# Development of Talimogene Laherparepvec (T-VEC, IMLYGIC®), First FDA Approved Genetically Modified Oncolytic Virus

## - Perspectives of Clinical Pharmacology

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# Outline

- Introduction of genetically modified virus-based products
- Overview of talimogene laherparepvec (T-VEC) development pathway
  - Unique construct of T-VEC design
  - Mechanism of action and indications
  - Dose and administration
  - Filing history and current status
- Clinical pharmacology support of T-VEC development
  - Preclinical/clinical study design
  - Biodistribution/shedding study results
  - Bioanalytical support
  - Prescribing information and medication guide
- Regulatory advances and perspectives

# Human Gene Therapy

Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

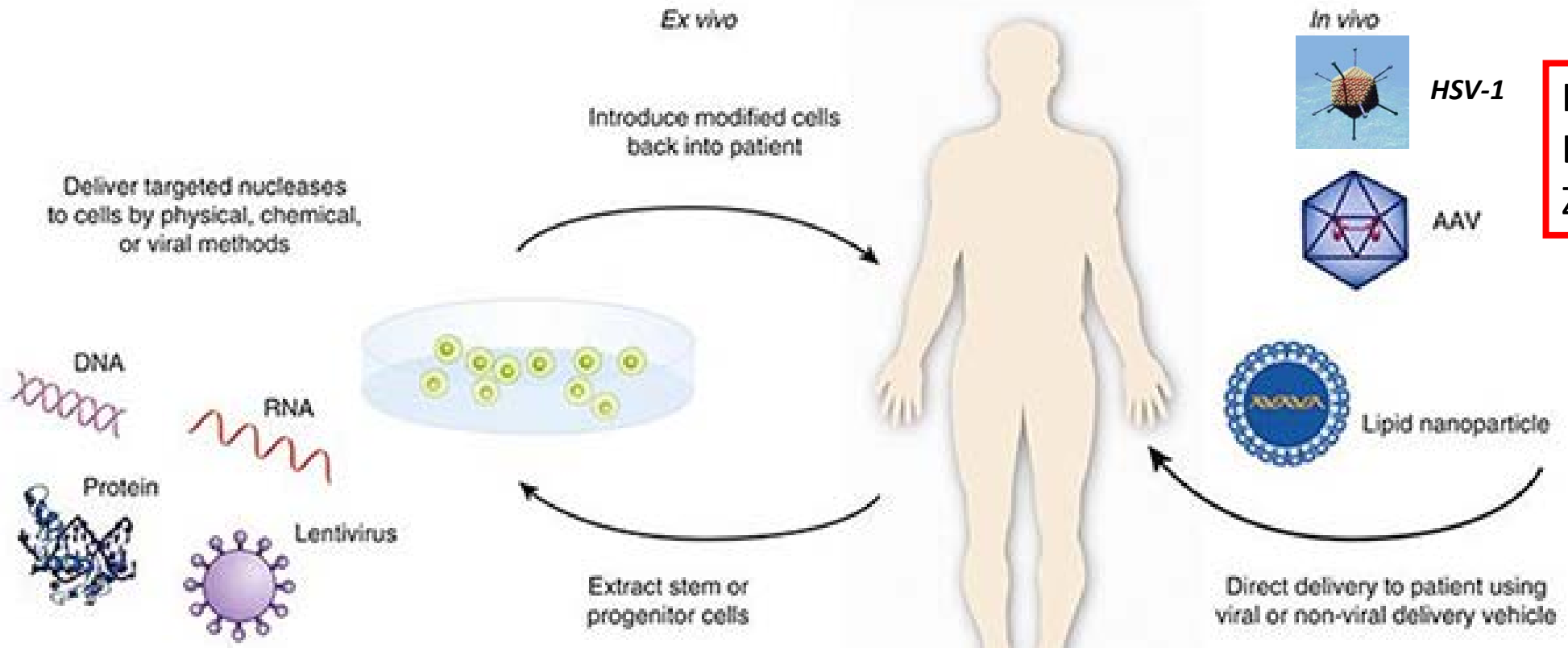
Gene therapies can work by several mechanisms:

- Replacing a disease-causing gene with a healthy copy of the gene
- Inactivating a disease-causing gene that is not functioning properly
- Introducing a new or modified gene into the body to help treat a disease

Gene therapy products are being studied to treat diseases including cancer, genetic diseases, and infectious diseases.

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

# Types of Human Gene Therapy Products




IMLYGIC® 2015
LUXTURNA® 2017
ZOLGENSMA®2019

KYMRIAH® 2017
YESCARTA® 2017

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy

# Approved Genetically Modified Virus-based Drugs

| | Indication | Vector | Route | Dose | Treatment duration | Nonclinical Biodistribution | Clinical biodistribution | Clinical shedding | Key safety warning |
|---|---|---|---|---|---|---|---|---|---|
| **IMLYGIC®** | Melanoma | HSV-1 | Intra-lesional injection | $10^6$, $10^8$ plaque-forming units (PFU) per mL | Q3W (first dose) then Q2W | Tumor, blood, spleen, liver, lymph node, kidney, heart, lung, gonads, salivary gland | Blood | Urine, oral mucosa, anogenital, inj. lesion, ext. dressing | Herpetic infection |
| **LUXTURNA®** | RPE65 mutation-associated retinal dystrophy | AAV2 | Subretinal injection | $1.5 \times 10^{11}$ vector genomes (vg) per eye | Single dose | Eyes, spleen, liver, lymph node<br>Not in gonads | Blood, tears | Tears | Retinal infection |
| **ZOLGENSMA®** | Pediatric spinal muscular atrophy | AAV9 | IV infusion | $1.1 \times 10^{14}$ vg per kg | Single dose | CNS (brain, spinal cord), muscle | Liver. spleen, heart, lung, pancreas, lymph node, muscles, nerves, kidney, intestines, spinal cord, brain, thymus | Saliva, urine, stool | Acute serious liver injury |

# Overview of T-VEC Development Pathway

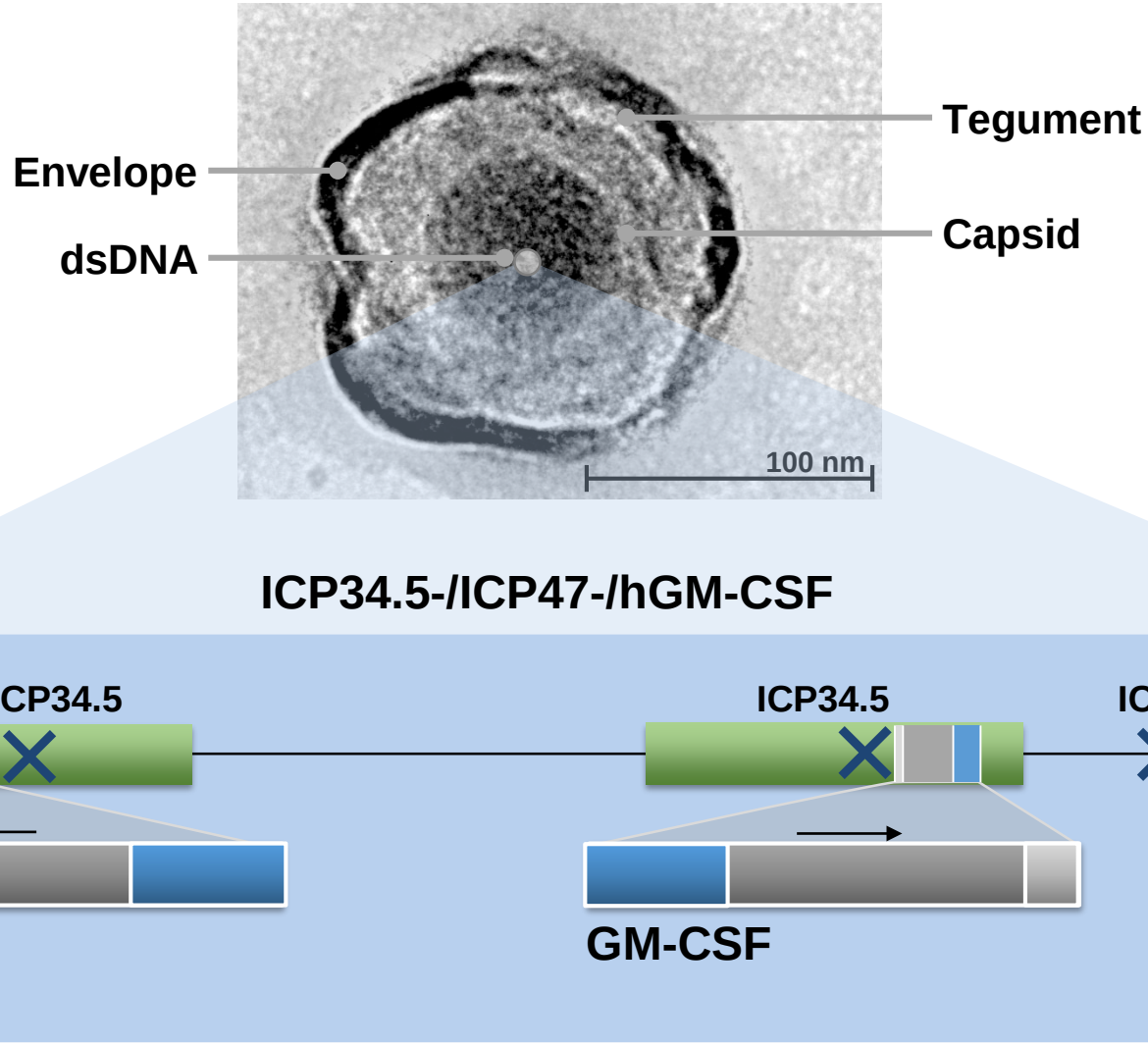
# Talimogene Laherparepvec

- Innovative oncolytic immunotherapy based on herpes simplex virus type 1 (HSV-1)
- Deletion of both copies of ICP34.5 attenuates neurovirulence
- Efficiently replicates in tumors but not normal tissues
- Retains sensitivity to anti-viral agents
- Results in tumor cell lysis for local control
- Results in release of tumor-derived antigens and GM-CSF to initiate a systemic anti-tumor immune response

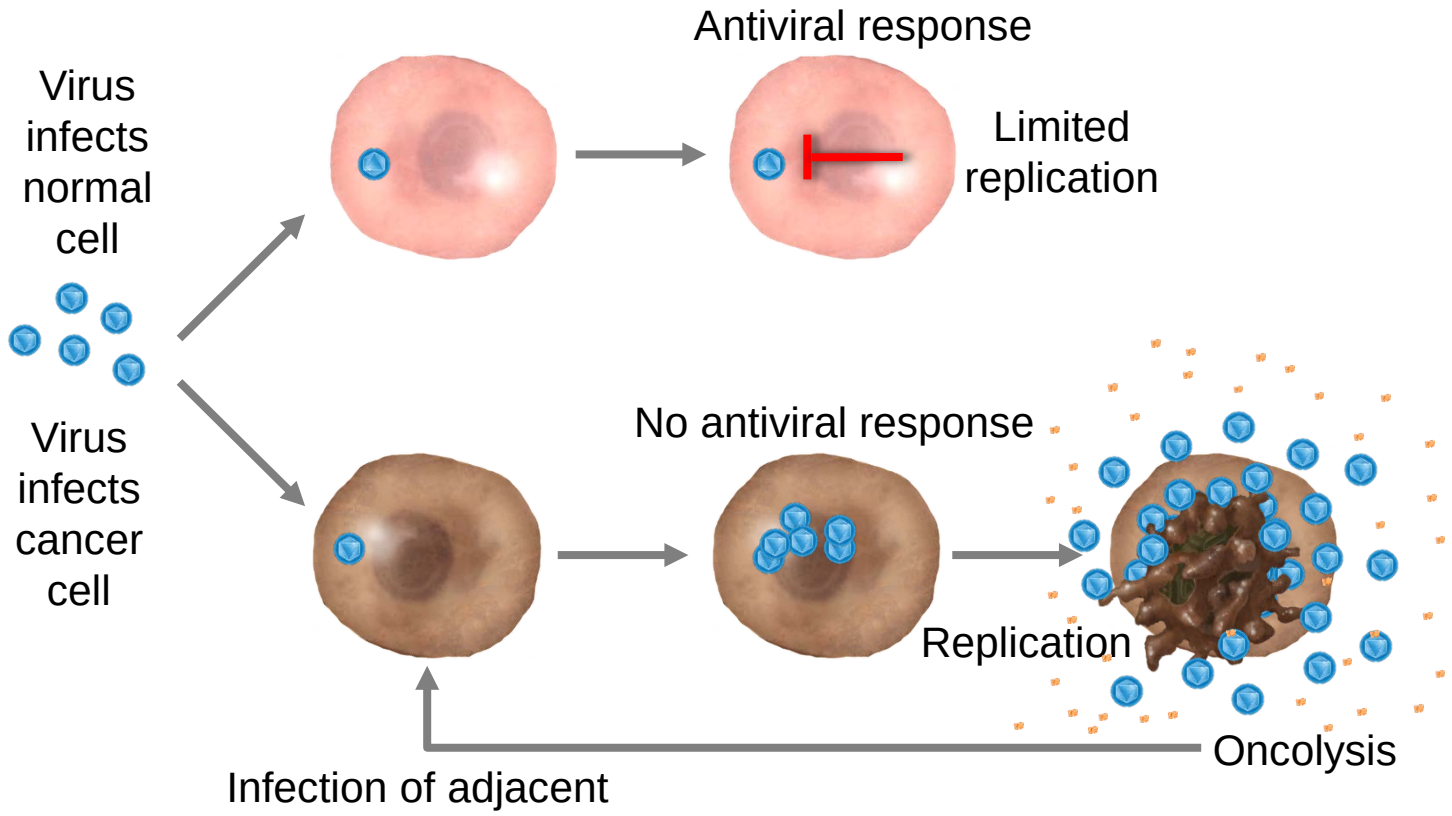
GM-CSF: granulocyte macrophage colony stimulating factor

# Talimogene Laherparepvec

## An HSV-1 Derived Oncolytic Immunotherapy



# Deletion of ICP34.5: Tumor-Selective Replication



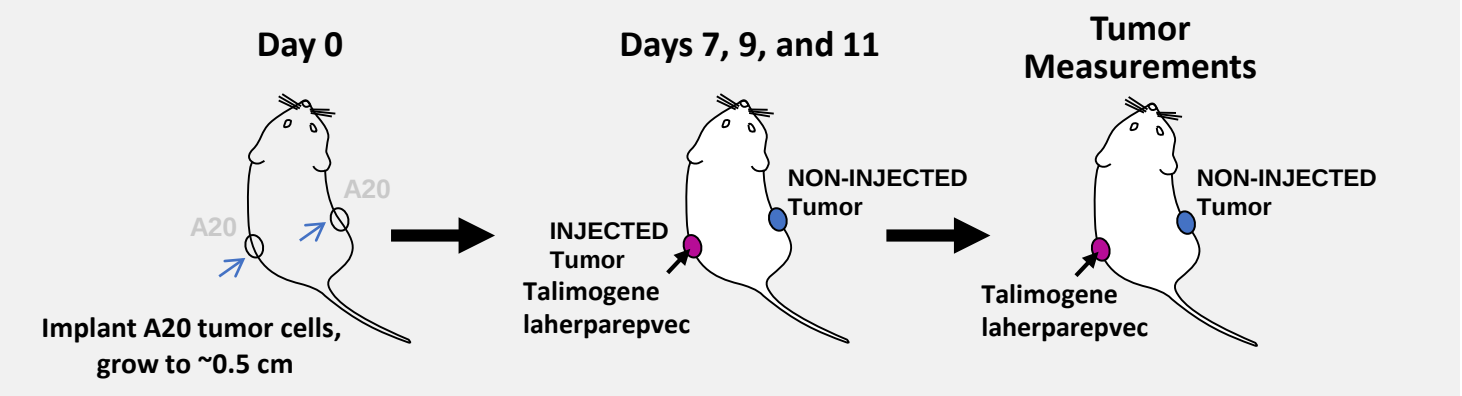

The figure was adapted from Hawkins L, et al. *Lancet Oncol.* 2002;3:7-26.

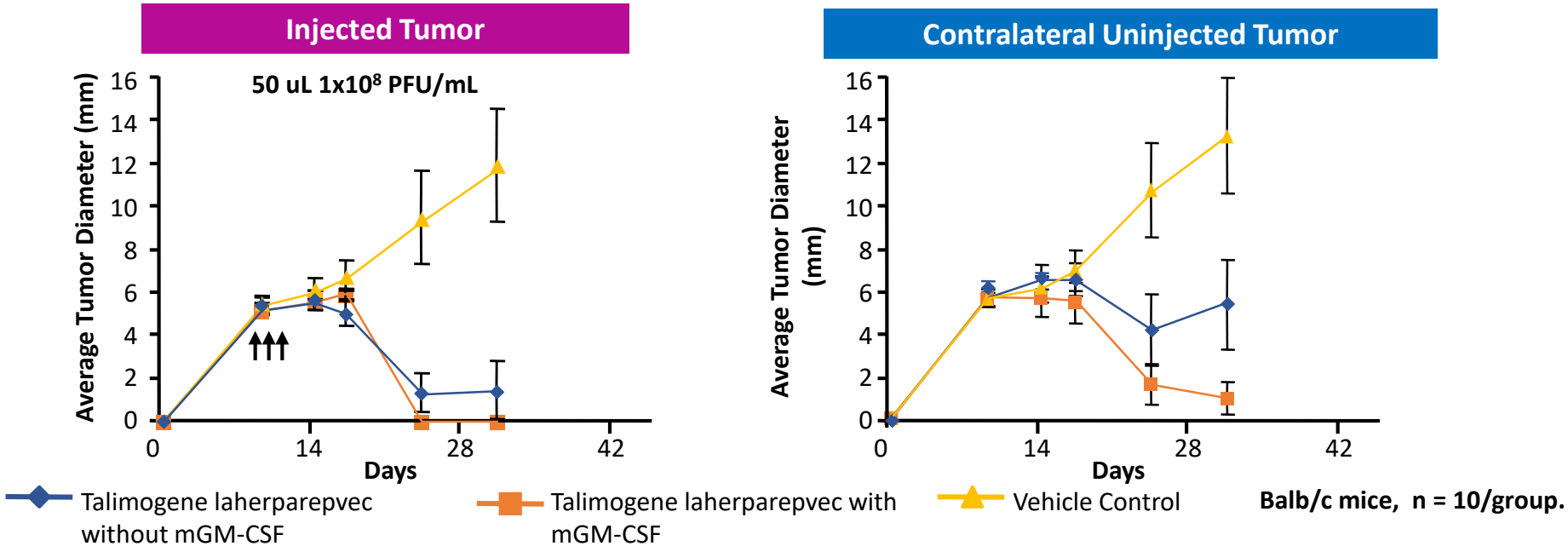
# Viral Safety Considerations

- Deletion of ICP34.5 markedly reduces neurovirulence compared to wild-type HSV-1 in mouse models[1,2]
- Administered intracerebrally, the $LD_{50}$ was $10^5$, ~10,000-fold reduction in virulence[1,2]
- Functional viral thymidine kinase maintains susceptibility to acyclovir[3]


1. Chou J, et al. *Science*. 1990;250:1262-1266.
2. Bolovan CA, et al. *J Virol*. 1994;68:48-55.
3. Liu BL, et al. *Gene Ther*. 2003;10:292-303.

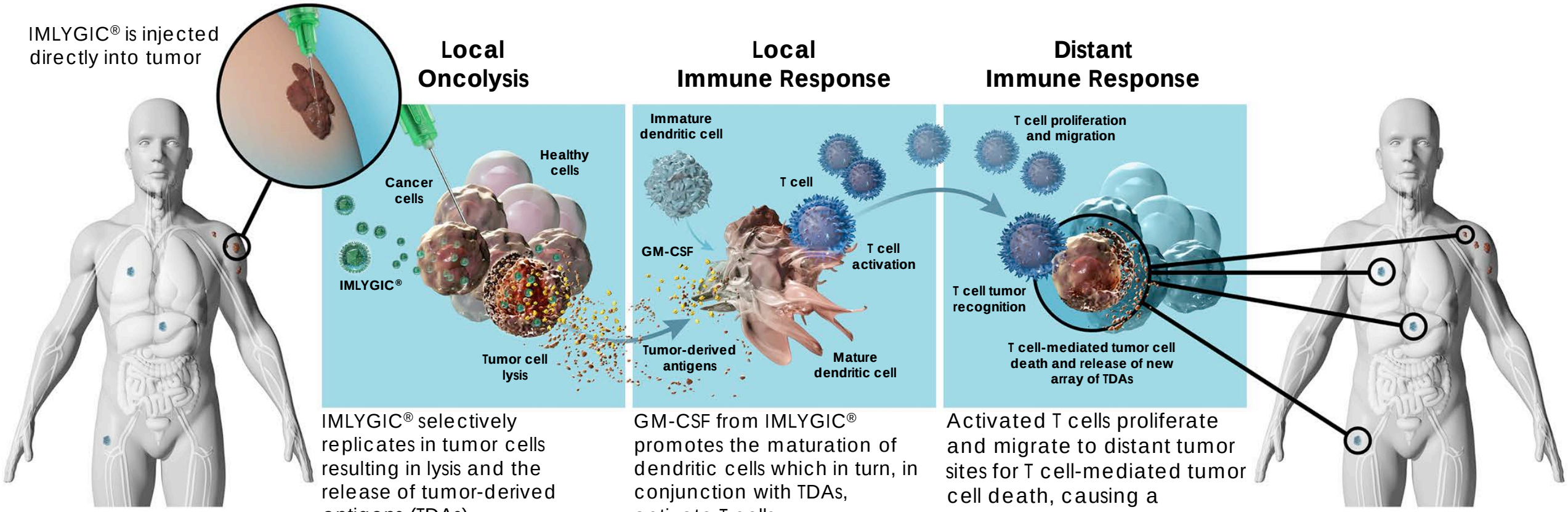
# Systemic Effect of Murine Talimogene Laherparepvec (mT-VEC) with GM-CSF




Liu et al. *Gen Ther.* 2003;10:292-303.

# Dual Mechanisms of Action of Talimogene Laherparepvec: HSV-1–Derived Oncolytic Immunotherapy Designed to Produce Local and Systemic Effects




IMLYGIC® selectively replicates in tumor cells resulting in lysis and the release of tumor-derived antigens (TDAs)

GM-CSF from IMLYGIC® promotes the maturation of dendritic cells which in turn, in conjunction with TDAs, activate T cells

Activated T cells proliferate and migrate to distant tumor sites for T cell-mediated tumor cell death, causing a systemic antitumor response*

*this figure depicts the proposed mechanism of action and is not meant to imply clinical efficacy.

# Clinical Studies with T-VEC

## Monotherapy

### Clinical Pharmacology

**Study 001/01**
Phase 1 (N=30)
Safety/BD
Completed*

**Study 20120324**
Phase 2 (N=61)
Biodistribution+ Shedding
Completed

### Melanoma

**Study 002/03**
Phase 2 (N=50)
Unresectable
Completed*

**Study 005/05**
Phase 3 (N=436)
Unresectable
Completed*

**Study 20110266** Phase 2
(N=150)
Neoadjuvant
Ongoing

**Study 20120325**
Phase 2 (N=112)
Biomarker
Ongoing

**Study 20140270**
Phase 1 (N=18)
Japan
Ongoing

### Non-Melanoma

**Study 005/04**
Phase 1 (N=17)
Pancreatic
Completed

**Study 20110261**
Phase 1b (N=18)
Pediatric Solid Tumors
Ongoing

## Combination

### Melanoma

**Study 20110264** Phase 1/2
(N=217)
+ ipilimumab
Ongoing

**Study 20110265** Phase 1b/3
(N=21/692)
+ pembrolizumab
Ongoing

**Study 20180115**
Phase 2 (N=100)
+ pembrolizumab in PD-1
Experienced
Pending

### Non-Melanoma

**Study 004/04**
Phase 1/2 (N=17)
SCCHN +CT & RT
Completed

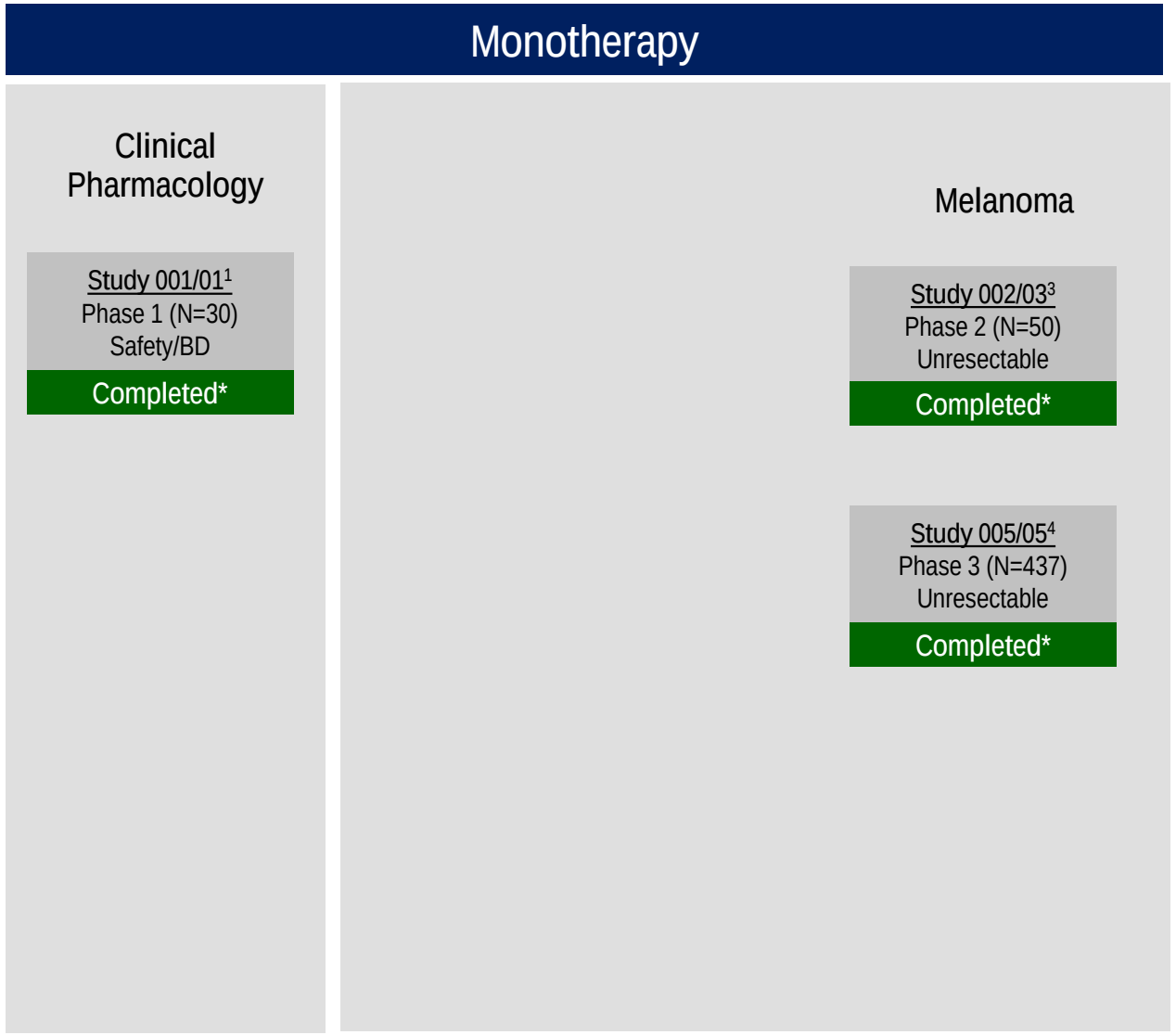
**Study 20130232**
Phase 1b
SCCHN (N=36) +pembrolizumab
Ongoing

**Study 20140299**
Phase 1b
TNBC/mCRC
(N=36)
+ atezolizumab
Ongoing

**Study 20140318**
Phase 1b/2 (N=244)
Alternative Injection Multi-Tumor
Basket Study
Ongoing

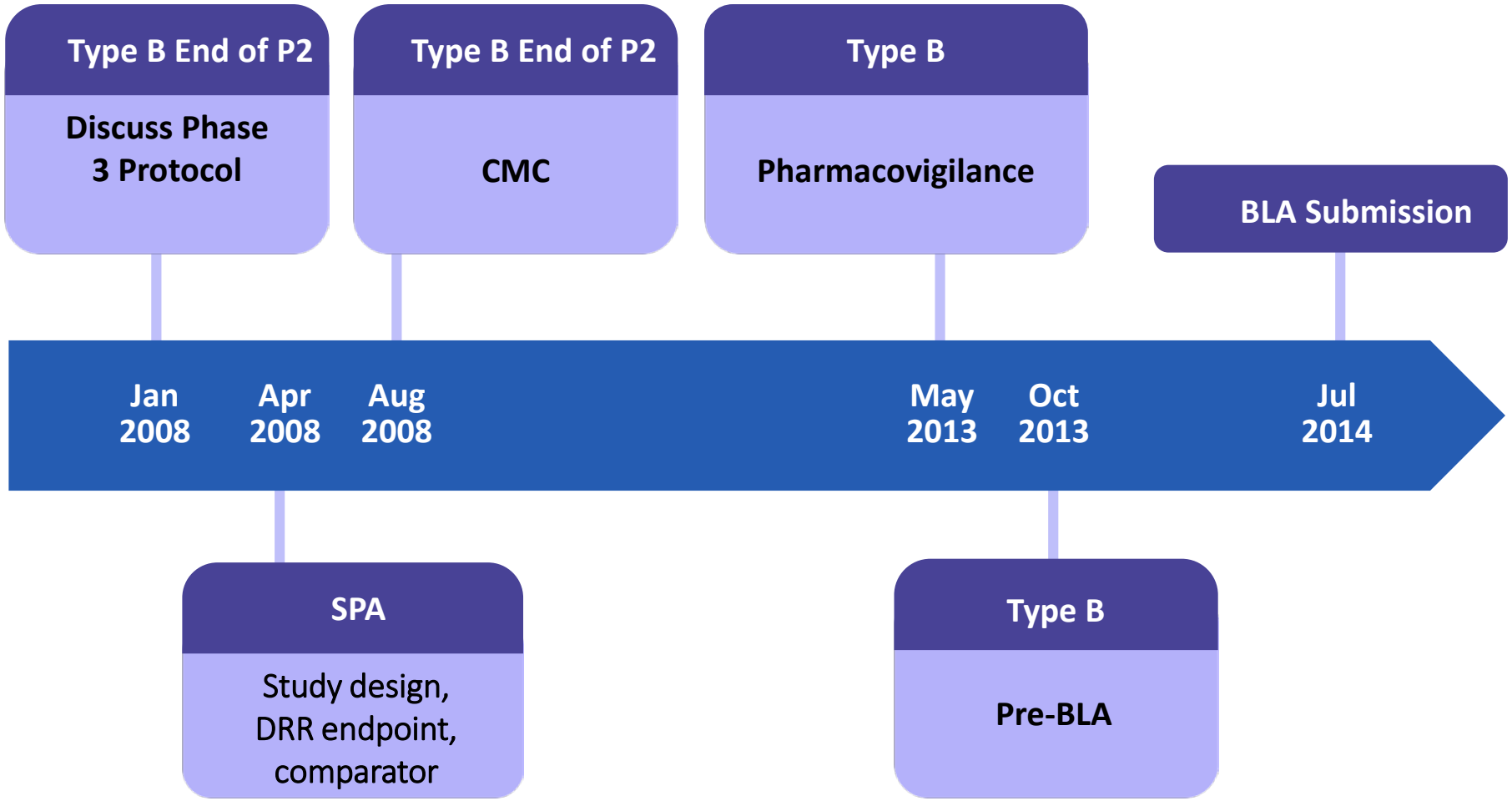
Registry and extension studies not included in this figure. Clinical trials information available at: www.clinicaltrials.gov.

# Key Studies Contributing to the BLA




Registry and extension studies not included in this figure. Clinical trials information available at: www.clinicaltrials.gov.

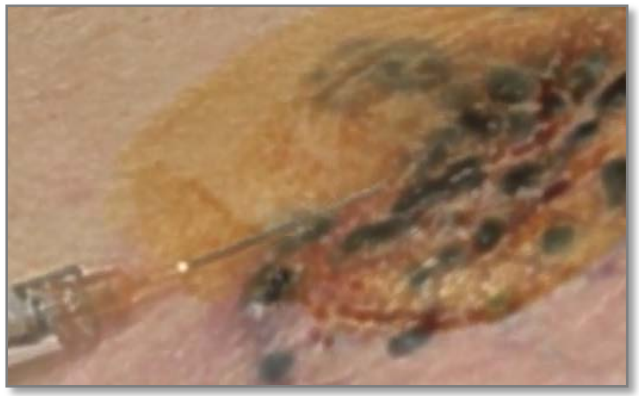
# Key Regulatory Interactions for BLA

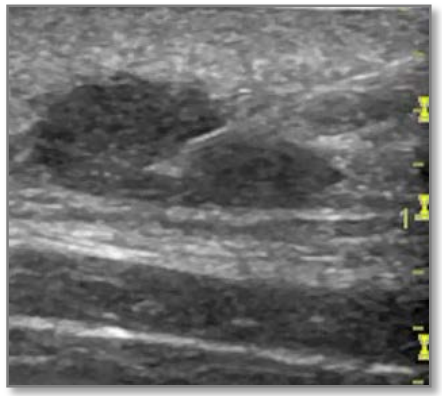



CMC: chemistry, manufacturing, and control; SPA: special protocol assessment; BLA: Biologics License Application

# Method of Administration

- Talimogene laherparepvec administered into cutaneous, SC, or nodal lesions (+/- ultrasound guidance)[1,2]
- No injections of visceral lesions permitted[1]
- Limits on amount to be injected per lesion by size (see table)[1,2]
- No specific limits on number of lesions injected per visit[1]
- Precedence to be given to new lesions, then larger lesions[1]





| Lesion Size (Diameter)[1,2] | Talimogene Laherparepvec Injection Volume[1,2] |
|---|---|
| > 5.0 cm | ≤ 4.0 mL |
| > 2.5 cm to 5.0 cm | ≤ 2.0 mL |
| > 1.5 cm to 2.5 cm | ≤ 1.0 mL |
| > 0.5 cm to 1.5 cm | ≤ 0.5 mL |
| ≤ 0.5 cm | ≤ 0.1 mL |

This total dose administered in any one treatment session should not exceed 4.0 mL[1]


1. Andtbacka RHI, et al. *J Clin Oncol*. 2015;33:2780-2788.
2. Andtbacka RHI, et al. Poster presented at: American Society of Clinical Oncology Annual meeting, 2015

# IMLYGIC® (Talimogene Laherparepvec) is the first and only oncolytic virus therapy approved by FDA

IMLYGIC®
(talimogene laherparepvec)
INTRALESIONAL INJECTION

- IMLYGIC® is the first and only modified oncolytic virus (HSV-1 based) immunotherapy approved in melanoma in the US and approved in EU
- Approval based on the Phase 3 OPTiM trial in unresectable metastatic melanoma[1]
  - Eightfold improvement in durable response (CR/PR maintained ≥6 months) with IMLYGIC® vs GM-CSF (16.3% vs 2.1%, p<0.0001)
- Clinical proof of concept has been demonstrated with IMLYGIC® in combination with Checkpoint inhibitors combination therapy
  - A large randomized phase 2 study demonstrated a doubling of overall response (38% vs.18%) and complete response (13% vs 7%) with the combination of IMLYGIC® plus Yervoy vs. Yervoy alone in patients with stage IIIB-IVM1c unresectable melanoma[2]
  - A single arm phase 1b study of IMLYGIC® plus Keytruda demonstrated a overall response rate of 67% with a complete response rate of 43%[3]
    - In studies combining with checkpoint inhibitors, IMLYGIC® was well tolerated and had no overlapping toxicities
- A phase 3 study (n=696) of IMLYGIC® plus Keytruda® vs. Keytruda® alone for first line treatment of advanced melanoma patients is fully enrolled and results will be available based on event driven analyses
- Neoadjuvant clinical data is available for IMLYGIC® in patients with advanced resectable melanoma
  - In an interim one year landmark analysis, IMLYGIC® demonstrated a recurrence free survival (RFS) of 55.8% vs. 39.3% for the upfront surgery arm


1. Andtbacka RHI et al. *J Clin Oncol* 2015
2. Chesney J et al, *Clin Oncol* 2017
3. Ribas A, Cell 2017

# T-VEC Specific Development Consideration

**MOA/Efficacy**

- Viral replication and oncolytic effect in tumor cells
- Systemic anti-tumor immune response due to GM-CSF expression
- Effectiveness of the virus due to previous HSV-1 exposure
- Efficacy upon re-treatment

**Safety**

- Viral shedding and accidental exposure to healthcare providers and close patient contacts
- Risk of herpetic infection in immunocompromised individuals
- Risk of viral latency and reactivation
- Viral sensitivity toward acyclovir upon infection

**PK**

- Kinetics of viral clearance in the blood and urine
- Biodistribution in different tissues
- Development of a specific assay for T-VEC DNA
- Development of an assay for infectivity due to live virus

# Key Nonclinical Pharmacology Studies Results

- Tumor killing effect observed in multiple cancer cell lines
- Anti-tumor effect observed on un-injected tumors
- Systemic activation of tumor specific T cells
- Anti-tumor effect in mice previously exposed to HSV
- Protection against tumor cell re-challenge following clearance of established tumors with T-VEC
- Demonstrated susceptibility to acyclovir

# Key Nonclinical Toxicology Studies Results

- High and multiple doses of T-VEC (>60-fold of clinical dose) are well tolerated following SC, IV, or IT administration
- Toxicology findings consistent with normal anti-viral immunity following HSV infection
- Systemic viremia was observed in immunodeficient mice
- Does not accumulate or persist in reproductive tissues
- No effect on embryo-fetal viability and development
- Negligible transfer of viral DNA from mother to fetus (<0.001%)

# Nonclinical Biodistribution Studies in Mice

| Study | Route | Dose Frequency | Dose (PFU) | Sample Collection |
|---|---|---|---|---|
| 4648-00030 | SC, IV | Single | $0.6x10^7$ (n=15/sex/ route) | blood, urine, injection site, spleen, lung, liver, heart, kidney, gonads, eyes, brain, trigeminal ganglion, nerve |
| 4648-00027 | SC | Multiple (Q3Dx5) | $1x10^7$ (n = 9/sex) | blood, urine, injection site, spleen, lung, liver, heart, kidney, gonads, eyes, brain, trigeminal ganglia, duodenum |
| 4648-00028 | SC | multiple (QWx5) | $1x10^7$ (n = 15/sex) | blood, urine, tissues (same as for 4648-00027) |
| 115857 | Intra-tumoral | Multiple (Q3Dx3) | $1x10^5$ or $5x10^5$ (n=24/sex/ dose) | blood, injection site, spleen, lung, liver, heart, kidney, gonads, eyes, brain, trigeminal ganglion, bone marrow, lymph node, additional specimens from possible sources for viral shedding (feces, lachrymal glands, nasal mucosa, and salivary glands) |

# Intratumoral Biodistribution/Shedding Study in Mice

Treatment Frequency: Once every 3 days (Days 1, 4 and 7) for a total of 3 doses

Treatment Groups

| Group | Dose Volume (mL/mouse) | Concentration (PFU/mL) |
|---|---|---|
| 1-2 | 0.05 | 0 (vehicle control article) |
| 3-4 | 0.05 | $2 \times 10^6$ |
| 5-6 | 0.05 | $1 \times 10^7$ |

| Group | Number of Animals | Dose (PFU/mouse) | Scheduled Euthanasia (Study Days) |
|---|---|---|---|
| 1 | 14 (Female) | Vehicle[a] | 8, 14 |
| 2 | 14 (Male) | Vehicle[a] | 8, 14 |
| 3 | 24 (Female) | $1 \times 10^5$ | 8, 14, 91 |
| 4 | 24 (Male) | $1 \times 10^5$ | 8, 14, 91 |
| 5 | 24 (Female) | $5 \times 10^5$ | 8, 14, 91 |
| 6 | 24 (Male) | $5 \times 10^5$ | 8, 14, 91 |

# Incidence Rate of T-VEC DNA Detection

| | | Tumor | Whole Blood | Brain | Gonads | Heart | Kidney | Liver | Lung | Lymph node (Mesenteric) | Salivary glands | Spleen |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days 8-91 | Positive | 35 | 12 | 2 | 1 | 5 | 3 | 7 | 3 | 7 | 1 | 15 |
| | Tested | 91 | 91 | 91 | 91 | 91 | 91 | 91 | 91 | 91 | 91 | 91 |
| | %Positive | 38% | 13% | 2% | 1% | 5% | 3% | 8% | 3% | 8% | 1% | 16% |
| Last positive | | Day 91 | Day 50 | Day 91 | Day 8 | Day 49 | Day 49 | Day 91 | Day 49 | Day 91 | Day 49 | Day 91 |

- Rate of detection highest in tumor tissue
- Levels of viral DNA in tumor tissue were over 50-fold or higher compared to other tissues
- Tissues associated with viral clearance: spleen (16%), liver (8%) and lymph node (8%)
- Highly perfused tissues: heart (5%), kidney (3%) and lung (3%)
- Brain (2%, 2/91 samples)

# Nonclinical Results Guided the Design of Clinical Biodistribution/Shedding Study

- Blood
  - 13% of samples are positive
  - last positive sample occurred 43 days after the last dose
  - viral levels in blood are a small fraction of those found in tumor (~0.006%)
- Urine
  - detected in 22% of animals within 24 hours post-dose
- Salivary gland
  - one sample had detectable viral DNA on Day 42
- T-VEC DNA not detected in lachrymal glands, nasal mucosa or feces

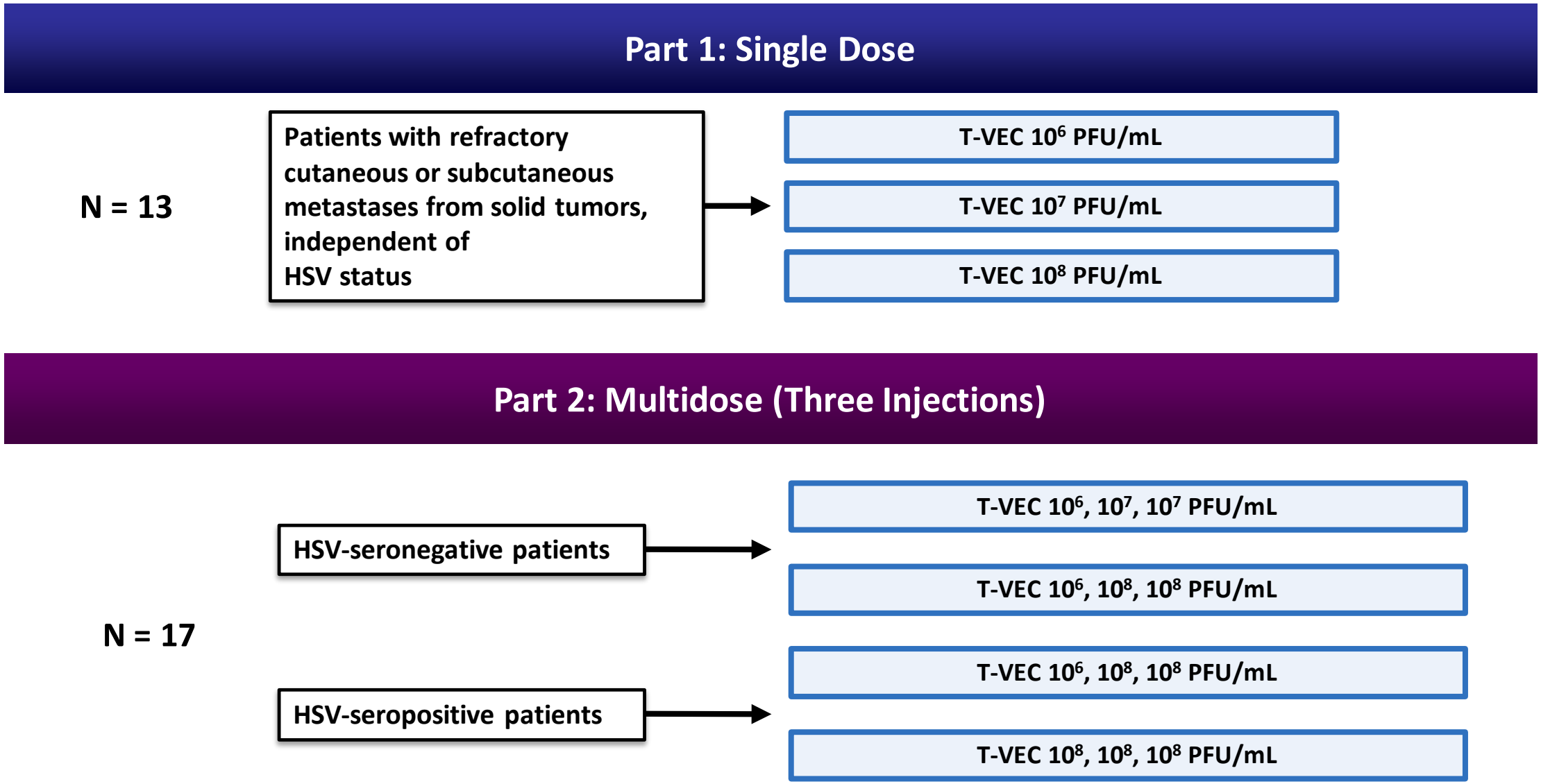
# Objectives of Clinical Pharmacology Program

- Evaluate the dosing regimen
- Evaluate anti-HSV-1 seroconversion
- Measure GM-CSF expression in tumor tissue and blood
- Understand the kinetics of viral clearance through biodistribution in the blood and urine
- Assess shedding from injected tumors, exterior of the dressing, oral mucosa, anogenital area and suspicious herpetic lesions

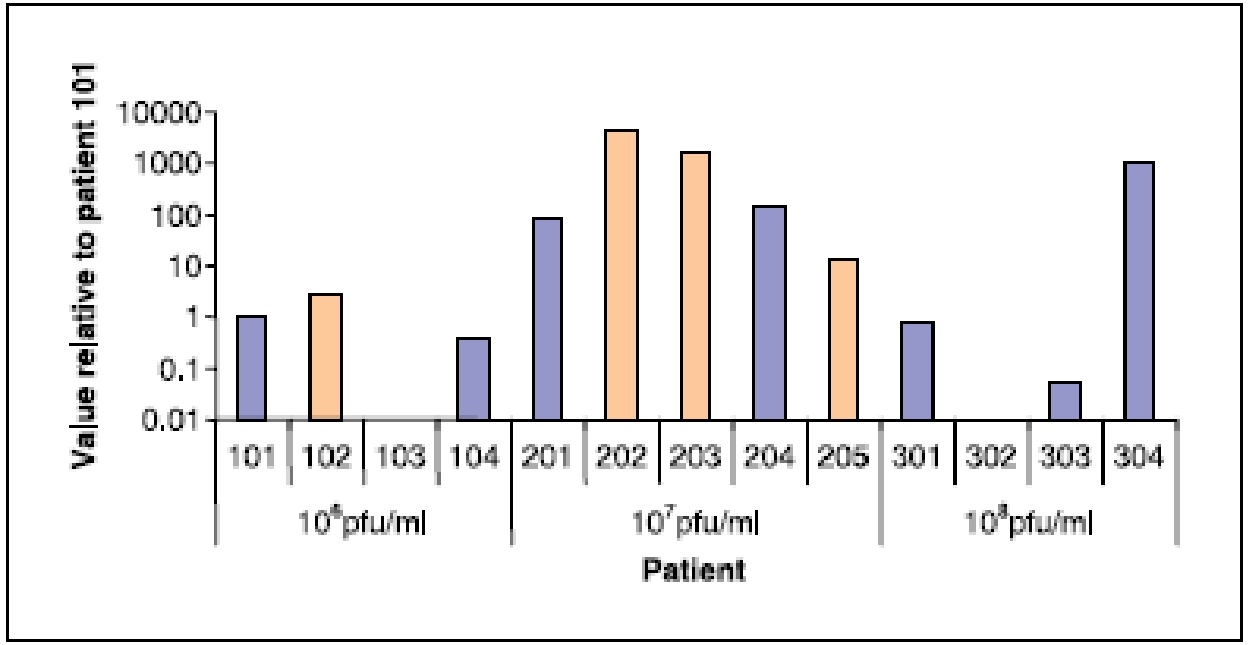
# Clinical Biodistribution/Shedding Assessment

| Study | Phase | N | Dose | T-VEC DNA in blood and urine | Live Viral Shedding From Tumor and Exterior of Dressing Swabs | Suspicious herpetic lesion swabs | GM-CSF |
|---|---|---|---|---|---|---|---|
| **001/01** | 1 | 30 | Part 1: $10^6$, $10^7$, or $10^8$ PFU/mL single dose<br>Part 2: $10^6$, $10^7$, or $10^8$ PFU/mL multiple doses | √ | √ | √ | √ |
| **002/03** | 2 | 50 | $10^6$ and $10^8$ PFU/mL, multiple doses | √ | √ | √ | |
| **005/05** | 3 | 436 | $10^6$ and $10^8$ PFU/mL, multiple doses | | | √ | |
| **324** | 2 | 60 | $10^6$ and $10^8$ PFU/mL, multiple doses | √ | √ | √ | |

# Phase 1 First-In-Human Study



# GM-CSF mRNA in Tumor Biopsies After Injection




- mRNA detected 48 hours after administration
- Detected in both seronegative and seropositive subjects
- Did not seem dose dependent

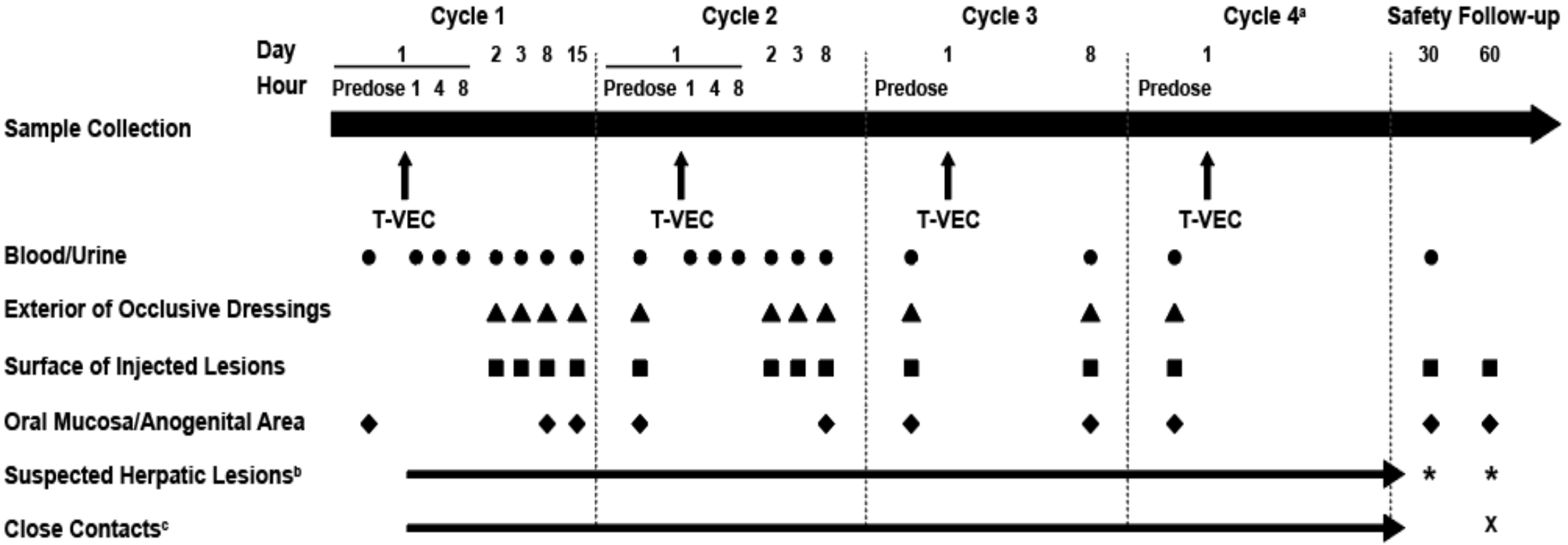
Clin Cancer Res 12(22): 6737-47 (2006)

# Dosing Regimen and Seroconversion

- In HSV seronegative patients, more pronounced local reactions and febrile influenza-like syndromes were observed with doses > $10^6$ pfu/mL
- Majority seronegative patients seroconverted in 3 weeks
- The initial dose of $10^6$ pfu/mL was sufficient for seroconversion
- The $10^8$ pfu/mL was well tolerated and was the highest dose studied in clinical studies
- $10^6$ pfu/mL followed by $10^8$ pfu/mL was found to be tolerable in both seronegative and seropositive patients

# A Phase 2, Multicenter, Single-arm Biodistribution and Shedding Study in Subjects with Melanoma

**Primary Objective: To estimate the proportion of subjects with detectable T-VEC DNA in the blood and urine any time after administration of T-VEC within the first 3 cycles**



# Assay Summary for T-VEC DNA and Infectivity

**Quantitative polymerase chain reaction (qPCR) assay**

- Validated and specific to T-VEC DNA
- Sensitive with LLOQ at 24, 18, and 1.76 copies/µg DNA for urine, swab, and blood samples, respectively

**Plaque assay**

- Considered gold standard as viral infectivity assay
- Detect live virus
- Formation of plaques in cells are quantified and expressed as plaque forming unit (PFU) per mL

**$TCID_{50}$ assay**

- Detect live virus
- Quantify the amount of virus required to create a cytopathic effect in 50% of inoculated Vero cells; virus titer is calculated as $TCID_{50}$/mL
- Sensitive and more robust

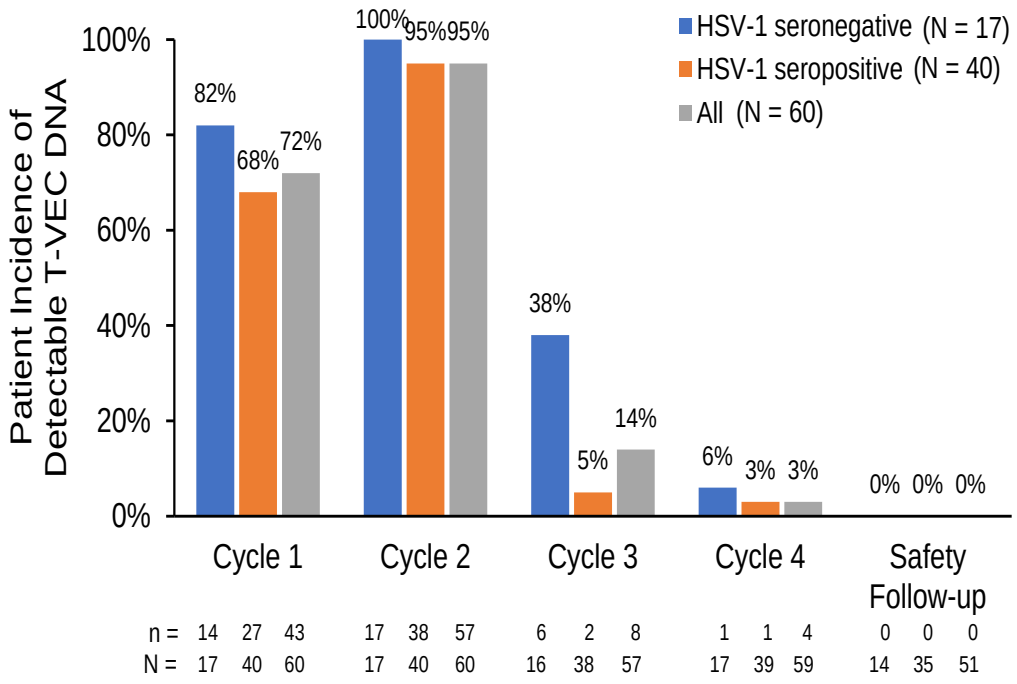
# T-VEC DNA Detection and Infectivity Results

| Sample type | Subjects, n/N (%) | Samples, n/N (%) |
|---|---|---|
| **Blood** | 59/60 (98%) | 383/1094 (35%) |
| **Urine** | 19/60 (32%) | 31/1088 (3%) |
| **Swabs of Injected Lesions** | 60/60 (100%) | 741/1520 (49%) |
| Viral Infectivity | 7/60 (12%) | 8/740 (1.1%) |
| **Exterior of Occlusive Dressing** | 48/60 (80%) | 212/1085 (20%) |
| Viral Infectivity | 0 | 0 |
| **Oral mucosa** | 8/60 (13%) | 12/964 (1.2%) |
| Viral Infectivity | 0 | 0 |
| **Anogenital system** | 5/26 (19%) | 7/448 (1.6%) |
| Viral Infectivity | 0 | 0 |
| **Suspicious Herpetic Lesions** | 3/19 (16%) | 4/37 (11%) |
| Viral Infectivity | 0 | 0 |

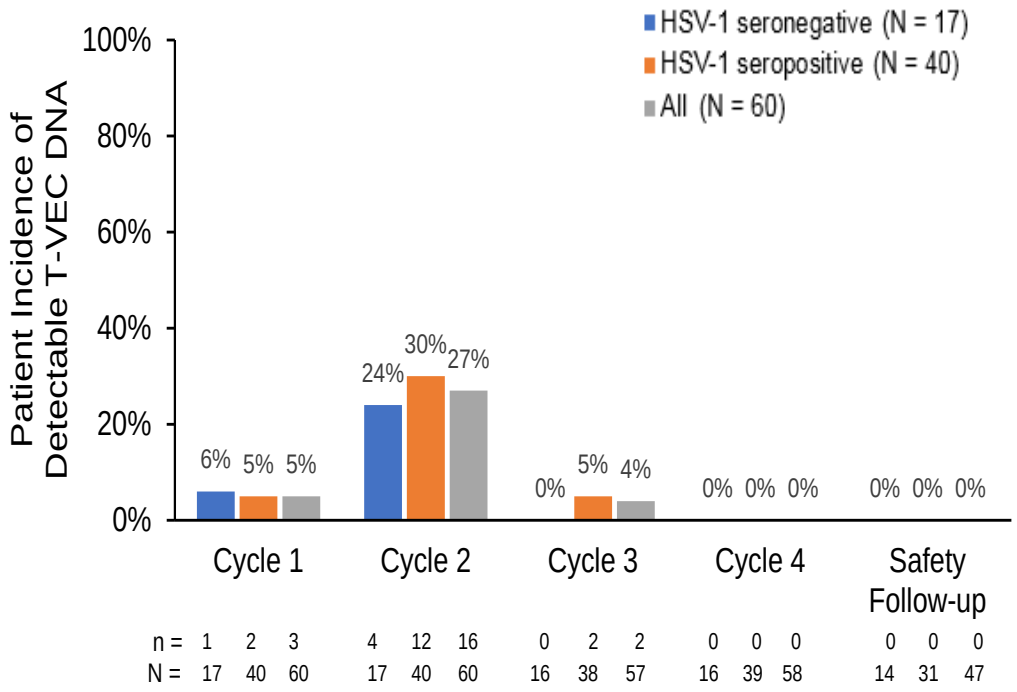
EBioMedicine 47:89-97 (2019)

# T-VEC Biodistribution in Blood and Urine by Cycles

## Blood



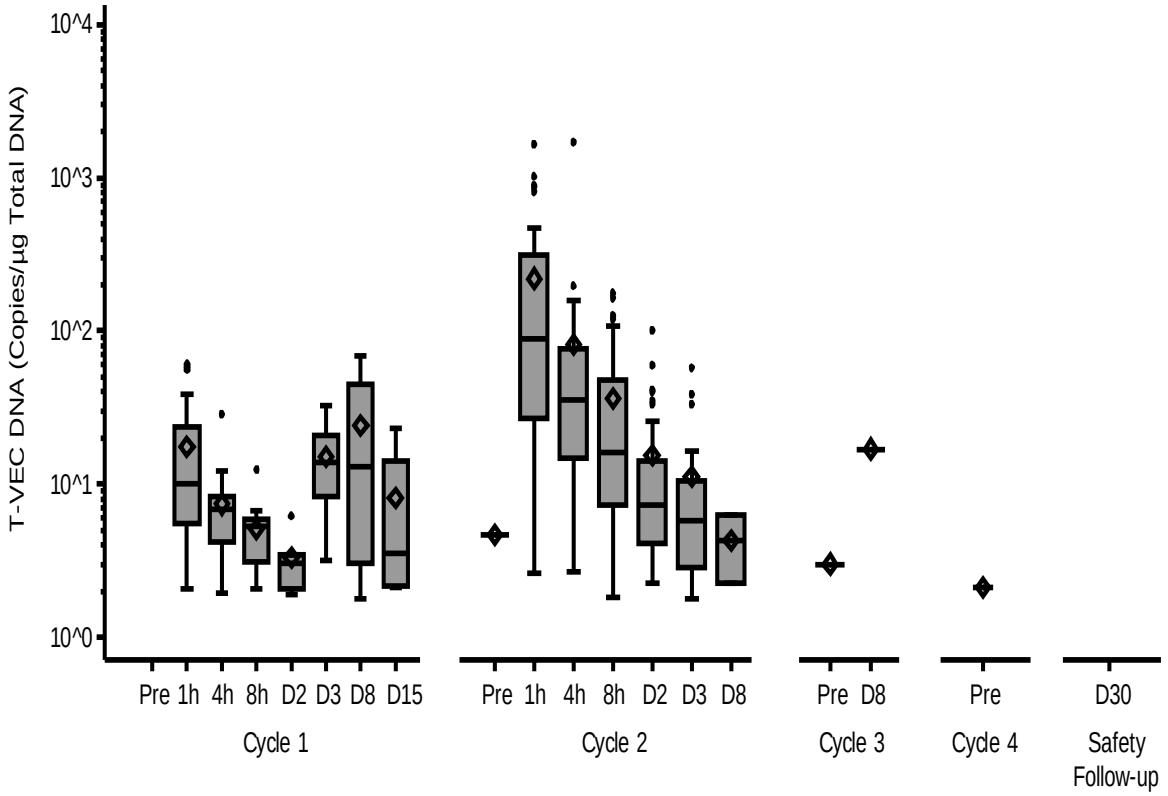

## Urine



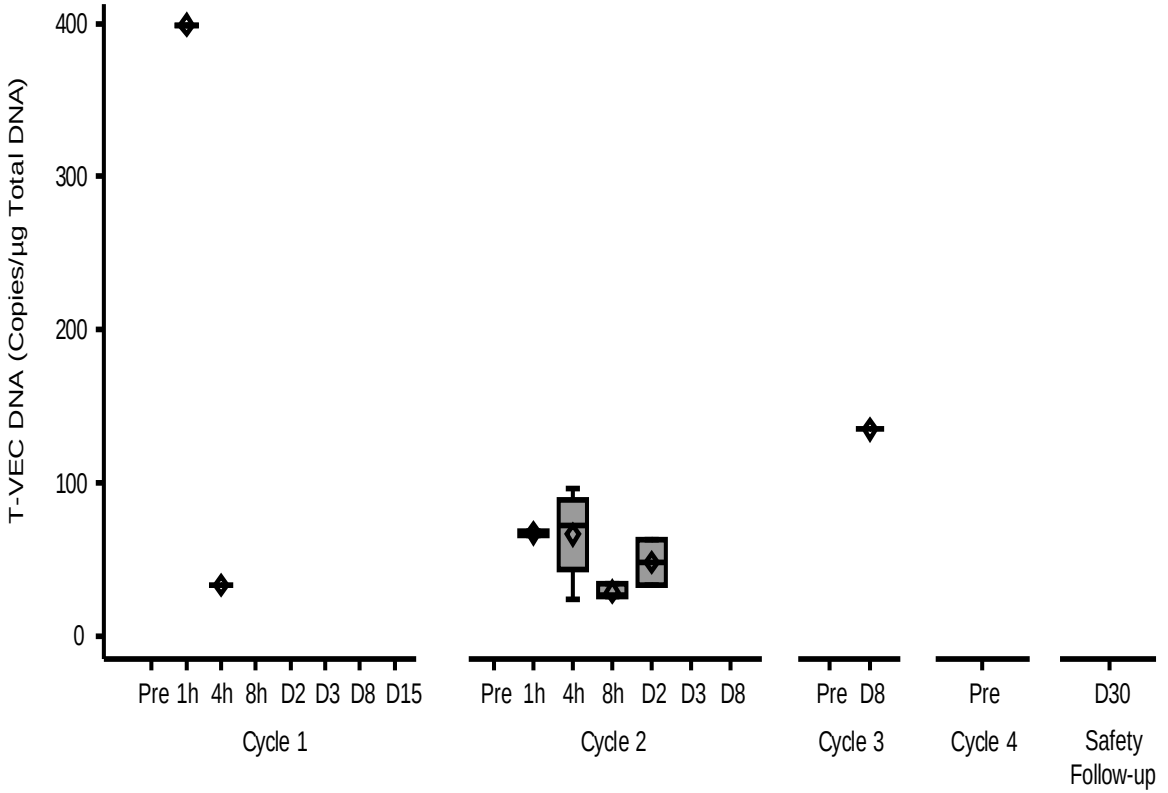

EBioMedicine 47:89-97 (2019)

# T-VEC DNA Levels in Blood and Urine by Cycles

## Blood




## Urine




EBioMedicine 47:89-97 (2019)

# Summary of Biodistribution and Shedding Results

## Biodistribution (within the body)

- Higher incidence of positive T-VEC DNA in blood in HSV-1 seronegative patients
- The amount of DNA in blood was highest during cycle 2
- Rapid decline potentially due to immune responses and cleared from blood by the end of treatment

## Viral shedding (excretion/secretion)

- The incidence of positive urine samples was low and DNA was detected highest during cycle 2
- No DNA detection in urine at Cycle 4 and at the follow-up visit
- Overall incidence in swabs of the oral mucosa and anogenital area was low (1-2% of samples)

## Viral detection on the surface of injected lesions and exterior dressing

- DNA detection was high on the surface of injected lesions and 14% subjects tested positive during the safety follow-up
- 1.1% samples from the surface of injected lesions tested positive for live virus. No samples were positive for viral infectivity after cycle 2 or during safety follow-up (up to day 60)
- Live virus was NOT detected on the exterior surface of occlusive dressing

# IMLYGIC® Prescribing Information
## (Based on Biodistribution/Shedding Results in Initial 20 Patients)

**Detection methods**

- IMLYGIC® viral DNA levels in various tissues and secretions were determined using a quantitative polymerase chain reaction (qPCR) assay.
- Infectious IMLYGIC® at the injection sites and at some potential herpetic lesions was also quantified using viral infectivity assays.

**Biodistribution/shedding in blood and urine**

- IMLYGIC® DNA was present in the blood of 17 (85%) patients and in urine of 4 (20%) patients.
- The peak levels of IMLYGIC® DNA in the urine were detected on the day of treatment.

**Viral detection on the surface of injected lesions and exterior dressing**

- Infectious IMLYGIC® virus was detected at the site of injection in 3 (15%) patients at a single time point each and all within the first week after the initial injection.
- The exterior of the occlusive dressings was positive in 14 (70%) patients. However, no infectious virus was detected on the exterior of the occlusive dressing.
- The number of patients with measurable levels of DNA on the exterior of occlusive dressings declined over time with no measurable DNA by the third treatment in 13 patients tested.

# Herpetic Lesions and Viral Transmission

## Suspicious herpetic lesions

- Of 19 patients with lesions of suspected herpetic origin, four of 37 swabs taken from three patients had detectable T-VEC DNA
- None were positive for infectivity based on $TCID_{50}$ assay

## Viral transmissibility

- 3 close contacts and 2 investigators reported exposure or signs and symptoms of suspected herpetic origin
- None had detective T-VEC DNA

# Medication Guide on IMLYGIC® Handling

**What should I avoid while getting IMLYGIC®?**

IMLYGIC® virus can spread to other areas of your body or to your close contacts (household members, caregivers, sex partners, or persons sharing the same bed).

Do the following to avoid spreading IMLYGIC® to other areas of your body or to your close contacts:

- Avoid direct contact between your treatment sites, dressings, or body fluids and close contacts (for example, use condoms when engaging in sexual activity, avoid kissing close contacts if either has an open mouth sore).
- Wear gloves while putting on or changing your dressings.
- Keep treatment sites covered with airtight and watertight dressings for at least 1 week after each treatment (or longer if the treatment site is weeping or oozing).
- If the dressing comes loose or falls off, replace it right away with a clean dressing.
- Place all used dressings and cleaning materials in a sealed plastic bag and throw them away in the garbage.
- Do not touch or scratch the treatment sites.

With proper handling, administration, and post-injection care, T-VEC can be administered safely in patients with minimal risk of transmission to close contacts.

# Clinical Pharmacology Considerations for Oncolytic Virus Therapy – *An FDA Perspective*

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*American Society of Clinical Pharmacology & Therapeutics (ASCPT)*
*October 29, 2019*

# Outline

- Introduction to Oncolytic Virus (OV)
- Clinical Pharmacology Considerations of OV Therapy
- Future Perspectives of OV Therapy
- Regulatory Resources for OV Product Development

# Oncolytic Virus

- Virus that infects and lyses cancer cells but not normal cells*
- Types
  - Naturally occurring (unmodified)
  - Genetically engineered
    - Conditional viral replication (selectively infect and replicate in tumor cells)
    - Expression of transgene with therapeutic or immune modulating effects

*NCI Dictionary of Cancer Terms
https://www.cancer.gov/publications/dictionaries/cancer-terms/def/oncolytic-virus

# Clinical Pharmacology Considerations

- Study Design Considerations
- Pharmacokinetic, Pharmacodynamic and Immunogenicity Assessments
- Biodistribution
- Viral Shedding

# Study Design Considerations

- Route of Administration
  - Intratumuoral, intravenous, intraperitoneal, etc.

- Dose and Dosing Schedule
  - Dose: preclinical data, available clinical data from similar OVs, available immunity information, dose ranging study data
  - Dosing schedule: preclinical data (anti-tumor effect) and available OV pharmacokinetic information

# Pharmacokinetic, Pharmacodynamic & Immunogenicity Assessments

- Pharmacokinetic (PK) Assessment
  - Systemic (blood) viral concentration-time profile
  - Viral presence within tumor sites (if possible)
  - Measure both viral transgene and infectivity using qPCR and infectivity assays
  - Evaluate PK profiles for co-transgene expression (if applicable)

- Pharmacodynamic Assessment: Biomarkers
  - Tumor lysis/Cytotoxic biomarkers
  - Tumor microenvironment modulation biomarkers

- Immunogenicity Assessment

# Biodistribution Assessment – Use of Animal Data

- Determines distribution and persistence of the product in both target and non-target tissues
- Study Design
  - Product formulation
  - Animal sex
  - Sample size
  - Appropriate safety endpoints
  - Sampling schedule
    - Expected time of peak levels
    - Several later time points to evaluate the persistence and clearance of product sequences from tissues

# Biodistribution Assessment - Use of Animal Data (cont'd)

- Tissue Collection
  - Recommended sample tissues, at a minimum: blood, injection site(s), gonads, brain, liver, kidneys, lung, heart, and spleen
  - Other sampling tissues considerations

- Tissue Analysis
  - A quantitative, sensitive assay such as qPCR

# Viral Shedding Assessment

- Viral Shedding – virus excretes outside of body (urine, fecal, dressing, swabs, saliva, etc.) - Elimination

- Viral Shedding Evaluation in Clinical Studies
  - Collect shedding data in Phase 1 trials: OV products are classified as replication competent. The data collection may continue in Phase 2 and Phase 3 studies.
  - Shedding study design
    - Biological characteristics
    - Route of administration
  - Sample collection
    - Frequency, duration, types of samples collected, storage conditions
  - Analytical assays
    - a quantitative, sensitive assay like qPCR, and
    - an infectivity or growth-based assay

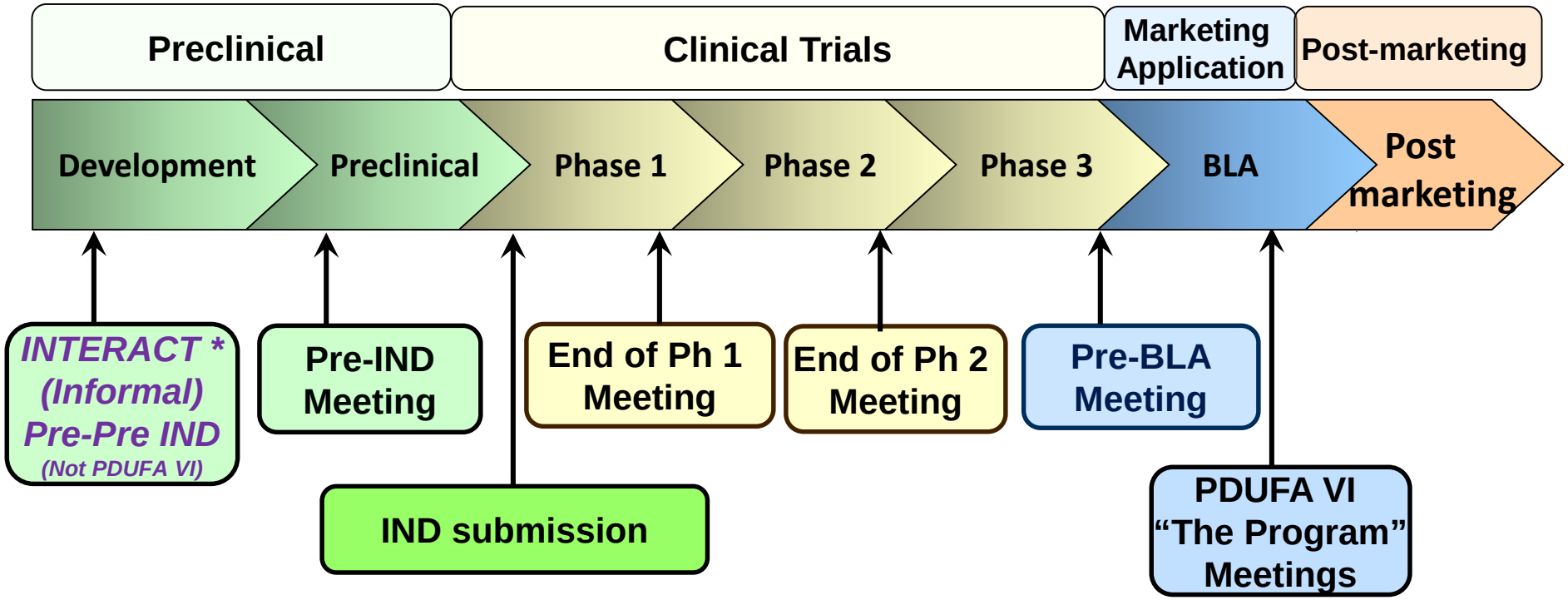


FDA Guidance for Industry - Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products (August 2015)

# Future Considerations

- Combination with check-point inhibitors, chemotherapy agents, and CAR T-cell therapy.
- Bioanalytical assays method development and validation
- Biomarkers qualification
- PK/PD modeling for OV therapy

# Opportunities for Interaction During Product Development



# FDA Guidances

- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015) https://www.fda.gov/media/106369/download
- Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products (August 2015) https://www.fda.gov/media/89036/download
- Long Term Follow-Up After Administration of Human Gene Therapy Products (Draft, July 2018)

  https://www.fda.gov/media/113768/download
- Biomarker Qualification: Evidentiary Framework (Draft, December 2018)

  https://www.fda.gov/media/122319/download

# References


- ICH Considerations – Oncolytic Viruses (October 2009) https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-22.pdf

- IPRP Reflection Paper – Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products (April, 2018)

  http://development.iprp.backend.dev6.penceo.com/sites/default/files/2018-09/IPRP_GTWG_ReflectionPaper_BD_Final_2018_0713.pdf

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- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm


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