



THIRD ANNUAL  
**ISSPP**  
**Congress 2022**

*International Society  
for the Study of Pleura  
and Peritoneum*



**NOVEL THERAPEUTIC AGENTS FOR PLEURA & PERITONAL CANCERS**

# Oncolytic Viruses and Combination Immunotherapy Strategies for GI Peritoneal Carcinomatosis

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*Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura*

# Disclosures

- Consultant for Amgen, Ipsen, and ViraTherapeutics.

*This presentation and/or comments will be free of any bias toward or promotion of the above referenced company or its products and/or other business interests.*

*This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.*

*This presentation has been peer-reviewed and no conflicts were noted.*

*The off-label/investigational use of OLVI-VEC (formerly denominated as GL-ONC1) will be discussed.*

# Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

## STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

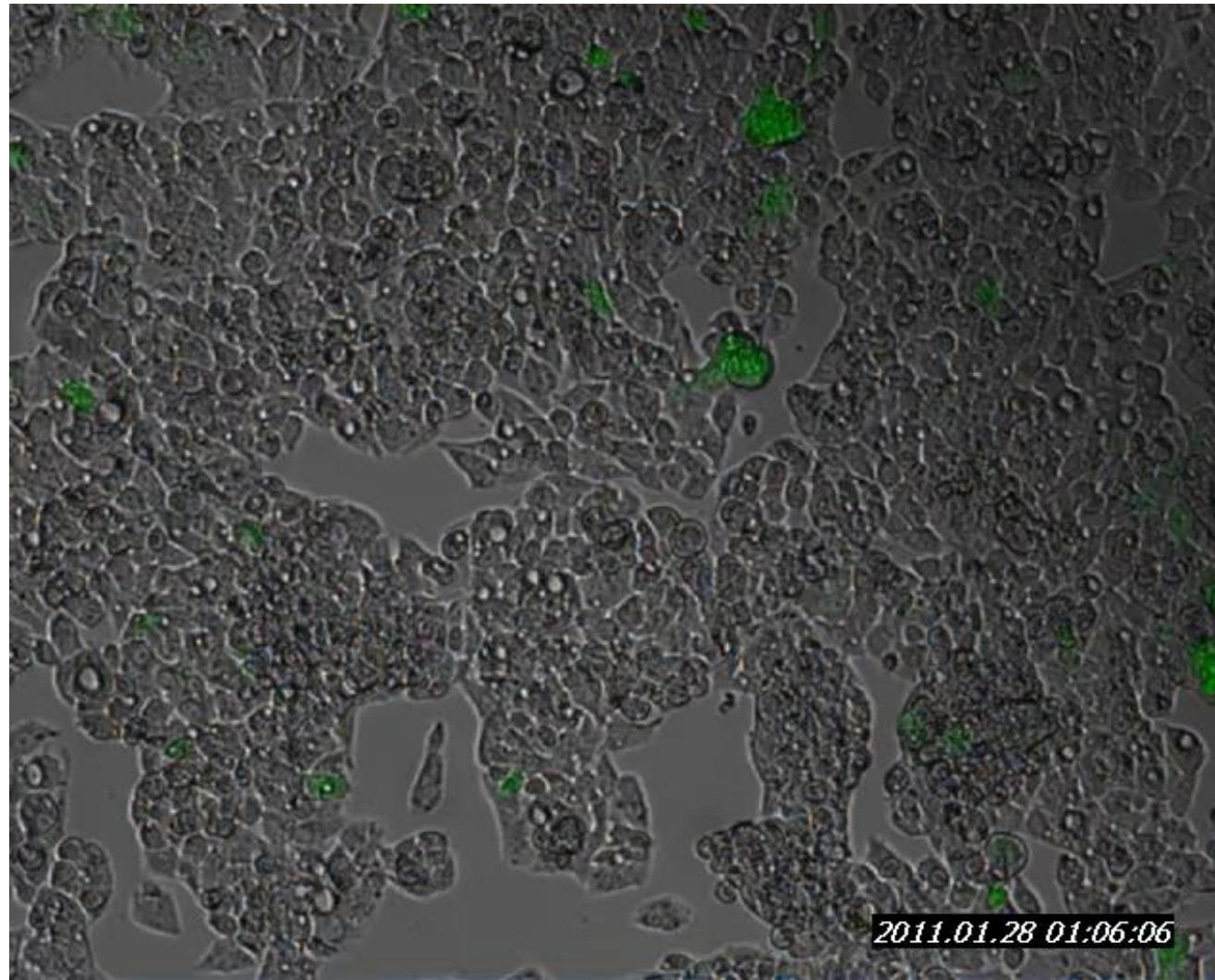
*The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.*

## The following CLC & IB components will be addressed in this presentation:

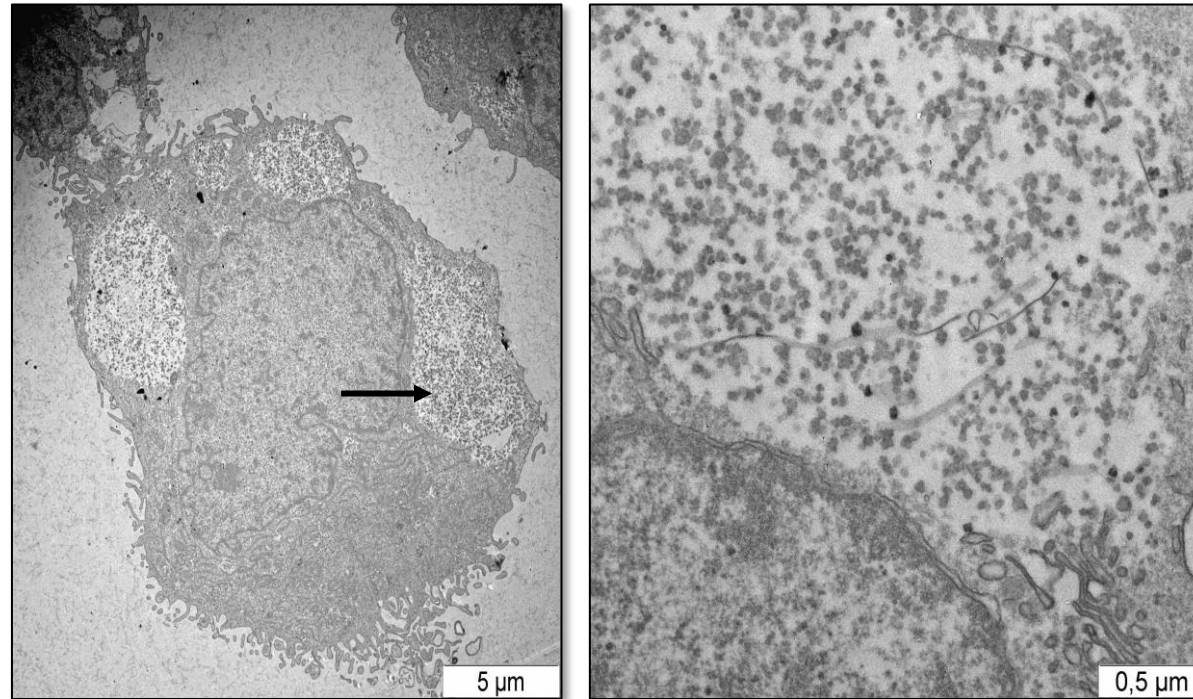
- Commonalities and differences among individuals with GI peritoneal carcinomatosis
- Possible bias aspects in taking part in clinical studies evaluating virotherapy as a new treatment option for GI peritoneal carcinomatosis



# IMMUNOVIROTHERAPY



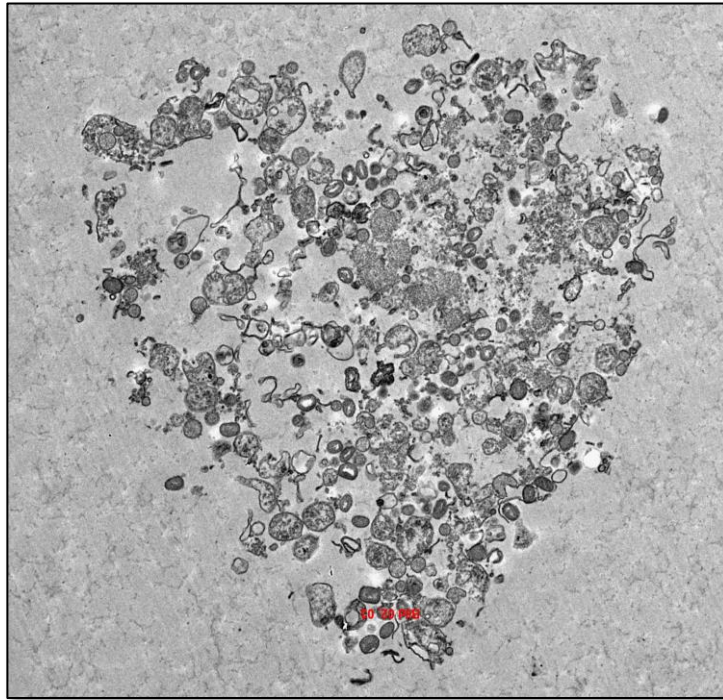
# IMMUNOVIROTHERAPY



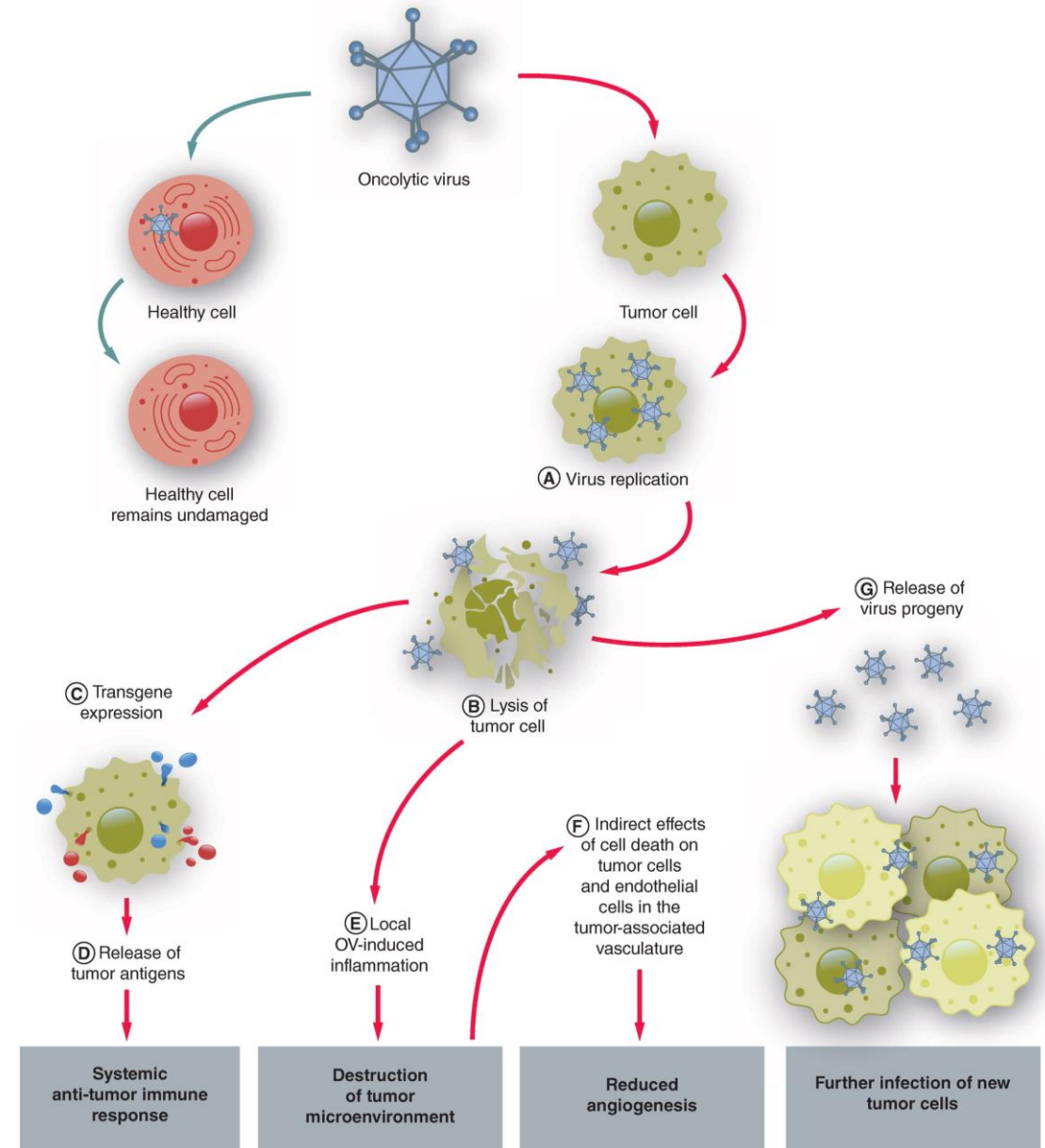
EM pictures obtained from Prof. Schaller/B. Fehrenbacher, Dermatology Tübingen, Germany



# IMMUNOVIROTHERAPY

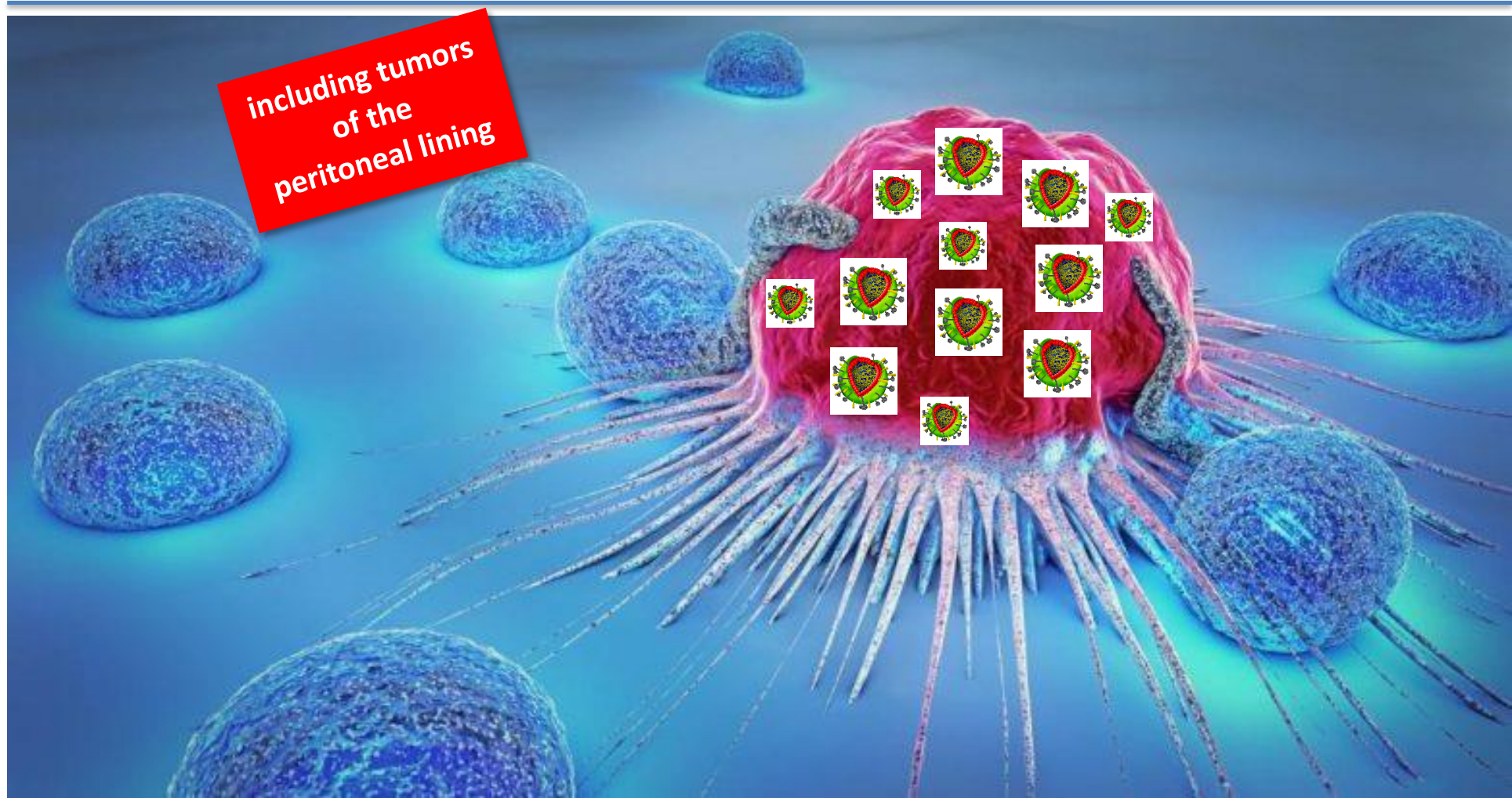


EM pictures obtained from Prof. Schaller/B. Fehrenbacher



Lauer & Beil, Future Oncol. 2022 Jul 12

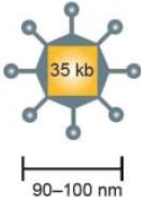
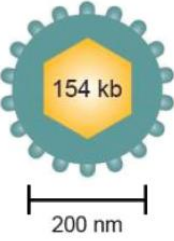


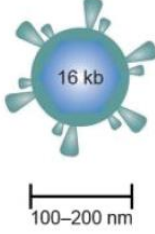
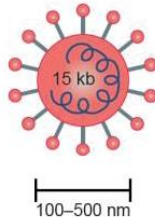
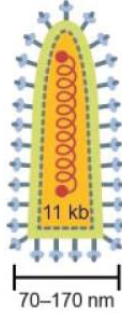

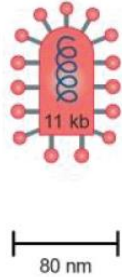

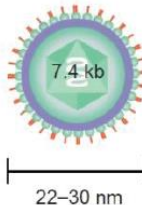
→ ALL tumor types are principally accessible to oncolytic virus-mediated destruction





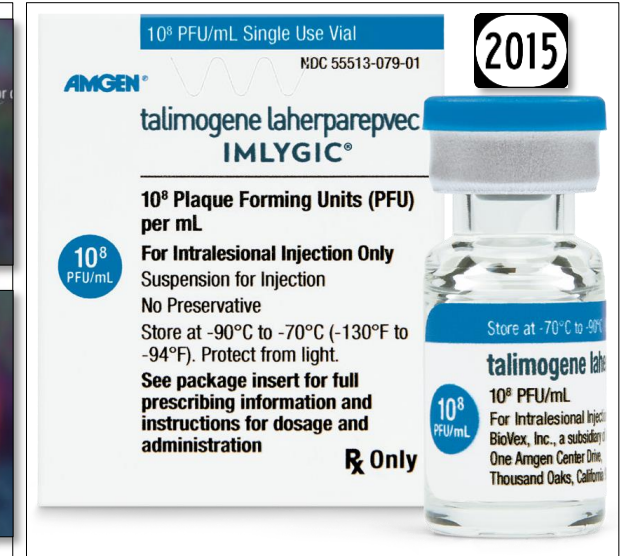
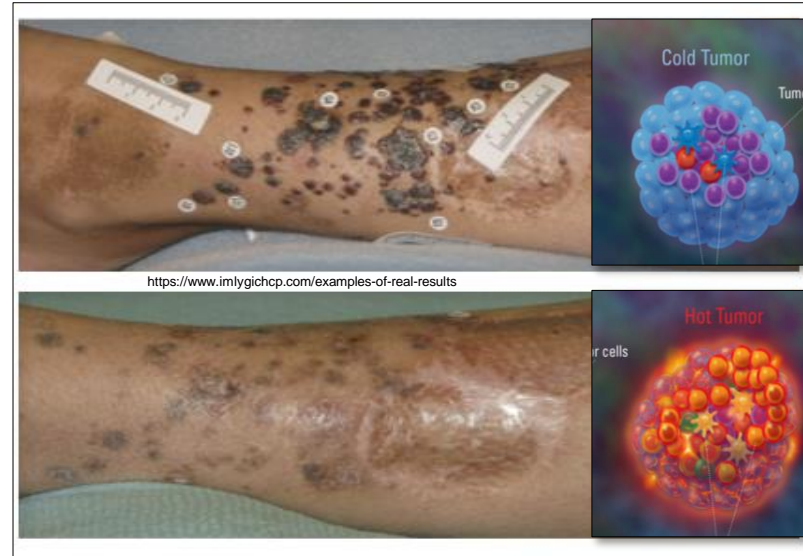
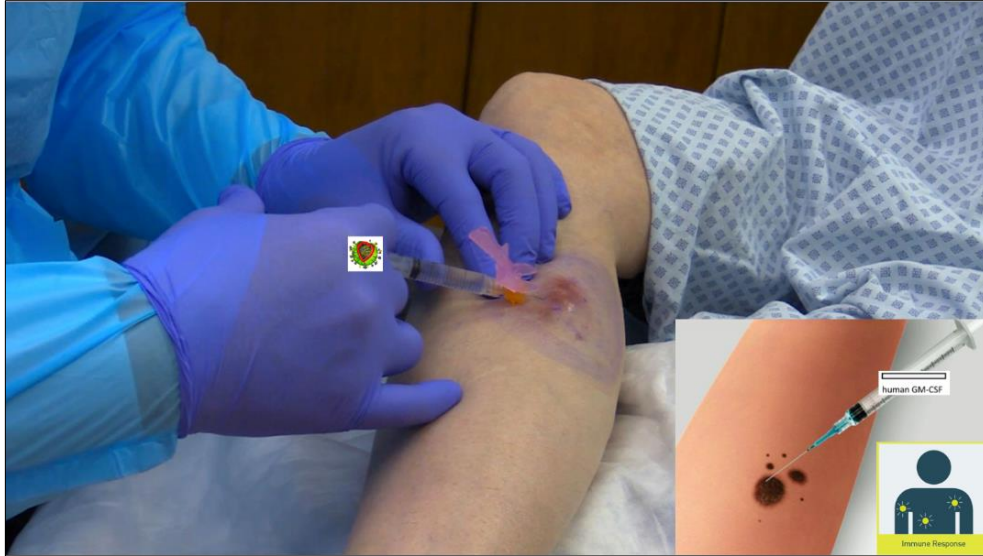
→ many types of viruses are able to perform a profound tumor cell oncolysis

Table 1. Properties of key oncolytic viruses.

Virus	DNA				RNA						
	Adenovirus	Herpes simplex virus	Parvovirus H1	Vaccinia virus	Measles vaccine virus	Newcastle disease virus	Maraba virus	Reovirus	Vesicular stomatitis virus	Poliovirus	Coxsackie virus
Genome size and diameter	 <p>Adenovirus</p>										
Capsid symmetry	Icosahedral	Icosahedral	Icosahedral	Complex	Icosahedral	Helical	Helical	Icosahedral	Helical	Icosahedral	Icosahedral
Envelope	Naked	Enveloped	Naked	Complex coats	Enveloped	Enveloped	Enveloped	Naked	Enveloped	Naked	Naked
Site of replication	Nucleus and cytoplasm	Nucleus and cytoplasm	Nucleus and cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm	Cytoplasm

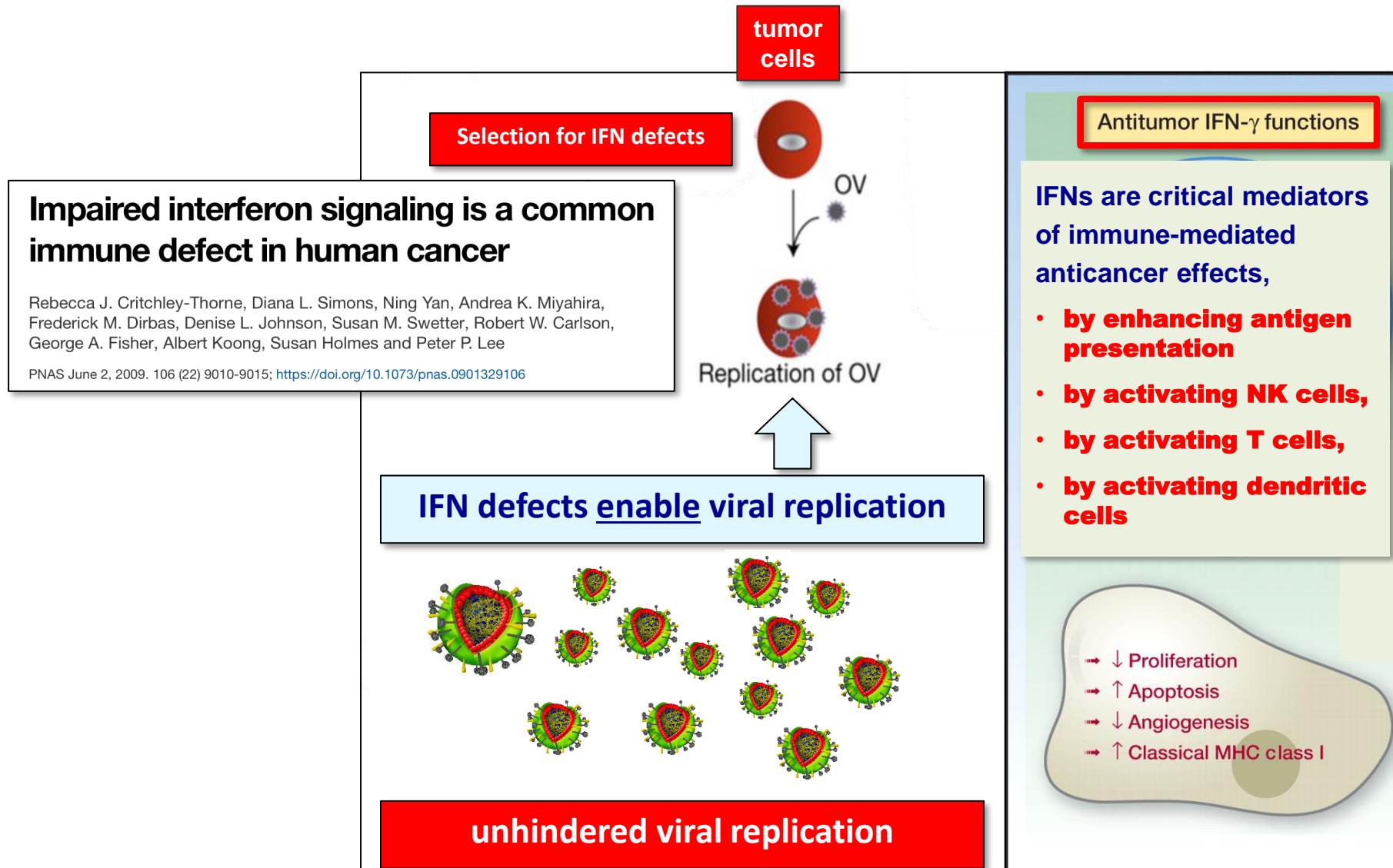


# IMMUNOVIROTHERAPY

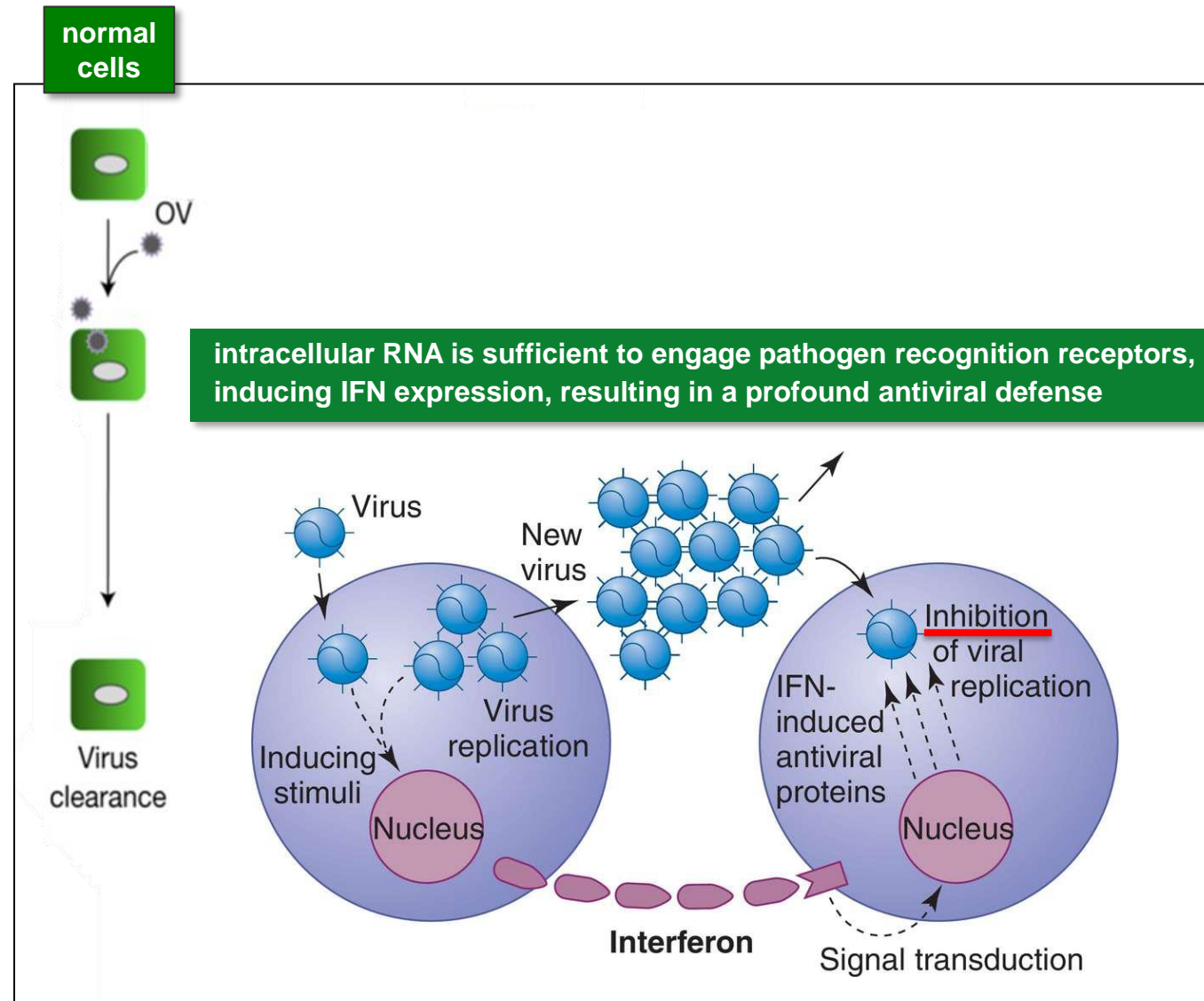


**abscopal effects** ➤ shrinkage not only of virus-treated, but also of untreated tumor sites

# Tumor cells: → Selection for IFN defects



# Normal cells: → intact virus defense





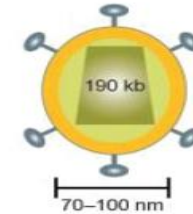
# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

Cancer Therapy: Clinical

Sponsor: Genelux Corporation, San Diego

Clinical  
Cancer  
Research

Vaccinia Virus



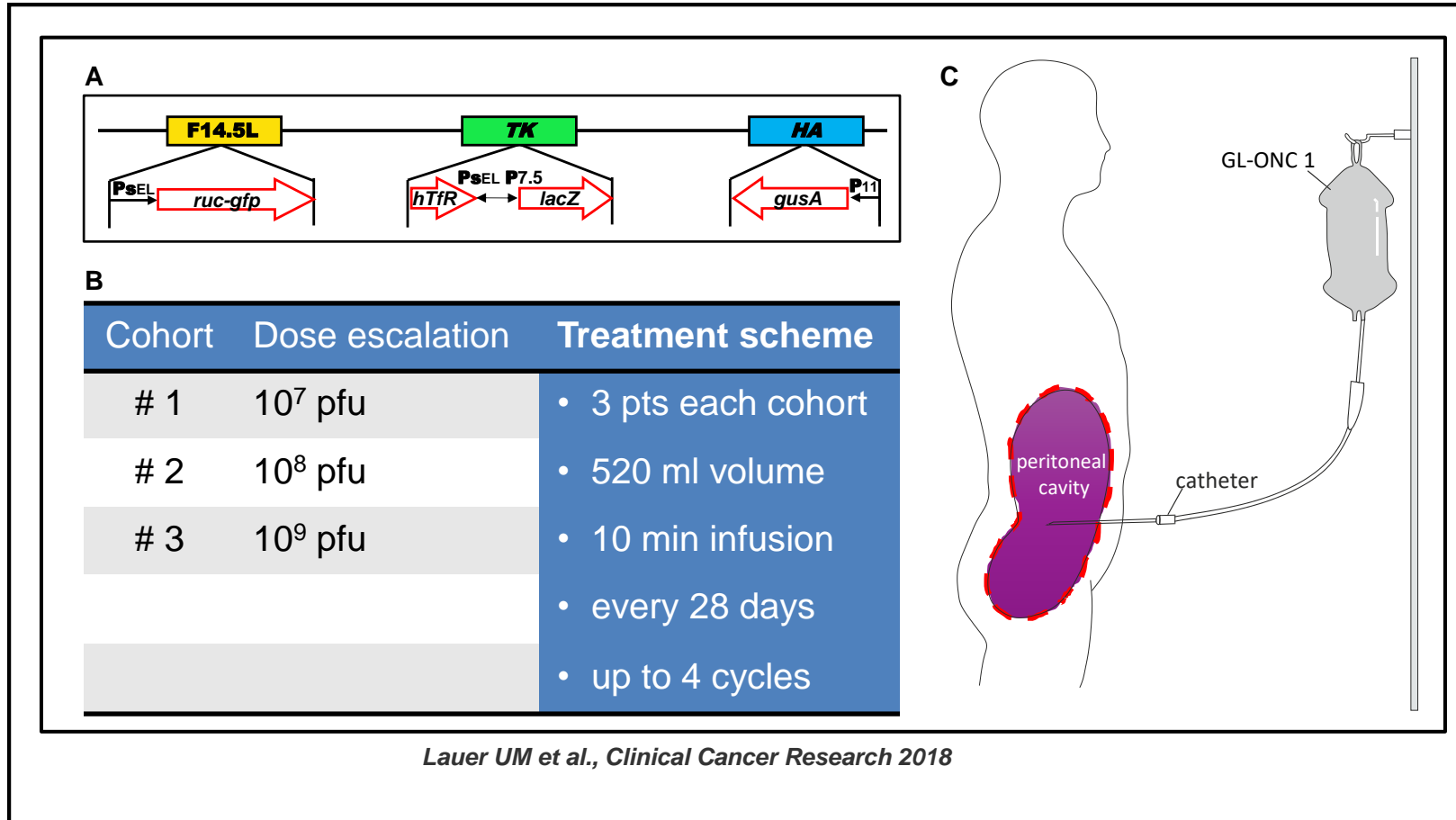
## Phase I Study of Oncolytic Vaccinia Virus GL-ONC1 in Patients with Peritoneal Carcinomatosis

Ulrich M. Lauer<sup>1,2</sup>, Martina Schell<sup>1</sup>, Julia Beil<sup>1,2</sup>, Susanne Berchtold<sup>1</sup>, Ursula Koppenhöfer<sup>1</sup>, Jörg Glatzle<sup>3</sup>, Alfred Königsrainer<sup>3</sup>, Robert Möhle<sup>4</sup>, Dominik Nann<sup>5</sup>, Falko Fend<sup>5</sup>, Christina Pfannenberger<sup>6</sup>, Michael Bitzer<sup>1</sup>, and Nisar P. Malek<sup>1</sup>

[Clin Cancer Res; September 15, 2018 \(NCT01443260\)](#)



# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis



# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

<b>Drug-Related Events</b> <i>number of occurrences (number of patients)</i>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
<b>Gastrointestinal disorders</b>				
Diarrhoea	2 (2)	-	-	-
Nausea	4 (2)	1 (1)	-	-
Vomiting	4 (4)	-	-	-
Flatulence	3 (1)	-	-	-
Abdominal pain	6 (4)	1 (1)	2 (2)	-
Ascites	-	-	6 (2)	-
<b>Generalized symptoms</b>				
Fatigue	1 (1)	-	2 (1)	-
Pyrexia	16 (8)	3 (3)	-	-
Chills	2 (1)	-	-	-
<b>Abnormal blood parameters</b>				
Alanine aminotransferase increased	-	1 (1)	-	-
Aspartate aminotransferase increased	-	-	1 (1)	-
Alkaline phosphatase increased	1 (1)	-	-	-
Creatinine increased	2 (2)	-	-	-
Gamma-glutamyltransferase increased	-	-	1 (1)	-
Lymphocyte count decreased	-	19 (7)	7 (5)	-
C-reactive protein increased	-	20 (7)	-	-
Hyperhidrosis	1 (1)	-	-	-
Cough	1 (1)	-	-	-
Pain in extremity	1 (1)	-	-	-
Herpes simplex virus infection	2 (2)	-	-	-



# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

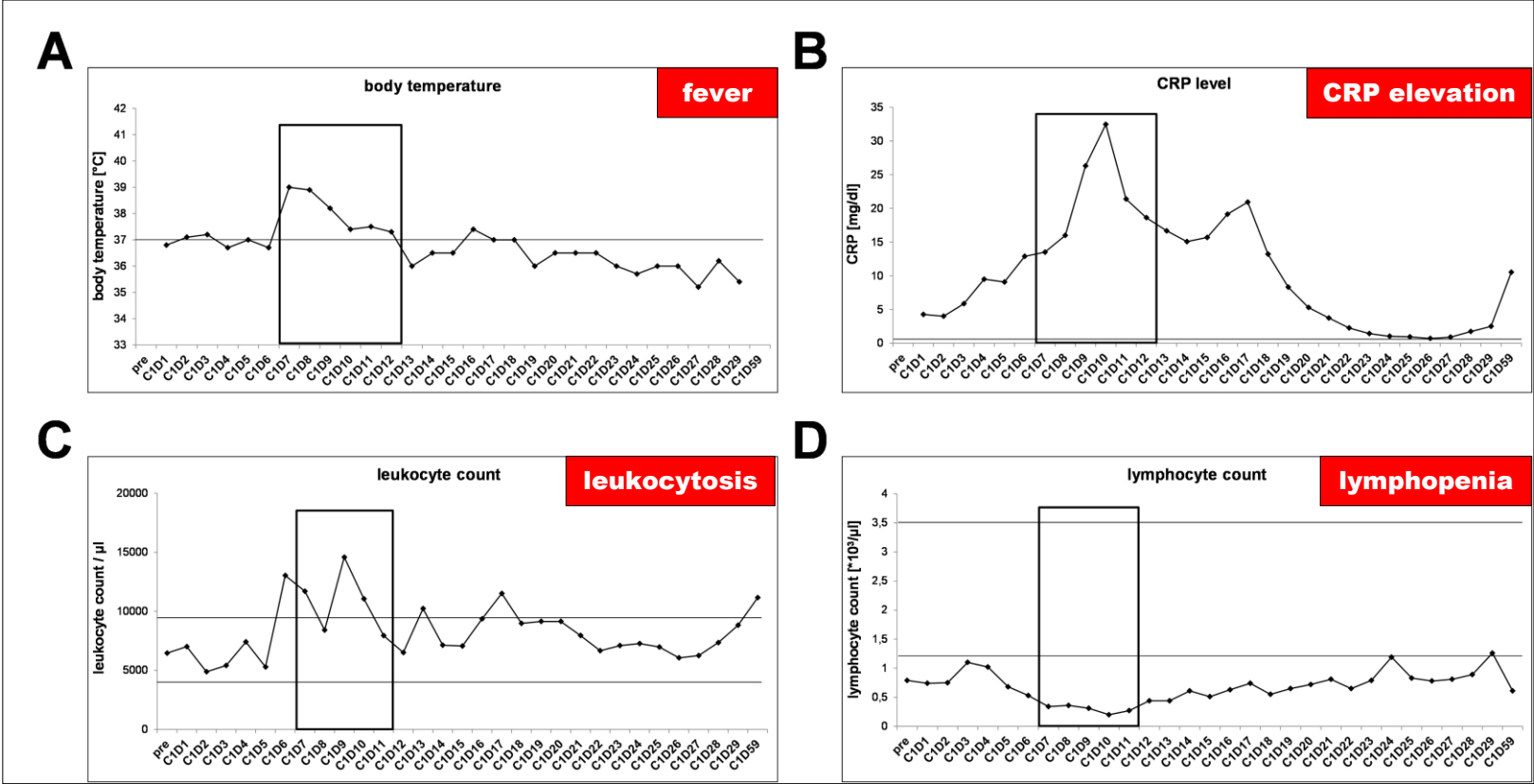
Table S1. GL-ONC1 shedding analysis (patient 01)

Treatment days	urine	sputum	anal swab	full blood	blood cells	blood cell lysates
pre	neg.	neg.	neg.	neg.	neg.	neg.
C1D1	neg.	neg.	neg.	neg.	neg.	neg.
C1D2	neg.	neg.	neg.	neg.	neg.	neg.
C1D3	neg.	neg.	neg.	neg.	neg.	neg.
C1D5	neg.	neg.	neg.	a	a	a
C1D8	neg.	neg.	neg.	neg.	neg.	neg.
C1D9	a	a	a	neg.	neg.	neg.
C1D10	neg.	neg.	neg.	neg.	neg.	neg.
C1D11	a	a	a	neg.	neg.	neg.
C1D12	neg.	neg.	neg.	neg.	neg.	neg.
C1D13	a	a	a	neg.	neg.	neg.
C1D14	a	a	a	neg.	neg.	neg.
C1D15	neg.	neg.	neg.	neg.	neg.	neg.
C1D16	a	a	a	neg.	neg.	neg.
C1D22	neg.	neg.	neg.	neg.	neg.	neg.
C1D59	neg.	neg.	neg.	neg.	neg.	neg.

<sup>a</sup> not analysed at that time point

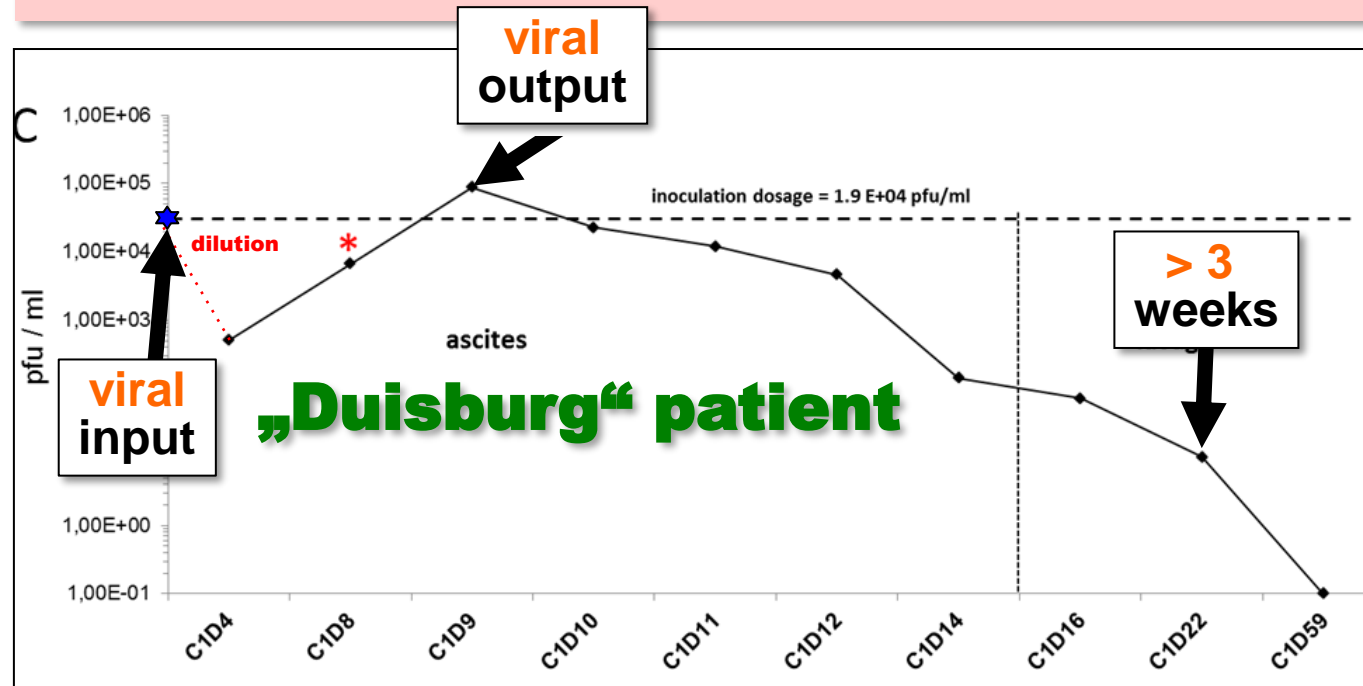
# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

## Inflammatory response



# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

## Time pattern of *in-patient* virus production

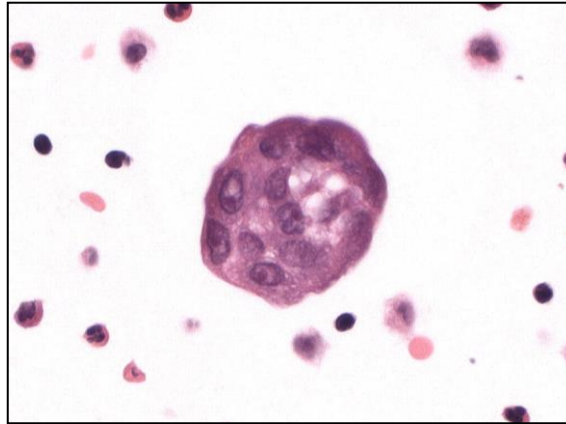


→ **Lowest GL-ONC1 virus dosage ( $10^7$  pfu)**  
**sufficient to achieve a prolonged**  
**"in patient" generation of new viral particles**

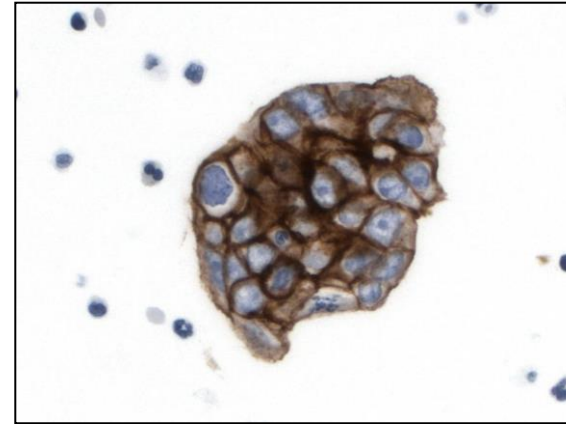


# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

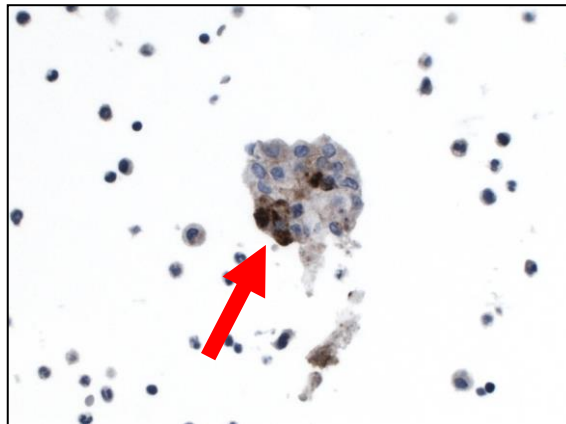
➔ Direct evidence of tumor cell colonisation



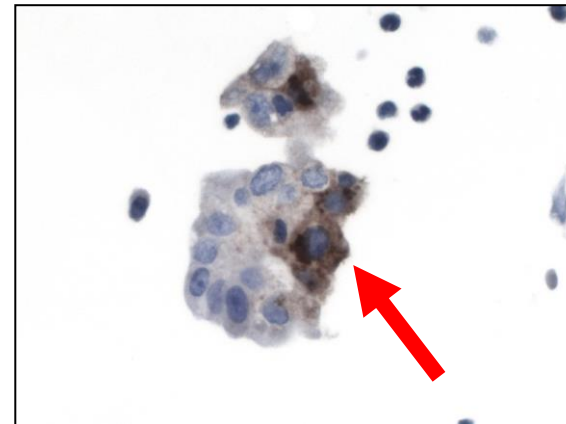
HE (400x); day 5 liquid (ascites) biopsies



BerEp4 (400x)



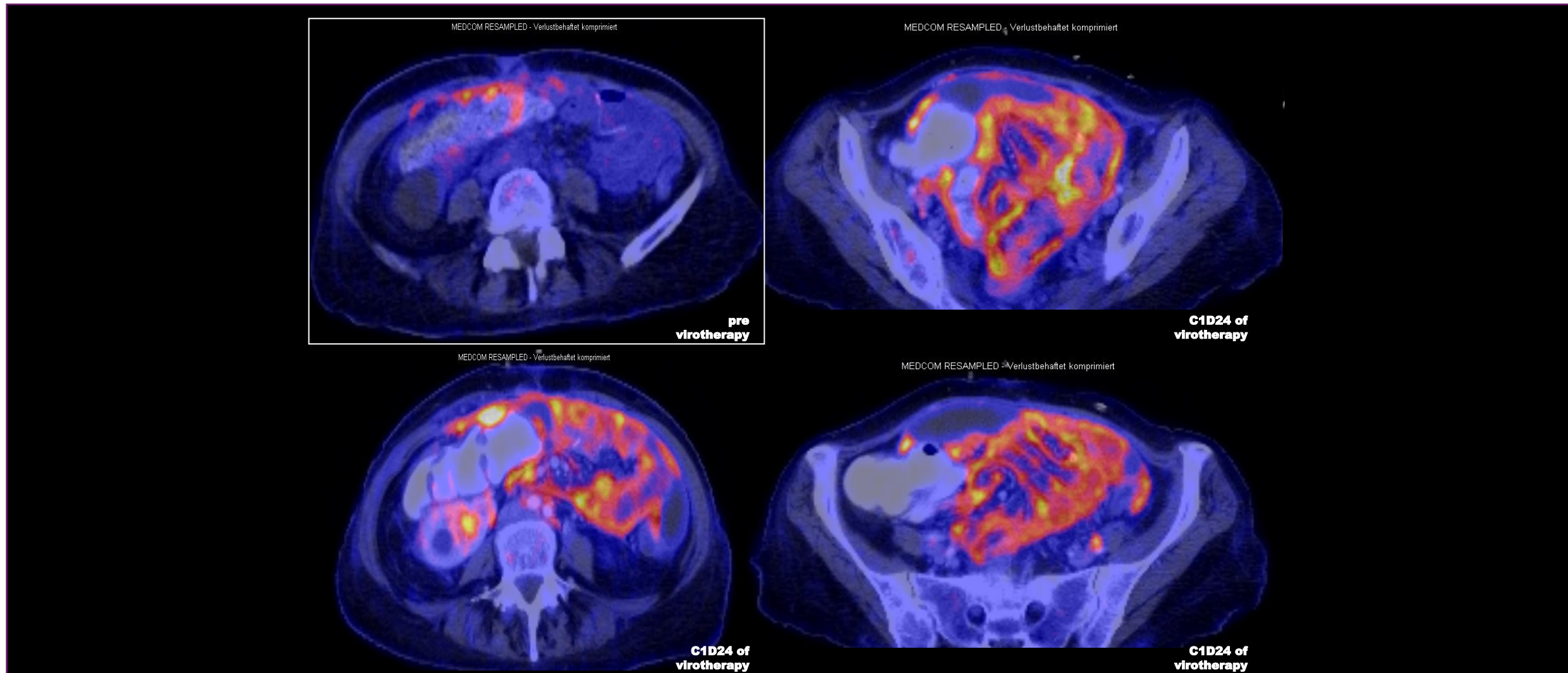
Vacc (400x)



Vacc (630x)

Clin Cancer Res; 24(18) September 15, 2018

# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis



Clin Cancer Res; 24(18) September 15, 2018

# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis



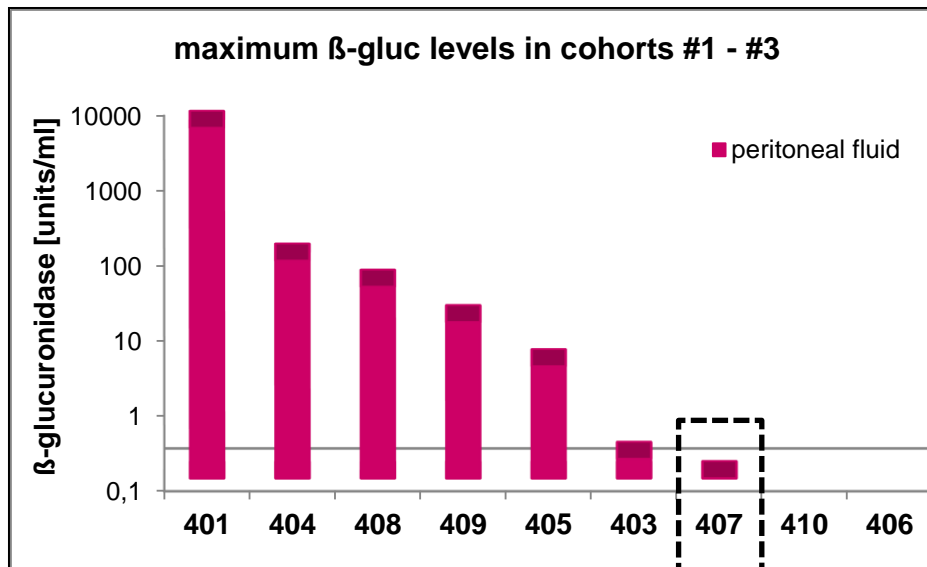
study patient with no extraperitoneal tumor

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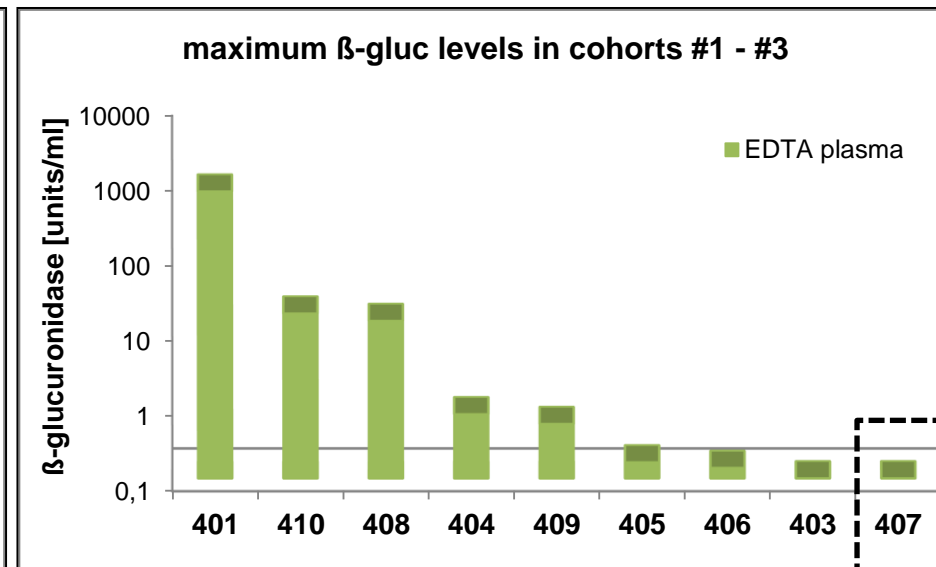


# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

→ Efficient **oncolysis** in 8 out of 9 study patients



non-responder  
patient

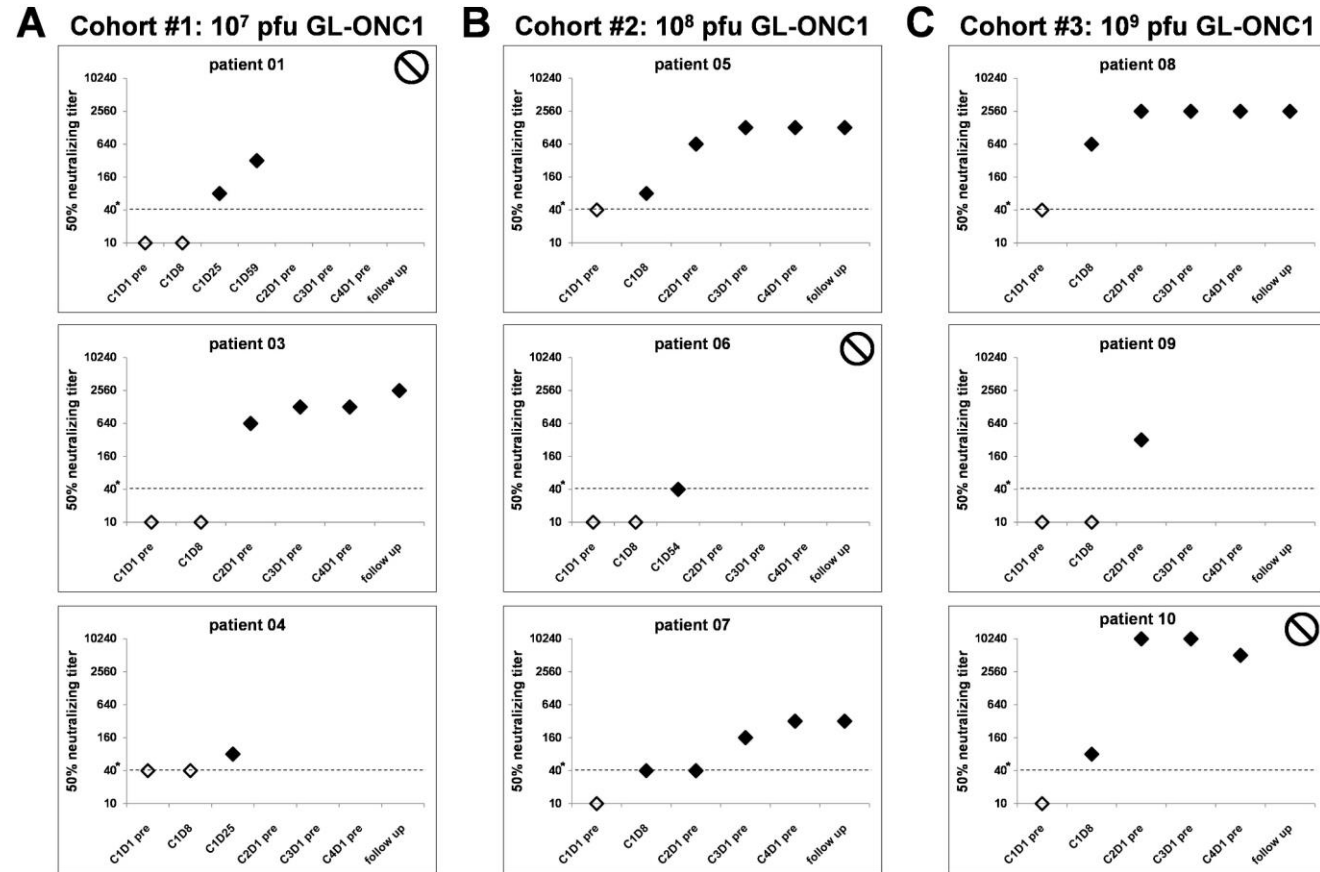


non-responder  
patient

→ **90% oncolysis efficiency (cycle 1)**

# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

## Development of neutralizing activities against GL-ONC1




# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

Dosage of GL-ONC1	Analysis of tumor response				Dosage s ( $\Sigma = 24$ )	Months since last dosage *	RECIST 1.1 (prim. target lesions)	CHOI (target lesions)	Status
	Pt. ID	Age	Tumor entity	Vacc.					
1 x 10 <sup>7</sup> pfu (cohort 1)	401	62	gastric	-	1	32	n.d.	n.d.	---
	2.7.2012 = C1D1 7.1.2021 = †	403	mesothelioma	+	4	<b>disease stabilization for 9 years</b>			
	404	47	gastric	+	1	29	n.d.	n.d.	---
1 x 10 <sup>8</sup> pfu (cohort 2)	405	62	ovarian	+	4	23	PD°	PD°	---
	406	40	ovarian	-	1	22	n.d.	n.d.	on CTx
	407	55	ovarian	+	4	19	SD°	PD°	on CTx
1 x 10 <sup>9</sup> pfu (cohort 3)	408	65	mesothelioma	+	4	15	PD°	PD°	on CTx
	409	68	CUP (adeno)	+	2	16	SD+	PD+	---
	410	39	mesothelioma	-	3	15	SD+	PR+	---

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# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

Vaccinia virus GL-ONC1 (i.p.) in peritoneal carcinomatosis		
<div>SUMMARY</div> <div></div>		PROOF-OF-PRINCIPLE
	STEP 1	<input checked="" type="checkbox"/> Tumor cell colonization
	STEP 2	<input checked="" type="checkbox"/> In-patient virus replication
	STEP 3	<input checked="" type="checkbox"/> Tumor cell oncolysis
	STEP 4	<input checked="" type="checkbox"/> Anti-viral immune response
	Overall	<input checked="" type="checkbox"/> Safety

# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input type="checkbox"/>	Active, not recruiting	<a href="#">GL-ONC1 Oncolytic Immunotherapy in Patients With Recurrent or Refractory Ovarian Cancer</a>	<ul style="list-style-type: none"> <li>Ovarian Cancer</li> <li>Peritoneal Carcinomatosis</li> <li>Fallopian Tube Cancer</li> </ul>	<ul style="list-style-type: none"> <li>Biological: <b>GL-ONC1</b> alone, or in combination with chemotherapy with or without bevacizumab</li> </ul>	<ul style="list-style-type: none"> <li>Gynecologic Oncology Associates Newport Beach, California, United States</li> <li>AdventHealth Cancer Institute Orlando, Florida, United States</li> </ul>
2	<input type="checkbox"/>	Terminated	<a href="#">Safety and Effect of GL-ONC1 Administered IV Prior to Surgery to Patients With Solid Organ Cancers Undergoing Surgery</a>	<ul style="list-style-type: none"> <li>Solid Organ Cancers</li> </ul>	<ul style="list-style-type: none"> <li>Biological: <b>GL-ONC1</b></li> </ul>	<ul style="list-style-type: none"> <li>UC San Diego Moores Cancer Center La Jolla, California, United States</li> </ul>
3	<input type="checkbox"/>	Active, not recruiting	<a href="#">Intra-pleural Administration of GL-ONC1, a Genetically Modified Vaccinia Virus, in Patients With Malignant Pleural Effusion: Primary, Metastases and Mesothelioma</a>	<ul style="list-style-type: none"> <li>Lung Cancer</li> </ul>	<ul style="list-style-type: none"> <li>Biological: <b>GL-ONC1</b></li> </ul>	<ul style="list-style-type: none"> <li>Memorial Sloan Kettering Cancer Center New York, New York, United States</li> </ul>
4	<input type="checkbox"/>	No longer available	<a href="#">Expanded Access to Provide GL-ONC1 for the Treatment of Advanced Cancers With No Standard of Care</a>	<ul style="list-style-type: none"> <li>Advanced Stage Cancer (Solid Tumor Disease for 4 Patients)</li> <li>Acute Myeloid Leukemia (6 Patients)</li> </ul>	<ul style="list-style-type: none"> <li>Biological: <b>GL-ONC1</b></li> </ul>	<ul style="list-style-type: none"> <li>Florida Hospital Cancer Institute Orlando, Florida, United States</li> </ul>
5	<input type="checkbox"/>	Completed	<a href="#">A Study of GL-ONC1, an Oncolytic Vaccinia Virus, in Patients With Advanced Peritoneal Carcinomatosis</a>	<ul style="list-style-type: none"> <li>Peritoneal Carcinomatosis</li> </ul>	<ul style="list-style-type: none"> <li>Biological: <b>GL-ONC1</b></li> </ul>	<div>NCT01443260 (phase 1b)</div> <ul style="list-style-type: none"> <li>University Hospital Tuebingen Tuebingen, Germany</li> </ul>
6	<input type="checkbox"/>	Completed	<a href="#">Safety Study of Attenuated Vaccinia Virus (GL-ONC1) With Combination Therapy in Head &amp; Neck Cancer</a>	<ul style="list-style-type: none"> <li>Cancer of Head and Neck</li> </ul>	<ul style="list-style-type: none"> <li>Biological: <b>GL-ONC1</b></li> </ul>	<ul style="list-style-type: none"> <li>Moores UC San Diego Cancer Center La Jolla, California, United States</li> </ul>
7	<input type="checkbox"/>	Completed	<a href="#">Safety Study of GL-ONC1, an Oncolytic Virus, in Patients With Advanced Solid Tumors</a>	<ul style="list-style-type: none"> <li>Advanced Cancers (Solid Tumors)</li> </ul>	<ul style="list-style-type: none"> <li>Biological: <b>GL-ONC1</b></li> </ul>	<ul style="list-style-type: none"> <li>Royal Marsden Hospital Surrey, United Kingdom</li> </ul>

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input type="checkbox"/>	Recruiting	<a href="#">Efficacy &amp; Safety of Ovi-Vec and Platinum-doublet + Bevacizumab Compared to Platinum-doublet + Bevacizumab in Platinum-Resistant/Refractory Ovarian Cancer (OnPrime, GOG-3076)</a>	<ul style="list-style-type: none"> <li>Platinum-resistant Ovarian Cancer</li> <li>Platinum-refractory Ovarian Cancer</li> <li>Fallopian Tube Cancer</li> <li>(and 4 more...)</li> </ul>	<ul style="list-style-type: none"> <li>Biological: olvimulogene nanivacirepvec</li> <li>Drug: Platinum chemotherapy: carboplatin (preferred) or cisplatin</li> <li>Drug: Non-platinum chemotherapy: Physician's Choice of gemcitabine, taxane (paclitaxel, docetaxel or nab-paclitaxel) or pegylated liposomal doxorubicin</li> <li>Drug: Bevacizumab (or biosimilar)</li> </ul>	<ul style="list-style-type: none"> <li>AdventHealth Cancer Institute Orlando, Florida, United States</li> </ul>

# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

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2	<input type="checkbox"/>	Terminated	<a href="#">Safety and Effect of GL-ONC1 Administered IV Prior to Surgery to Patients With Solid Organ Cancers Undergoing Surgery</a>	<ul style="list-style-type: none"> <li>Solid Organ Cancers</li> </ul>	<ul style="list-style-type: none"> <li>Biological: <b>GL-ONC1</b></li> </ul>	<ul style="list-style-type: none"> <li>UC San Diego Moores Cancer Center La Jolla, California, United States</li> </ul>
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6	<input type="checkbox"/>	Completed	<a href="#">Safety Study of Attenuated Vaccinia Virus (GL-ONC1) With Combination Therapy in Head &amp; Neck Cancer</a>	<ul style="list-style-type: none"> <li>Cancer of Head and Neck</li> </ul>	<ul style="list-style-type: none"> <li>Biological: <b>GL-ONC1</b></li> </ul>	<ul style="list-style-type: none"> <li>Moores UC San Diego Cancer Center La Jolla, California, United States</li> </ul>
7	<input type="checkbox"/>	Completed	<a href="#">Safety Study of GL-ONC1, an Oncolytic Virus, in Patients With Advanced Solid Tumors</a>	<ul style="list-style-type: none"> <li>Advanced Cancers (Solid Tumors)</li> </ul>	<ul style="list-style-type: none"> <li>Biological: <b>GL-ONC1</b></li> </ul>	<ul style="list-style-type: none"> <li>Royal Marsden Hospital Surrey, United Kingdom</li> </ul>


  

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	<input type="checkbox"/>	Recruiting	<a href="#">Efficacy &amp; Safety of Ovi-Vec and Platinum-doublet + Bevacizumab Compared to Platinum-doublet + Bevacizumab in Platinum-Resistant/Refractory Ovarian Cancer (OnPrime, GOG-3076)</a>	<ul style="list-style-type: none"> <li>Platinum-resistant Ovarian Cancer</li> <li>Platinum-refractory Ovarian Cancer</li> <li>Fallopian Tube Cancer</li> <li>(and 4 more...)</li> </ul>	<ul style="list-style-type: none"> <li>Biological: olvimulogene nanivacirepvec</li> <li>Drug: Platinum chemotherapy: carboplatin (preferred) or cisplatin</li> <li>Drug: Non-platinum chemotherapy: Physician's Choice of gemcitabine, taxane (paclitaxel, docetaxel or nab-paclitaxel) or pegylated liposomal doxorubicin</li> <li>Drug: Bevacizumab (or biosimilar)</li> </ul> <p><b>NCT02759588 (phase 2 part)</b></p>	<ul style="list-style-type: none"> <li>AdventHealth Cancer Institute Orlando, Florida, United States</li> </ul>

# IMMUNOVIROTHERAPY → other clinical studies

**NCT02759588**


Gynecologic Oncology 163 (2021) 481–489



Contents lists available at ScienceDirect

**Gynecologic Oncology**

journal homepage: [www.elsevier.com/locate/ygyno](http://www.elsevier.com/locate/ygyno)



## A phase 1b study of intraperitoneal oncolytic viral immunotherapy in platinum-resistant or refractory ovarian cancer<sup>1</sup>

Madhavi Manyam<sup>a</sup>, Amanda J. Stephens<sup>a</sup>, Jessica A. Kennard<sup>a</sup>, Jane LeBlanc<sup>b</sup>, Sarfraz Ahmad<sup>a,\*</sup>, James E. Kendrick<sup>a</sup>, Robert W. Holloway<sup>a</sup>

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<sup>b</sup> Office of Clinical Research, AdventHealth Cancer Institute, Orlando, FL 32804, USA

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**HIGHLIGHTS**    **Olvi-Vec (USAN: olvimulogene nanivacirepvec; laboratory name: GLV-1 h68; also known as GL-ONC1)**

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- Intraperitoneal Olvi-Vec was well tolerated in this phase 1 study of platinum-resistant/refractory ovarian cancer.
- Nausea, fever, and abdominal distension were the most common treatment-related adverse events.
- The ORR with monotherapy Olvi-Vec was 9%, stable disease ≥15 weeks was 46%, median PFS was 15.7 (95% CI: 5.7–34.5) weeks.
- Three patients had extended overall survival (33.6 to 59+ months) following additional cytotoxic therapies.
- Virus-induced tumor-specific T-cell activation in blood and CD8+ T-cell infiltration into tumor tissue were demonstrated.

**OUTLOOK based on phase 1b data:**

**Recommended phase 2 (RP2) dosage =  
3 × 10<sup>9</sup> pfu/day i.p. on two consecutive days**



# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

IGCS20\_1308 phase-2 trial (NCT02759588)

12 **ONCOLYTIC VACCINIA (OLVI-VEC) PRIMED  
IMMUNOCHEMOTHERAPY IN PLATINUM-RESISTANT/  
REFRACTORY OVARIAN CANCER**

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<sup>2</sup>M King, <sup>1</sup>J LeBlanc, <sup>2</sup>K Lopez, <sup>1</sup>M Manyam, <sup>1</sup>N McKenzie, <sup>2</sup>K Mori, <sup>1</sup>A Stephens,  
<sup>1</sup>S Ahmad. <sup>1</sup>AdventHealth Cancer Institute, USA; <sup>2</sup>Gynecologic Oncology Associates, USA

10.1136/ijgc-2020-IGCS.12

**2 days of  $3 \times 10^9$  pfu Olvi-Vec i.p.** followed by intravenous carboplatin-doublet (CD)  $\pm$  bevacizumab (Bev); then, maintenance with single-agent therapies  $\pm$  Bev; 27 patients enrolled

- majority of patients achieved RECIST response with median PFS exceeding their prior line of therapy

full publication awaited

# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

## Clinical Studies

## Cancer Research

### Oncolytic Measles Virus Expressing the Sodium Iodide Symporter to Treat Drug-Resistant Ovarian Cancer

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NCT00408590

#### Abstract

Edmonston vaccine strains of measles virus (MV) have significant antitumor activity in mouse xenograft models of ovarian cancer. MV engineered to express the sodium iodide symporter gene (MV-NIS) facilitates localization of viral gene expression and offers a tool for tumor radiovirotherapy. Here, we report results from a clinical evaluation of MV-NIS in patients with taxol- and platinum-resistant ovarian cancer. MV-NIS was given intraperitoneally every 4 weeks for up to 6 cycles. Treatment was well tolerated and associated with promising median overall survival in these patients with heavily pretreated ovarian cancer; no dose-limiting toxicity was observed in 16 patients treated at high-dose levels ( $10^8$ – $10^9$  TCID<sub>50</sub>), and their median overall survival of 26.5 months compared favorably with

other contemporary series. MV receptor CD46 and nectin-4 expression was confirmed by immunohistochemistry in patient tumors. Sodium iodide symporter expression in patient tumors after treatment was confirmed in three patients by <sup>123</sup>I uptake on SPECT/CTs and was associated with long progression-free survival. Immune monitoring posttreatment showed an increase in effector T cells recognizing the tumor antigens IGFBP2 and FR $\alpha$ , indicating that MV-NIS treatment triggered cellular immunity against the patients' tumor and suggesting that an immune mechanism mediating the observed antitumor effect. Our findings support further clinical evaluation of MV-NIS as an effective immunovirotherapy. *Cancer Res*; 75(1); 22–30. ©2014 AACR.

All patients (n=16) underwent laparoscopy for placement of an intraperitoneal catheter. MV-NIS was infused in a volume of 500 mL over 30 minutes. Treatment was repeated monthly for up to 6 cycles. Dose levels:  $10^8$  and  $10^9$  TCID<sub>50</sub>.

#### RESULTS:

- intraperitoneal administration of MV-NIS is safe
- compelling survival outcomes were observed, further prospective testing is warranted

# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

Molecular Therapy  
**Oncolytics**  
Original Article

Molecular Therapy: Oncolytics Vol. 25 June 2022



## Intraperitoneal oncolytic virotherapy for patients with malignant ascites: Characterization of clinical efficacy and antitumor immune response

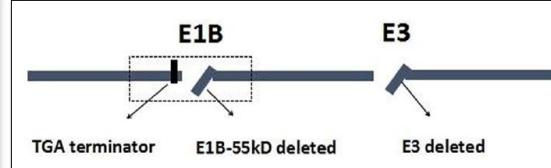
Yalei Zhang,<sup>1,2,3</sup> Ling Qian,<sup>1,2,3</sup> Kun Chen,<sup>1,2</sup> Sijia Gu,<sup>1,2</sup> Jia Wang,<sup>1,2</sup> Zhiqiang Meng,<sup>1,2</sup> Ye Li,<sup>1,2</sup> and Peng Wang<sup>1,2</sup>

<sup>1</sup>Department of Integrative Oncology, Fudan University Shanghai Cancer Center, 270 Dong An Road, Shanghai 200032, China; <sup>2</sup>Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

Oncolytic viruses mediate antitumor responses through direct tumor cell lysis and induction of host antitumor immunity. However, the therapeutic efficacy of oncolytic viruses against malignant ascites has rarely been explored. This study aimed to evaluate the efficacy, safety, and immunomodulatory effect of an intraperitoneal injection of human type 5 recombinant adenovirus (called H101) against malignant ascites. **Forty patients with malignant ascites were recruited and treated with intraperitoneal H101 in the Fudan University Shanghai Cancer Center.** The 4-week clinical responses were determined by an objective assessment of ascites volume change. The ascites response rate and ascites control rate were 40% (16/40) and 75% (30/40), respectively. The major adverse events following intraperitoneal H101 administration were mild-to-moderate abdominal pain (8/40, 20.0%) and fever (11/40, 27.5%); no grade III/IV adverse events were observed. Mass cytometry and immunocytological analysis at baseline, and days 7 and 14 post-treatment showed that intraperitoneally injected H101 led to marked tumor cell depletion, increased dendritic cell and CD8<sup>+</sup> T cell densities. H101-mediated tumor-specific immune activation on day 14 post-treatment was further identified by enzyme-linked immunospot assay. **In conclusion, intraperitoneal H101 administration was well tolerated and effective in treating malignant ascites; thus, its immune activation ability may be a promising tool in combination with immunotherapy.**

on the role of VEGF in promoting ascites production.<sup>10–12</sup> Catumaxomab, a chimeric antibody targeting CD3 and epithelial cell adhesion molecule (EPCAM), has been reported to improve the quality of life in patients with MA.<sup>13</sup> However, the risk of severe adverse effects, including fatal bowel perforation for the potent VEGF inhibitor aflibercept,<sup>11,14</sup> and hepatobiliary toxicity for catumaxomab, has limited the application of these treatments in patients with heavy disease burden.<sup>15</sup> Therefore, the identification of new treatment strategies against MA is critical.

Oncolytic viruses (OVs) are emerging therapeutic agents that can selectively target cancer cells and trigger immune activation. The application of OVs in combination with cancer immunotherapy in various solid tumors has become a promising therapeutic strategy.<sup>16–18</sup> Although extensive clinical data for OVs in treating solid tumors have been reported, studies on the therapeutic efficacy of OVs in treating MA are limited. The dense stroma and hypoxic microenvironment within a solid tumor mass limit the effectiveness of viral infection and intratumoral penetration of OVs.<sup>19,20</sup> In contrast, the microenvironment within MA may create a favorable condition for OV infection and OV-induced immune activation, indicating the feasibility of OVs to treat peritoneal malignancies and MA. A preclinical study reported that vesicular stomatitis virus, another type of OV, exerted a suppression effect on cancer cells from ascites and alleviated ascites accumulation in MA models.<sup>21</sup> Intraperitoneal

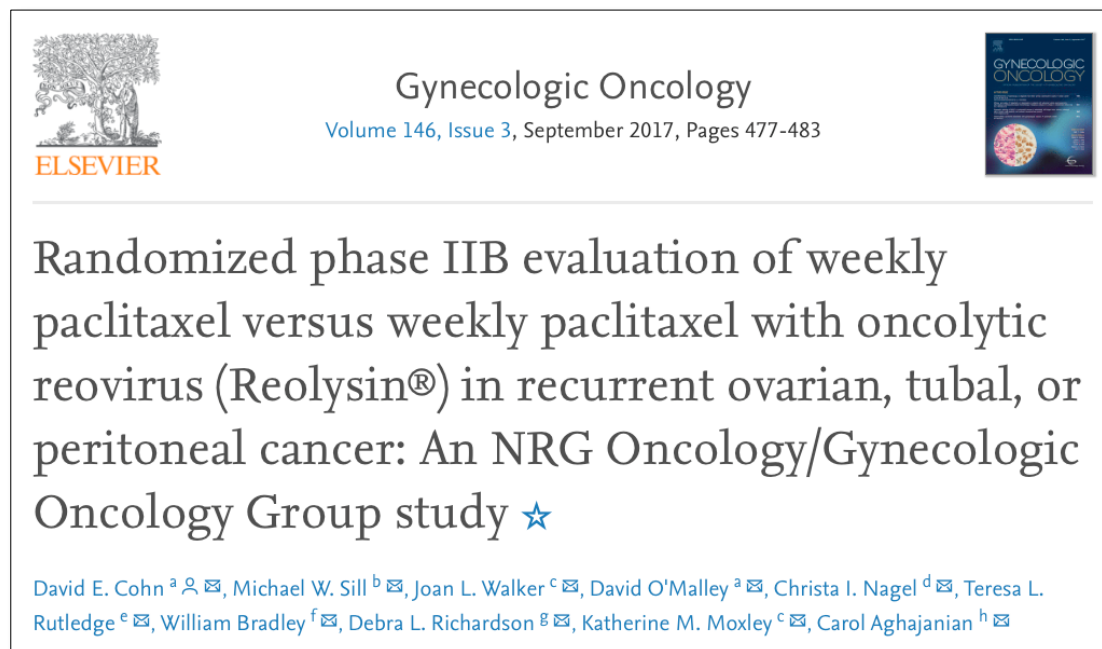


**H101 (Oncorine®)**, a recombinant oncolytic type 5 adenovirus with specific genetic modifications:

- the gene encoding the anti-apoptotic E1B55K protein that inactivates p53 was deleted, enabling selective replication only in cancer cells with aberrant p53 function
- a partial E3 region was also deleted to improve the safety of H101
- on days 1 and 3, H101 is injected i.p. through a peritoneal drainage catheter
- $5.0 \times 10^{11}$  vp for a small amount ascites
- $1 \times 10^{12}$  vp -  $1.5 \times 10^{12}$  vp for medium amount ascites
- $2 \times 10^{12}$  vp for the massive amount ascites

**A prospective Phase II Study of Intraperitoneal Injection of Oncolytic Viruses H101 for Patients With Refractory Malignant Ascites (NCT04771676)**

# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis



REOVIRUS,  $3 \times 10^{10}$  TCID<sub>50</sub>/day was administered IV over 60 min (on days 1-5 of each cycle after paclitaxel); paclitaxel was administered at 80 mg/m<sup>2</sup> as a continuous IV infusion on days 1, 8, 15 every 4 weeks.

## NEGATIVE RESULT

Addition of REOVIRUS to weekly paclitaxel in women with recurrent ovarian cancer led to NO improvement in PFS or other measures of patient outcome.

**Results from this study do NOT support further investigation of this combination in this patient population at these doses and schedule.**

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# IMMUNOVIROTHERAPY in Peritoneal Carcinomatosis

## SUMMARY

- oncolytic viruses effectively infect and destroy peritoneal cancer cells
- many viruses such as vaccinia virus, measles virus, adenovirus can be used
- anti-tumoral / anti-viral immune responses are triggered
- regularly, a virus-induced peritonitis is triggered
- i.p. application can be performed safely with only minor transient side effects
- combination with other anti-cancer medications is feasible
- further preclinical / clinical studies are required



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**NOVEL THERAPEUTIC AGENTS FOR PLEURA & PERITONAL CANCERS**

# Oncolytic Viruses and Combination Immunotherapy Strategies for GI Peritoneal Carcinomatosis

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*Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura*