Trials and Tribulations of Management of Peritoneal Metastasis from Gastric Cancer

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Disclosures

**FUNDING**

- **Department of Defense CA180425 (PI)**, 2019-2021: “Discovery of Immune Biomarkers That Predict Response to a Novel Chimeric Immuno-Oncolytic Virus Encoding Anti-PD-L1 in Gastric Cancer Peritoneal Carcinomatosis”

- **SU2C Gastric Cancer Interception Award (PI: A. Chen & S. Rhyeom; COH Site PI: Woo)** 2020-2022: Early Detection of Diffuse and Intestinal Gastric Cancer

- **Department of Surgery Research Support (PI)** 2021-2022: Translation of oncolytic viruses in the treatment of advanced GI cancers; and development of a precision oncology platform for the personalized therapy for gastric cancer peritoneal carcinomatosis

**Scientific Advisory Board:** Imugene LTD

**Consulting:** J&J | ETHICON

**Acknowledgement:** CF33-hNIS-antiPDL1 (CHEKVAC) and CF33-hNIS (VAXINIA), the CF33-oncolytic viruses discussed in this presentation has been licensed to Imugene, LTD.
“YANGHEE” → YANG = Bright & HEE=Hope

- Surgery Residency at Columbia University Medical Center, NYP
- Research Fellowship at MSKCC, NYC
- Clinical Fellowship in Upper GI/Robotic Surgery at Yonsei University, Severance Hospital, S. Korea
- Assistant Professor/Director, Gastric Cancer Program at CUMC/NYP
- Joined City of Hope 7/2015 to direct the surgical innovation program and lead gastric cancer care and build international collaborations
Greetings from Our Multidisplinary Team at COH

• The GCWG at COH is a multidisciplinary and translational team of experts in stomach and gastroesophageal junction tumors
• Building clinical and research collaborations to optimized GC care and find more and better cures
Greetings from Gastric Cancer Session
Faculty & Friends at the 3rd ISSPP Congress on October 13-14, 2022
In Pursuit of More Cures for All Patients with Gastric Cancer

- Goal: to achieve long-term survival and to preserve or provide improved QoL
- By bringing the best of scientific discoveries and surgical innovation to GC care

The diagnosis of GC begins patient’s war to protect life.

We fight different battles to find that winning strategy for one – but together we fight for more cures for all
Horizon of Hope for Stomach Cancer Patients

- GC outcomes are improving in US
- GC outcomes can continue to improve
  - More accurate staging
  - Better locoregional surgical control
  - More and better systemic options
  - Better multimodal treatment strategies
  - Tumor-specific, patient tailored multidisiplinary best practices
- Unfortunately, survival for Stage IV patients remains poor and unacceptable
- We need more and better cures

<table>
<thead>
<tr>
<th>STAGE</th>
<th>5-yr Survival 2012</th>
<th>5 yr Survival 2017</th>
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<tr>
<td>Stage IA</td>
<td>71%</td>
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<tr>
<td>Stage IV</td>
<td>4%</td>
<td>5%</td>
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<tr>
<td>OVERALL</td>
<td>25%</td>
<td>31%</td>
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</table>

5-YEAR OVERALL SURVIVAL for Stomach Cancer Patients in the U.S. BY NATIONAL CANCER DATABASE has reached = 42% (2014-2021)
Best Practice Management Strategies for GC

EGC (cT1a-b, N0)
- EMR / ESD
- Gastrectomy D1+ LND

Locally AGC (cT2 or N+ and M0)
- MSI High
- MSS

+/- Neoadjuvant Therapy

Radical Gastrectomy
D2 NLD

Radical Gastrectomy,
D2 LND &
Combined resection

+/- Adjuvant Therapy

Met GC (M1)
- Chemotherapy
- Targeted therapy
- Immunotherapy
- Palliative
- Radiation?
- Palliative Surgery
- Conversion Surgery
- Supportive Care

Clinical Trials & Precision Oncology → More and Better Cures
Systemic Therapies in GC with PM

- Over 94 randomized control trials have achieved significant improvement in GC
- But failures of current therapy in the peritoneum are high in resectable GC patients
- Rarely, are effects of systemic therapy on PM specifically measured or reported in clinical trial → leaves many questions unanswered
- Few PM directed trial designs and PM specific endpoints exist in clinical trial literature

Survival in Months compared to Best Supportive Care (4 months)

- 5-FU Alone: 7.0 mo
- Docetaxel + Cisplatin + 5-FU: 9.2 mo
- Capecitabine + Cisplatin (XP): 10.5 mo
- 5-FU + Oxaliplatin (FLO): 10.7 mo
- Epirubicin + Oxaliplatin Capecitabine (EOX): 11.2 mo
- Trastuzumab + CDDP + 5FU or Capcitabine: 13.8 mo
- Overall Response Rate: ~17 mo

Overall Response Rate
- 2021 Pembrolizumab + trastuzumab + fluorouracil + cisplatin or capecitabine + oxaliplatin
- 2017-2018 Pembrolizumab MSI-H or dMMR solid tumors

Pembrolizumab
- 74% in pembro arm
- 52% in placebo arm (P<0.0001)
PM is Leading Site of Metastases and Cause of Therapeutic Failure in GC

PM is the most common site of distant metastases in GC
60% at autopsy

Leading distant metastatic site at time of initial diagnosis
43% in the U.S. GC patients

Highest rate of recurrent disease occurs in the peritoneum
56% after FLOT + gastrectomy with D2

OVERALL SURVIVAL = 3.3 TO 11.0 MONTHS
Disparities in GCPM

- **Younger Adults** under 40 years old more likely to present with synchronous PM (32.0% vs. 10.5–25.9%, \( P < 0.0001 \)), and have worse OS. CCR (2000–2012)

- **Hispanic Americans** present with 14.8% PM vs 9.7% in Asian Am. vs. 7.5% in NHW. CCR (2004-2014)

- Disease often not detected on cross-sectional imaging and not measurable for RECIST based clinical trials

- **An urgent unmet cancer care need of health disparities**

Kim Y et al. Epidemiol Health. 2015; Kahn et al 2019; Li et al 2022
Barriers To Treatment of Peritoneal Carcinomatosis

- PC poses distinct therapeutic challenges
  - Difficult to diagnose → Delay in identification until high tumor burden can be seen on CT or becomes symptomatic
  - Blood-peritoneal barrier protect peritoneal tumors from systemic (IV) therapy can’t reach PM easily
  - Immunosuppressive environment that prevent effective drug delivery and promote drug resistance
  - Disease often not measurable → Patients do not qualify for clinical trials
  - Thus, little is known about the effects of established drugs or novel therapies in PC patients
Diagnostic Laparoscopy for Peritoneal Staging

- Positive peritoneal cytology in gastric cancer is classified as M1 disease by the 7th Edition of American Joint Committee on Cancer staging system

- NCCN recommends staging laparoscopy with cytology for clinical stage T1b or greater

- Best performed prior to neoadjuvant chemotherapy
- Repeated for patients with low PCI score after systemic therapy if considering conversion surgery
- Surveillance laparoscopy in at-risk patients for peritoneal metastases after curative intent surgery
- As tolerated if peritoneal tumor biopsy for genomic testing would benefit development of therapeutic strategy

Pre-neoadjuvant therapy in patient with cT3N1M0 demonstrating diffuse peritoneal carcinomatosis. Photo from OR 2020

A lower PCI score has been associated with better prognosis, and patients with limited peritoneal metastases might be appropriate candidates for cytoreductive surgery and hyperthermic intraperitoneal Chemotherapy (HIPEC); however, evidence is limited and risks must be balanced carefully against uncertain benefits.
Treatment Strategies for GC PM

**Systemic chemo plus CRS**

Multidisciplinary treatment for patients with stage IV gastric cancer: the role of conversion surgery following chemotherapy

Beom, SH et al. BMC Cancer, 2018
South Korea

**Systemic chemo plus one-time HIPEC (one or two chemo agents) plus CRS**

Phase II Trial of Laparoscopic Hyperthermic Intraperitoneal Chemoperfusion for Peritoneal Carcinomatosis or Peritoneal Cytology in Patients with Gastric Adenocarcinoma

Badgewell, B et al. ASO, 2020

**Systemic chemo plus repeat HIPEC (two chemo agents)**

The median OS
- 5 of 19 patients received CRS
- From diagnosis of PC = 30.2 months
- From the first laparoscopic HIPEC was 20.3 months.

All patients were given systemic therapy prior to HIPEC

Rau, B et al. Gastric Cancer, 2019
Germany

**The median OS was 13.0 months.**

- PCI 0-6 = 18 mo
- PCI 7-15 = 12 mo
- PCI 16-39 = 5 months (p = 0.002)

PCI score matters and is prognostic

Systemic therapy can improve PC
38 yo M with GC PM Diffuse-Type

- T.L. diagnosed in December 2019 and was given 6-12 months at time of diagnosis
- Sought other opinions and other tx options
- International multi-institutional multidisciplinary strategy was developed

- Systemic therapy → HIPEC x 2 → 3 clinical trials
- Significant QoL decline and complications
- True Warrior in our fight against GC PM
- T.L. lived 2 years and 9 months and leaves behind his wife, 4 yr and 6 yr sons, and sisters and mother
PIPAC Another Option for GCPM?
Emerging Trial Results in PIPAC ISSPP

Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications

Mohammad Alyami, Martin Hüblner, Fabian Grass, Naouel Bakrin, Laurent Villeneuve, Nathalie Laplace, Guillaume Passot, Olivier Vuhan Kepenekian

Current Status

- Over 42 Clinical Trials
- Over 528 GCPM patients treated
- Over 12,500 PIPAC procedures in 40 countries
- 1-12 PIPACs/patient
- Safe and feasible
- 79% stable disease or decreased ascites
- 10-20 months survival
- May prolong survival
- On-going trials in Europe and Singapore

Treatment Strategies

- PIPAC alone or in combination with systemic therapy
  - 1st line = All; 2nd line = Half; 3rd line = Few
  - Goal is to repeat PIPAC every 6–8 weeks for at least three procedures
  - Delay of the systemic chemotherapy is 2 weeks before and after each PIPAC procedure.

Phase I Device Registry trial open in U.S. at COH, Northwell, Mayo Clinic (T. Dellinger, PI)
Co-I at COH – PIPAC for Stomach

Lancet Oncol 2019; 20 e368-77
Clinical Trials of PIPAC in GC

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<td>Adjuvant PIPAC in Gastric Cancer Patients</td>
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<td>Neoadjuvant Chemotherapy With PISOXO for Locally-invaded-gastric Cancer (LIGC)</td>
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<td>Oncological Benefits of Pressurized Intraperitoneal Aerosol Chemotherapy (ePIPAC)</td>
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<td>Pressurized Intraperitoneal Aerosol Chemotherapy (PIPA) in Gastric Cancer</td>
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<td>PIPAC in Multimodal Therapy for Patients With T3-4 Gastric Cancer</td>
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<td>Neoadjuvant Systemic and Peritoneal Chemotherapy for Advanced Gastric Cancer and Primary Peritoneal Neoplasms</td>
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<td>PIPAC for the Treatment of Peritoneal Carcinomatosis</td>
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<td>Study of Efficacy and Safety of PIPAC in Gastric Cancer and Primary Peritoneal Neoplasms</td>
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<td>Pressurized Intraperitoneal Aerosol Chemotherapy (PIPA) and Electrostatic PIPA (ePIPA) With Paclitaxel in Patients With Peritoneal Carcinomatosis</td>
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<td>Pressurized Intraperitoneal Aerosol Chemotherapy (PIPA) in Gastric Carcinomatosis. Phase II Randomized Study</td>
<td>GC and other</td>
<td></td>
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</table>

Total of 16 trials registered on clinicaltrials.gov

- Completed 3
- Recruiting 8
- Active not recruiting 2
- Unknown 2
- Suspended 1
### Indications for GC PC Patients:
- Biopsy proven GC PC
- Progressed on 2-lines of systemic therapy

### Laparoscopic procedure
- Repeat 3 times every 6 weeks
- Short hospital stay ~24 hr

**PI:** T. Dellinger at COH, A. Merchea at Mayo; L. Whalen at Northwell.

**Co-I:** Raoof, Perrelta, Woo
First US GC Patient Undergoing PIPAC with COH TEAM

Extra-abdominal view

Intra-abdominal view

LIMITED BY NO CONCURRENT SYSTEMIC THERAPY

Extra-abdominal view
Proposal for phase I dose-escalation trial to evaluate the safety and tolerability of docetaxel PIPAC in combination with first-line standard of care therapy in gastric cancer patients with peritoneal metastases

Kevin M Sullivan1, Raghav Sundar2, Joseph Chao1, Samuel Kiempner2, Daneng Li1, Alexander Jung1, Sue Chang1, Rifat Mannan1, Paul Frankel1, Wei Peng Yong3, I Benjamin Paz1, Thanh Hue Dellinger1, Mustafa Raoof1, Jimmy So2, Yuman Fong1, Yanghee Woo1

1 City of Hope National Medical Center, Duarte, CA. 2 National University of Singapore. Singapore. Singapore. 3 Massachusetts General Hospital, Boston, MA

BACKGROUND
- Peritoneal metastases (PM) from gastric cancer (GC) often progress within 3 months of standard of care first line systemic chemotherapy
- PIPAC has demonstrated safety in clinical trials in gastric, gynecologic, appendiceal, and colorectal PM outside of the U.S.
- Cisplatin/doxorubicin PIPAC in patients with unresectable GC showed overall survival (OS) of 19 months and 14.3% of patients became resectable with <10% major complications (Alyami M et al. Eur J Surg Oncol 2021)
- A phase II study of cisplatin/doxorubicin PIPAC in 26 patients showed 40% complete response, partial response, or stable disease, including 36% histologic complete or major regression. (Struller F et al. Ther Adv Med Oncol 2019)
- Safety of docetaxel PIPAC in combination with systemic therapy has not been established.

METHODS
- Eligibility: Patients with GC PM who have received ≥ 3 months of first-line therapy consisting of IV oxaliplatin and fluorouracil (5-FU) plus leucovorin +/- trastuzumab or pembrolizumab
- Exclusion criteria: extraperitoneal disease, progression, contraindications for laparoscopy, poor performance status, or bowel obstruction
- Dose escalation schedule follows the 3+3 design (lead-in cohort 50 mg/m2, then 75, 100, and 125 mg/m2) plus SOC chemotherapy

RESULTS
- Primary endpoint: incidence and severity of AEs and dose limiting toxicity (DLT)
- Secondary endpoints:
  - Peritoneal tumor response (by peritoneal regression grade score)
  - PCI score
  - Imaging [RECIST 1.1]
  - Progression free and OS rates
- Exploratory endpoints: Longitudinal blood, urine and tissue specimens collected for translational correlates including pharmacokinetics, circulating biomarkers, immune profiling, and single-cell multi-omics studies.

CONCLUSIONS
The goal of this phase I trial is to evaluate the safety, tolerability and MTD of combination docetaxel PIPAC and systemic therapy for GC PM in the first line setting.

Abstract ID: PAP.2022.0190

Yanghee Woo, MD | yhwoo@coh.org
Hope for More and Better Cures for GC PM

Target the best of science and innovation for the cure and care of patients with GC PM

Type of Therapy
- Surgery
- Regional Therapy
- Systemic Therapy

Type of AGENTS
- Immunotherapy
- Gene Therapy
- Oncolytic Viruses & CAR-T Cell Therapies
- Ablative Therapy?

New Methods of Peritoneal Disease Assessment

New Combination Strategies

Innovative Methods of Drug Delivery

PM Specific Clinical Trial Designs?

PM Specific Clinical Trial Endpoints

Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura
Novel Anti-Cancer Immune Agents For GCPM?

- **Oncolytic Viruses**
  - Naturally occurring or synthetically created viruses that kill cancer
  - Tracks to and infects cancer cells
  - Selectively replicates in and express transgenes in the host cell
  - Alter immune TME
  - Many in clinical trials
  - TVEC only approved OV in US

- **CAR-T Therapy**
  - Chimeric antigen receptor T cell therapy
  - Establishes tumor-targeting T cells by recognizing a specific receptor on the tumor
  - Can regulate T-cell expansion and perseverance

- **Cancer Vaccines**
  - Antigen-specific antibody & adaptive immune responses that target antigen expressing cancer cells
  - Increases neoantigen presentation
  - Long-term memory
  - Potential for treatment and prevention

Images:
- [Imugene, Sidney Australia](https://www.imugene.com)
- [Bioworld.com](https://www.bioworld.com)
Many different oncolytic viruses have long been explored for cancer treatments

Now reemerging as agents of cancer gene therapy
Oncolytic Viruses for Cancer Gene Therapy

- **Inherent properties** for cancer cell targeting
  - Selectively replicate in and lyse cancer cells by utilizing abnormalities in host’s cancer cell genome
  - Stimulate a robustly complex immune response both limiting direct oncolysis and enhancing anti-cancer immunity

- **Genetically engineered** to decrease virulence and improve efficacy
  - Better viral gene editing techniques
  - More efficient OV production
  - Improved understanding of the immune TME
  - Rapidly increasing molecular targets provide enormous opportunity for OV’s to delivery more effective cancer gene therapy

Wan PKT et al. Molecular Therapy, 2020
Strategies to Enhance Anti-Cancer Immunity

• OVs can alter the immune TME by taking over the host’s cancer cell genome to express
  – Immune stimulatory
    ✓ GM-CSF, IL-2, IL-12, TNF-α
  – Immune modulatory
    ✓ anti-PD-1, anti-PD-L1, anti-CTLA4
  – Anti-angiogenic
    ✓ Cytosine deaminase, TK, VEGFR
  – Stromal degradation
    ✓ hyaluronidase, collagenase, and matrix metalloproteinase

• Radiolabeling agents for imaging and therapeutic targeting
  • hNIS (\(^{123}\)I, \(^{124}\)I, \(^{125}\)I, \(^{131}\)I, \(^{99m}\)TcO\(_4\))

Oncolytic Viruses for Cancer Gene Therapy

2005 in China Oncorine (H101) – genetically engineered adenovirus, the world’s first recombinant oncolytic virus to gain regulatory approval for SCC of H&N/esophagus; planned trial in lung ca: deletions of E1B-55k and viral gene E3

2015 in USA TVEC (Talimogene laherparepvec, Amgen) - genetically engineered HSV-1 the first immuno-oncolytic therapy approved in the US in Oct. and in Europe Dec. for unresectable melanoma; now being tested for unresectable solid tumors: two gene deletions, one gene addition (GM-CSF)

2021 worldwide – numerous OVs are currently under clinical trials and being developed in the preclinical stages including our novel CF33-platform of chimeric orthopoxviruses
# Trials in Immuno-Oncolytic Viruses

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<th>Transgene</th>
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<td>Pexa-Vec (VV)</td>
<td>GM-CSF</td>
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<td>Tbio-6517 (VV)</td>
<td>FLT3 ligand, IL-12, and anti-CTLA-4</td>
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<td>Solid tumors, TNBC, MSS</td>
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<td>GL-ONC1 (VV)</td>
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<td>Ovarian ca, PC, CRS</td>
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<td>ONCR-177 (HSV-1)</td>
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<td>PD-L1</td>
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<td>TMV-018 (Measles virus)</td>
<td>Cytosine deaminase</td>
<td>5-FC to 5-FU</td>
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Optimization of Immuno-Oncolytic Viral Therapy

Challenges to OV Therapy: Off target effects - physical barriers to tumor penetration - anti-viral immunity - high dosing requirements – long-time for clinical translation

Ensuring Safety – Enhancing Oncolyis → 2005 - 2021 → Tumor tracking - Dx Imaging – Harnessing Immune Modulation
New Chimeric Oncolytic Virus Platform (CF33)

- Genetic mixture of several different orthopox strains with known safety profiles to generate 100 recombinant viral chimera
- Through high throughput testing of NCI 60 human cancer cells lines identified CF33 to possess high oncolytic potential
CF33 has a unique dsDNA viral genome that did not previously exist in nature.

- Genetic mapping of CF33 shows:
  - Ankara (177,923 bp)
  - Cowpox Brighton (224,499 bp)
  - IHD-W clone IHDW1 (195,821 bp)
  - Lister (187,893 bp)
  - Rabbitpox Utrecht (197,731 bp)
  - Racoonpox Herman (214,699 bp)
  - Western Reserve Vaccinia (194,711 bp)

- Safe strains with limited tropism for normal human cells
- Effectively kills treatment resistant cancer types including TNBC, PDAC, and diffuse gastric cancer
CF33 More Potent Compared to Other OVs

- Preclinical Studies in various solid tumors
  - TNBC, Lung Ca
  - Colorectal Ca
  - Pancreatic Ca
  - Gastric Ca
- CF33 has 2-3 logs higher inherent oncolytic potency than other OVs currently in clinics
  - 10e3-10e5 pfus (immunocompromised)
  - 10e6-10e7 pfus (immunocompetent)
CF33-OV Can Deliver Functional Protein to the Cancer Cells

Two Gene Deletion and Two Gene Insertion

Anti-DDDDK-Tag binds to virus produced single chain anti-PD-L1 protein

Zhang Z. et al. JACS. 2020
Functional Transgene Expression Allows Imaging

- **Bioluminescent Tracking of OV and Tumor In Vivo**
  - CF33-Fluc
  - J2R Thymidine kinase
  - Fluc
  - (days): 1, 3, 5, 7, 20, 30
  - IV OV Injection

- **PET Imaging of Anti-Tumor Efficacy In Vivo**
  - CF33-hNIS
  - J2R Thymidine kinase
  - hNIS
  - IT OV Injection

- **Ex vivo Detection of Cancer Cells Ex Vivo**
  - CF33-GFP
  - J2R Thymidine kinase
  - S5
  - GFP
  - Woo Y et al. Data not yet published

Chaurasiya S. et al. Cancer Gene Therapy, 2019
Warner SG et al. MTO, 2019
CF33-OVs Synergistic Tumor Kill with anti-PD-L1

PD-L1 upregulated with CF33-hNIS- ΔF14.5 (double gene deletion and one addition) at MOI 3

Synergistic antitumor efficacy of CF33-hNIS- ΔF14.5 seen with 10e7pfus (IT) + antiPD-L1 Ab (100 μg) treatment

CF33-hNIS-anti-PDL1 Imaging and Treatment of PC

- After IT injection of SQ tumors CF33-OV tracks to tumor cells in peritoneum
- Infected tumors are identified by I124 PET scan (viral presence confirmed by RT-PCR)
- Eliminated PC in two animals
CF33-hNIS-antiPDL1 virus primes pancreatic ductal adenocarcinoma for enhanced anti-PD-L1 therapy

Zhifang Zhang, Annie Yang, Shyambabu Chaurasiya, Anthony K. Park, Jianming Lu, Sang-In Kim, Susanne G. Warner, Yate-Ching Yuan, Zheng Liu, Haiyong Han, Daniel Von Hoff, Yuman Fong & Yanghee Woo

Cancer Gene Therapy (2021) | Cite this article

A

AsPC-1

IFNγ + CF33-hNIS-aPDL1

CF33-hNIS-Δ

Control

Isotype

BxPC-3

PD-L1

FLAG tag

DAPI

Merged

AsPC-1

MFI of PD-L1

IFNγ +

CF33-hNIS-aPDL1

Isotype

+ – – – + – – + – + – – + – – + – – +

BxPC-3

MFI of PD-L1

p < 0.01

p < 0.01

FLU

Merged

BxPC-3 + IFNγ

PBS CF33-hNIS-Δ CF33-hNIS-aPDL1
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| 1   |       | Recruiting | **CF33-hNIS-antiPDL1 for the Treatment of Metastatic Triple Negative Breast Cancer** | • Anatomic Stage IV Breast Cancer AJCC v8  
• Metastatic Triple-Negative Breast Carcinoma  
• Prognostic Stage IV Breast Cancer AJCC v8 | • Biological: Oncolytic Virus **CF33**-expressing hNIS/Anti-PD-L1 Antibody | • City of Hope Medical Center  
Duarte, California, United States |
| 2   |       | Recruiting | **A Study of CF33-hNIS (VAXINIA), an Oncolytic Virus, as Monotherapy or in Combination With Pembrolizumab in Adults With Metastatic or Advanced Solid Tumors** | • Solid Tumor  
• Solid Carcinoma  
• Solid Tumor, Adult  
• (and 2 more...) | • Biological: CF33-hNIS  
• Biological: Pembrolizumab | • City of Hope Medical Center  
Duarte, California, United States  
Barbara Ann Karmanos Cancer Institute  
Detroit, Michigan, United States  
NEXT Oncology  
Fairfax, Virginia, United States |
Investigation of CF33-hNIS-antiPDL1 Against GC

<table>
<thead>
<tr>
<th></th>
<th>Phase contrast</th>
<th>GFP</th>
<th>Merged</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF33-GFP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASCITES FLUID FROM STOMACH CANCER PATIENT
Next Steps: Investigator Initiated Clinical Trials for OVs in GCPM

Phase I Trial Evaluating the Safety and Efficacy of Intraperitoneal CF33-hNIS-antiPDL1 of Primary GC Tumors in Patients with Synchronous Peritoneal Metastases Who Failed Second Line Therapy?

• **Eligibility:**
  - Patients with GC cancers with peritoneal metastasis
  - ECOG 0-1

• **Endpoints:**
  - Safety and antitumor activity
  - Progression-free survival and overall survival
  - Pathologic and cytologic tumor response
  - Immune biomarkers of response/resistance

• **Correlative Endpoints:**
  - cfDNA detection of recurrence/progression
  - Molecular Signatures of Response in Peritoneal TME
Furthermore → CAR-T & OV Combination Strategy

- Advocating and working to bring the generation of Targeted Immunotherapies to Patients with GC, with PM and with GCPM
- OnCARlytics plus CD19 CAR-T Cell Therapy
- TAG72 CART Cell Therapy

Next steps: preclinical in vivo studies in GC and GC PC → prepare for first in-man
How Does OVs and CAR-T Cell Combinations Work?

- OVs will find and infect cancer cells and express targetable Proteins on the Cancer Cells
- The CAR-T Cells then recognize the target protein on the cancer cell
- Patient’s Immunity is activated to kill the cancer cells
### How Genomics of GC PC Impact OV Therapy?

**Increasing Association with Peritoneal Dissemination**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bormann</td>
<td>Type IV</td>
</tr>
<tr>
<td>Lauren</td>
<td>Diffuse Type</td>
</tr>
<tr>
<td>Singapore-Duke</td>
<td>Mesenchymal</td>
</tr>
<tr>
<td>TCGA</td>
<td>GS</td>
</tr>
<tr>
<td>ACRG</td>
<td>MSS/EMT</td>
</tr>
<tr>
<td>Stromal/vascular</td>
<td>VM/I and VM</td>
</tr>
</tbody>
</table>

**Will tumor-specific genomic profiles direct OV therapy?**

- Lauren: Diffuse Type
- Singapore-Duke: Mesenchymal
- TCGA: GS
- ACRG: MSS/EMT
- Stromal/vascular: VM/I and VM

### Current Molecular Targets in GC/GEJ Tumors

<table>
<thead>
<tr>
<th>Drug Targets</th>
<th>Prevalence in GC</th>
<th>Drugs</th>
<th>FDA</th>
<th>Line of Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERRB2</td>
<td>Amplification/Overexpression 10-34%</td>
<td>Trastuzumab</td>
<td>Approved</td>
<td>First-line</td>
</tr>
<tr>
<td>VEGFR2</td>
<td>Overexpression Up to 50%</td>
<td>Ramucirumab</td>
<td>Approved</td>
<td>Second-line</td>
</tr>
<tr>
<td>PD-L1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td>Overexpression</td>
<td>Nimotuzumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>Amplification / Overexpression Up to 40%</td>
<td>Onartuzumab / AMG337</td>
<td>Phase II/III Trial</td>
<td></td>
</tr>
<tr>
<td>ATM</td>
<td>Loss of Protein Up to 60%</td>
<td>Olaparib</td>
<td>Phase III</td>
<td></td>
</tr>
<tr>
<td>CDK4/6</td>
<td>Amplification Up to 15%</td>
<td>LEE001</td>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td>Identifiable</td>
<td>OV induced ?</td>
<td>HOV2, HOV3 HOV-CD19 CAR-T</td>
<td>Preclinical pending IND</td>
<td></td>
</tr>
</tbody>
</table>

• How will OV therapy contribute to the emerging body of treatment options for solid tumors?
Preclinical Studies
- Preparation for First-in Man

Clinical Trial Design
- IRB

FDA Approval for Clinical Studies
- IND
- IDE

Toxicity & Safety
- Animal studies
- Biodistribution
- Persistence profile

Manufacturing
- GMP production
- Process control
- Quality control
- Release testing

Analysis of Clinical Trial Outcomes
- Studying immune biomarkers of therapeutic response & identifying potential co-targets

Preclinical Studies

Funding
- Grants – Philanthropy – Industry

Multinational Collaborations for Clinical Trials
"If you know the enemy and know yourself, you need not fear the result of a hundred battles. If you know yourself but not the enemy, for every victory gained you will also suffer a defeat. If you know neither the enemy nor yourself, you will succumb in every battle." – Sun Tzu in the Art of War
Join Together to Develop the New Strategies!

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A Takasashi (Mexico)
M Jung (Sweden)
And Growing...

**ISSPP & the U.S PIPAC Consortium**

Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura
Thank you for your attention!

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