Forward Looking Statements

This presentation contains certain forward looking statements relating to the company’s business prospects and the development and commercialization of pelareorep, a first-in-class systemically administered immuno-oncology agent for solid tumors and heme malignancies. These statements are based on management’s current expectations and beliefs and are subject to a number of factors which involve known and unknown risks, delays, uncertainties and other factors not under the company’s control which may cause actual results, performance or achievements of the company to be materially different from the results, performance or other expectations implied by these forward looking statements.

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Introductions

Dirk Arnold, MD, PhD  Director, Asklepios Tumor Center, University Hamburg, Germany, ESMO board member
Matt Coffey, PhD  President and CEO
Kirk Look, CA  Chief Financial Officer
Rita Laeufle, MD, PhD  Chief Medical Officer
Andrew de Guttadauro  Global Head of Business Development
Michael Moore  Vice President, Investor Relations & Corporate Communications
Grey Wilkinson, PhD  Scientist, Translational Medicine
Agenda

01 Pelareorep Overview

02 Biomarkers and Their Impact on Regulatory Approval

03 REO 024: Efficacy & Biomarker Data

04 Impact of Biomarkers on Clinical & Business Development
Pelareorep Overview
What is Pelareorep?

Non-pathogenic proprietary isolate of the unmodified reovirus

Unarmed IV delivered double stranded RNA (dsRNA) oncolytic virus that creates an inflamed phenotype in tumor tissue
Pelareorep at a Glance: Immune Stimulation

- **Non-infected**
  - Cancer cell
  - No T cell recognition or killing

- **Infected with pelareorep**
  - T cell
  - T cells recognize infected cancer cells, moderate T cell killing and engage memory effect

- **Infected with pelareorep and anti-PD-1/PD-L1 added**
  - T cells recognize infected cancer cells, increased T cell killing and increased memory effect (via checkpoint inhibitor)
Pelareorep at a Glance: Efficacy and Safety

First IV delivered immuno-oncolytic virus to demonstrate overall survival benefit in a randomized study in metastatic breast cancer

1,100+ patients treated, 900+ intravenously

No maximum tolerated dose (MTD) reached to date

ITT Population

Test Arm (paclitaxel/pelareorep) 17.35 months
Control Arm (paclitaxel) 10.35 months

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No maximum tolerated dose (MTD) reached to date

First IV delivered immuno-oncolytic virus to demonstrate overall survival benefit in a randomized study in metastatic breast cancer

Test Arm (paclitaxel/pelareorep) 17.35 months
Control Arm (paclitaxel) 10.35 months

Bernstein V et al. Abstract CT131, AACR 2017
Pelareorep treatment has shown an enhanced overall survival benefit across cancer indications.

Tolerable and safe with encouraging benefit in 2y-survival in single arm Ph 2 studies:

**Overall survival in REO-017 Single Arm Pancreatic Cancer study**

- Pelareorep + Gemcitabine 2y-OS = 24%

**Overall survival in NCI-8601, Randomized Pancreatic Cancer study**

- All patients, N= 73
  - Test Arm (Carbotax + pelareorep) 9%
  - Control Arm (Carbotax) 20%
- Excluding crossover patients, N= 56
  - Test Arm (Carbotax + pelareorep) 24%
  - Control Arm (Carbotax) 20%

Systemically delivered pelareorep in combination with chemotherapy achieves 1 & 2 year-survival rates of 46% & 24% in pancreatic cancer patients.

Mahalingam et al. ESMO, 2015, P-175. and Noonan et al. Molecular Therapy, 2016, 24:1150–11.
Biomarkers and Their Impact on Regulatory Approval
A biomarker is an indicator of biological processes or a characteristics that either:

- Can identify or characterize a disease or its severity or prognosis
- Can identify patients that may need a specific treatment
- May serve as a guide to optimize treatment
- Is subject to change during a disease or an intervention
- Can be used as surrogate endpoint in clinical studies to accelerate approval of a new compound

The importance of biomarkers continues to grow in all areas of clinical practice and, whether to predict, diagnose, or monitor disease, biomarkers are useful and important in every step of patient care!
Prognostic Versus Predictive

Barratt et al., Lancet 2002
Susan McCune, MD, Center for Drug Evaluation and Research, FDA:

“Biomarker-based strategies allow for a more biology-targeted approach to drug development and may enable time and cost savings through leaner, more focused clinical trials that have a higher overall probability of success with respect to both efficacy and safety.”

“Biomarkers can be used to identify the mechanism of action of a drug…”

“FDA recognizes biomarker development as a high priority area for future research and collaboration among stakeholders and is taking action to better understand biomarkers used in drug development.”

“...we need a whole new generation of biomarkers that are more informative and that can tell developers earlier whether or not their drug may have toxicity or ...may not work at all, and to get that early read on what’s going to be successful. And so those biomarkers are ones that have yet to be developed”.

- J. Woodcock FDA

The Importance of Biomarkers in Clinical Studies

Conventional clinical study approach:

Is using clinical outcomes such as survival or disease progression. Collection of information on these endpoints take many years.....

Biomarker-driven clinical study approach:

may predict drug efficacy more quickly than conventional endpoints.

“Potential to accelerate product development”

On-Treatment Biomarker: Influence on Clinical Treatment Decisions

On-treatment biomarkers

- offer the potential for monitoring of treatment response, treatment-associated toxicity, and onset of treatment resistance

- markers for response to available cancer therapies move treatment toward a fully individualized therapeutic approach

- can be detected in blood or in tissue
On-Treatment Biomarker: Influence on Clinical Treatment Decisions

Phase II, non comparative, study
Target accrual: 27 pts

- mCRC pts RAS and BRAF wt
- FOLFIRI/ FOLFOXIRI + Cetuximab
  - PD
  - ≥ 6 Months
  - ORR 22%
  - DCR 54%
  - ctDNA for RAS/BRAF mutations (ddPCR+NGS)

- FOLFOX/XELOX/ FOLFOXIRI + Bevacizumab
  - PD
  - ≥ 4 Months
  - Irinotecan + Cetuximab
  - Study treatment: Irinotecan 180 mg/sqm iv
    Cetuximab 500 mg/sqm iv
  - ≥ 4 months
  - Time between the end of 1st-line therapy and the start of 3rd-line ≥4 months

Rossini et al., ASCO 2018
CRICKET trial: Phase 2 single-arm study of re-challenge with cetuximab + irinotecan as 3rd-line therapy in RAS and BRAF WT pts with acquired resistance to 1st-line cetuximab- and irinotecan-containing therapy

CTDNA, circulating tumor DNA
On-Treatment Effect

Pelareorep’s Promotion of an Inflamed Phenotype

Pre-treatment
Lack of PD-L1 staining

One week after pelareorep + carfilzomib
>90% PD-L1 staining

7-8 Days
REO 024: Efficacy & Biomarker Data

A Phase Ib study of pembrolizumab in combination with pelareorep and chemotherapy in patients with advanced pancreatic adenocarcinoma
Detailed results were presented last week at AACC.

Exploratory analysis of T cell repertoire dynamics upon systemic treatment with the oncolytic virus pellarovirus in combination with pembrolizumab and chemotherapny in patients with advanced pancreatic adenocarcinoma (Abstract #2272)

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Abstract
Background: Pancreatic cancer is an intrinsically lethal disease that, when treated, involves most of the patients (WHO). Systemically administered pembrolizumab in combination with pellarovirus (P) and 2 weekly subcutaneous (wks) of paclitaxel (PTX) and carboplatin (CARBO) are the standard of care treatments for patients (pts) with advanced pancreatic adenocarcinoma (PDAC). We have previously demonstrated the safety and therapeutic efficacy of the combination therapy. Thus, we hypothesized that pancreatic in combination with pembrolizumab and chemotherapeutic agents (PTX+CARBO) can significantly reduce the progression of PDAC.

Methods: We conducted a Phase I/II trial evaluating the safety and efficacy of the combination of Pellarovirus (P), Pembrolizumab (PTX), and Carboplatin (CARBO) in patients with advanced PDAC. A total of 40 patients were enrolled and treated with Pellarovirus (P), Pembrolizumab (PTX), and Carboplatin (CARBO) in cycles of 21 days. Safety was assessed based on occurrence of adverse events (AEs) which included a spectrum of skin, gastrointestinal, and autoimmune reactions. AEs were recorded and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Results: We conducted a Phase I/II trial evaluating the safety and efficacy of the combination of Pellarovirus (P), Pembrolizumab (PTX), and Carboplatin (CARBO) in patients with advanced PDAC. A total of 40 patients were enrolled and treated with Pellarovirus (P), Pembrolizumab (PTX), and Carboplatin (CARBO) in cycles of 21 days. Safety was assessed based on occurrence of adverse events (AEs) which included a spectrum of skin, gastrointestinal, and autoimmune reactions. AEs were recorded and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Background cont.

Background cont.

Safety Findings

Safety was tolerable in all patients without an increase in Grade 4 toxicity.

Study Hypothesis

We hypothesized that pembrolizumab in combination with chemotherapy and pembrolizumab in patients with advanced pancreatic adenocarcinoma (PDAC) significantly reduces the progression of PDAC.

Methods

Immuno-sequencing of the TCR repertoire of patients with advanced PDAC was performed using the ImmunoSEQ assay developed by Adaptimmune Biotechnologies. Seattle, WA. DNA for the analysis was extracted from peripheral blood mononuclear cells (PBMCs) obtained at baseline and during treatment with pembrolizumab and pembrolizumab in combination with chemotherapy. The TCR repertoire was analyzed using the ImmunoSEQ assay to identify changes in the TCR repertoire.

Results

The median frequency of TCR repertoire in patients with advanced PDAC was significantly higher than the frequency of TCR repertoire in healthy controls. The frequency of TCR repertoire was significantly higher in patients with advanced PDAC who received pembrolizumab and pembrolizumab in combination with chemotherapy than in patients with advanced PDAC who received pembrolizumab alone. The frequency of TCR repertoire was significantly lower in patients with advanced PDAC who received pembrolizumab and pembrolizumab in combination with chemotherapy than in patients with advanced PDAC who received pembrolizumab alone.

Conclusions

Pembrolizumab and pembrolizumab in combination with chemotherapy significantly reduces the progression of PDAC. The TCR repertoire is an important biomarker for evaluating the response to immunotherapy. The TCR repertoire is a potential target for developing personalized immunotherapy for patients with advanced PDAC.
T cell receptors (TCRs) contain both constant and variable domains

- The **variable domains** confer antigen specificity and allow the adaptive immune system to continually recognize new targets
- Within the variable domain, the **most highly variable region is the CDR3** and this is what we target for immune repertoire sequencing
- The immunoSEQ assay allows for the quantification of **clonality**
Clonal Expansion or Clonality is a Critical Marker of Immune Activation

Purely diverse = 0

- Clonality indicates how evenly distributed the abundances of unique clones are in a sample.
- Values range on a scale from 0 to 1

Relative abundance of top 25 clones in a sample:

Monoclonal = 1
Hypothesis:
Pelareorep in combination with chemotherapy and pembrolizumab alters the peripheral T cell repertoire.

- Does pelareorep create novel T cell clones via release of neoantigens? and/or
- Does pelareorep expand existing T cell clones?

2L Relapsed Metastatic Adenocarcinoma of the Pancreas (MAP) n = 11

21 day cycle:
- pelareorep 4.5x10^10 TCID_{50} IV
- Pembrolizumab 2 mg/kg IV
- Gemcitabine or 5-flourouracil or irinotecan

Primary endpoint:
- Dose-limiting toxicities

Secondary Endpoints:
- ORR
- PFS
- OS
- biomarkers

Cycle 1 Cycle 2 Cycle 3

D1 D2 D8 21 D1 D2 D8 21 D1 D2 D8 21

Chemotherapy, Pelareorep, Pembrolizumab

BX = Biopsy = blood draw for TCR-seq

A Phase 1b Study of Pembrolizumab in Combination with Pelareorep and Chemotherapy in Patients with Advanced Pancreatic Adenocarcinoma
Efficacy findings

6 efficacy evaluable patients:

- One patient: Partial Response (PR), starting 6.5 mos. after the start of therapy, lasting 17.4 mos.
- Two patients: Stable Disease (SD), for 6 and 9.5 mos. respectively

Disease control was achieved in 50% of the 6 efficacy-evaluable patients
Low Morisita Indices Over Time Suggests High Repertoire Turnover with Significant Creation of New Clones

- Morisita Index (MI)
  - takes into account both repertoire overlap and clonal frequencies between the two samples.
  - A perfectly identical repertoire is 1, and two completely disparate samples would be 0.
  - Normal variation over a month is ~0.9 – 0.95.

Between baseline and c2 d1:
- Median MI is 0.83 - with 3 samples below 0.6. This suggests significant peripheral repertoire turnover.
- 86% of peripheral clonal expansion is observed from new clones ➔ indicative of T cell priming.
Peripheral Clonality at Baseline: Correlates with Progression Free Survival

- Variables were treated as continuous variables for cox regression
  - Clonality was scaled to a unit of 0.1
- Clonality is correlated with progression free survival and show a stronger p-value at baseline
- Higher peripheral clonality is associated with longer progression free survival
Variables were treated as continuous variables for cox regression.

- Clonality was scaled to a unit of 0.1

- Clonality is correlated with overall survival and show a stronger p-value at cycle two, day 1.

- Higher peripheral clonality is associated with better outcome.
Long Term Survivors Have Greater Peripheral Clonality

Patients with a clinical response or longer survival: Higher Peripheral Clonality after one cycle of treatment (at cycle 2, day 1)

Long term survivors:  > 6 months
Short term survivors: < 6 months
Early Expanded Clones Most Strongly Correlate With Survival Time (Pre-Pembrolizumab)

- Both high numbers of early and durable clone are associated with longer overall survival times
- The strongest correlation is seen with the number of early expanded clones
- Early vs. late clonal expansion may be influenced by the type of response of the virus is eliciting

Types of Expanded Clones

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Cycle 2</th>
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<tr>
<td>Day 8</td>
<td>Day 1</td>
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Early Expanded Clones: $R = 0.58, p = 0.099$

Durable Expanded Clones: $R = 0.44, p = 0.24$

Late Expanded Clones: $R = 0, p = 1$

Spearman Rho Correlations
Summary & Next Steps

Patients classified as

- “Long term survivors” have higher levels of T cell clonality
- “Short term survivors” have lower levels of T cell clonality in peripheral blood after one cycle of treatment

All the observations of this initial study will be validated in randomized P2 studies in BC and GI cancer

A study by Hopkins et al. has also shown that on-treatment peripheral T cell clonality associates with survival in MAP pts treated with nivolumab and a pancreatic cancer vaccine (Hopkins, A.C., et al. JCI Insight, 2018. 3(13)).
Impact of Biomarkers on Clinical & Business Development
Influence on Oncolytics’ Clinical Development Program

**WHY**
- Increase the number of patients that can be safely and successfully treated with an immunotherapy combination
- Overcome resistance of current checkpoint indication
- Potentially offer a chemo – limiting/free treatment approach

**HOW**
- Include a prospective biomarker program in our clinical studies
- Work closely with academia (thought leaders) and FDA
- Prospectively collect biomarker and correlate them with overall response rate

**WHAT**
- For metastatic breast cancer optimize our registration study – Identify patients that derive the best benefit from the treatment
- Expand in multiple indications
# Pelareorep Clinical Studies

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<tr>
<th>Programs</th>
<th>Indication</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<td><strong>Breast Cancer</strong></td>
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<td>pelareorep + combination</td>
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<td>pelareorep +</td>
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<td>pelareorep +</td>
<td>Pancreatic Cancer</td>
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<td><strong>Multiple Myeloma</strong></td>
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<td>pelareorep +</td>
<td>R/R MM</td>
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Biomarker Impact on Business Development

**FASTER**

Quicker time to trial readout

**BETTER**

Potential to de-risk trial investment via higher probability of trial clinical success

**CHEAPER**

Trials make for more palatable investment opportunities
Thanks for your time