2

# Oncolytic virus overview
*Dr. Dmitriy Zamarin*

3. ONCOS-102 in melanoma – Dr. Alex Shoushtari
4. ONCOS-102 in mesothelioma
5. Summary & closing

targovax


Memorial Sloan Kettering Cancer Center™

# Systemic immunomodulation with *in situ* oncolytic vaccines

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# The idea of using pathogens for treating cancer

1800

1850

1900

1950

1970

1990

2005

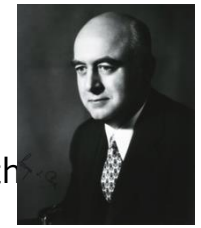
2015

**1850-1900** – reports of natural tumor regressions coinciding with human infections

William Coley

**1891**-William B. Coley uses live Strep. pyogenes to treat head and neck cancer

**1910**-De Pace et. al - patient with advanced cervical cancer treated with rabies vaccine experiences complete remission



George T. Pack

**1940's**-George T. Pack – treated melanoma with rabies vaccine; some remissions were seen.

**1950's**- clinical trials with Hepatitis B, West Nile virus, Adenovirus, Russian Far Eastern Encephalitis viruses

Chester Southam

**1960's-1990's**-clinical trials with attenuated human viruses and animal viruses

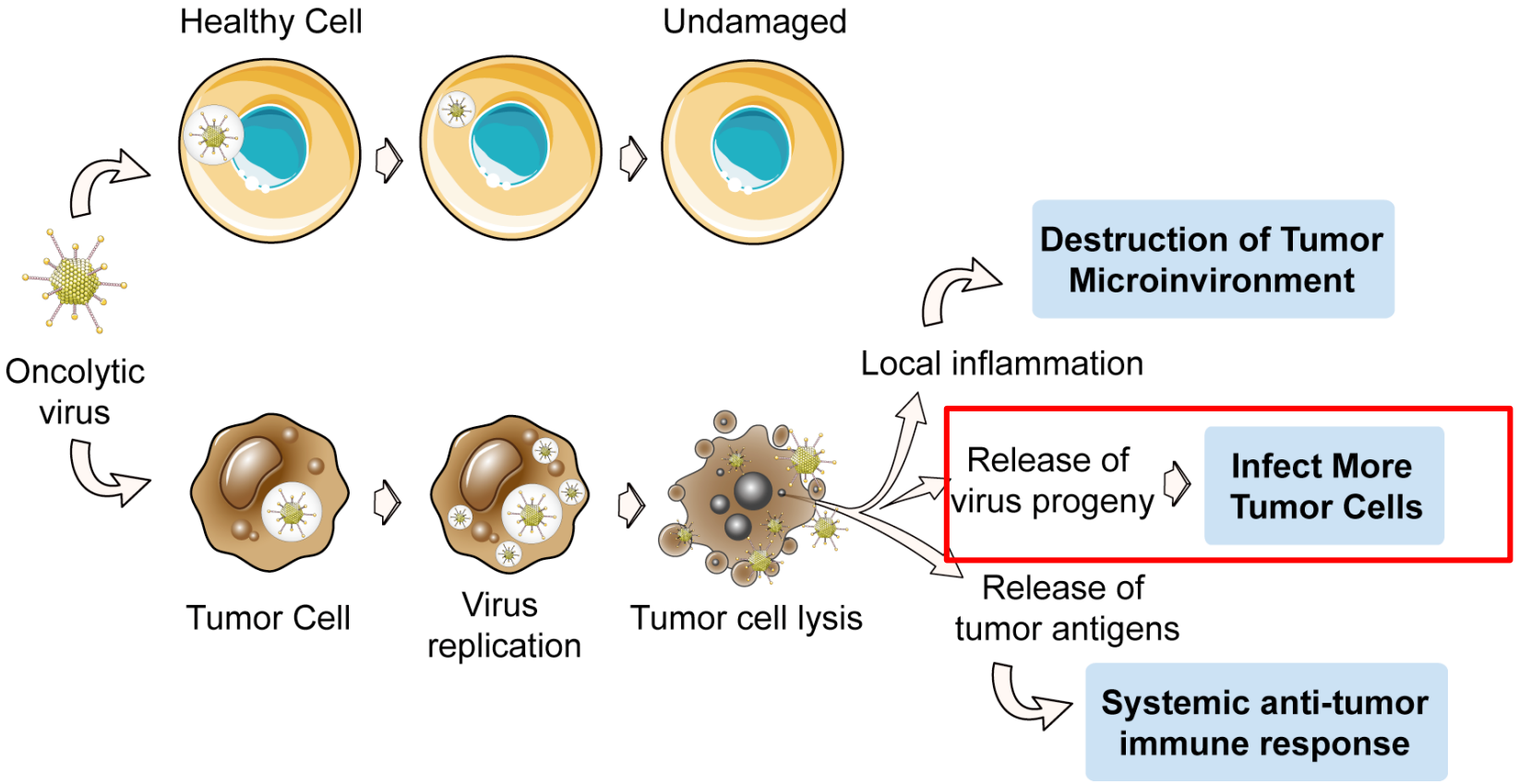
**1990's-present** – Genetically engineered viruses

**2005**- 1st approved oncolytic virus (China)

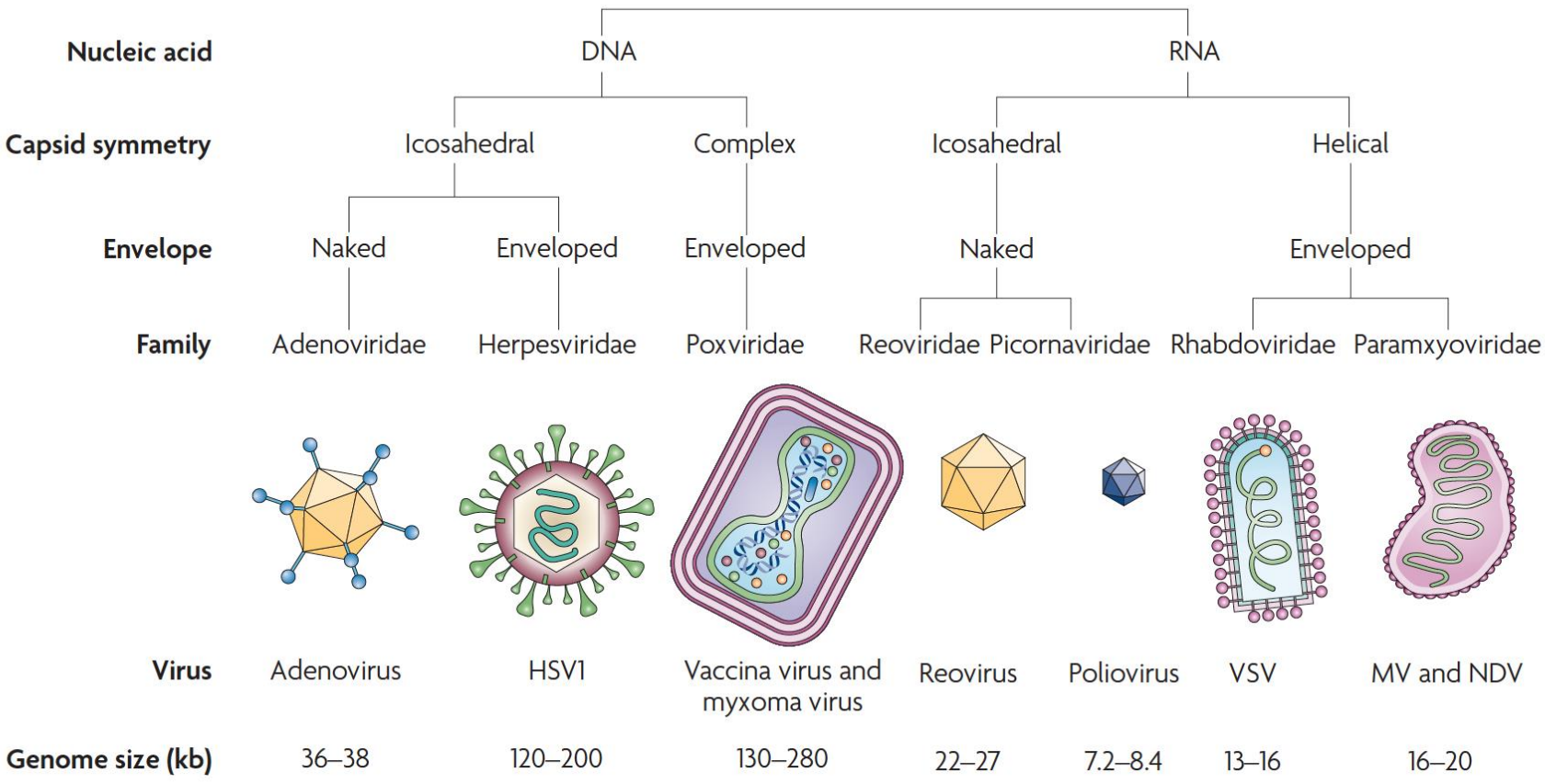
**2013**-1st positive phase III trial (talimogene laherparepvec)

**2015**- T-vec approved for advanced melanoma

# How oncolytic viruses work



# Not all oncolytic viruses are created equal




**Dogma: replicating and lytic viruses are better anti-cancer agents than non-lytic viruses**



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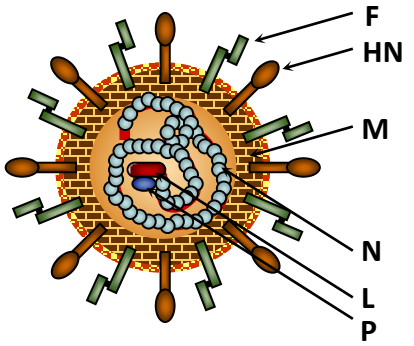
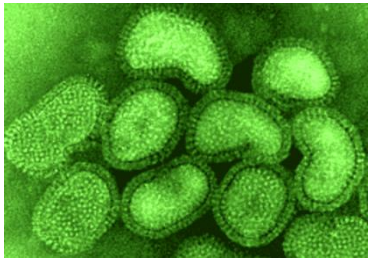
# Current efforts (non-exhaustive list, closest to clinical development)

- **HSV-1 (Amgen and at least 5 other companies );** T-vec phase III in melanoma complete and FDA-approved; combination trials with anti-PD-1 and anti-CTLA-4 in melanoma ongoing. Head and neck Ph III trial terminated in 2011.
- **Vaccinia (Jennerex, Genelux, Western Oncolytics).** JX-594 had encouraging results in early trial with HCC; less promising in a later study. GL-ONC1 is in phase I for IP for carcinomatosis, intrapleural for mesothelioma, IV for solid tumors.
- **Myxoma (academic).** Pre-clinical
- **Reolysin (Oncolytics).** Multiple clinical trials in various indications; most recently in combination with chemotherapy.
- **Coxsackie A21 (Viralytics).** Phase II for intralesional administration (CALM study, melanoma) showed promise. Currently in phase I IV for different cancer types; including with pembro combination for lung.
- **Poliovirus (academic).** Encouraging data in glioblastoma (given intratumorally)
- **Adenovirus (Oncos, Cold Genesys, PsiOxus, academic).** Oncos: Ad5-GM-CSF; completed phase I study with IT administration, results pending (evidence of immune activation based on poster presentations). PsiOxus: chimeric Ad11p/Ad3, in phase I for colon cancer (IV).
- **VSV (Viread).** Phase I ongoing in HCC.
- **Maraba (Turnstone).** Phase I ongoing in combination with adenovirus prime-boost in patients with MAGE-A3 expressing cancers
- **Measles (academic).** Phase I in ovarian, head and neck, multiple myeloma, GBM, mesothelioma. Promising results in ovarian and multiple myeloma so far.
- **NDV (academic and industry).** Several phase I studies completed in multiple tumor types using virulent virus strain, with promising results. Currently in development with non-virulent strains.
- **Seneca Valley (Neotropix).** Phase I completed in neuroendocrine tumors.

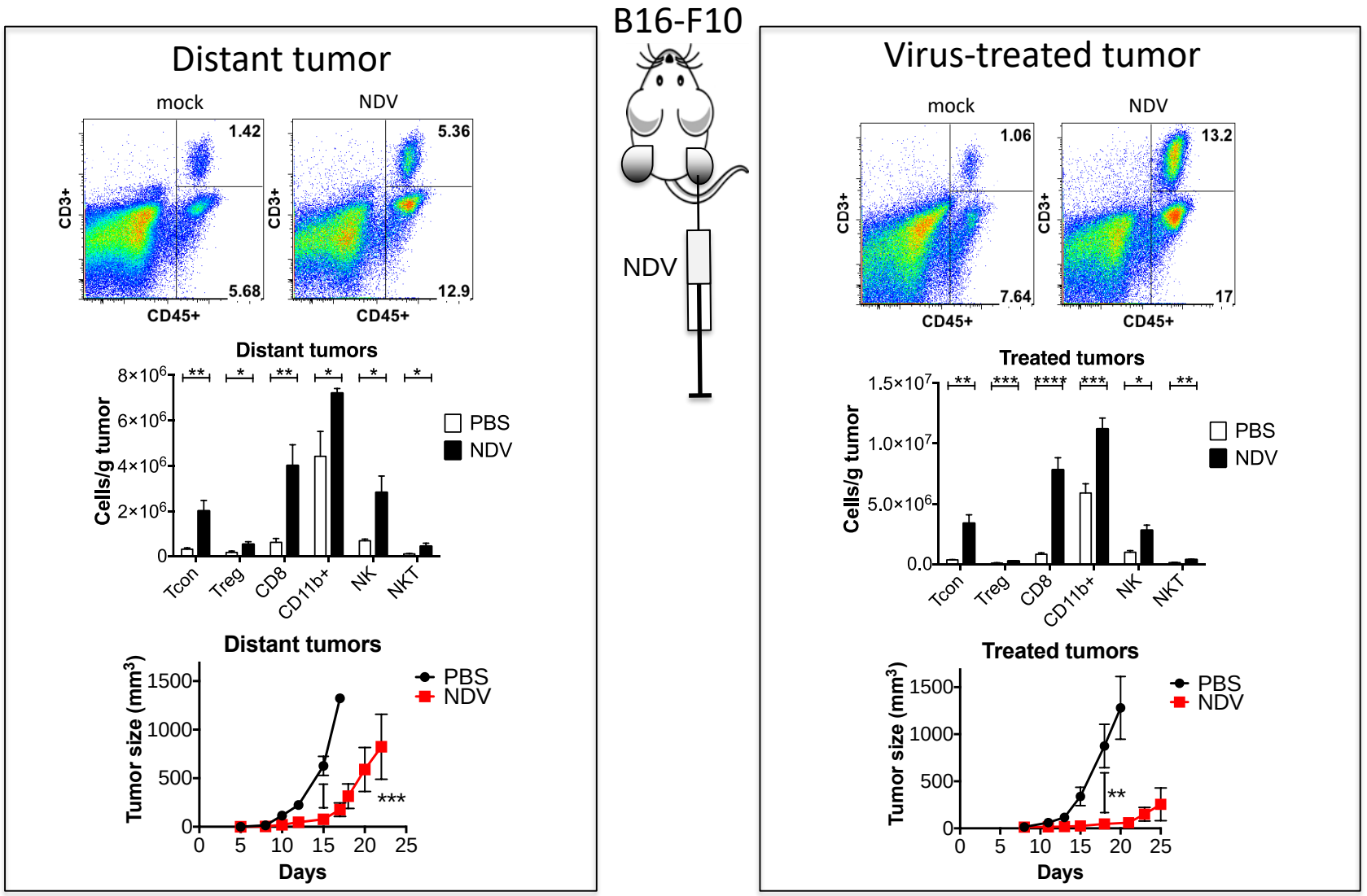
# Newcastle Disease Virus (NDV)

- Negative-strand RNA virus, member of Paramyxoviridae family (same as mumps, HPIV, measles), which **do not integrate into mammalian genome**
- Causes contagious bird disease affecting many domestic and wild avian species, but poses **no hazard to human health**
- Readily **infects the majority of cancer cells** due to ubiquity of the receptor (sialic acid)
- Specificity for cancer cells is mediated by selective viral replication in cells with **deficient innate immune responses and cells resistant to apoptosis**
- Pathogenicity in birds is primarily determined by the fusion protein cleavage site sequence



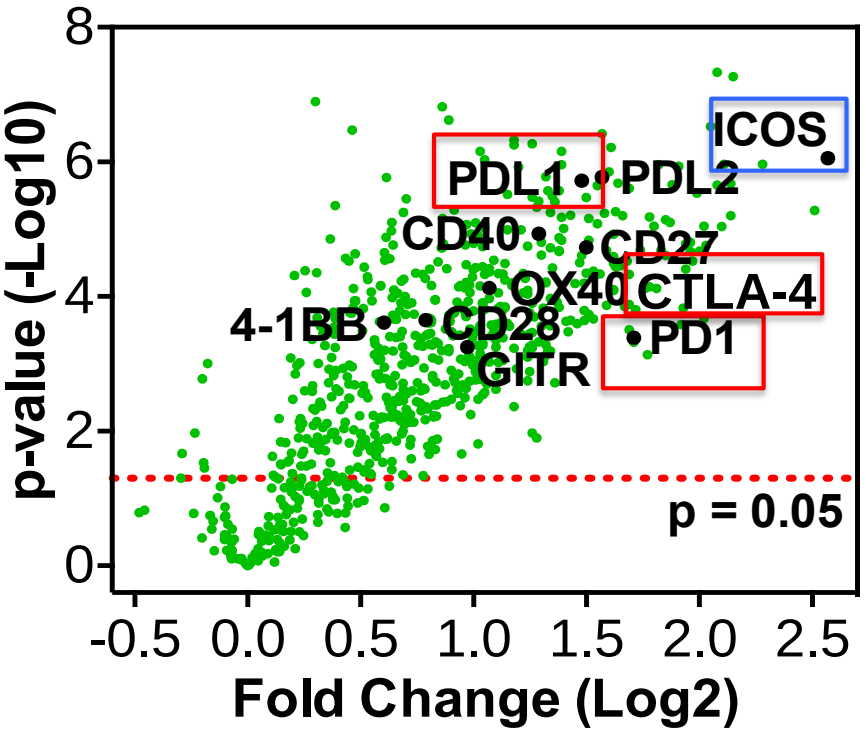
# Intratumoral NDV induces local and distant TIL infiltration

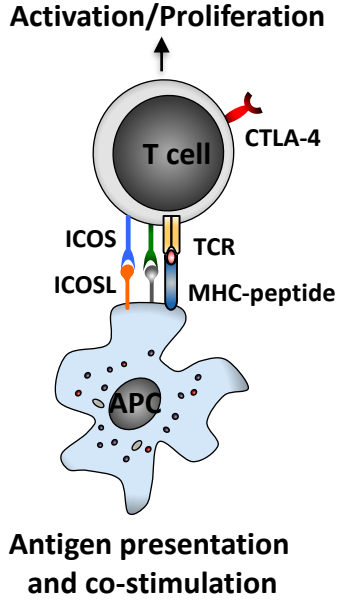




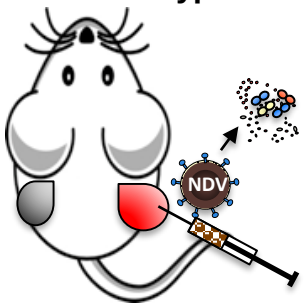

Zamarin D, Wolchok JD, Allison JP. *Science Translational Medicine.* 2014 5:226ra

# NDV upregulates a range of immune inhibitory and activating pathways in tumors

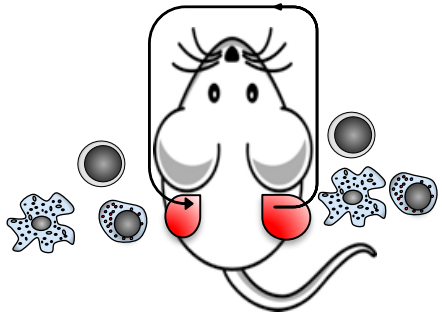


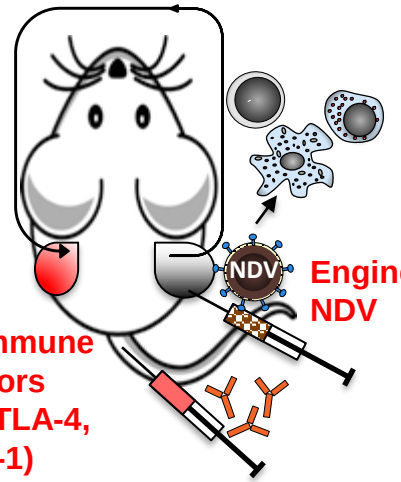




Early: direct action of type I IFN




Late: response to TIL infiltration

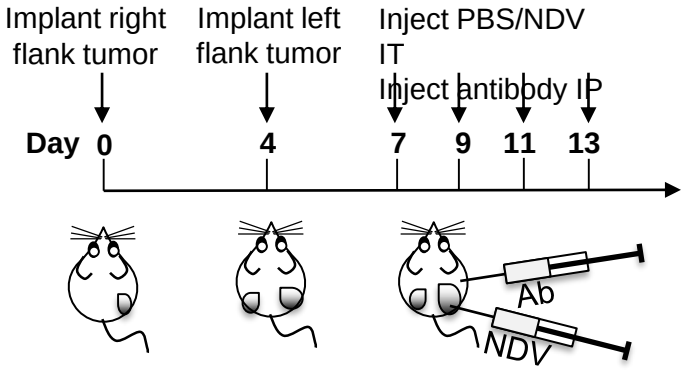




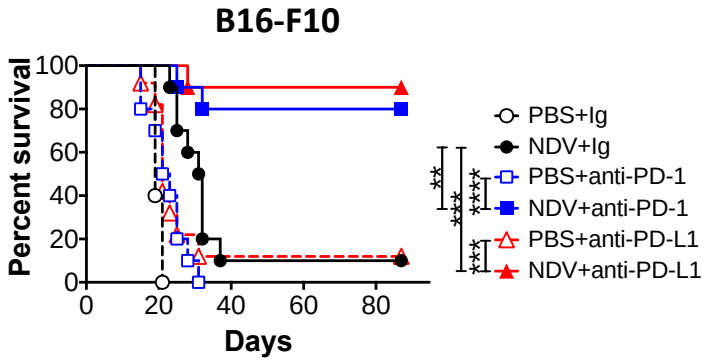


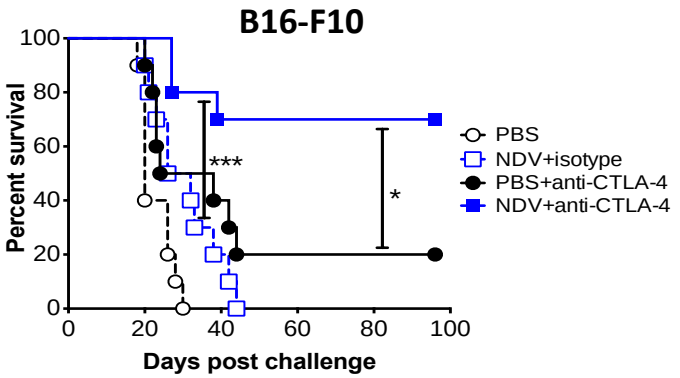

Zamarin et al., *J. Clin. Invest*. 2018 *in press*

# NDV potentiates the efficacy of systemic immune checkpoint blockade in models sensitive and resistant to NDV lysis

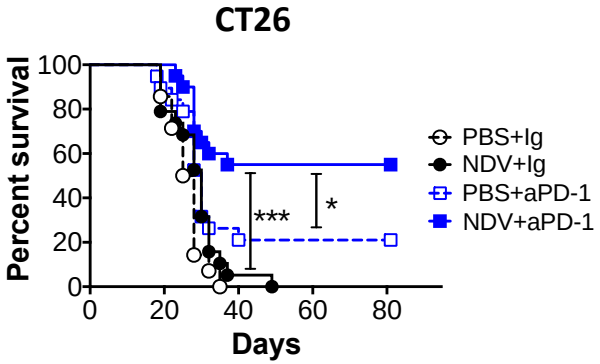


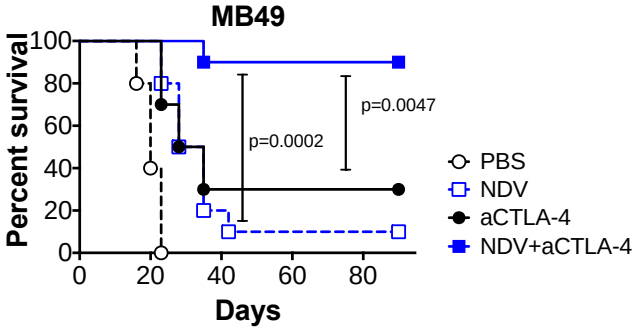

NDV-sensitive




NDV-resistant

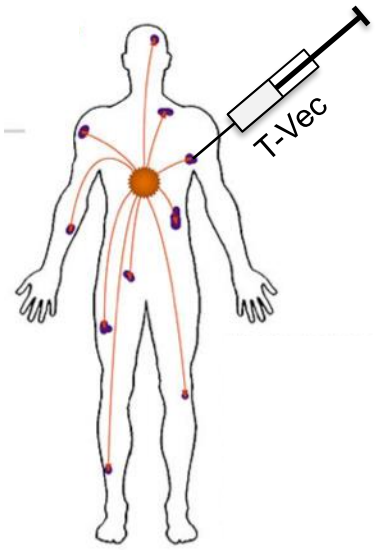


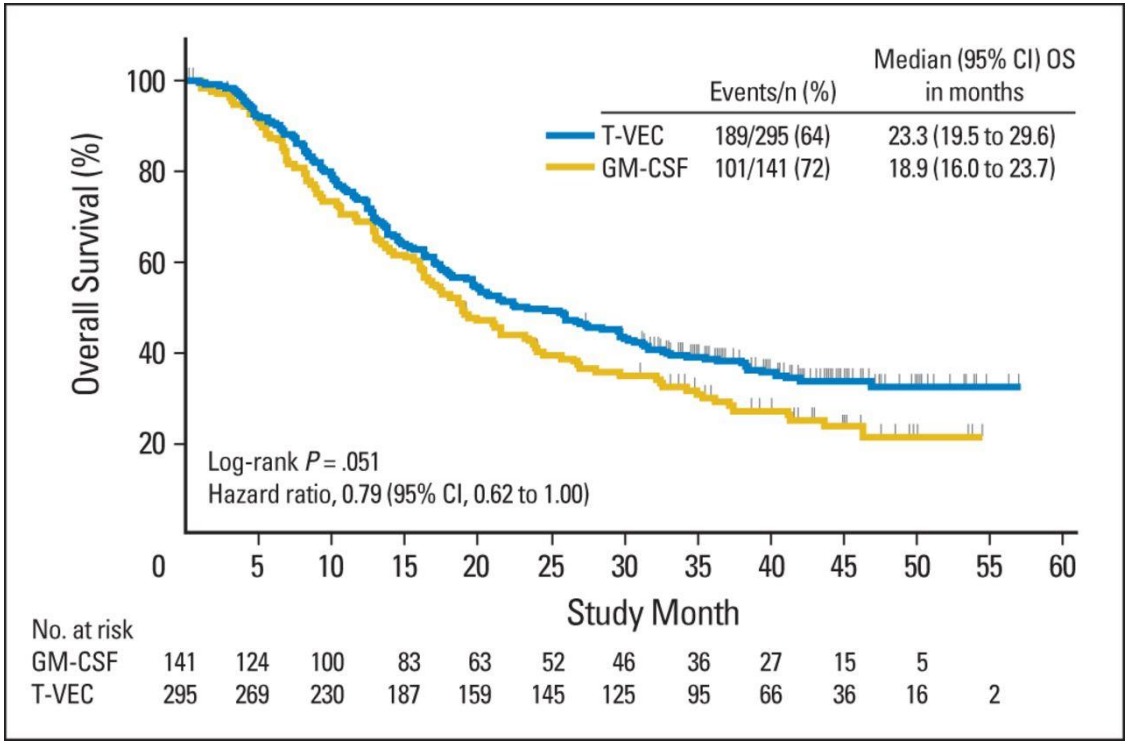






Zamarin et al., *J. Clin. Invest*. 2018 *in press;* Zamarin D, et al., *Science Translational Medicine.* 2014 5:226ra

# OPTiM, a randomized phase III trial of talimogene laherparepvec (T-VEC: HSV-GM-CSF) versus subcutaneous GM-CSF for the treatment of advanced melanoma



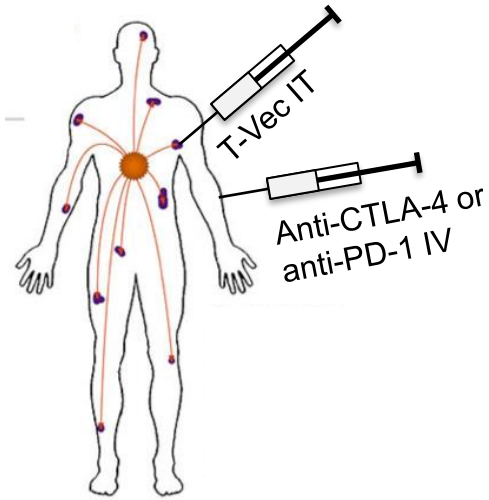




T-vec was approved by FDA in 10/2015

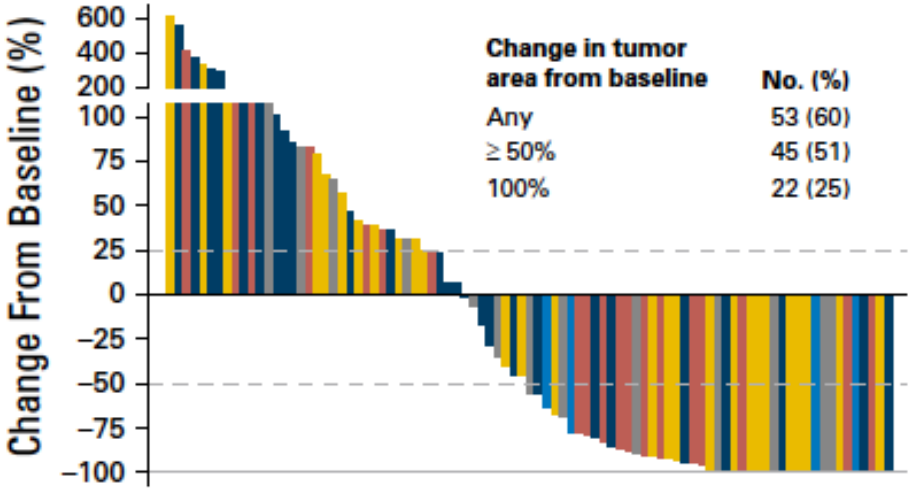


Andtbacka et al., JCO 2015

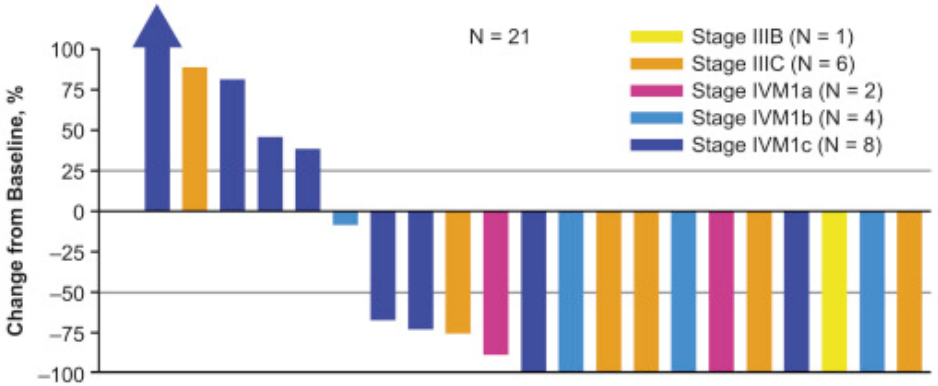
# Intratumoral T-vec potentiates the efficacy of systemic anti-CTLA-4 and anti-PD-1 therapy in melanoma




Tvec + anti-CTLA-4 (ORR 39%)



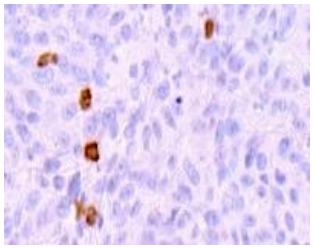

Tvec + anti-PD-1 (ORR 62%)



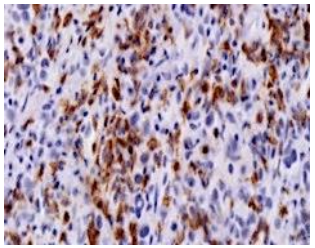



Chesney et al., JCO 2017; Ribas et al, Cell 2017

# Summary: locoregional and systemic immune modulation approaches can lead to systemic anti-tumor immunity

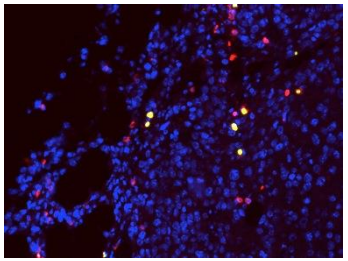


No response to CPI



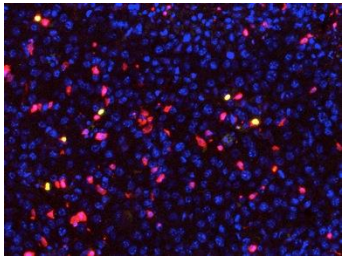
Response to CPI

PBS

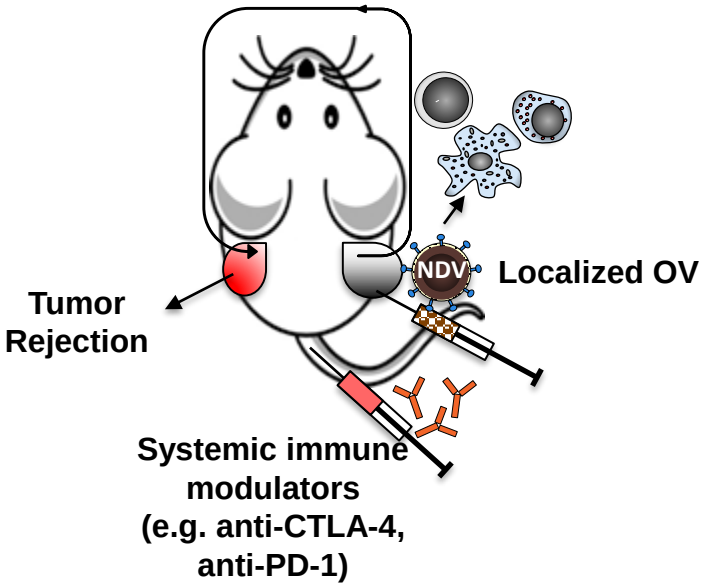


No response to CPI

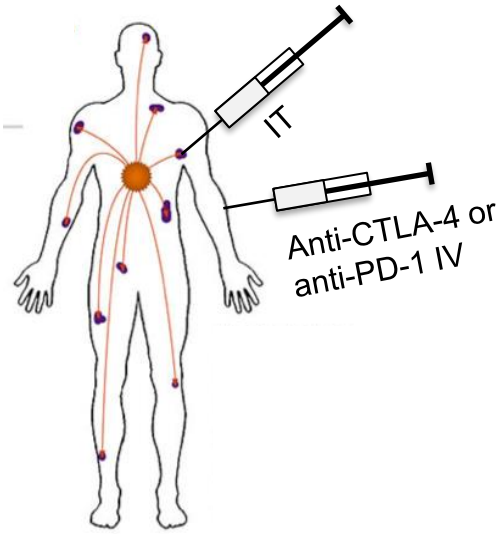
NDV



Response to CPI



# *In situ* oncolytic vaccines in combination with ICB overcome the need for systemic oncolytic virus delivery

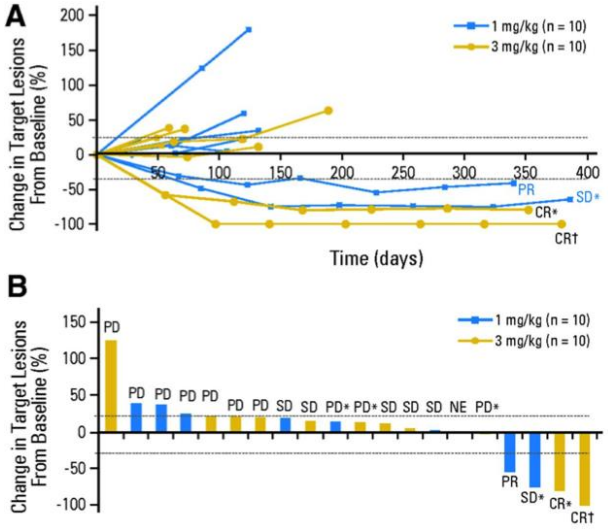



## Methods for delivery of *in situ* oncolytic vaccines

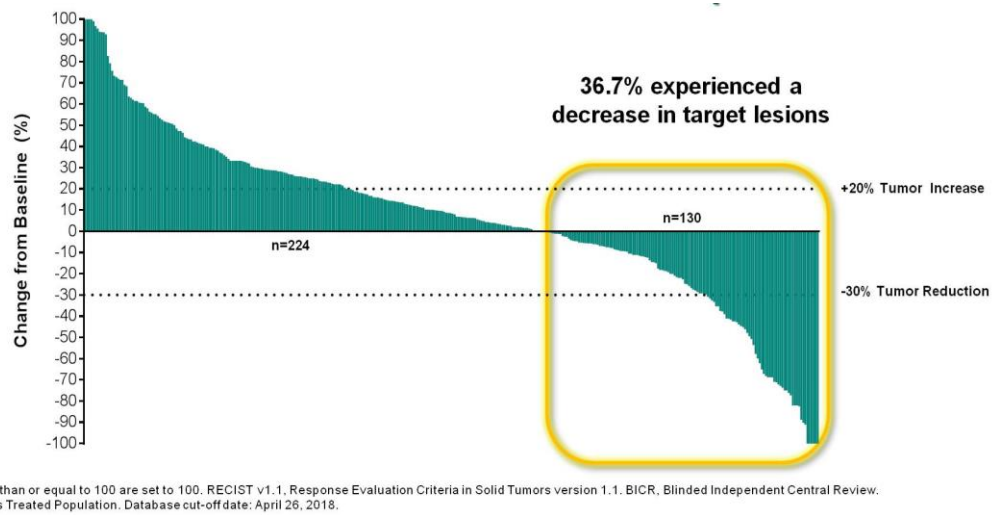
- Intravenous
- Intratumoral
  - Direct injection of accessible lesions
  - Image guided
  - Endoscopic
- Intraperitoneal catheter
- Intrapleural catheter
- Intraarterial
  - Hepatic artery infusion pump

# Combination oncolytic immunotherapy for peritoneal cancers

# PD-1 blockade as a single agent has limited activity in ovarian cancer




**ORR 15%**




Values higher than or equal to 100 are set to 100. RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. BICR, Blinded Independent Central Review. All Subjects as Treated Population. Database cut-off date: April 26, 2018.

**ORR 9%**

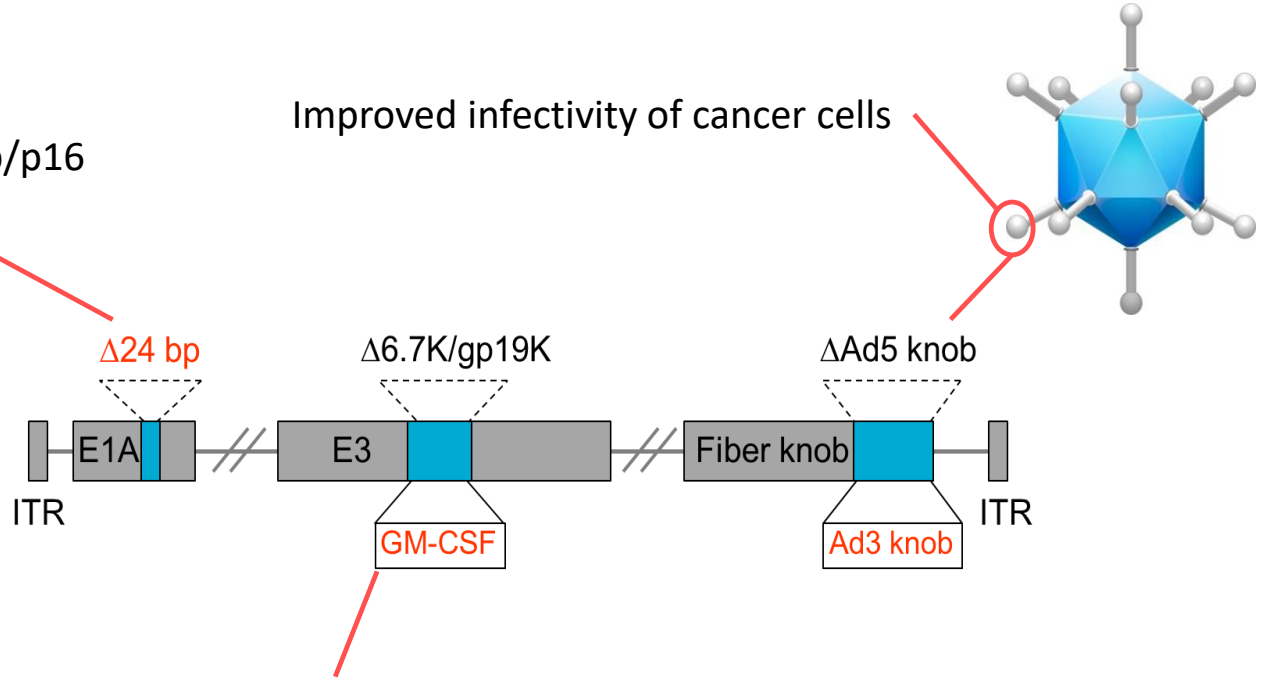


Hamanishi et al., JCO 2015, Matulonis et al., ASCO 2018

# Background on ONCOS-102

Selective replication in Rb/p16 defective cancer cells

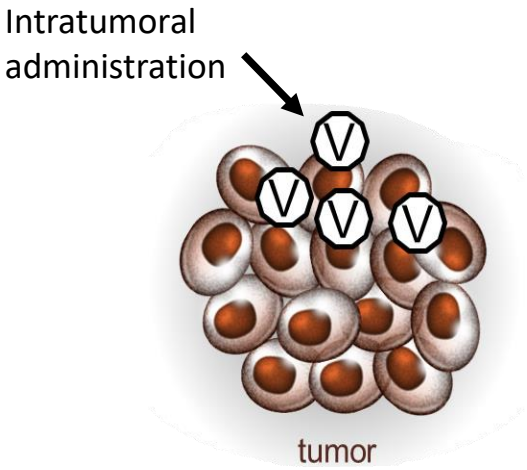
Improved infectivity of cancer cells

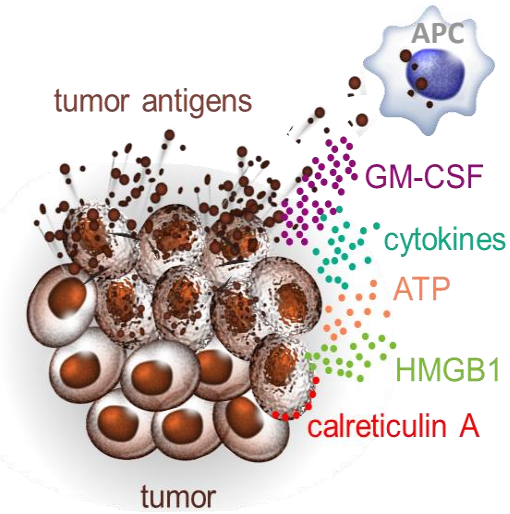


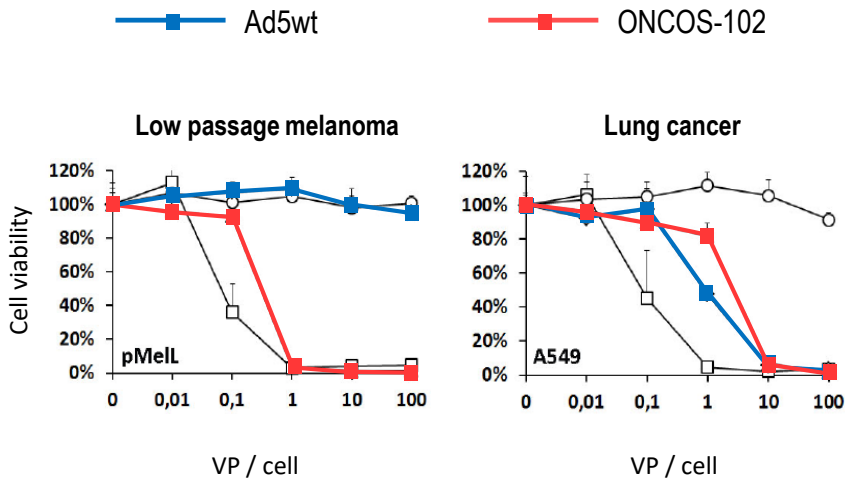

Transgene expression coupled to virus replication
-> expression only in tumor cells

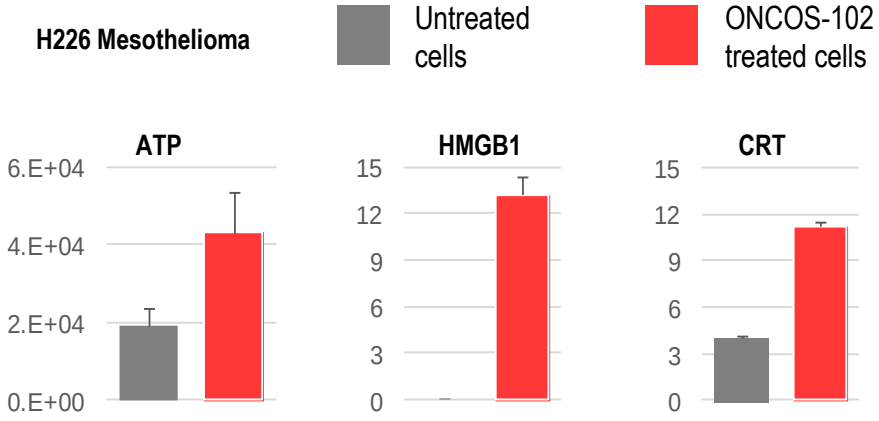
- 115 cancer patients with solid refractory tumors were treated with ONCOS-102 in Advanced Therapy Access Program (ATAP)
- ONCOS C1 trial

# ONCOS-102 replicates in cancer cells and induces immunogenic cell death

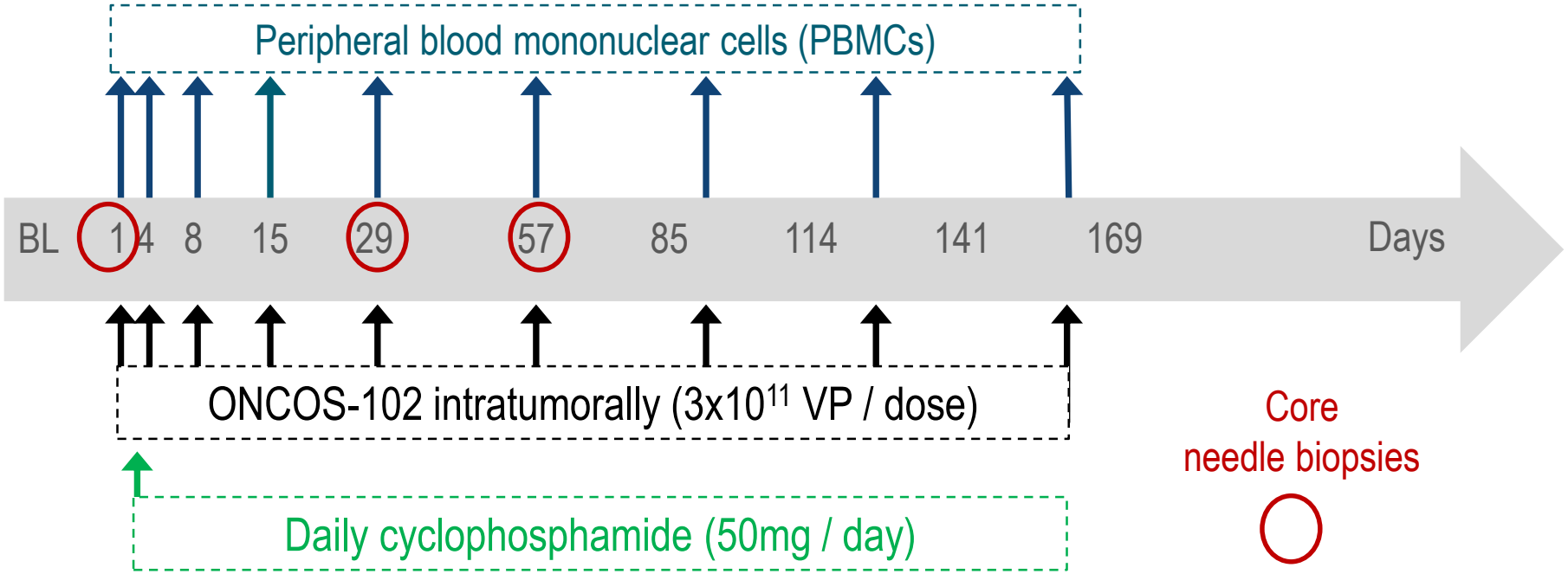


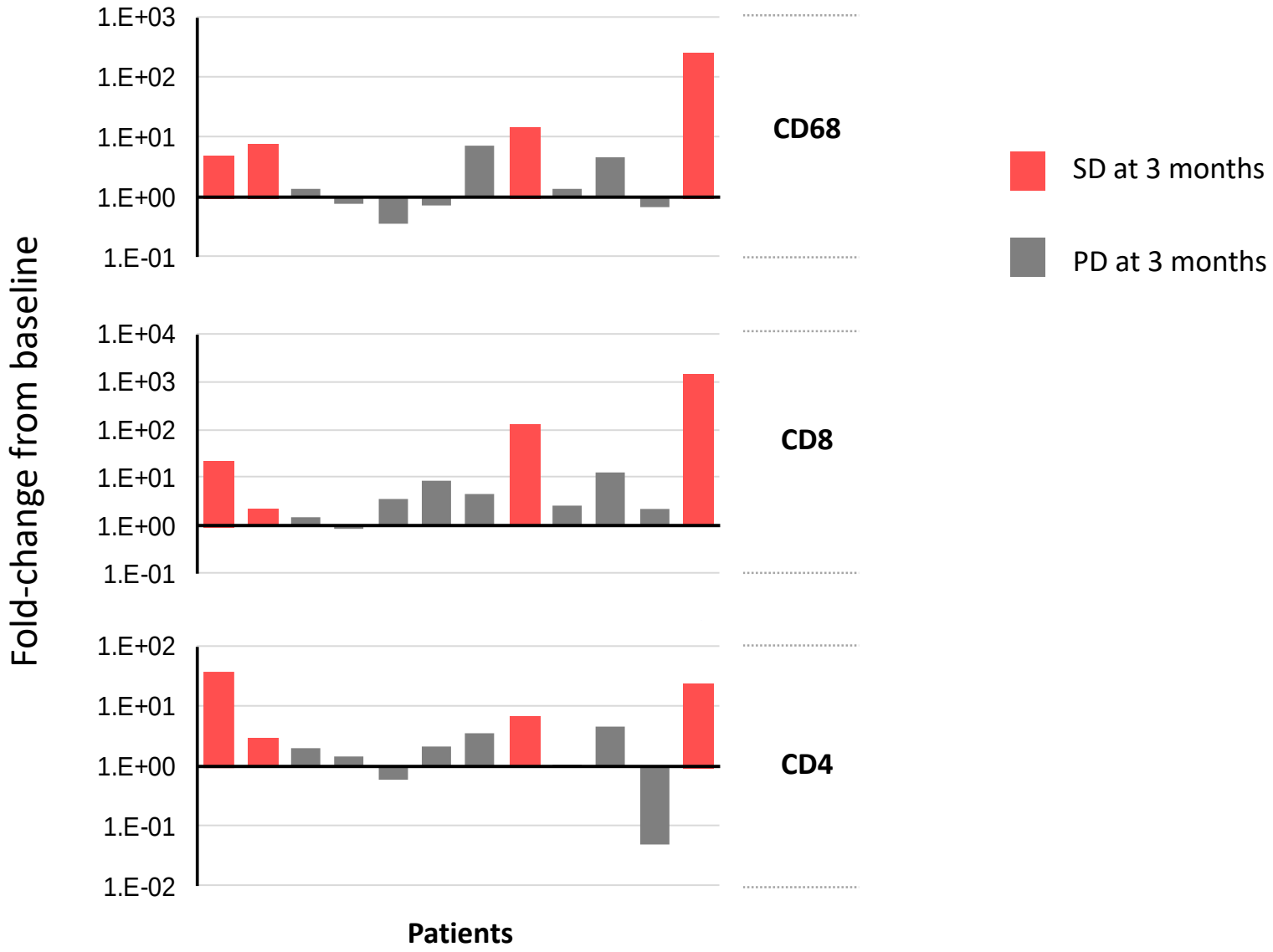



# Phase I study of intratumoral ONCOS-102 with low dose cyclophosphamide in patients with advanced solid tumors

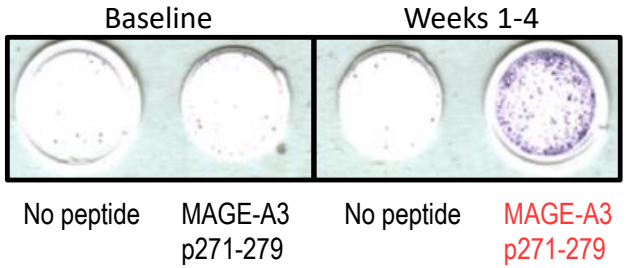


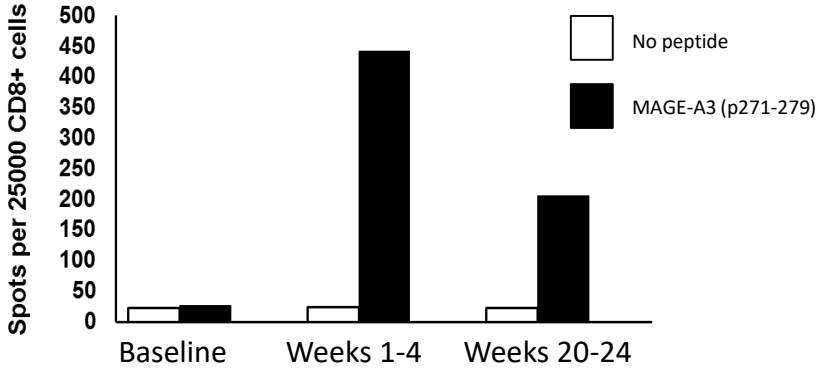
# Several immune cell subsets were attracted into tumors following ONCOS-102



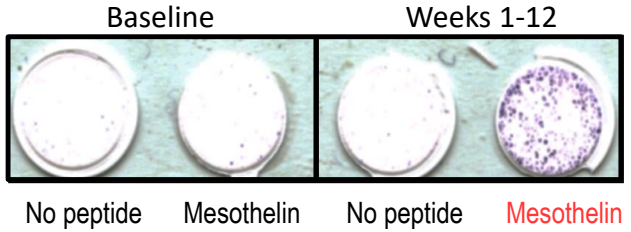
# Local ONCOS-102 administration leads to induction of systemic tumor-specific CD8+ T cell response

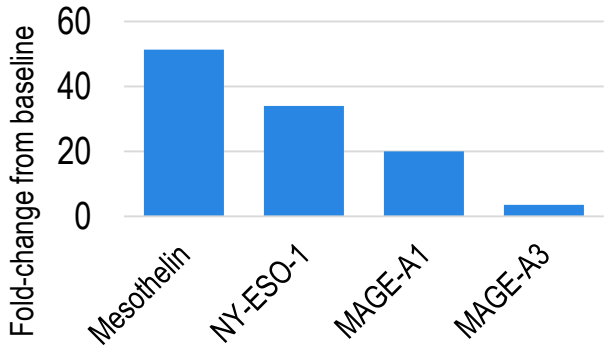
**Mesothelioma pt FI1-14**: induction of MAGE-A3 specific CD8+ T cells



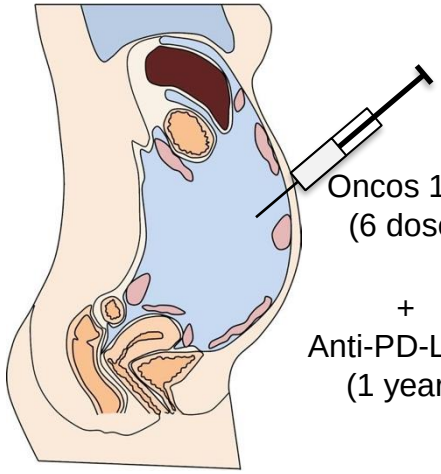

**OvCa pt FI1-19:** multiple tumor-specific CD8+ T cell populations induced by ONCOS-102




NY-ESO-1 specific CD8+ T cells present 17 mo after previous ONCOS-102 treatment, alive and SD >24 mo

# A Phase I/II study to investigate the safety and biologic and anti-tumor activity of ONCOS-102 in combination with PD-L1 blockade in patients with peritoneal malignancies



Oncos 102 IP
(6 doses)

+

Anti-PD-L1 IV
(1 year)

| Phase I | Phase II | Endpoints |
|---|---|---|
| **3 + 3 design** | **Optimal Simon 2 stage design** | **Primary**<br>• Feasibility<br>• Safety<br><br>**Secondary**<br>• Efficacy (ORR, CBR at 24 weeks, PFS)<br><br>**Exploratory**<br>• Immune biomarkers |
| 2 virus dose cohorts:<br>1. $1x10^{11}$ pfu<br>2. $3x10^{11}$ pfu<br>(6-12) | 1. Platinum-resistant/ refractory ovarian cancer (18+15)<br>2. Colorectal cancer (13+14)<br>3. Other intraperitoneal (e.g. mesothelioma, pancreas, endometrial) (30)<br>Additional expansion cohorts? | |

LUDWIG CANCER RESEARCH

CANCER RESEARCH INSTITUTE

PI: Zamarin

# Update

- 7 patients enrolled and treated to date
- Dose escalation is ongoing