ONCOLYTICS BIOTECH INC

Unleashing the Power of the Immune System to Fight Cancer

Investor Presentation
September 2024

Forward-Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended and forward-looking information under applicable Canadian securities laws (such forward-looking statements and forward-looking information are collectively referred to herein as "forward-looking statements"). Forward-looking statements contained in this presentation include statements regarding our belief as to the potential, mechanism of action and benefits of pelareorep as a cancer therapeutic; our stated goals and objectives; our potential registration opportunities in breast and pancreatic cancer and the milestones and next steps associated therewith and the anticipated timing thereof; our anticipated cash runway; our key milestones in 2024 and beyond; our development strategy; and other statements related to anticipated developments in Oncolytics' business and technologies. In any forward-looking statement in which Oncolytics expresses an expectation or belief as to future results, such expectations or beliefs are expressed in good faith and are believed to have a reasonable basis, but there can be no assurance that the statement or expectation or belief will be achieved. Such forward-looking statements involve known and unknown risks and uncertainties, which could cause Oncolytics' actual results to differ materially from those in the forward-looking statements. Such risks and uncertainties include, among others, the availability of funds and resources to pursue research and development projects, the efficacy of pelareorep as a cancer treatment, the success and timely completion of clinical studies and trials, Oncolytics' ability to successfully commercialize pelareorep, uncertainties related to the research and development of pharmaceuticals, uncertainties related to the regulatory process and general changes to the economic environment. We may incur expenses or delays relating to such events outside of our control, including public health crises such as pandemics and epidemics, which could have a material adverse impact on our business, operating results and financial condition. Investors should consult Oncolytics' quarterly and annual filings with the Canadian and U.S. securities commissions for additional information on risks and uncertainties relating to the forward-looking statements. Investors are cautioned against placing undue reliance on forward-looking statements. The Company does not undertake to update these forward-looking statements, except as required by applicable laws.

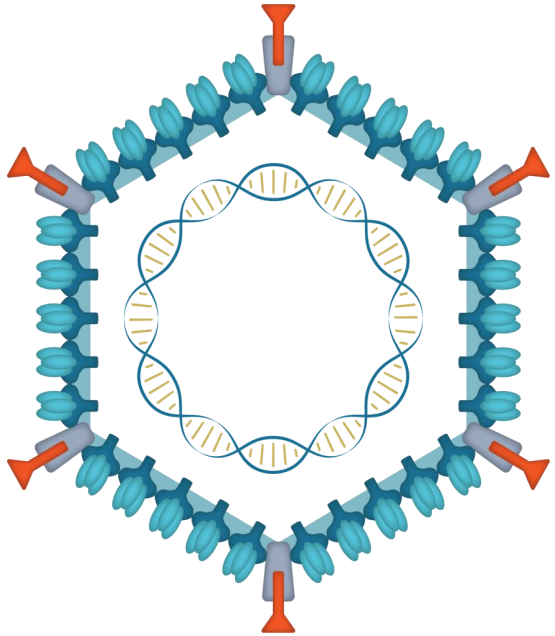
Pelareorep in Breast & Pancreatic Cancer: Overview & Highlights

Non-pathogenic, unmodified immunotherapy

- Targets cancer cells, but not normal cells
- Administered IV, delivers dsRNA into tumors
- Strong safety profile – has been given to >1,100 patients
- 147 patents provide extensive IP protection

Pela activates the immune system

- Induces anti-tumor innate and adaptive immune responses
- Makes tumors visible to the immune system
- Synergizes with chemotherapy and immuno-therapeutics including checkpoint inhibitors
- Clinical evidence showing changes to TME



Clear registration path in two indications

- Strong efficacy signal in breast and pancreatic cancer
- Fast Track designation for both indications
- Efficient registration path identified for both indications with potential for accelerated approval for breast cancer

Experienced team

- Extensive oncology drug development experience
- Track record of success in bringing new drugs to the market
- Decades of experience in manufacturing and product development
- Distinguished Scientific Advisory Board

dsRNA: double-stranded RNA; TME: tumor microenvironment

Pelareorep is a First in Class Immunotherapeutic Agent

- **Non-genetically modified, non-pathogenic reovirus**
- **IV administration allows direct targeting of both primary and metastatic tumors**
- **Manufactured at commercial scale; requires no special handling**

Selectively replicates in cancer cells

↓

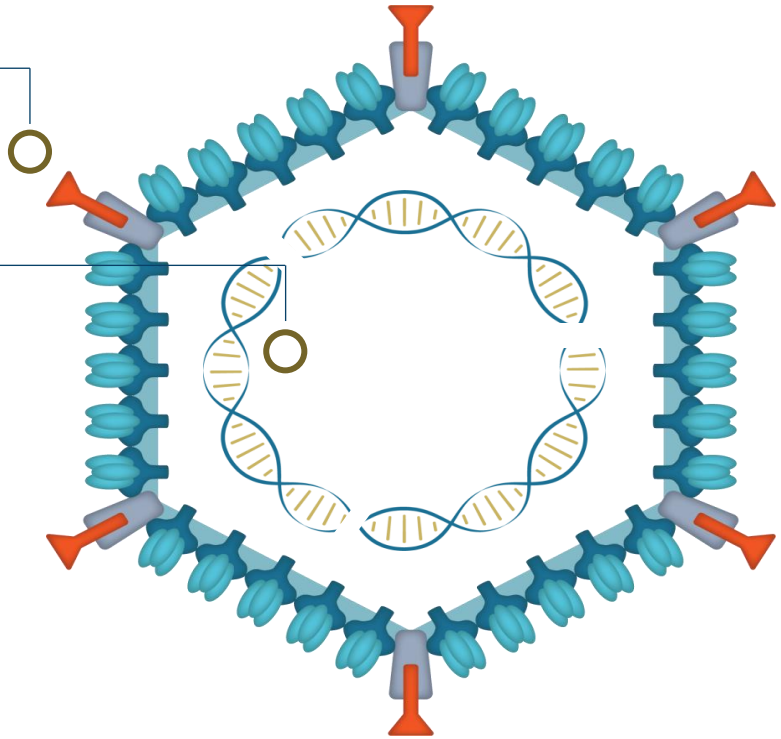
Leads to accumulation of double-stranded RNA

↓

Stimulates chemokine expression to make tumors visible to the immune system

and

Induces anti-tumor cellular immune responses including expansion of tumor-infiltrating lymphocytes



Oncolytics illustration, 2024

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Pelareorep in HR+ / HER2- Breast Cancer

Pelareorep Offers New Options in the Evolving HR+/HER2- Advanced/Metastatic Breast Cancer Treatment Pathway

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Hormonal and targeted treatment lines

First-line treatment

- Endocrine therapy
- CDK4/6 inhibitors

Second-line treatment

- Endocrine therapy
- CDK4/6 inhibitors
- Targeted therapy

Post-hormonal treatment lines

Third-line treatments

Antibody-drug conjugate therapy, e.g., T-DXd (Enhertu)*

or

Traditional chemotherapy (if T-DXd ineligible)

Pelareorep + paclitaxel

3rd-line option for pts ineligible for T-DXd

Fourth-line treatments

Chemotherapy

Pelareorep + paclitaxel

4th-line option for pts who fail T-DXd‡

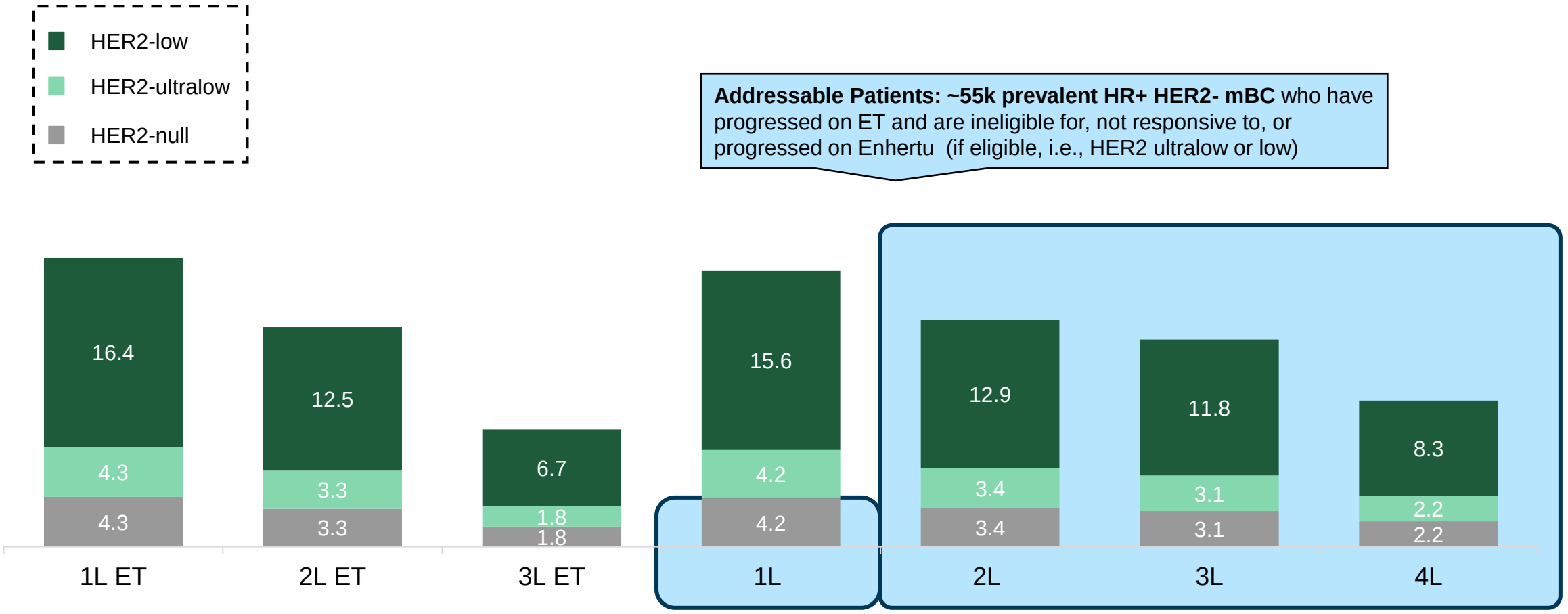
* Anticipated based on Destiny-Breast06 results (ASCO 2024)

‡Due to progression on or inability to tolerate T-DXd

The HR+/HER2- mBC Segment Post Enhertu Represents ~55K Addressable Patients

Projected 2027 HR+ mBC Treated Prevalence Across Lines of Therapy in U.S.

(# of patients in 1,000s, Not Mutually Exclusive)

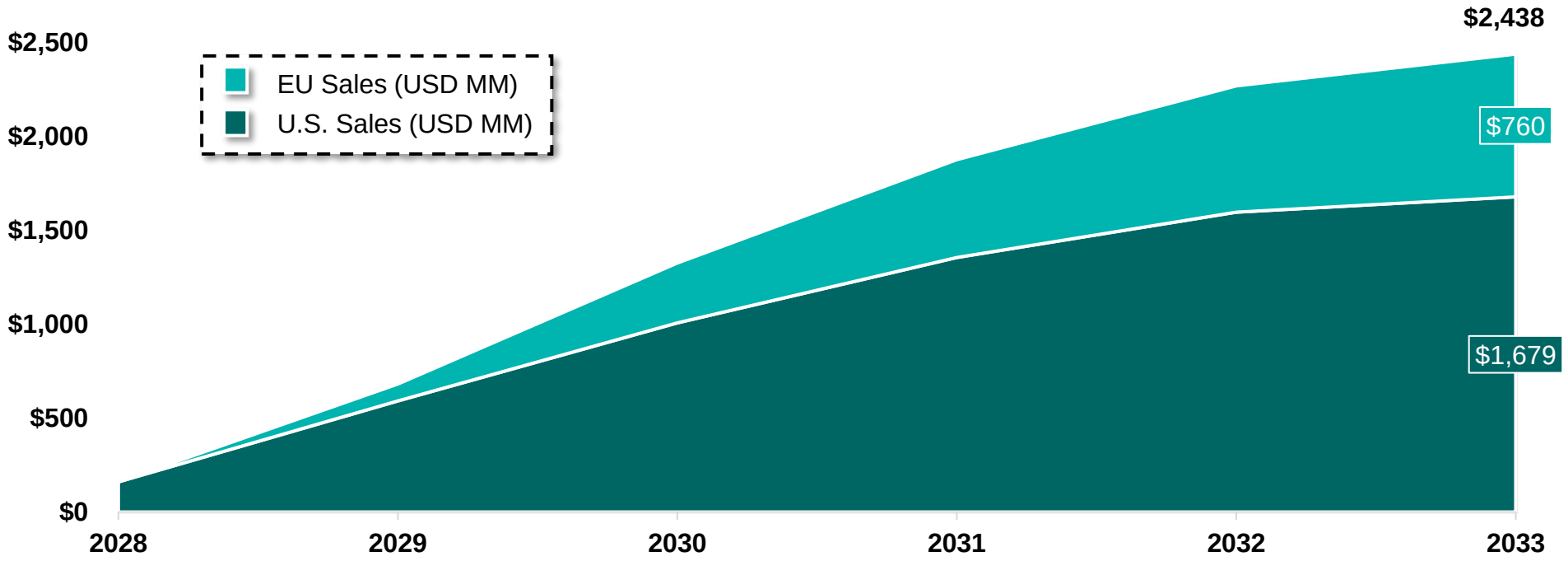


Addressable Patients Methodlogy in Appendix. Sources: Gampenrieder, Simon Peter et al. "Landscape of HER2-low metastatic breast cancer (MBC): results from the Austrian AGMT_MBC-Registry." Breast cancer research : BCR vol. 23,1 112. 14 Dec. 2021, doi:10.1186/s13058-021-01492-x; Schettini, Francesco et al. "Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer." NPJ breast cancer vol. 7,1 1. 4 Jan. 2021, doi:10.1038/s41523-020-00208-2Mehta, Sandhya et al. "Prevalent of 'HER2 ultra-low' among patients with advanced breast cancer with historical IHC0 status." Journal of Clinical Oncology vol. 42, 16. 29 May 2024, doi.org/10.1200/JCO.2024.42.16_suppl.e1315; Tarantino, Paolo et al. "HER2-Low Breast Cancer: Pathological and Clinical Landscape." Journal of clinical oncology : official journal of the American Society of Clinical Oncology vol. 38,17 (2020): 1951-1962. doi:10.1200/JCO.19.02488; DESTINY-BREAST04; DESTINY-BREAST06

Pelareorep Potential Peak Sales: $2.4 Billion

Projected U.S. & EU sales of Pelareorep in HR+ mBC

(Sales in USD MM)



Treated patients

Total U.S Pela Patients	966	3,414	5,577	7,200	8,132	8,197
Total EU5 Pela Patients	-	995	3,517	5,745	7,416	8,376
Total US and EU5 Pela Patients	966	4,409	9,094	12,945	15,548	16,572

Sources: GlobalData HER2 negative BC Global Drug Forecast & Market Analysis to 2030; GlobalData Price Intelligence Database; Redbook; ICER

Pelareorep-Based Therapy Provides Clinical Benefit in Breast Cancer

Phase 1 study of pelareorep in advanced breast cancer

Phase 1	Pelareorep has single agent activity in HR+/HER2- breast cancer

Phase 2 study in metastatic breast cancer (mBC): Paclitaxel *vs.* pelareorep + paclitaxel

IND-213	Pelareorep + paclitaxel provided survival benefit of >10 months in heavily pretreated patients

Phase 2 study in HR+/HER2- mBC: Paclitaxel *vs.* pelareorep/paclitaxel *vs.* paclitaxel/pelareorep/avelumab

BRACELET-1	Pelareorep + paclitaxel provided 5.7-month progression-free survival benefit and approximately 14-month survival benefit following CDK4/6 therapy compared to paclitaxel monotherapy

Pelareorep Treatment Led to a Statistically Significant Improvement in mOS in Phase 2 Breast Cancer Trial IND-213

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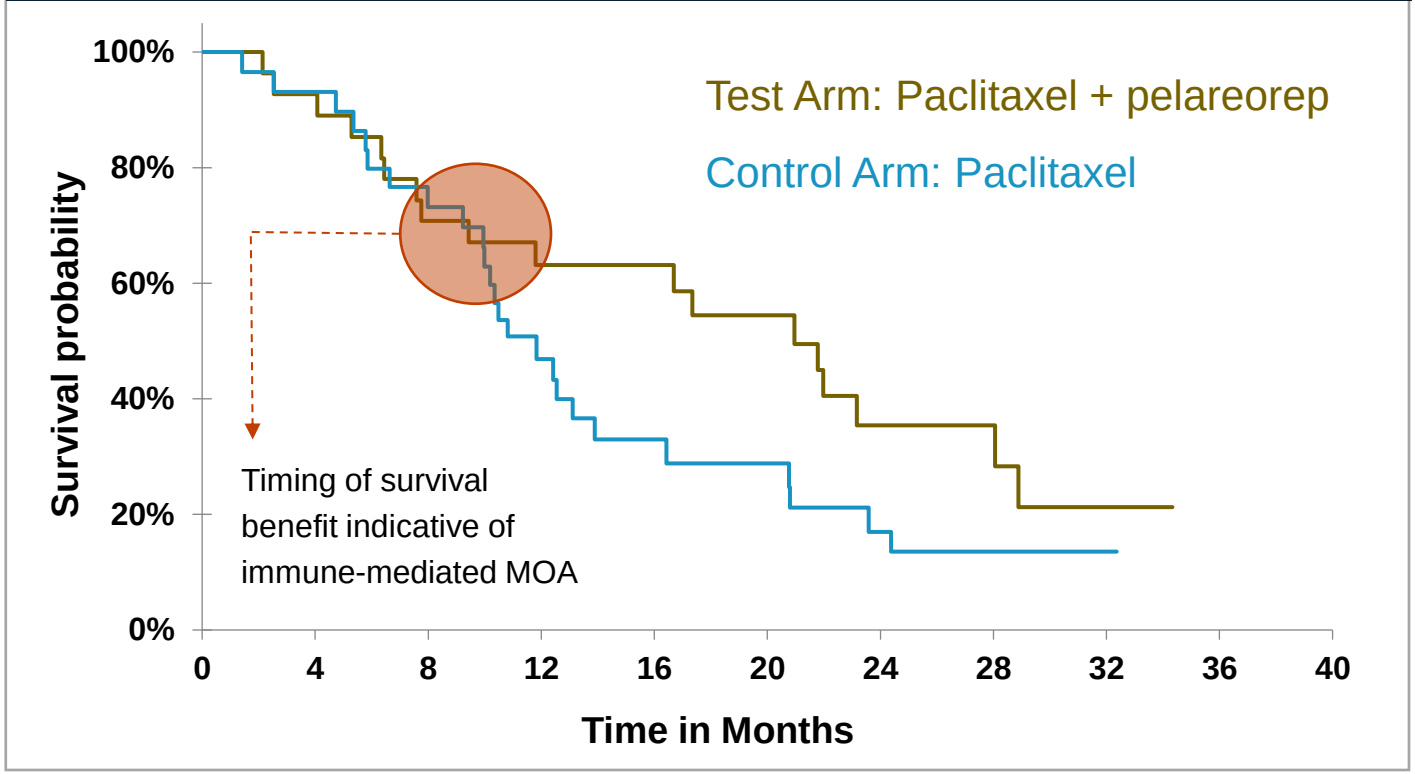
Phase 2 All Subtypes (n = 74)

HR	0.65
p	0.1 (powered to 90%)
mOS	17.4 months vs. 10.4 months
Test	n = 36
Control	n = 38

HR+/HER2- Patients (n = 57)

HR	0.60
p	0.1 (powered to 90%)
mOS	21.0 months vs 10.8 months
Test	n = 28
Control	n = 29

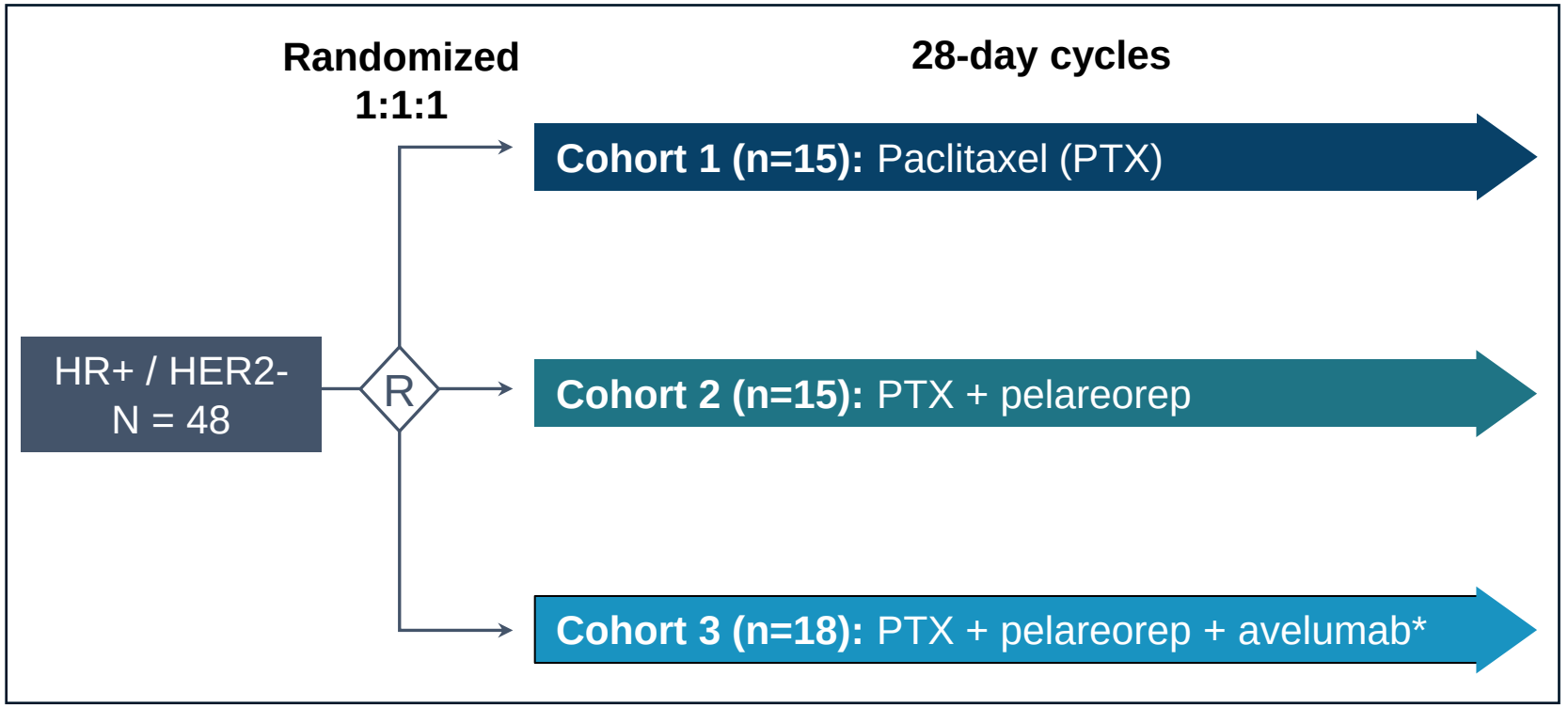
Overall survival for the HR+/HER2- patients in IND-213 study of metastatic breast cancer (n = 57)



Near doubling of mOS in HR+/HER2- patients with pelareorep treatment

mOS: Median Overall Survival; HR: hazard ratio

BRACELET-1 Study Design



Key Eligibility Criteria

- No prior chemo for metastatic disease
- Progressed on at least 1 hormone-based therapy with a CDK 4/6 inhibitor

Primary Endpoint

- Overall response rate (ORR) at week 16

Other Endpoints

- Progression-free survival
- Overall survival
- Peripheral and tumor T cell clonality
- Safety and tolerability assessments

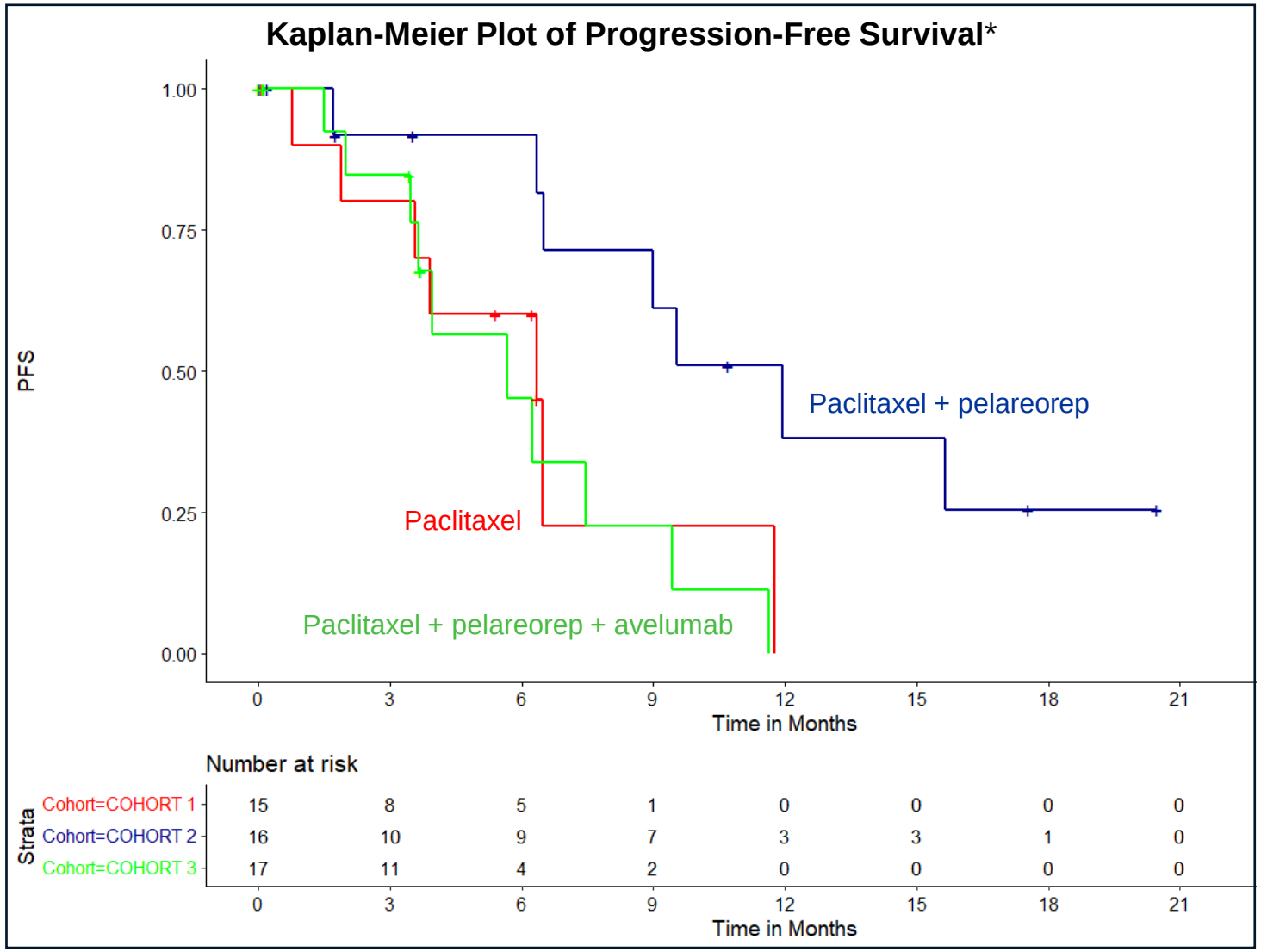
Study Objectives

- To assess the clinical benefit of pelareorep combination therapy in patients who had received CDK4/6 therapy
- To assess whether avelumab added any additional benefit

Collaborators

Avelumab (Bavencio®)
*Includes 3 patient safety run-in

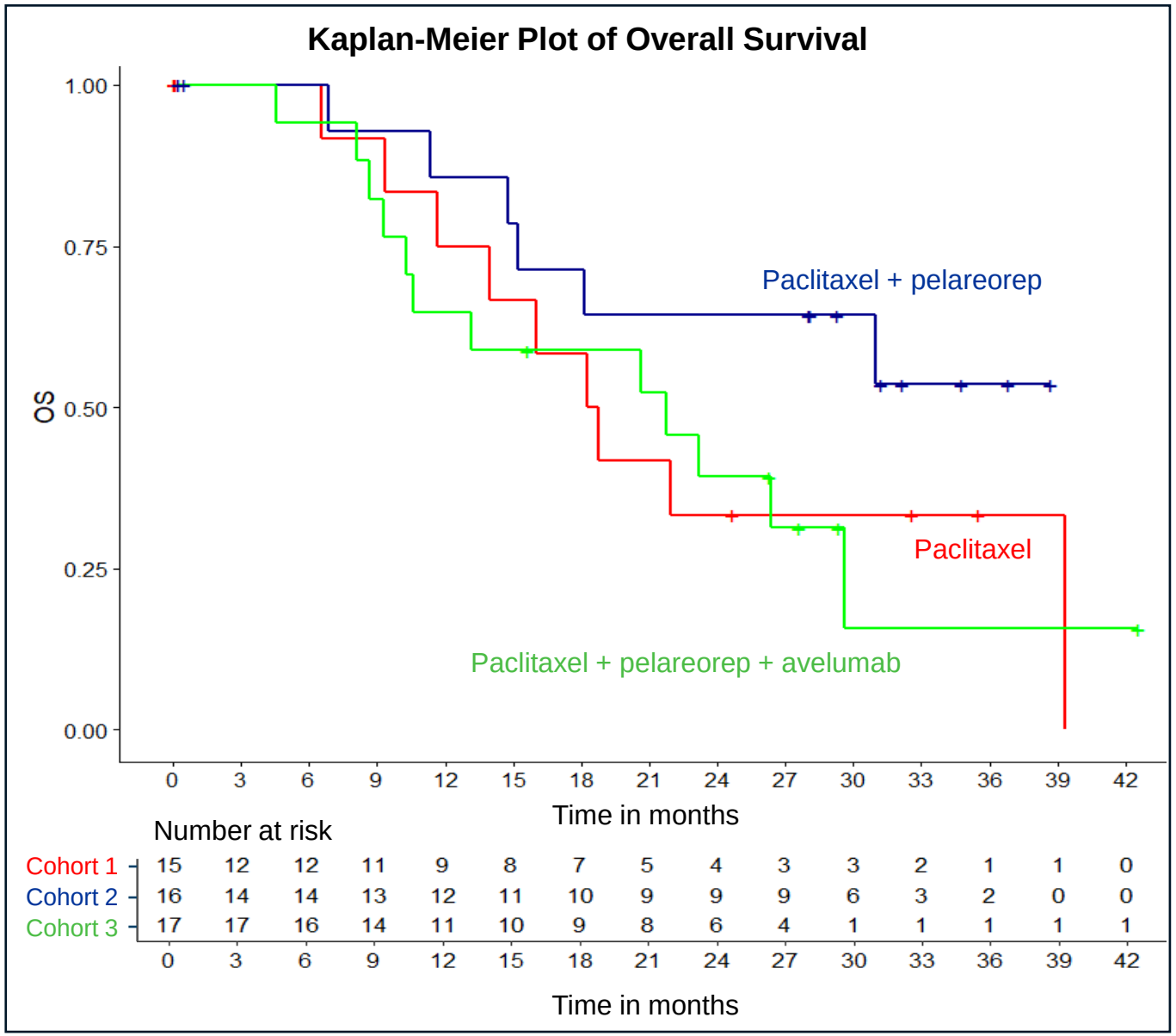
BRACELET-1 Study Showed Robust Improvement in Progression-free Survival (PFS) for the Pelareorep + Paclitaxel Arm



	Paclitaxel (PTX)	PTX + pelareorep	PTX + pelareorep + avelumab
Median PFS (months)	**6.4**	**12.1**	**6.4**
Hazard ratio vs. PTX	**-**	**0.39**	**1.43**

*Progression-free survival is defined as the time from randomization to the first documented disease progression per RECIST v1.1 or death from any cause, whichever occurs first.

BRACELET-1 Study Showed Meaningful Improvement in Overall Survival (OS) for the Pelareorep + Paclitaxel Arm



	Paclitaxel (PTX) Cohort 1	PTX + pela Cohort 2	PTX + pela + avelumab Cohort 3
Median OS (months)	**18.2**	**Not reached**	**21.7**
		Estimate: 32.1*	
Hazard ratio vs. PTX alone	**-**	**0.48**	**1.08**

*This estimate assumes patients survived only until the next per protocol follow-up in 4 months. Had the patients survived only one day past their final follow-up visits, the estimated median OS would be 28.7 months.

BRACELET-1: Data Show Benefits in Pelareorep + Paclitaxel Arm

Response Measures[1]	PTX Monotherapy (n=15)	PTX + Pelareorep (n=16)	PTX + Pelareorep + Avelumab (n=17)
Confirmed ORR	13.3%	**37.5%**	17.6%
Median PFS (months)	6.4	**12.1**	6.4
Median OS (months)	18.2	**Not Reached** ***Estimate: 32.1****	21.7
Hazard Ratio for OS	-	**0.48**	1.08
24-Month OS Rate (%)	33%	**64%**	39%

[1] Tumor responses based on RECIST version 1.1
ORR: Overall response rate; PTX: paclitaxel
PFS: progression-free survival; OS: overall survival

*This estimate assumes patients survived only until the next per protocol follow-up in 4 months. Had the patients survived only one day past their final follow-up visits, the estimated median OS would be 28.7 months.

Pelareorep's Favorable Overall Safety Highlighted by BRACELET-1 Safety Summary

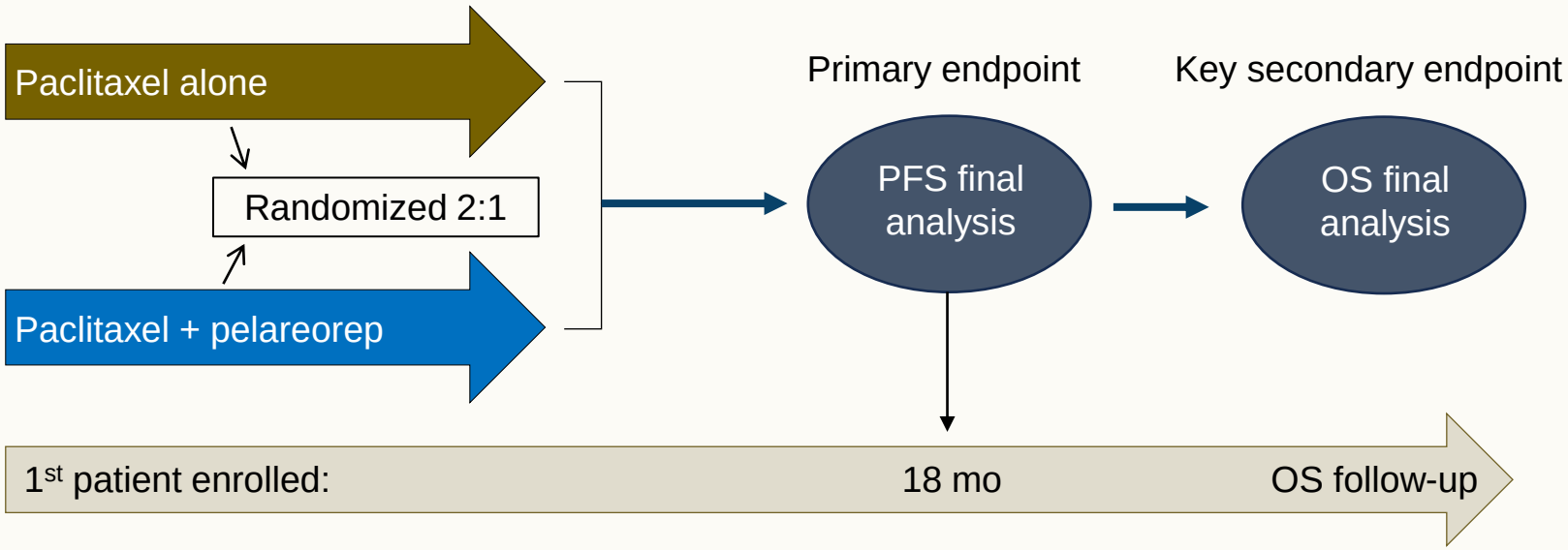
Fifteen Most Common Adverse Events[1,2] as Attributed to Study Drug(s)

	Paclitaxel (PTX) (n=12)		PTX + Pelareorep (n=16)		PTX + Pelareorep + Avelumab (n=17)	
Grade	Any	≥ 3	Any	≥ 3	Any	≥ 3
Alopecia	6 (50%)	-	9 (56%)	-	8 (47%)	-
Anemia	7 (58%)	-	5 (31%)	-	10 (59%)	1 (6%)
Anorexia	4 (33%)	-	5 (31%)	-	5 (29%)	-
Chills	-	-	7 (44%)	-	5 (29%)	-
Diarrhea	1 (8%)	-	6 (38%)	1 (6%)	8 (47%)	2 (12%)
Fatigue	5 (42%)	-	12 (75%)	2 (12%)	8 (47%)	1 (6%)
Infusion related reaction	1 (8%)	-	3 (19%)	-	9 (53%)	1 (6%)
Leucopenia	2 (17%)	-	3 (19%)	1 (6%)	11 (65%)	5 (29%)
LFT[3] Abnormality	3 (25%)	-	6 (38%)	2 (12%)	9 (53%)	2 (12%)
Lymphopenia	3 (25%)	-	3 (19%)	1 (6%)	4 (24%)	2 (12%)
Nausea	4 (33%)	-	7 (44%)	-	8 (47%)	-
Neuropathy	3 (25%)	-	8 (50%)	1 (6%)	10 (59%)	1 (6%)
Neutropenia	3 (25%)	1 (8%)	5 (31%)	3 (19%)	10 (59%)	6 (35%)
Proteinuria	2 (17%)	-	6 (38%)	-	4 (24%)	1 (6%)
Pyrexia	-	-	8 (50%)	-	11 (65%)	-

Safety data presented by Clark et al. at ASCO 2023, [1]Adverse Events collected using CTCAE V5.0, [2]Only the 45 randomized patients who received any study therapy included in this analysis, [3] Liver function test abnormality

Efficient Path to Registration Through Large Phase 2 Study

Study design



- FDA agrees with study population and primary endpoint (Type C meeting)
- Follows development model used for Ibrance, Enhertu (and others)

Total study size:

- Expected to be ≤200 patients

Target population:

- Advanced or metastatic breast cancer
- HR+/HER2-low or 0
- Failed hormonal therapy
- Ineligible or failed ADC therapy

Primary endpoint:

- Progression-free survival

Additional endpoint:

- Overall survival

A successful study expected to support a BLA or greatly de-risk a registrational Phase 3 trial

FDA Type C Meeting Outcome – May 2024: Alignment on Key Elements of the Planned Registration-Enabling Study

Summary of key outcomes

- FDA agreed that the proposed study population is appropriate (i.e., patients who failed hormonal therapy and received either 0 or 1 line of ADC therapy)
- FDA agreed that PFS is acceptable primary endpoint. They noted that OS should also be formally tested.
- FDA provided guidance on what constitutes a clinically meaningful benefit

General comments:

- The tone of the discussion was very collegial with a thoughtful dialogue between Oncolytics and the FDA medical reviewers

ADC: antibody-drug conjugate; PFS: progression-free survival; OS: overall survival

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Pelareorep in Gastrointestinal Cancer

GOBLET Study Design

Phase 1/2 multiple indication biomarker, safety & efficacy study

Advanced / Metastatic Pancreatic Cancer
1L n=12

→ Pelareorep + Atezolizumab + Gemcitabine + Nab-paclitaxel
Success Criteria ≥ 3 responses

Newly Diagnosed Pancreatic Cancer
1L n=15

→ Pelareorep + mFOLFIRINOX +/- Atezolizumab
Success Criteria ≥ 6 responses

Unresectable Anal Cancer
≥2L n=10

→ Pelareorep + Atezolizumab
Success Criteria ≥ 2 responses

Primary Endpoints:
Safety
ORR

Secondary Endpoints:
PFS, OS

Exploratory Endpoints:
Biomarker and MOA assessments

L: line; mFOLFIRINOX: modified FOLFIRINOX; ORR: objective response rate; atezolizumab (Tecentriq®); PFS: progression-free survival; OS: overall survival; MOA: mechanism of action

Efficacy Signals Shown in Two Gastrointestinal Cancers

	First-line Advanced / Metastatic Pancreatic Cancer	Second-line or Later Anal Cancer
Status	Phase 1/2 updated data reported October 2023	Phase 1/2 initial data reported November 2023
Key Data	62% Objective response rate 7.2 months Median PFS 10.6 months interim Median OS 46% 12-month survival rate	37.5% Objective response rate Including a complete response
Next Steps	Advancing to a licensure-enabling study	Expansion of enrollment to confirm efficacy signal

Pancreatic cancer program has U.S. FDA Fast Track Designation

PFS: Progression-free survival; OS: Overall survival

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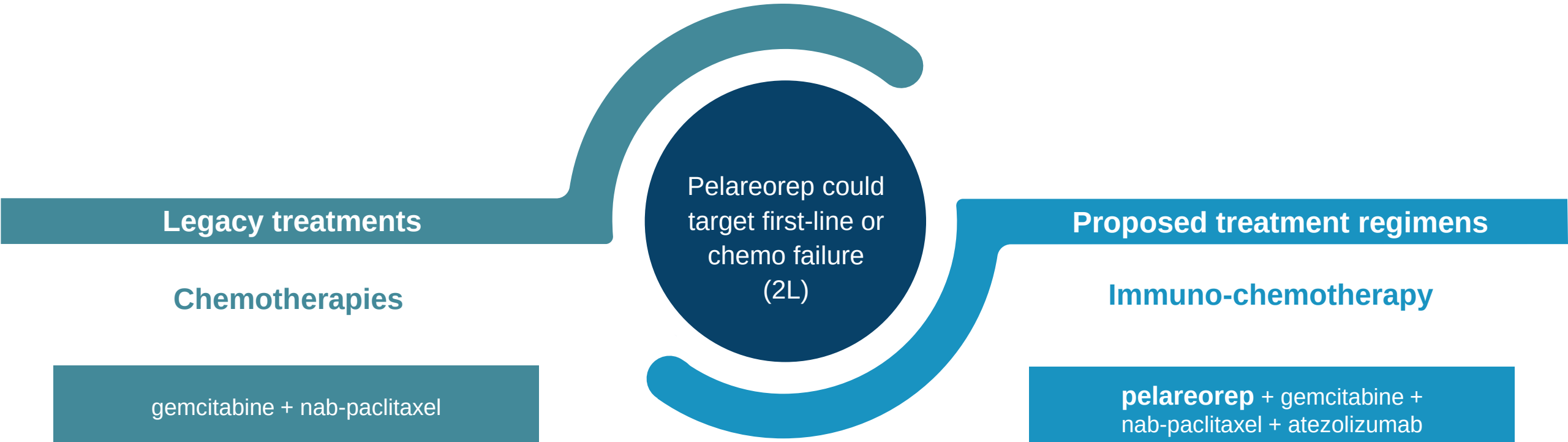
Pelareorep in Metastatic Pancreatic Cancer

Advanced/metastatic pancreatic ductal adenocarcinoma market



Legacy treatments

Chemotherapies

- gemcitabine + nab-paclitaxel
- mFOLFIRINOX

Proposed treatment regimens

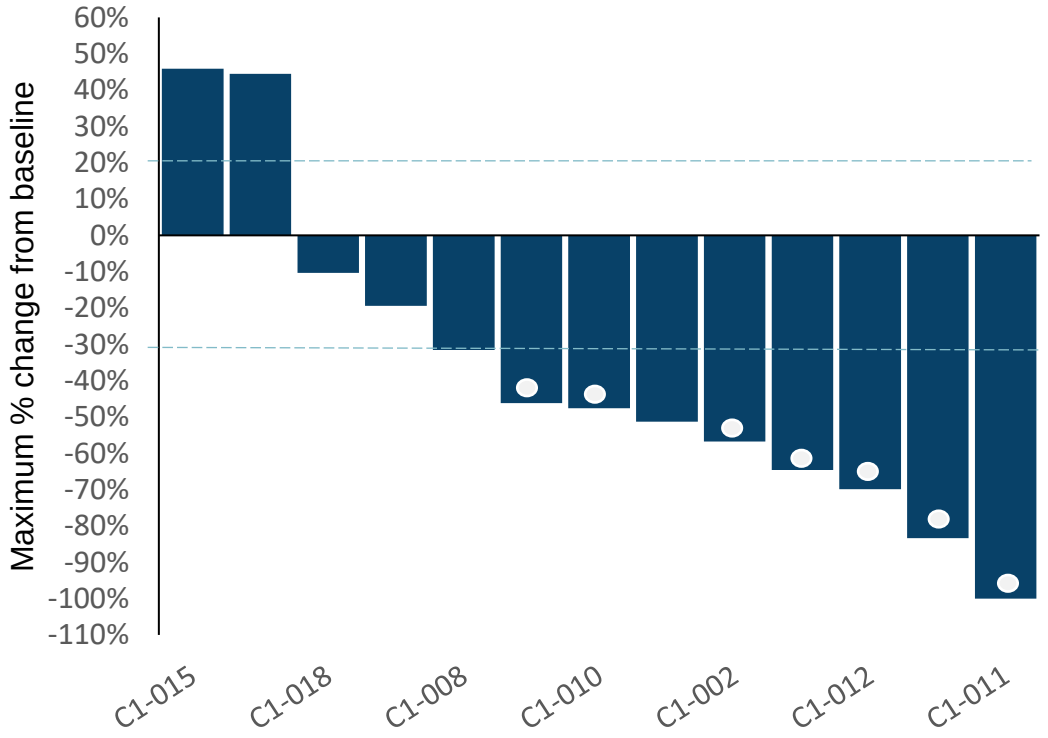
Immuno-chemotherapy

- **pelareorep** + gemcitabine + nab-paclitaxel + atezolizumab
- **pelareorep** + mFOLFIRINOX +/- atezolizumab

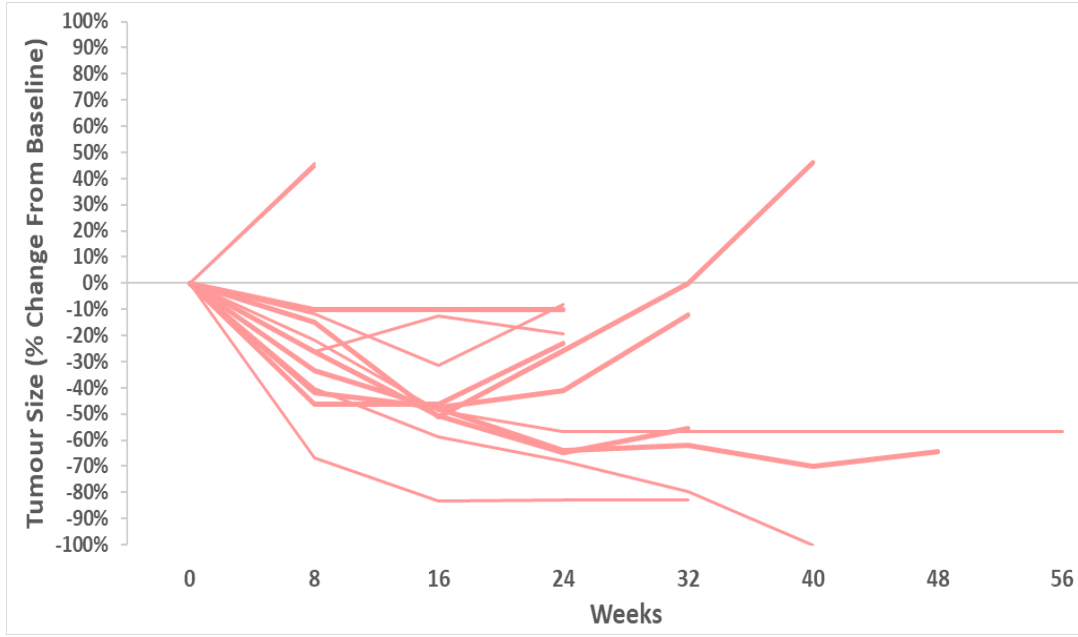
mFOLFIRINOX: modified FOLFIRINOX; chemo: chemotherapy; 2L: second-line

PDAC GOBLET Results Showing 62% ORR, Nearly Triple The Rate Seen in Prior Studies

Tumor Responses as of Sep. 18, 2023 cut off; All Patients/n=13



Tumor Responses Over Time; Evaluable Patients/n=11



Dotted lines represent cut-offs for PD (+20%) and PR (-30%)

Patients with a white dot have confirmed responses (2 or more consecutive scans with PR or CR)

PDAC: pancreatic ductal adenocarcinoma; ORR: Objective Response Rate; PD: Progressive Disease; PR: Partial Response; CR: Complete Response; Graph Source: ESMO 2023 poster

Next Steps: Finalize GCAR PDAC Registrational Trial Protocol and Initiate Study

Patient Population:

- Patients receiving 1L treatment for PDAC
- Prior Treatments: None
- Adaptive trial design to be based on positive GOBLET cohort 1 results

Treatment Regimen:

- Randomized trial of pelareorep + atezolizumab + gemcitabine + nab-paclitaxel vs. gemcitabine + nab-paclitaxel

Registrational Endpoints:

- **Primary Endpoint:** Overall Survival
- **Secondary Endpoints:** Progression-Free Survival, Overall Response Rate, and Translational Data

FDA Fast Track Designation

Trial plan to include study size, timing for the first interim analysis, and definition of clinical and translational endpoints

GCAR: Global Coalition for Adaptive Research; 1L: First-Line; PDAC: pancreatic ductal adenocarcinoma

mFOLFIRINOX Cohort Design

Strategic rationale: to investigate the use of pelareorep with another commonly used treatment regimen

Patient Population:

- Newly diagnosed metastatic PDAC patients (as defined by RECIST 1.1)
- To be supported by PanCAN Therapeutic Accelerator Grant

Treatment Regimen:

- Phase 1/2 randomized trial of pelareorep + mFOLFIRINOX vs. mFOLFIRINOX + pelareorep + atezolizumab (n=15/arm in Stage 1)

Endpoints: Based on Simon two-stage screened selection design:

- **Stage 1**: success criteria of ≥ 6 responses in the first 30 subjects
- **Stage 2**: success of ≥ 13 responses (41%):
- Study to include Translational Data

Safety run-in completed in Q3 2024

PDAC: pancreatic ductal adenocarcinoma; PanCAN: Pancreatic Cancer Action Network; mFOLFIRINOX: modified FOLFIRINOX

Pancreatic Cancer Opportunity Driven by Promising GOBLET Phase 1/2 Data & Supported by FDA Fast Track Designation

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GOBLET Study Shows Increased ORR	» An ORR of 62% was observed, representing a near doubling from historical controls compared to historical control trials[1-4]
Studies Show Survival Benefit	» Prior studies also showed clinically meaningful improvements in survival
Favorable Overall Safety	» GOBLET data indicate the treatment has been well tolerated with no safety concerns
Consistent Translational Data	» Translational data from GOBLET show that patients with increases in blood TILs showed a decrease in tumor volumes
Registrational Trial Plan and Beyond	» Registration-enabled study protocol being finalized after pelareorep selected for inclusion by GCAR » $5M PanCAN grant to explore pelareorep/mFOLFIRINOX regimen, H2 2024 safety run-in complete

ORR: objective response rate; mPFS: median progression-free survival; mOS: median overall survival; TILs: tumor-infiltrating lymphocytes; GCAR: Global Coalition for Adaptive Research; mFOLFIRINOX: modified FOLFIRINOX; PanCAN: Pancreatic Cancer Action Network; Sources: 1. Von Hoff D et al. N Engl J Med 2013; 369:1691-1703 DOI: 10.1056/NEJMoa1304369; 2. O'Reilly et al. Eur J Cancer. 2020 June ; 132: 112–121. DOI:10.1016/j.ejca.2020.03.005; 3. Karasic et al. JAMA Oncol. 2019 Jul 1;5(7):993-998. DOI: 10.1001/jamaoncol.2019.0684; 4. Tempero et al. Ann Oncol. 2021 May;32(5):600-608. DOI: 10.1016/j.annonc.2021.01.070.

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Pelareorep in ≥ Second-Line Unresectable Anal Cancer

Positive GOBLET Anal Cancer Data Meets Success Criteria, Expanding Enrollment, Highlights Synergy with CPI

Presented November 9, 2023 at the 2nd International Multidisciplinary Anal Cancer Conference (IMACC)

Patient Population:

- Patients with 2L, unresectable squamous cell carcinoma of the anal canal (SCCA)
- Prior treatments included chemotherapy and radiation therapy

Study Design & Treatment Regimen:

- Open-label, single arm, Simon Two-stage study of pelareorep + atezolizumab (n=10)

Enrollment Expanded:

- Stage 1 success criteria met; Stage 2 enrollment (18 patients) ongoing

Combined results could lead to a single-arm registration study

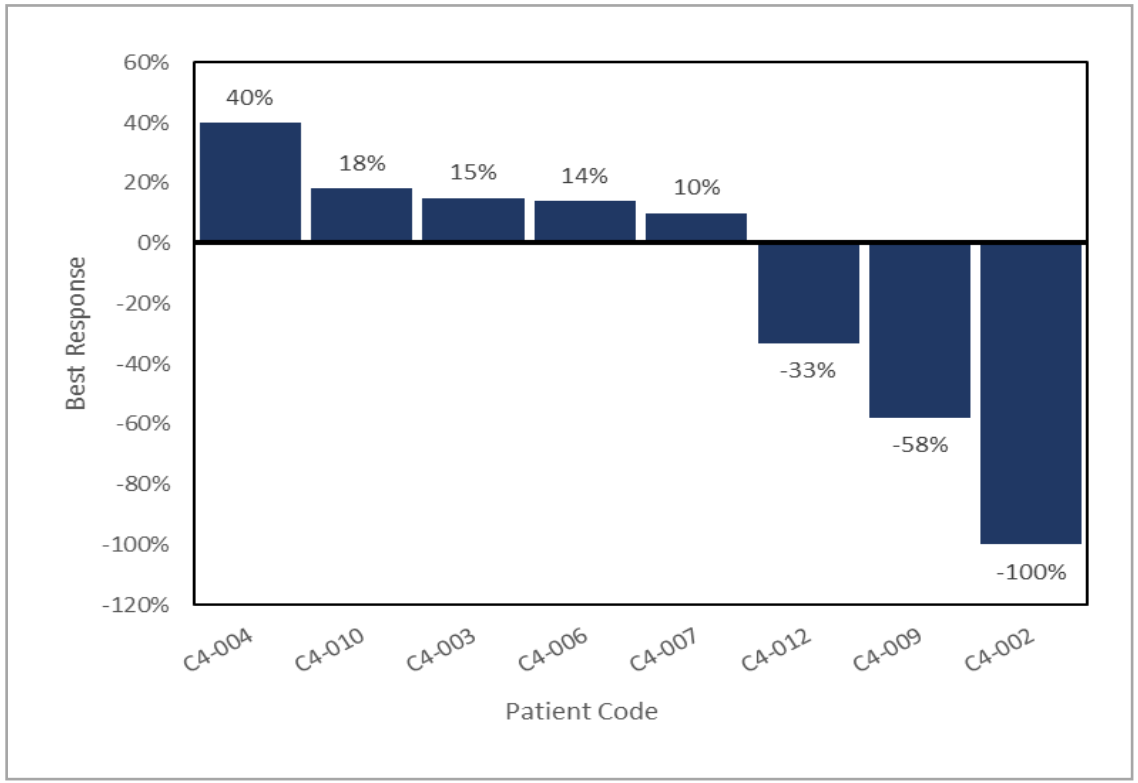
ORR of 37.5%, with 1 CR ongoing at 12 months and 2 PRs
Data satisfied the pre-specified success criteria for the study
Follow-up is ongoing

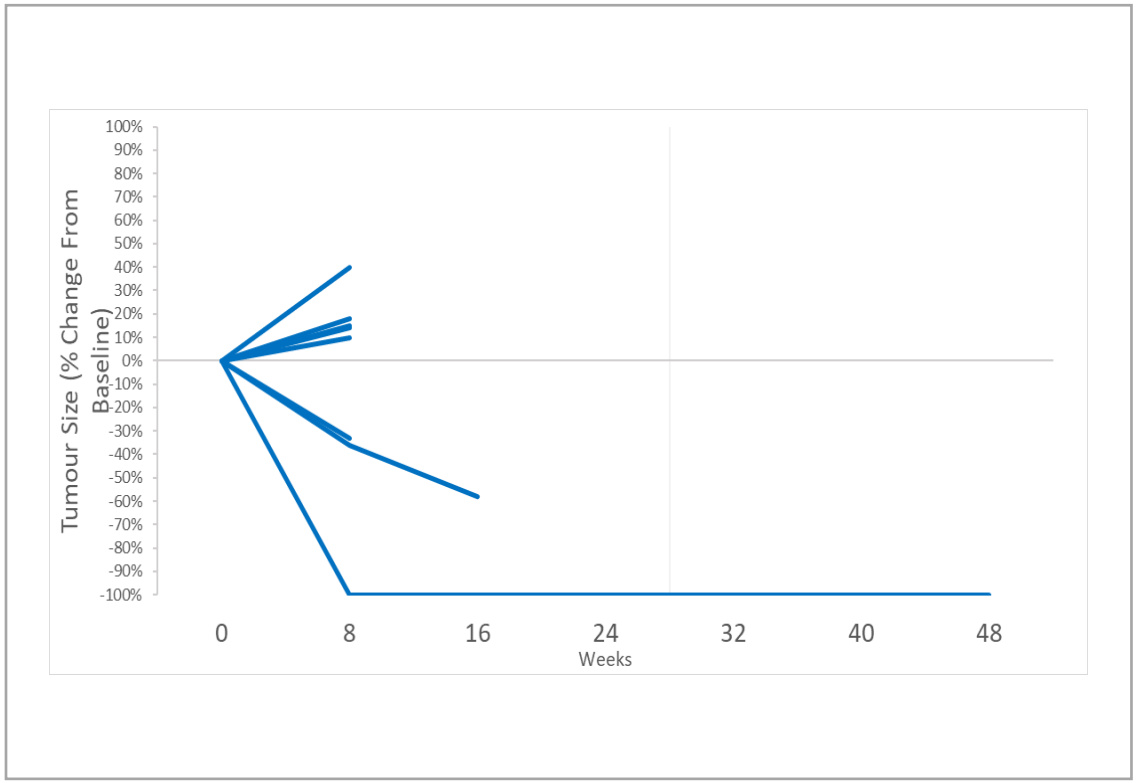
CPI: Checkpoint Inhibitor; 2L: Second-Line; ORR: objective response rate; CR: complete response; PR: partial response

Pelareorep-Atezolizumab Combination in Anal Cancer, ORR Exceeds Historical Efficacy Rates of Like Studies

ORR of 37.5% meets the pre-specified efficacy success criteria. Of 8 evaluable patients:

- 1 CR (ongoing at 12 months)
- 2 PR (one at week 8 and one ongoing at week 16)
- ~11% Average ORR reported in historical control trials of checkpoint inhibitor therapies[1-3]





ORR: objective response rate; CR: Complete Response; PR: Partial Response; Sources: 1. Sheela Rao (Frontier Oncol) 2022;
2. Marabelle et al Lancet Oncology (2022)/NCT02628067; 3. Sara Lonardi (2021) J. Immu Cancer/NCT03944252;

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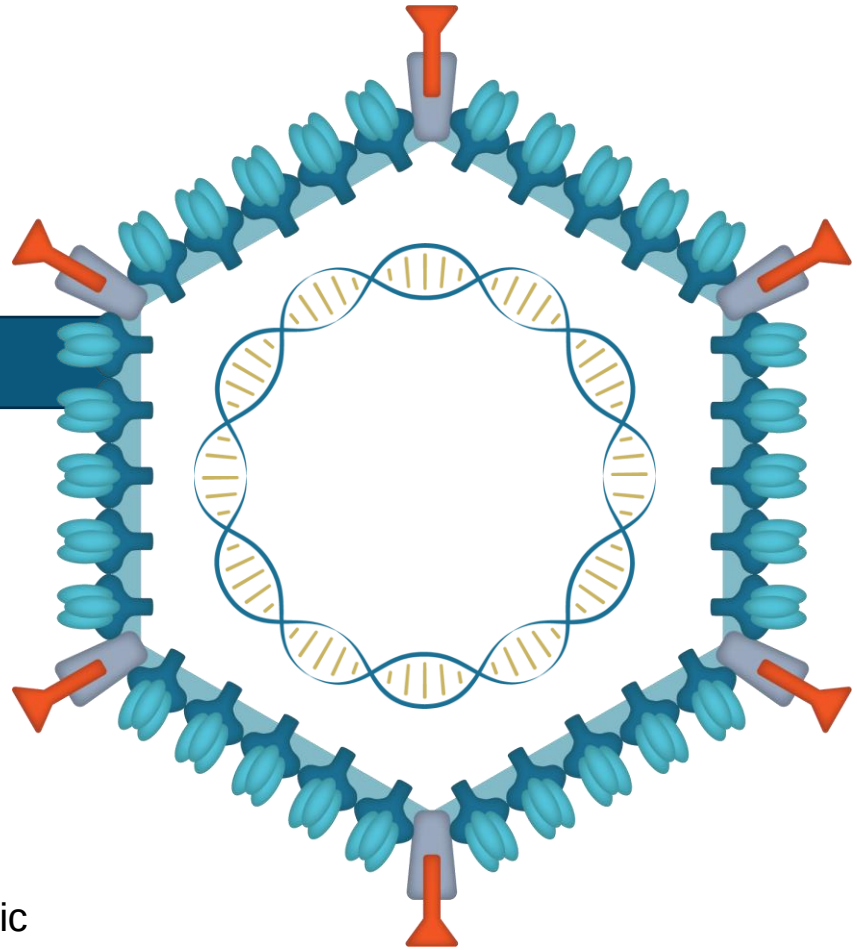
Intellectual Property, Management Team, Financials, Pipeline, Additional Information

Robust Intellectual Property Portfolio

149 patents issued worldwide, including **13 US** and **7 Canadian**

14 pending applications worldwide



Pelareorep issued patent claims cover:

- Compositions of matter comprising pelareorep
- Patent rights extend to at least the end of 2031
- Pharmaceutical use of pelareorep to treat neoplasia and cellular proliferative diseases
- Combination therapy with radiation, chemotherapy and/or immunosuppressants
- Methods for manufacturing pelareorep and screening for susceptibility to pelareorep
- Upon approval, eligible for minimum 12 years of U.S. market exclusivity for new biologic

Updated as of June 30, 2024

Innovative Leadership Team with Strong Immuno-oncology, Business Development, Clinical Trial and Finance Expertise

Matt Coffey, Ph.D., MBA
President and CEO

Kirk Look, CA, MSJ
Chief Financial Officer

Thomas Heineman, M.D., Ph.D.
Chief Medical Officer

Allison Hagerman, PEng, PMP, MBT
VP, Product Development

Christophe Degois
VP, Business Development

Amy Levin, RN, BSN
VP, Clinical Operations

Financials Overview

Financial Overview	
Ticker	ONCY: NASDAQ ONC: TSX
Avg. Daily Volume (1 mo*)	143,061
Shares Outstanding	76,986,033
Market cap[1]	~$79 M
Cash[2]	$24.9 M
HQ	San Diego, CA / Calgary, AB, Canada

Research Coverage	
Patrick Trucchio	H.C. Wainwright & Co.
John Newman	Canaccord Genuity
Jason McCarthy	Maxim Group
Douglas Miehm	RBC Capital Markets
Louise Chen	Cantor Fitzgerald
Douglas Loe	Leede Jones Gable
Soumit Roy	JonesTrading
Rahul Sarugaser	Raymond James

*Trading days from June 26, 2024 – July 29, 2024; 1. Market Cap as of Aug. 1, 2024;
2. Cash as of June 30, 2024

Pelareorep Has Expansive Potential, Starting with Breast and Gastrointestinal Cancers

Program	Collaborator	Combination	Phase 1	Phase 2	Registration-Enabling Study	Milestone
BREAST CANCER						
BRACELET-1 HR+/HER2- mBC	Pfizer MERCK	pela + PTX				OS data reported in Q3 2024
Planned Study	TBD	pela + PTX				Registrational Study Plan H1 2024
GASTROINTESTINAL CANCERS						
GOBLET cohort 1 1L Adv/Metastatic PDAC	Roche	pela + gem + nab-PTX + atezo				OS data pending
Adaptive Study 1L Adv/Metastatic PDAC	Roche GCAR	pela + gem + nab-PTX + atezo				Study initiation 2025
GOBLET cohort 5 Newly Diagnosed PDAC	Roche PANCREATIC CANCER ACTION NETWORK	pela + mFOL +/- atezo				Safety run-in complete Q3 2024
GOBLET cohort 4 ≥2L Unresectable Anal Cancer	Roche	pela + atezo				Enrollment Expansion H1 2024

mBC: Metastatic Breast Cancer; PDAC: pancreatic ductal adenocarcinoma; GCAR: Global Coalition for Adaptive Research; pela: pelareorep; PTX: paclitaxel; gem: gemcitabine; atezo: atezolizumab; mFOL: modified FOLFIRINOX; OS: Overall Survival; Adv: Advanced; 1L: First-Line; 2L: Second-Line

Why Did Avelumab Eliminate the Benefit of Pelareorep?

Avelumab is the only licensed anti-PD-L1 Ab with a native Fc region that retains FcγR binding

Hypothesis:

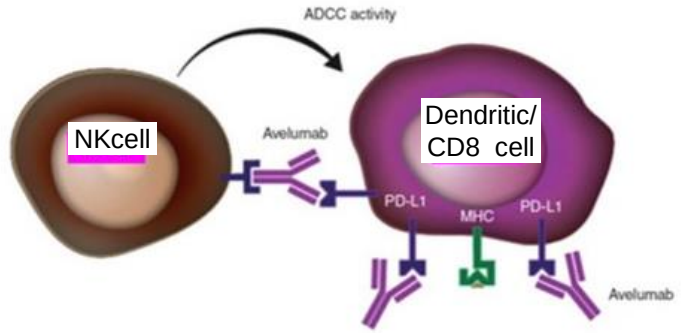
Binding of avelumab to Fc receptors impairs the expansion of T cell clones thereby diminishing the generation of potentially beneficial pelareorep-induced immune responses

Possible mechanisms are shown →

Evaluation of immune cell subsets of cancer patients treated with Avelumab, a fully human IgG1 anti-PD-L1 MAb capable of mediating ADC of human tumor cells

Lauren Lepone[1], Renee Donahue[1*], Italia Grenga[1], Caroline Jochems[2], Kwong-Yok Tsang[1], Simon Metenou[1], Jacob Richards[1], Christopher R Heery[1], Ravi Madan[3], James L Gulley[4], Jeffrey Schlom[1]

Avelumab binding to the FcγR on NK cells may induce ADCC-mediated killing of T cells

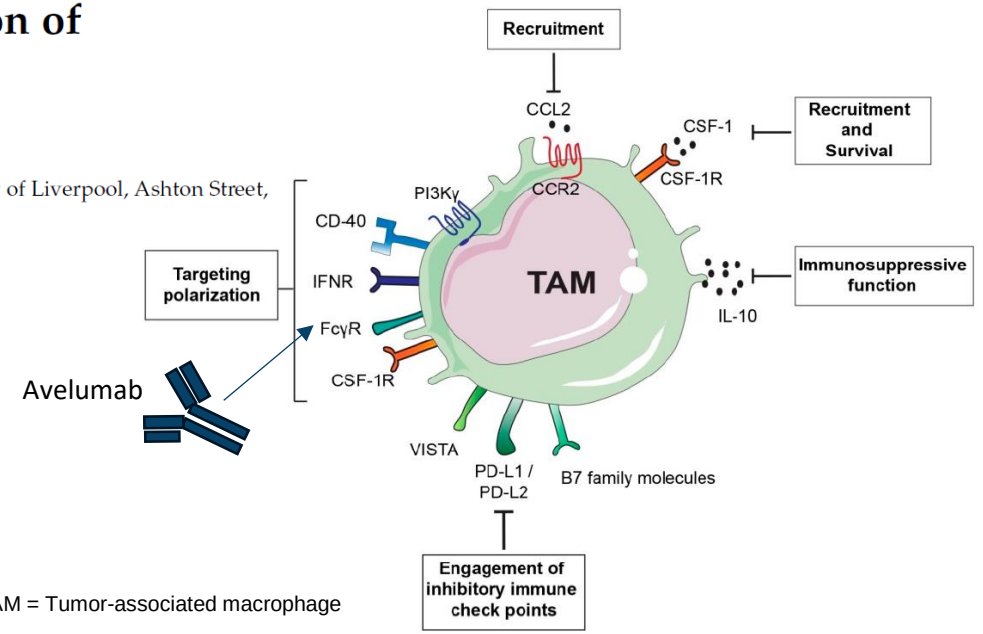


Macrophage-Mediated Subversion of Anti-Tumour Immunity

Valeria Quaranta and Michael C. Schmid *

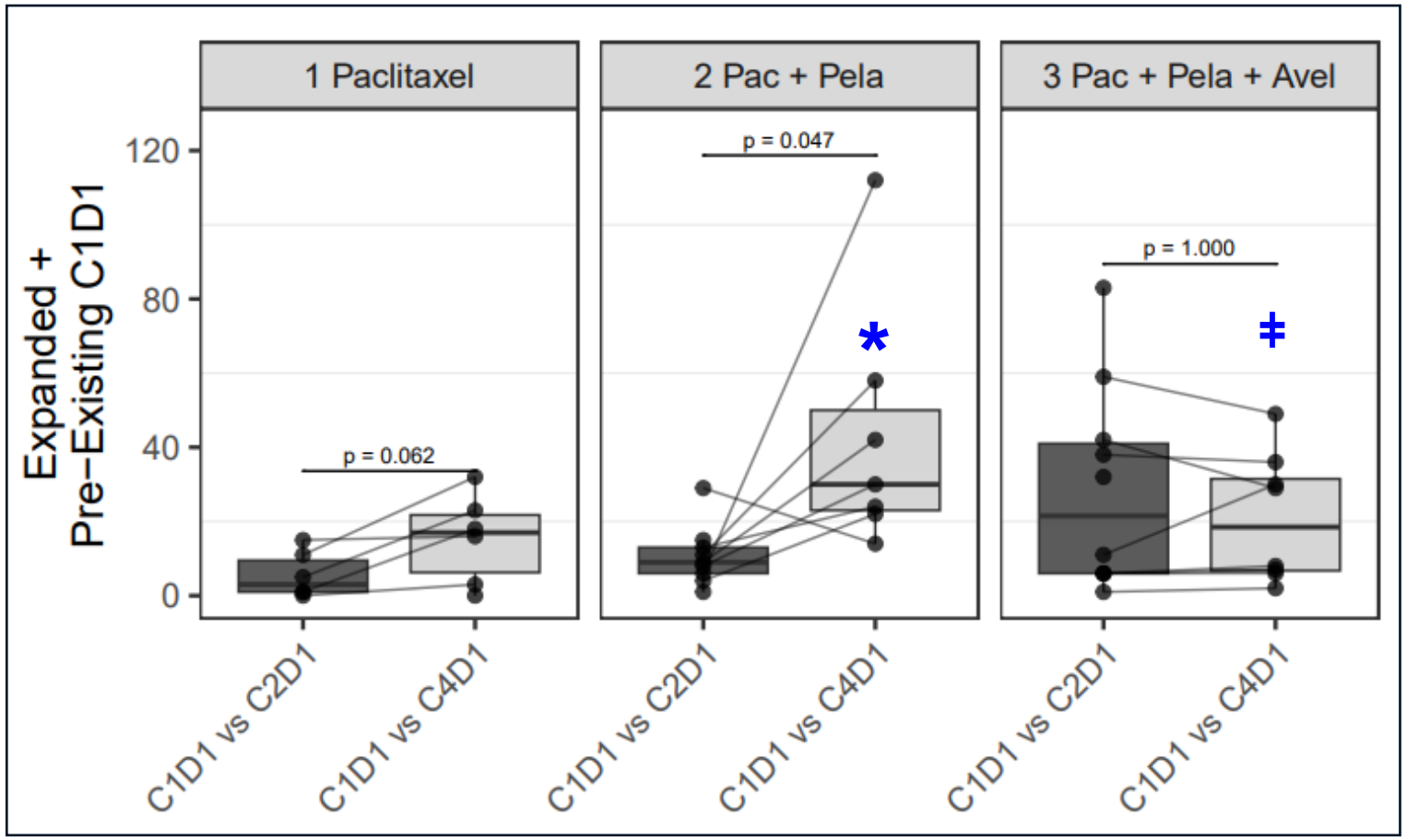
Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Ashton Street, Liverpool L69 3GE, UK

Binding of avelumab to the FcγR on TAMs may drive them to an immunosuppressive M2 phenotype



TAM = Tumor-associated macrophage

T Cell Expansion in BRACELET Patients Blocked by Avelumab



Pelareorep + paclitaxel:

Statistically significant expansion of T cell clones at Cycle 4 Day 1 (*)

Pelareorep + paclitaxel + avelumab :

No T cell expansion at Cycle 4 Day 1 (‡)

Pac = paclitaxel; Pela = pelareorep; Avel = avelumab

C = cycle; D = day

Pelareorep Expected to be Efficacious Following Progression on Enhertu (T-DXd)

- **Pelareorep is efficacious in heavily pre-treated breast cancer patients**
- **T-DXd failure results from reduced HER2 expression or deruxtecan resistance – neither should affect pelareorep's efficacy**[1]
- **T-DXd has no known immunosuppressive effects that would impair pelareorep's MOA**
  - T-DXd does not directly target immune cells, which are key to pelareorep's activity[2]
  - T-DXd is associated with leukopenia or neutropenia; however, these are transient are not expected to affect pelareorep's efficacy based on prior studies
- **T-DXd may stimulate anti-cancer immunity and enhance the effects of immune therapies**
  - Deruxtecan stimulates innate and adaptive immune responses through DNA damage-mediated effects[1]
  - T-DXd enhances tumor-infiltrating CD8+ T cells and MHC class I expression on tumor cells in mice[1]
  - T-DXd induces CXCL9/10/11 on HER2-positive gastric cells resulting enhanced anti-tumor immunity[2]

Sources: 1. Guidi, et al., Cancers, 2023; 2. Nakajima, et al., Nature Sci. Reports, 2021