RENAISSANCE OF REOVIRUS AS A TRUE IMMUNO-ONCOLOGY VIRAL AGENT FOR CANCER

Phacilitate Immuno Oncology Frontiers
Berlin, Germany
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Chief Medical Officer
What is REOLYSIN®?

- **Immuno-Oncolytic Virus (IOV)** for intravenous administration

- **Unmodified**, non-pathogenic, type 3 Dearing reovirus strain
  - Double-stranded RNA virus
  - Ubiquitous to the environment

- **Dual mechanism of action**: selective tumor cell lysis and anti-tumor immune response

- **Safe and Tolerable**
  - As monotherapy and in combo

- **Phase 3 ready asset**

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**IND.213 Trial- ITT population (n=74)**

- Statistically significant increase in OS in metastatic breast cancer when combined with paclitaxel (17.4 m) when compared to paclitaxel alone (10.4 m, HR=65, 80% CI 0.46-0.91, p=0.1)
1. **Direct tumor lysis** 1-20

Selective viral replication in permissive cancer cells leading to tumor cell lysis.

2. **Innate immunity** 21-37

Viral replication resulting in a cascade of chemokines/cytokines causing NK (natural killer) cells to recognize and attack cancer cells.

3. **Adaptive immunity** 24-28, 30, 32-39

Antigen presenting cells (APCs) display tumor-associated antigens (TAA) and viral-associated antigens (VAA) to educate T-cells to recognize and destroy cancer cells. Induces PD-1 & PDL-1 expression on T-cells & tumors.

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What makes cancer cells permissive to reovirus replication?

○ **Endogenous Factors**
  - Defective PKR signaling
  - Downregulation of the IFN-induced antiviral response
    - RAS activation and/or mutations in upstream downstream RAS effector proteins
    - Dysfunctional tumor suppressor genes (e.g., p53, ATM and Rb)
    - Tumor mutational burden

○ **Exogenous Factors**
  - Cellular stress from chemo/radio therapies
  - Reovirus modulation of interferon signaling

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Selective viral replication and lysis in breast cancer cell lines treated with REOLYSIN®

Cell Viability Assays

- Hs-578Bst (normal) Normal
- Cancer cells
- MCF7
- MDA-MB-468
- SK-BR-3
- MDA-MB-435S
- T-47D

Normalized cell viability graph showing the percentage of cells surviving as a function of multiplicity of infection (PFU/cell) for normal and cancer cell lines.

Clinical Studies with REOLYSIN® (pelareorep)

- A total of 1420 patients have been enrolled in 36 studies

- Various collaborators:
  - Investigators, US NCI, CCTG
  - 1029 pts. have received REOLYSIN
    - Intratumoral (91)
    - Intravenous (938)
  - Twenty publications with REOLYSIN IV
  - Six randomized, controlled phase 2 studies
REOLYSIN® – IV Monotherapy

- IND filed for IV administration in 2004
- Four Phase 1 studies in solid tumors with REOLYSIN IV
  - 126 patients with solid tumors were evaluated
  - Doses: $1 \times 10^8$ to $3 \times 10^{10}$ TCID$_{50}$ (1, 3 or 5 doses in a month)
  - No MTD was defined
    - Common, transient Grade 1/2 “flu-like syndrome” post-infusion
    - Transient treatment-related grade 2/3 neutropenia & lymphopenia
  - Disease Control Rate = 35%
    - PR in patient with anthracycline and taxane refractory mBC

Mita AC et al. JCO, 2009: 27(15s)- Abstract 10524
## TEAEs in ≥20% of Patients with Intravenous REOLYSIN® Monotherapy in Solid Tumors

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Dose Escalation</th>
<th>Fixed Dose Pelareorep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REO 004 (N=18)</td>
<td>REO 005 (N=33)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (38.9%)</td>
<td>19 (57.6%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7 (38.9%)</td>
<td>24 (72.7%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (33.3%)</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>6 (33.3%)</td>
<td>14 (42.4%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5 (27.8%)</td>
<td>9 (27.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (27.8%)</td>
<td>9 (27.3%)</td>
</tr>
<tr>
<td>Chills</td>
<td>4 (22.2%)</td>
<td>4 (12.1%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (22.2%)</td>
<td>8 (24.2%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (22.2%)</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (22.2%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (22.2%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1 (5.6%)</td>
<td>7 (21.2%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (5.6%)</td>
<td>7 (21.2%)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (11.1%)</td>
<td>2 (6.1%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1 (5.6%)</td>
<td>7 (21.2%)</td>
</tr>
<tr>
<td>Influenza-Like Illness</td>
<td>NR</td>
<td>10 (30.3%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>NR</td>
<td>1 (3.0)%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>NR</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>NR</td>
<td>5 (15.2%)</td>
</tr>
<tr>
<td>Platelet Count Decreased</td>
<td>NR</td>
<td>2 (6.1)%</td>
</tr>
</tbody>
</table>
60 y breast cancer patient refractory to anthracycline and taxane
PR with 34% decrease in tumor burden by RECIST
Successive shrinkage and achieved a PR by 5 cycles.

Co-Localization of Reovirus Protein, Caspase and/or NK cells in Tumor Metastasis after REOLYSIN® IV MT

A
IHC: reovirus protein (red stain)

B
RGB image to fluorescent green (caspase-3), red (reovirus), and yellow (co-expression)

C
RGB image to fluorescent red (reovirus protein), green (cKIT/NK cells), blue (hematoxylin)

Inflammatory Phenotype

Adair et al., Sci Transl Med. 2012, 4:138ra77,

Courtesy of Dr. Gerard Nuovo of the OSU Comprehensive Cancer Center and Phylogeny, Inc
Path 1. REOLYSIN® IV - Chemo Combinations

- Three Ph 1 dose escalation trials with REOLYSIN IV + Chemotherapy
  - Paclitaxel/carboplatin (REO 011), docetaxel (REO 010) and gemcitabine (REO 009)
  - MTD was not reached or defined
  - Disease control rate = 75%
    - Significant clinical and objective tumor responses in patients with refractory cancers
      - H&N, melanoma, breast, esophageal & gastric cancer
- Six randomized, controlled phase 2 studies with REOLYSIN IV
  - Pancreatic, breast, NSCLC, ovarian, prostate & colorectal cancer

IND.213 Randomized Controlled Trial in Metastatic Breast Cancer with Paclitaxel ± REOLYSIN® IV

Eligibility
- Advanced or metastatic BC for which paclitaxel is indicated
- Received at least one prior CT for advanced or metastatic BC (unless they have relapsed within 6 months of completion of adjuvant CT or have received taxane and/or anthracycline containing adjuvant CT)
- Prior RT at least 28 days prior to enrollment
- ECOG PS 0-2

Primary Endpoint: PFS
Secondary Endpoints: Tolerability, toxicity, ORR, OS, CTC counts, biomarkers

REOLYSIN IV
(3X10^{10} TCID_{50} D 1, 8, 15 q4w)

Paclitaxel
(80 mg/m^2, D 1, 8, 15 q4w)

Maximum 8 cycles or until PD, consent withdrawal or unacceptable drug-toxicity

Paclitaxel
(80 mg/m^2, D 1, 8, 15 q4w)

36 patients
38 patients

www.clinicaltrials.gov NCT01656538
Improved Median Overall Survival in Metastatic Breast Cancer with REOLYSIN® and Paclitaxel vs. Paclitaxel Alone

IND-213 randomized, controlled-Phase 2 study from CCTG

- Statistical significant improvement in OS in the combination arm by Phase 2 criteria
- Like many IOs, no differences in ORR and PFS

![Graph showing ITT Population](image)

Arm A (paclitaxel/REOLYSIN) 17.35 months
Arm B (paclitaxel) 10.35 months
HR 0.65 (80% CI 0.46-0.91, p=0.1)

HR(+)/Her2 (-) ~ 80%
TNBC ~ 18%
Prior chemo 100%
Prior anthracy ~ 90%
Prior taxanes ~ 50%

 Bernstein V et.al. Abst CT131, AACR 2017
IND213: OS Subgroup Analysis in mBC with REOLYSIN® and Paclitaxel vs. Paclitaxel Alone

Bernstein V et.al. Abst CT131, AACR 2017
IND213: Improved Median Overall Survival in HR+ HER2- mBC with REOLYSIN® and Paclitaxel vs. Paclitaxel Alone

Hsiao & Liu - Post Hoc Analysis - CYTEL 2017
## IND.213 Salvage Therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Arm A N=36</th>
<th>Arm B N=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy Within 4 weeks of last dose of protocol therapy</td>
<td>0 (0%)</td>
<td>4 (11%)*</td>
</tr>
<tr>
<td>Chemotherapy during follow-up</td>
<td>23 (64%)</td>
<td>22 (58%)</td>
</tr>
<tr>
<td>Hormonal Therapy during follow-up</td>
<td>7 (19%)</td>
<td>6 (16%)</td>
</tr>
</tbody>
</table>

* Generally reflects patients choosing to have paclitaxel off protocol when randomized to Arm B
IND.213: Percentage of ≥ Grade 3 Non-Hematologic AEs Occurring in ≥ 5% Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ARM A Paclitaxel/pelareorep N=43*</th>
<th>ARM B Paclitaxel N=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>46.5</td>
<td>47.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16.3</td>
<td>13.2</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>0.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>0.0</td>
<td>7.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3</td>
<td>7.9</td>
</tr>
<tr>
<td>Pain</td>
<td>2.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Fall</td>
<td>2.3</td>
<td>5.2</td>
</tr>
<tr>
<td>Cancer deaths on treatment</td>
<td>2.3</td>
<td>7.9</td>
</tr>
<tr>
<td>Breast pain</td>
<td>0.0</td>
<td>5.2</td>
</tr>
</tbody>
</table>

* Seven additional patients in the safety lead in phase

** p=0.1
IND.213: Percentage of ≥ Grade 3 Hematologic AEs Occurring in ≥ 5% Patients

<table>
<thead>
<tr>
<th>Laboratory Value</th>
<th>ARM A Paclitaxel/pelareorep N=43*</th>
<th>ARM B Paclitaxel N=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia**</td>
<td>10 (23.3%)</td>
<td>10 (26.3%)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>5 (11.6%)</td>
<td>11 (28.9%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (4.7%)</td>
<td>2 (5.3%)</td>
</tr>
</tbody>
</table>

* Seven additional patients in the safety lead in phase
** Only 1 patient on Arm A experienced febrile neutropenia
Pooled Safety Analysis in 547 pts Treated with Paclitaxel or Carbo-Tax ± REOLYSIN® IV

Flu-Like Syndrome common with REOLYSIN IV

- **AEs:** G1/2 fever, chills, fatigue, nausea, vomiting, diarrhea (dehydration)
- **Related SAEs:** fever, GI AEs and dehydration
  - The incidence of febrile neutropenia and/or infection was similar
  - **G3/4**-induced by chemotherapy do not seem to be modified by the addition of REOLYSIN
- **Hepatic and renal laboratory** values showed no significant differences between the two groups
  - Transient Grade 3/4 neutropenia and lymphopenia

Largest safety database with an intravenous IOV presented at ESMO 2017 (1193p)

Gutierrez AA et.al, ESMO 2017 Abst 1193P
Path 1: Chemo-Combos / Breast Cancer

Key Learnings

- REOLYSIN® IV acts as a systemic immunotherapy
- Consistent with other approved I-O therapies, the primary endpoint for the phase 3 study in mBC must be overall survival

Regulatory Milestones

- FDA Fast Track Designation - May 2017
- Successful FDA End-of-Phase 2 - August 2017
  - Clear regulatory pathway to registration in metastatic breast cancer
  - Overall agreement with Phase 3 study design (discussions on the final version ongoing)
- Next Step: EMA Scientific Advice Meeting
Phase 3 Randomized Controlled Trial in Metastatic Breast Cancer with Paclitaxel ± REOLYSIN® IV

Eligibility
- Advanced or metastatic HR+ HER2- BC
- Measurable disease
- Received at least one but no more than 2 prior CT for advanced or metastatic BC
- Received at least one hormone–based therapy which may or may not have included mTOR- or CDK4/6-inhibitors

REOLYSIN IV
(3×10^{10} TCID_{50} D 1, 2, 8, 9, 15, 16 q4w)
- Maximum 8 cycles or until PD, consent withdrawal or unacceptable drug-toxicity

Paclitaxel
(80 mg/m^2, D 1, 8, 15 q4w)

Enroll N=400 patients, 1:1

Interim Analysis 24-30 mo.

Planned final analysis ~36 mo.

Primary Endpoint: OS
Secondary Endpoints: ORR, PFS, biomarkers

Adaptively extended final analysis ~48 mo.
Path 2: Immunotherapy Combo’s

**REOLYSIN® IV + Pembrolizumab** (anti-PD-1 antibody) in pancreatic cancer
- Combo with gemcitabine (n = 6), 5-flourouracil (n = 3) or irinotecan (n = 2)
- Grade 3 / 4 TEAEs in 73%
- DCR 45%: PR (6 m) and 2 SD (126 and 221 d)
- On-treatment biopsy: reovirus infection in cancer cells and immune infiltrates

**Ongoing collaborations**

Mahalingam et.al. ASCO 2017  Abst e15753
Rajani, Viruses 2015, 7:588
Rajani, Mol Ther 2016,24:166
Path 3: Targeted/IMiD Combo’s

REOLYSIN® IV + Pomalidomide in multiple myeloma
- Establish safety profile
- Further characterize immune profile
- Ongoing collaboration with Celgene & Myeloma UK

REOLYSIN IV + Targeted Therapy in mBC
- In planning stage

Enhancement of Innate Immune Response:
REOLYSIN® + IMiDs

- REOLYSIN® alone
  - Activation of NK cells
  - Release of inflammatory cytokines

- REOLYSIN® + IMiDs
  - Increased activation of NK cells
  - Release of inflammatory cytokines

+ IMiDs
Acknowledgments

- Our patients & families worldwide
- Pioneers and their collaborators

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Dr R Vile
Dr S Nawrocki

Prof A Melcher
Prof K Harrington

Dr Sanjay Goel

Prof Hardev Pandha

Prof GP Cook

Dr. K Kelly

Dr L Seymour
Dr V Berstein

Dr K Gelmon
Dr B Eigl

Dr D Sborov

Dr. K Kelly