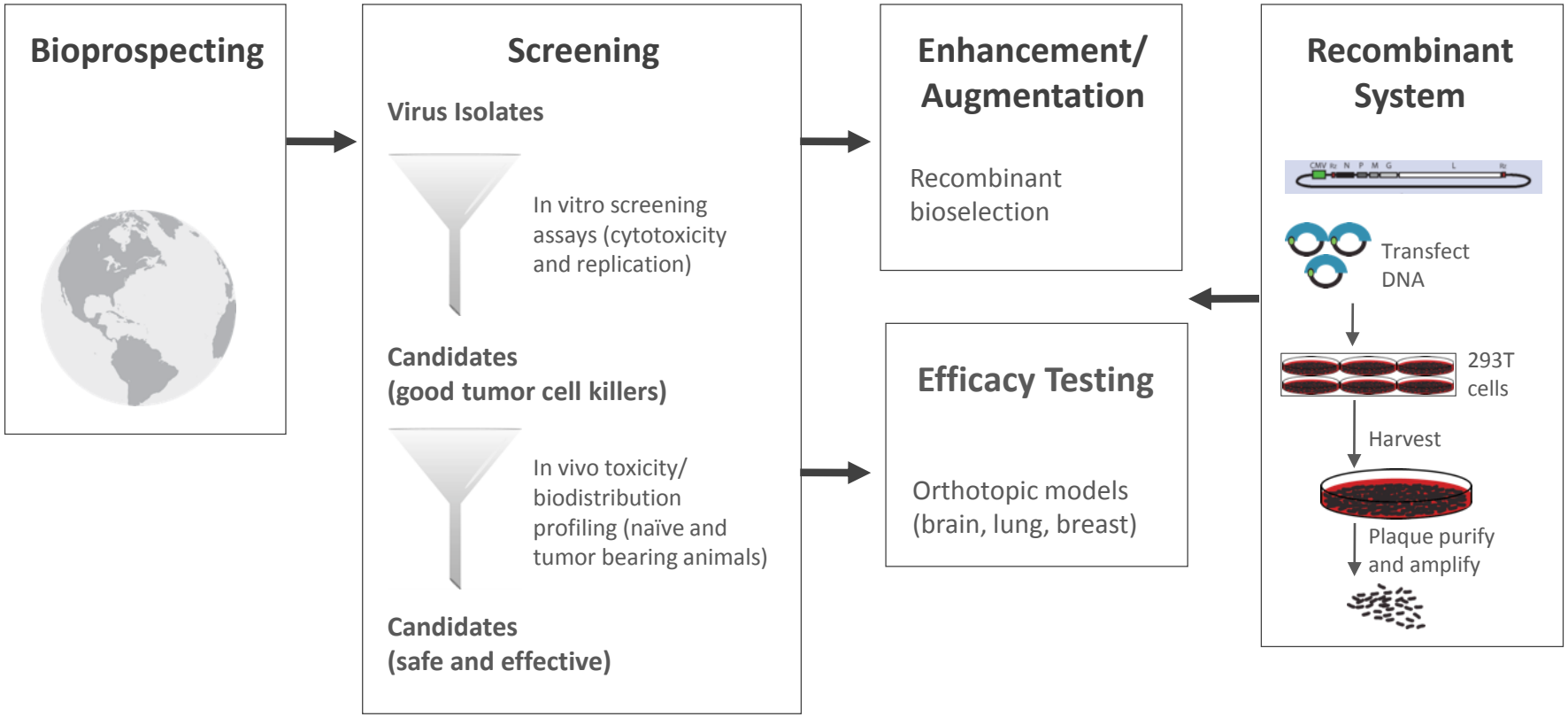
Systemic delivery of oncolytic virus enables lysis and microenvironment modulation at metastatic tumor sites throughout the body



Virus engineered to encode tumor antigens and act as ***T-cell vaccine*** to produce unprecedented CD8+ immune response



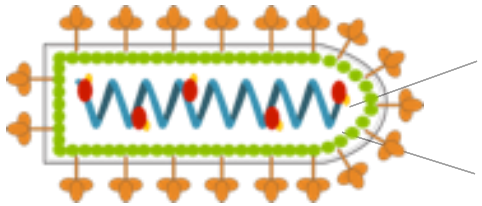
Bioselection Process Identified Optimal Virus



- Compared virus families in broad-based analysis leading to choice of rhabdoviridae
- Screened and evaluated over 200 different rhabdoviruses
- Selected Maraba virus based on broad potency and tumor selectivity

Maraba Oncolytic Virus Platform

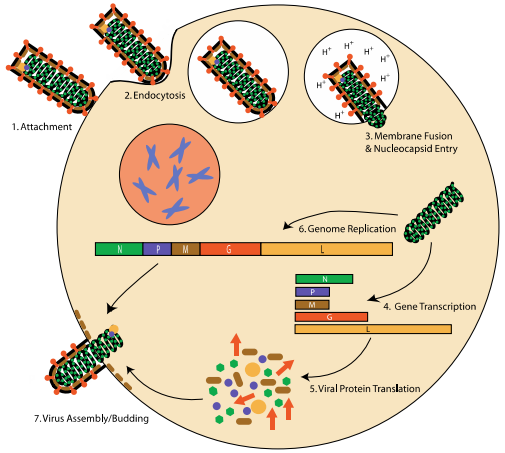
Rhabdovirus Structure



Single stranded negative sense RNA genome

Matrix protein (M) is involved in budding, silencing host gene expression, and apoptosis

Rhabdovirus Life Cycle



Maraba Virus

- Member of rhabdovirus family
- Isolated from Brazilian sand flies
- 11 kb RNA genome
- Broad tumor tropism with non-specific cell entry mechanism
- Induces cell death via apoptotic pathway

Key Features

- Little pre-existing immunity
- Cytoplasmic life cycle – no genotoxicity
- Genetically stable
- Fully functionalized recombinant system
- Multiple transgene capacity
- Easy to manufacture

Brun J, et al. Mol Ther. 2010 Aug;18(8):1440-9

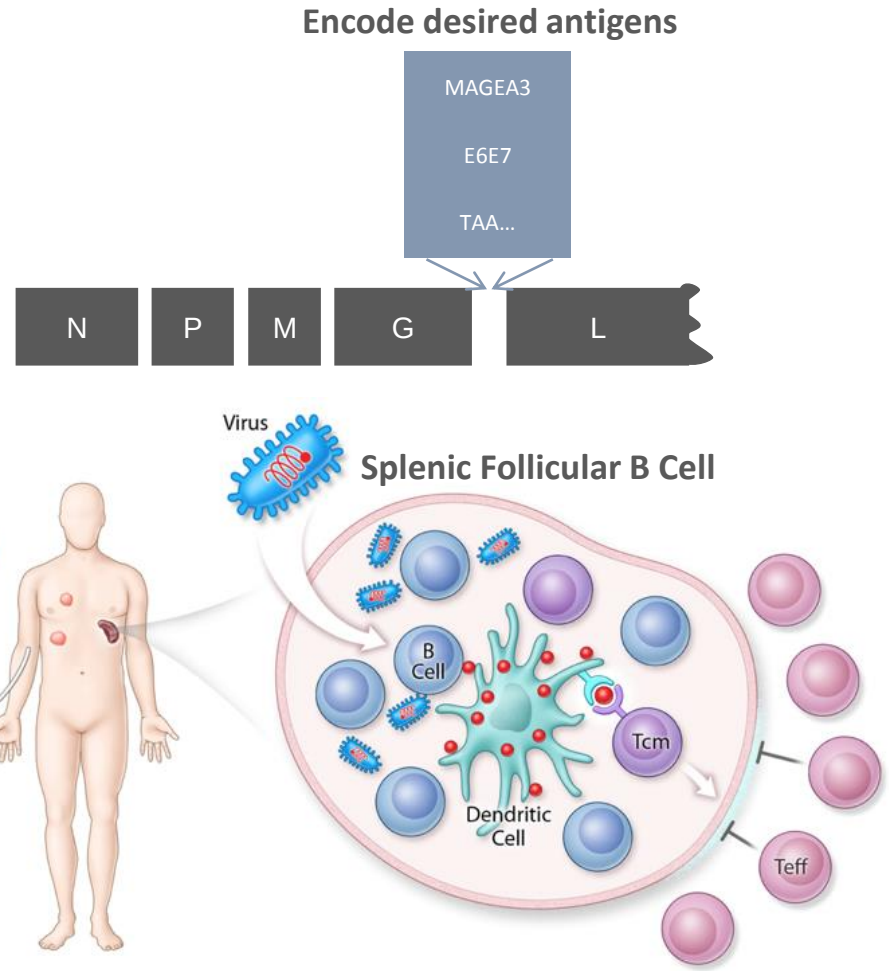
MG1 Mechanism of Direct T Cell Induction – Unique Biology Uncovered

MG1 as a Vaccine Vector

- MG1 engineered to encode any/multiple tumor antigens (4-5kb capacity) to specifically direct immune response
- MG1 effectively boosts pre-existing population of memory T cells (established by any mechanism)

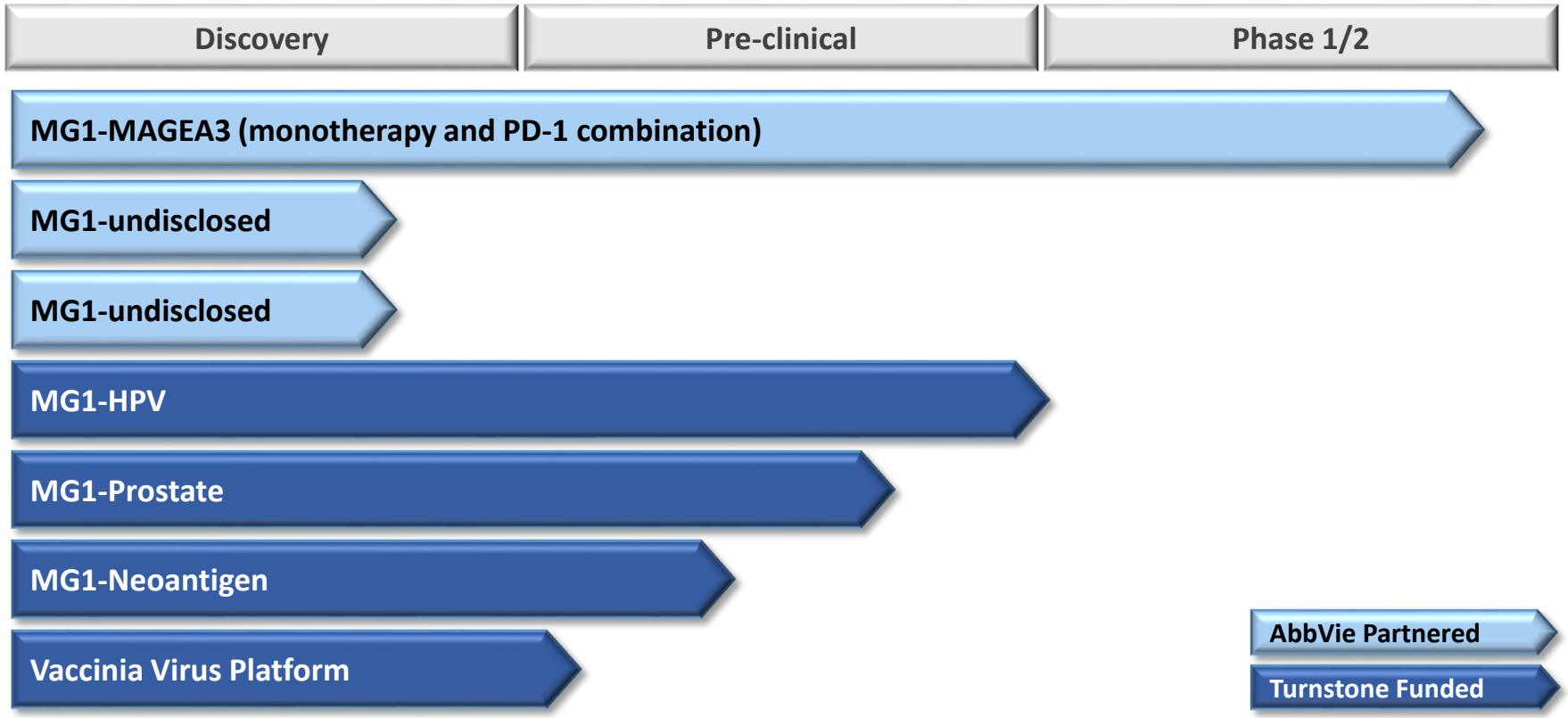
Unique Biology of T Cell Boosting

- Virus infects follicular B cells which provide antigen to follicular dendritic cells for presentation
- Central memory T cells are directly engaged and activated to boost responses
- No negative feedback from T effector cells (privileged compartment) – allows massive T cell response



Development Pipeline

TURNSTONE BIOLOGICS



MG1-MAGEA3 Monotherapy Study Overview

Trial Design

Eligibility Criteria:
Positive MAGE-A3 expressing tumor
No life prolonging standard therapy

Phase 1

Arm A
MG1-MAGEA3 alone

Arm B
Ad-MAGEA3 alone

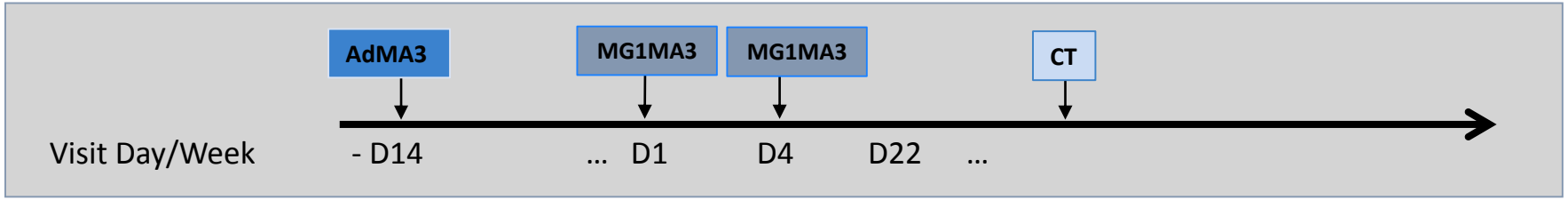
Arm C
1) Ad-MAGEA3 1E10 pfu + MG1-MAGEA3 1E10, 1E11, 3E11 pfu
2) Second dose step-up: MG1-MAGEA3 1E11 + 3E11 pfu, 1E11 + 1E12 pfu
3) Increased dosing frequency: MG1-MAGEA3 1E11 + 3E11 pfu x 3

Phase 2

Simon 2-stage
12 evaluable in each indication (NSCLC, breast, esophageal)
9 additional patients in indication that shows positive clinical activity

- Dose: Ad-MAGEA3 $1E10^{10}$ pfu + MG1-MAGEA3 (RP2D)
- H_o 5%, H_a 20%
- Power 80%, Alpha (1-sided) 0.1
- Success if ≧ 3 total responses observed in an indication

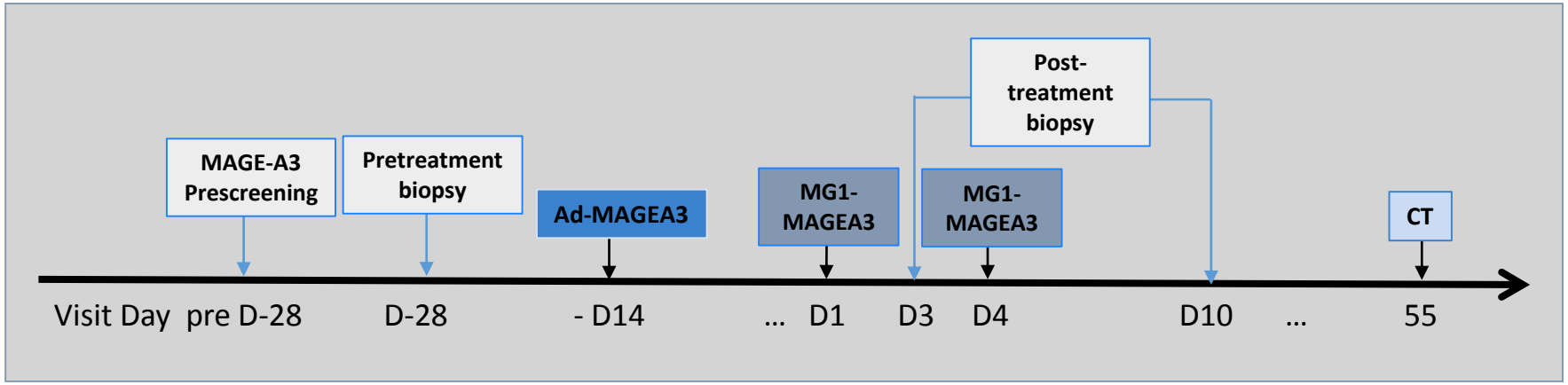
Treatment Regimen



MG1-MAGE A3 is Well Tolerated

- **Maximum tolerated dose (MTD) established:**
  - Ad-MAGEA3: 1 x 10^{10} pfu IM
  - MG1-MAGEA3: 1 x 10^{11} pfu IV
- **MG1-MAGEA3 treatment related AEs:**
  - The great majority occur in association with treatment 1 of MG1-MAGEA3; treatment 2 MG1-MAGEA3 shows markedly better safety profile
  - Generally acute and transient
  - **Most common**: Fever, fatigue, diarrhea, anorexia, nausea, chills, flu-like symptoms, and vomiting
- **Laboratory toxicity:**
  - Included generally transient, mild to moderate hypophosphatemia, cytopenia (anemia, leukopenia, and thrombocytopenia), increased creatinine, and transaminitis
  - Notably, hypophosphatemia was observed within 24 hours of treatment with MG1-MAGEA3 and was as severe as grade 4

High Content Study: Extensive Collection of Correlate Samples



- Biopsy analysis: Viral infection, change in immune microenvironment
  - MG1 delivery, innate immune changes
  - TIL infiltration
- Blood collection:
  - Immune monitoring: Days -14, 1, 8 15, 43 and 98
  - PK and viremia: Days 1, 4, 8, 15

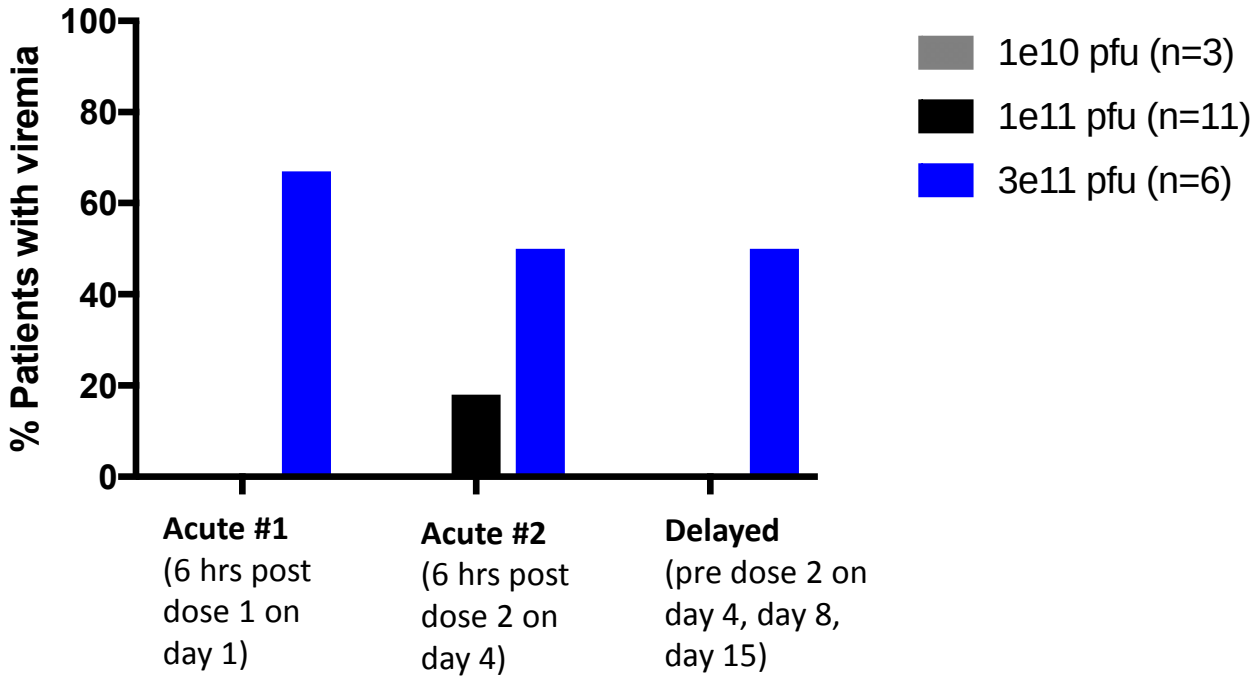
Major Goal of Phase 1 Study is to Establish Proof of Mechanism for MG1-MAGEA3

Four primary areas of focus for correlate data:

1. Evidence for MG1 reaching and replicating in tumors
2. Evidence for modification of tumor microenvironment
3. Evidence for robust immune response
4. Evidence for clinical responses

1a Evidence for MG1 Reaching and Replicating in Tumors

Dose-dependent systemic exposure of MG1-MAGEA3 demonstrated by Q-PCR analysis of whole blood



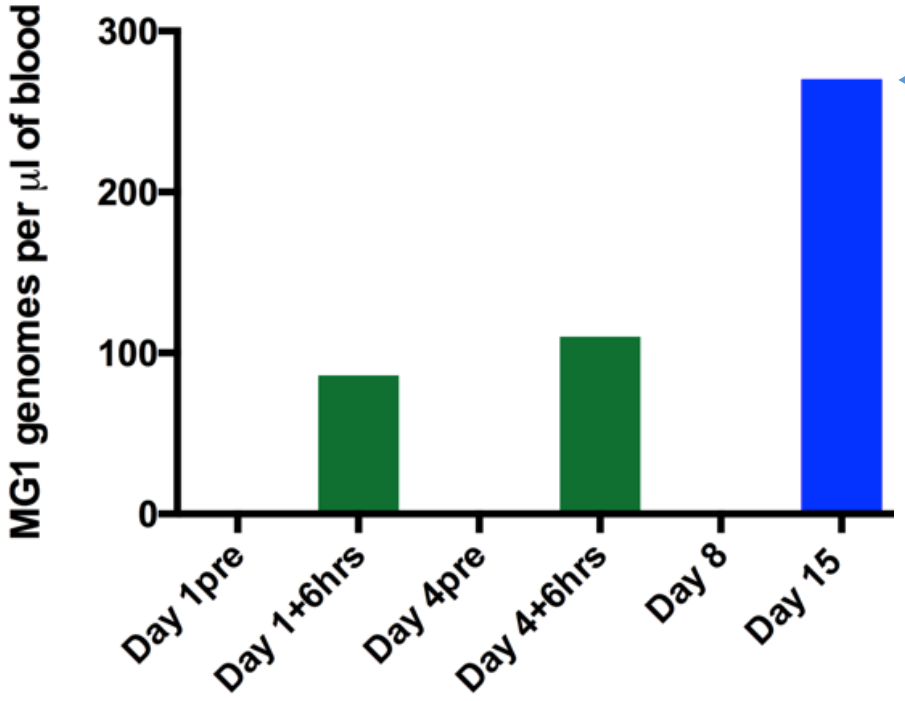
Acute (post-input) and delayed (non-input) circulating virus indicate dose levels sufficient for virus to reach and replicate in tumors

Reaching critical threshold with higher doses driving viral replication in tumors

- Delayed viremia only occurs through viral replication in tumors
- Only evidence for delayed viremia at 3e11 pfu dose level
- Data supports current strategy of dose optimization

1b Evidence for MG1 Reaching and Replicating in Tumors

Viremia analysis in patient receiving MG1-MAGEA3 reveals re-emergence of viral genomes in blood at high concentration in the absence of additional dosing – strong indication of viral replication occurring at tumor sites



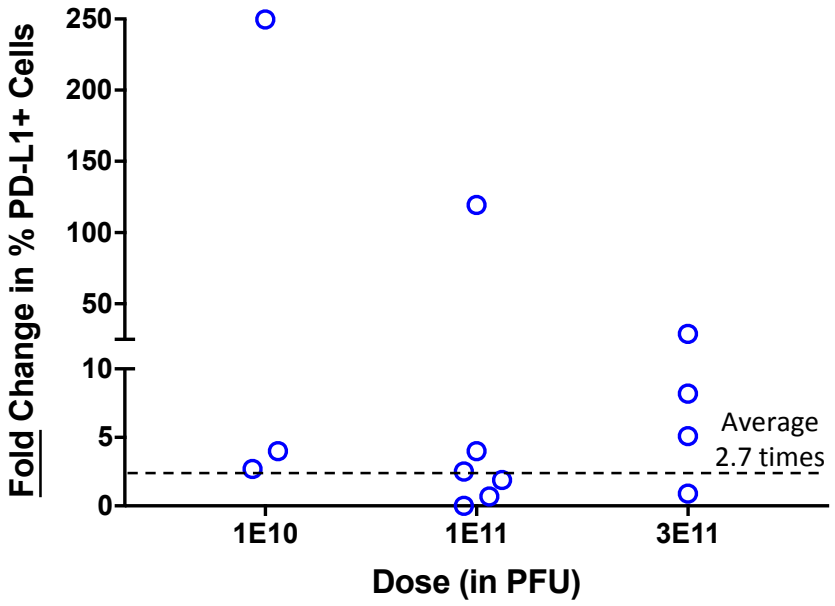
250 viral genomes per microlitre of blood – potentially representing over 1 billion genomes in the patient's bloodstream

2 Strong Evidence of Modifying Tumor Microenvironment

Average fold change pre- to post- treatment across all patients receiving MG1*

Anti-viral markers		Immunogenic markers	
18.0	IFIT1	8.9	CXCL10
15.9	ISG15	5.1	TNFSF10/TRAIL
12.8	MX1	4.6	IL6
13.5	IFIT2	2.8	CD80
6.5	IFITM1	2.4	IDO1
5.7	IFIH1/MDA-5	2.7	CD274 (PDL1)
5.0	DDX58/RIG-I	2.3	IL8
4.6	OAS1	2.7	CX3CL1
4.1	IRF7	2.3	HLA-B
3.6	IFI35	2.3	CCL2
2.6	STAT1	2.1	PDCD1LG2/PDL2
2.6	EIF2AK2/PKR	1.8	ICOS
2.8	TLR3	2.0	CD163
2.1	NOS2	2.0	IL1B
		2.1	CCL5
		2.0	HLA-A
		1.8	CXCL9

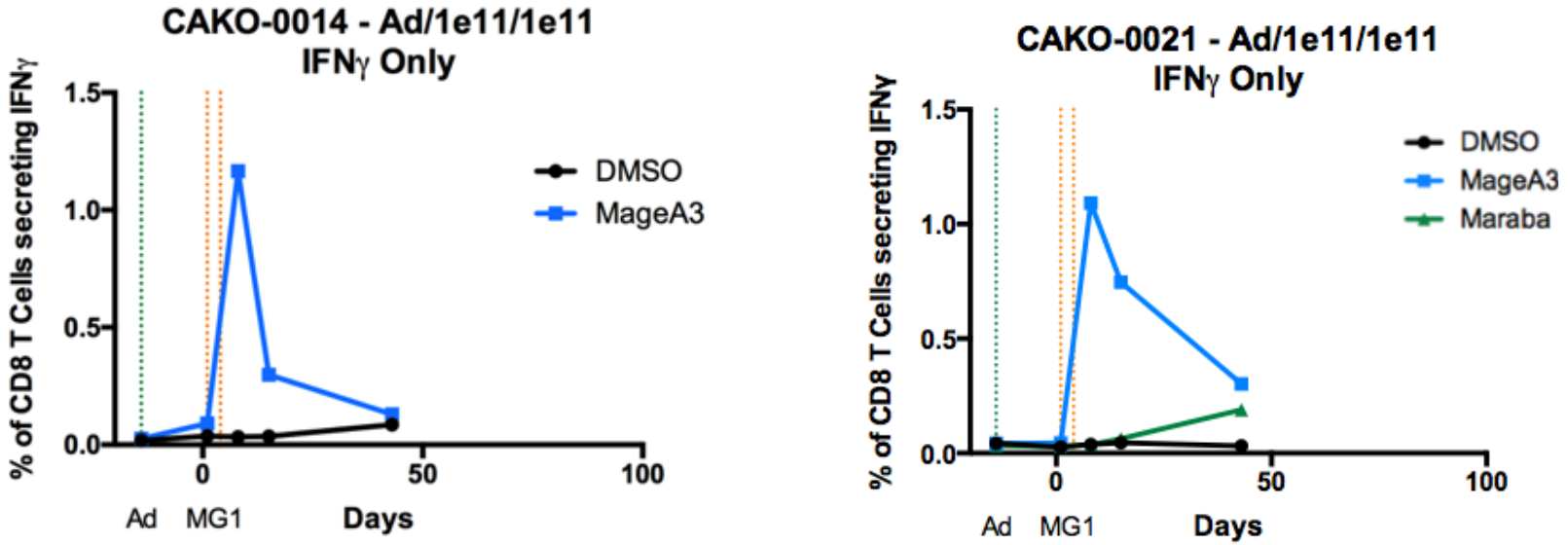
PD-L1 is reproducibly upregulated in tumors at early biopsy point (3 days post-treatment) – expectation of further increase at later time points



* Intratumoural gene expression analysis by nanostring assay comparing pre-MG1 and 48hr post-MG1 gene expression changes within tumor biopsies (Interim data as of Aug 2017 n=20 Arm C pts)

3 Unprecedented Magnitude of Immune Response

Immune responses for two patients at 1E11 dose of MG1-MAGEA3



Unprecedented immune responses to self-cancer-antigen observed

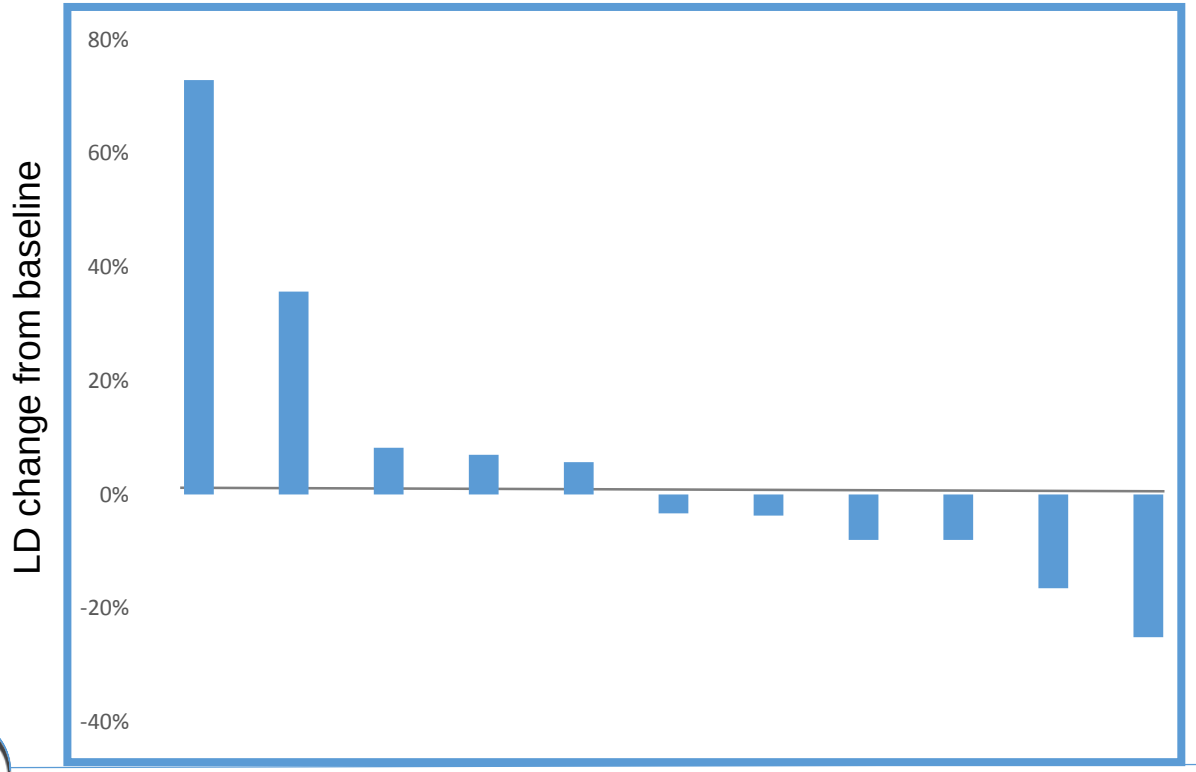
- 41% of all patients have strong immune response to MAGEA3 as detected by ELISpot without the need for ex vivo call expansion
- Multiple patients with >1% of CD8+ T cells positive for MAGEA3

Strong durability with immune response noted over 6 weeks post MG1-MAGEA3 boost at 1 x 10^{11} dose

4

Evidence for Clinical Benefit - Stable Disease and Tumor Shrinkage

Change in target tumor longest diameter from baseline to Week 9 in all evaluable 1 x 10^{11} PFU MG1 treated patients



Promising evidence of anti-tumor activity in dose escalation phase:

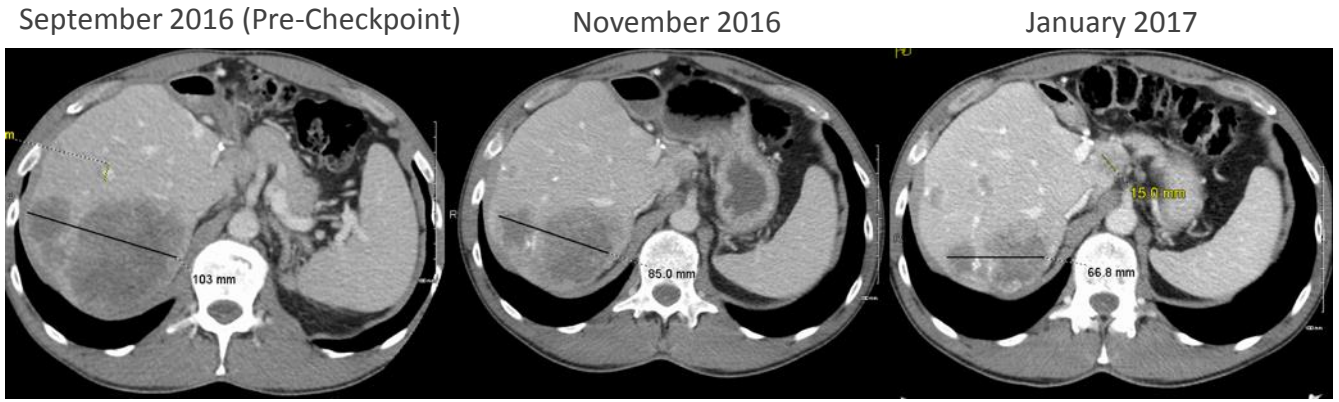
- 9/11 treated patients (81%) exhibit stable disease at Week 9
- 6/11 treated patients exhibit tumor shrinkage between 3-25% at Week 9

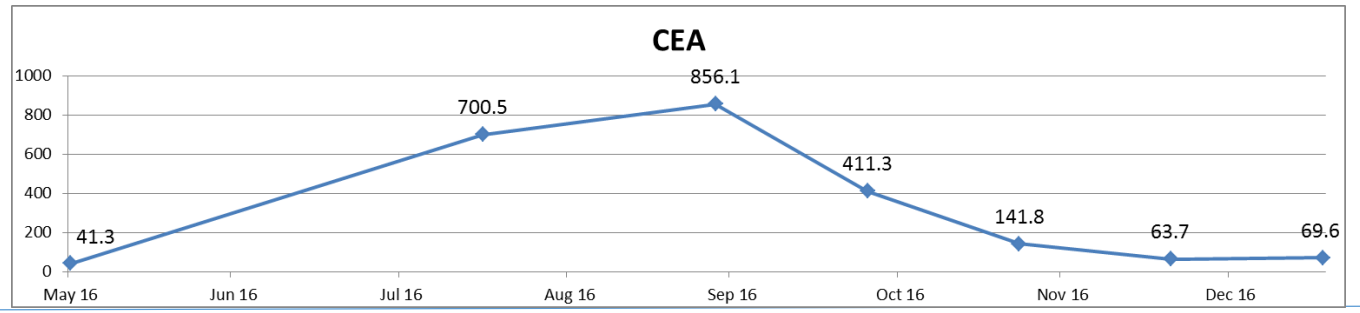
Data updated as of July 31, 2017

Subsequent Response to ICI

Response to ICI therapy in MSS colorectal patient after MG1-MAGEA3 therapy compelling given lack of single-agent ICI activity in this indication

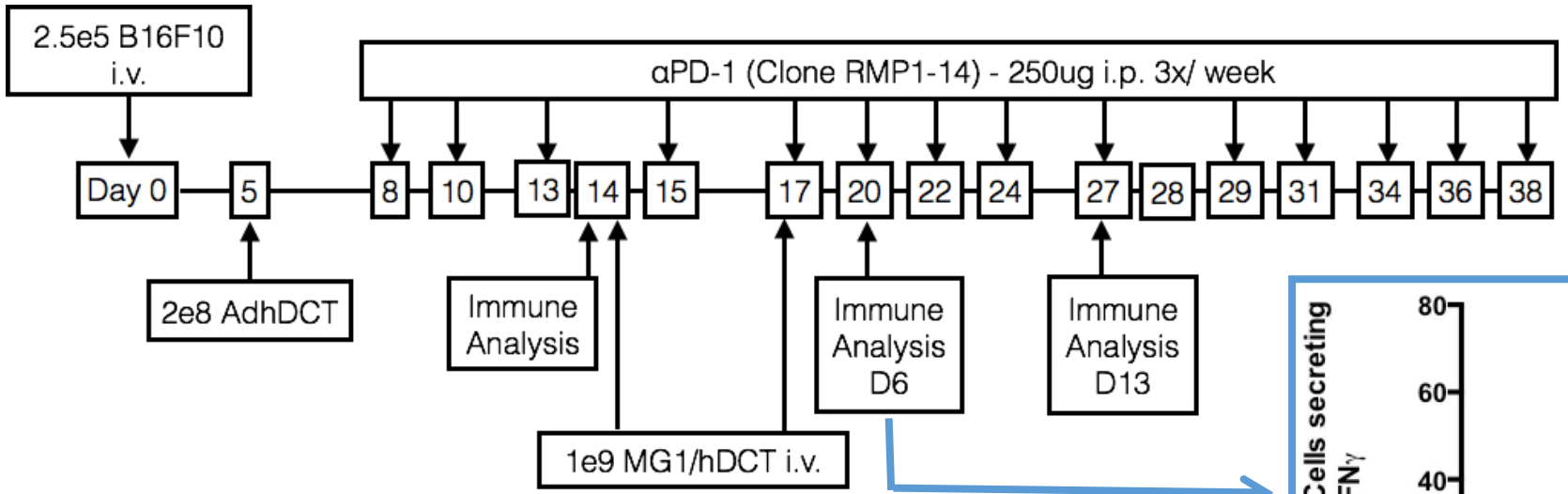
Radiographic and CEA response on PD-1 therapy after treatment with Ad/MG1-MAGEA3 at 3E11 pfu

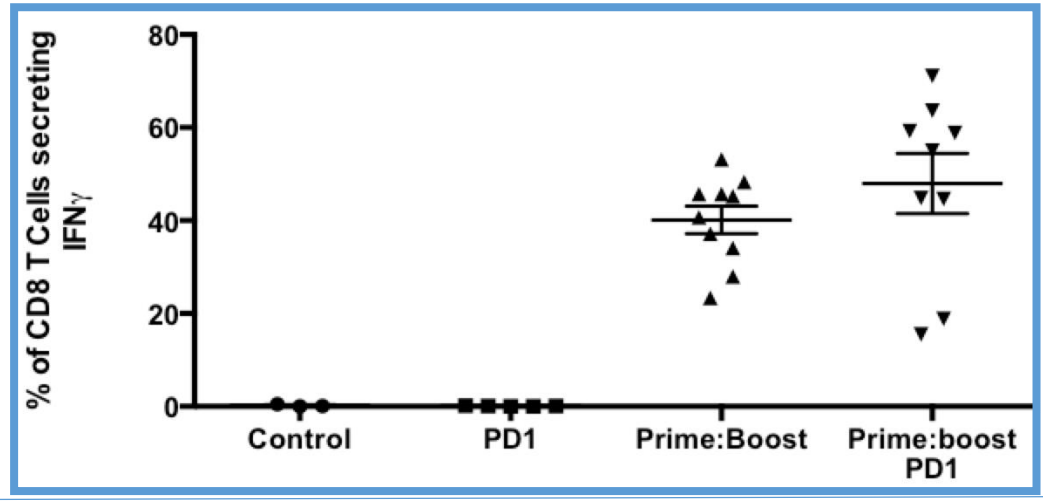




Evaluating the Efficacy of Anti-PD1 Treatment in Combination with Ad/MG1 Oncolytic Vaccine

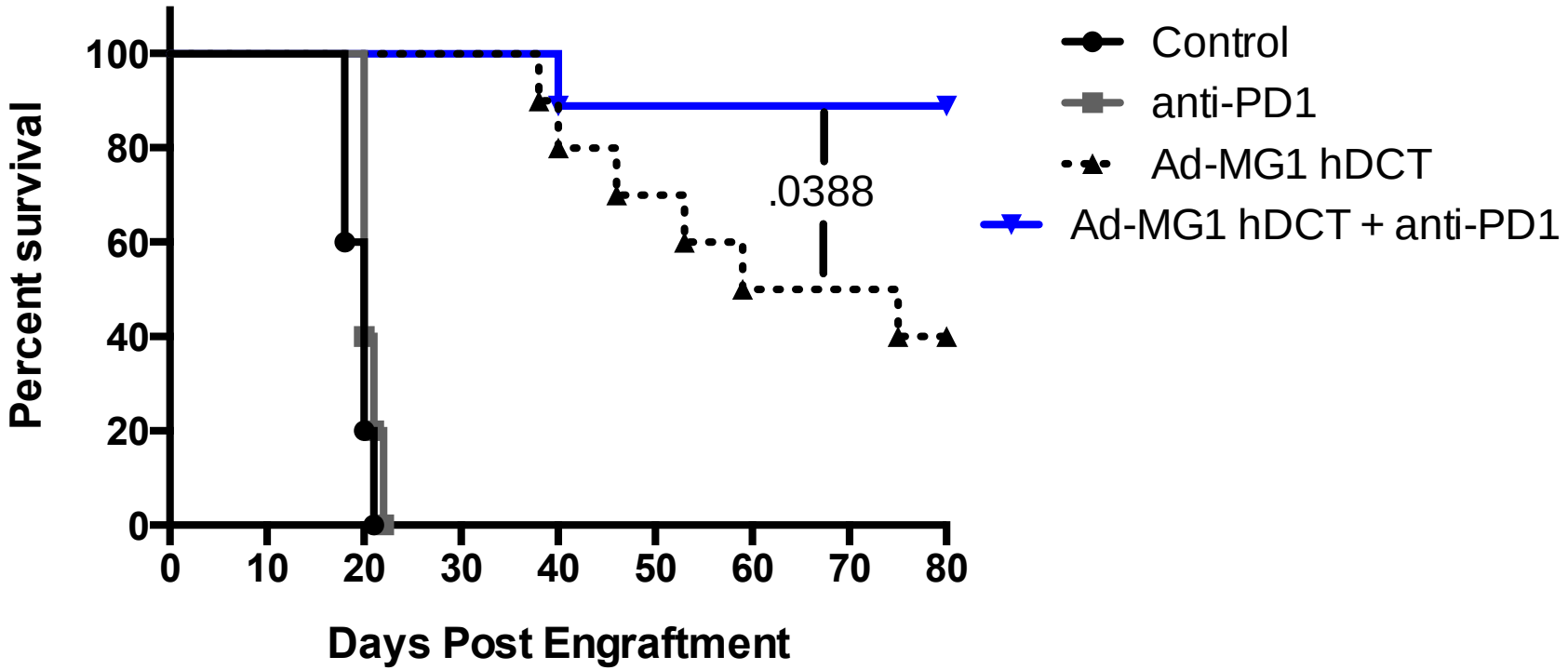
Murine B16-F10 Melanoma Metastatic Lung Model (DCT Endogenous Antigen)

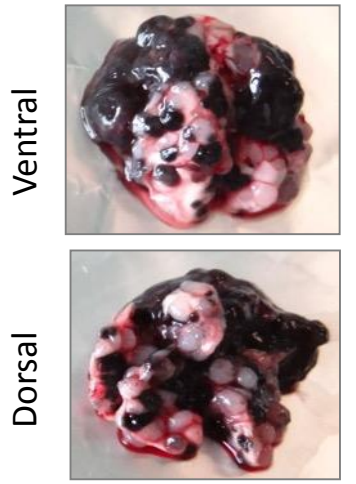




Evaluating the Efficacy of Anti-PD1 Treatment in Combination with Ad/MG1 Oncolytic Vaccine

- Treatment with Ad-MG1 hDCT sensitizes tumours to anti-PD1 antibody
- Anti-PD1 antibody alone does not have anti-tumour activity in this model





Lung tumor burden at time of MG1 dosing

AdMA3/MG1MA3 + Pembrolizumab – Sandpiper Trial

N = 52

Eligibility Criteria
- Squamous, non-squamous NSCLC
- Platinum-failure
- MAGE-A3 expressing tumour

Phase 1

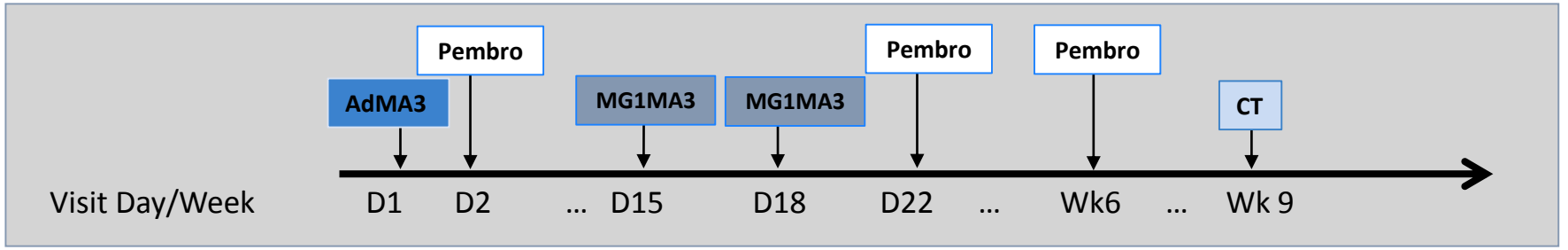
Ad-MAGEA3 IM
MG1-MAGEA3 IV
(1×10^{11}, 3×10^{11} pfu)
+ ICI

Phase 2

Ad-MAGEA3 IM
MG1-MAGEA3 IV
RP2D
+ ICI

Primary Endpoint
Ph1b: Safety
Ph 2: Response rate

Secondary endpoints
Ph 1b: ORR
Ph 1b & Ph 2: Safety
Ph 2: ORR (RECIST), ORR (irRECIST), time to response, response duration, PFS
Correlative endpoints: tumour microenvironment changes; anti-tumour CTL



Lessons and Take Home Messages

- MG1 Maraba is a promising emerging oncolytic virus that mediates IV infection of tumours and positively alters the tumour microenvironment
- MG1 Maraba oncolytic vaccine accesses unique splenic biology to drive very large anti-tumoural immunity
- MG1 Maraba oncolytic vaccine can enhance the activity of immune checkpoint inhibitors
- Pre-clinical data in mice and NHPs now being borne out in ongoing phase I trials