# 2024 VIRTUAL INVESTOR DAY: CLINICAL INSIGHTS & CLINICIAN DISCUSSION

September 26, 2024

# Forward-Looking Statements

Certain statements set forth in this presentation constitute “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. The words “anticipate,” “believe,” “expect,” “may,” “will” and similar expressions are intended to identify forward-looking statements. Forward-looking statements made in this presentation include, but are not limited to, statements concerning: the protein engineering capabilities of Mural Oncology plc (the “Company”); the potential therapeutic and commercial value, and anticipated safety profile, of the Company’s engineered IL-2, IL-12, and IL-18 cytokine programs and product candidates, including nemvaleukin alfa (“nemvaleukin”) as a cancer immunotherapy when used as monotherapy or in combination, and its broad potential utility across a wide array of tumor types and indications and its potential dosing optionality; the Company’s expectations regarding timelines and plans for the development of its engineered IL-2, IL-12, and IL-18 cytokines, including, for nemvaleukin, expectations related to ongoing clinical studies in the ARTISTRY development program, the ability of ongoing studies to support potential registration, and potential for expansion of the development program, including to explore novel combinations with other cancer treatments; the potential patient populations and market for the indications that the Company is pursuing; and the sufficiency of the Company’s existing cash resources for the period anticipated. You are cautioned that forward-looking statements are inherently uncertain. Although the Company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual results may differ materially from those expressed or implied in the forward-looking statements due to various risks, assumptions and uncertainties. These risks, assumptions and uncertainties include, among others: the inherent risks and uncertainties associated with competitive developments, preclinical development, clinical trials, recruitment of patients, product development activities and regulatory approval requirements; preclinical or interim results and data from ongoing clinical studies of the Company’s cytokine programs and product candidates may not be predictive of future or final results from such studies, results of future clinical studies or real-world results; future clinical trials or future stages of ongoing clinical trials may not be initiated or completed on time or at all; the Company’s product candidates, including nemvaleukin, could be shown to be unsafe or ineffective; changes in the cost, scope and duration of development activities; the U.S. Food and Drug Administration (“FDA”) may make adverse decisions regarding the Company’s product candidates; and those risks, assumptions and uncertainties described under the heading “Risk Factors” in the Company’s filings with the Securities and Exchange Commission (“SEC”), including its Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2024, and as may be updated in subsequent filings the Company may make with the SEC, which are available on the SEC’s website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Except as required by law, the Company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation.

# Highly Experienced Late-Stage Oncology Team

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**CEO**

glympse bio · Bristol Myers Squibb · MERCK · PhRMA RESEARCH PROGRESS HOPE

**Adam Cutler**
**CFO**

Q32 BIO · tem · Arbutus BIOPHARMA · CREDIT SUISSE

**Vicki Goodman, MD**
**CMO**

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**Maiken Keson-Brookes**
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# Mural at a Glance

Phase 2/3

## Late-Stage Trials:

- ✓ **Fully enrolled** for ARTISTRY-7 (Phase 3, PROC) and ARTISTRY-6 cohort 2 (Phase 2, mucosal melanoma)
- ✓ Ongoing discussions with FDA on ARTISTRY-6 potential **confirmatory evidence package**
- ✓ RP2D for **next generation dosing schedule** underway in ARTISTRY-6, cohorts 3 & 4 (phase 2, cutaneous melanoma )

## 2025 CATALYSTS:

- ➢ **Late Q1/Early Q2:** Interim OS for ARTISTRY-7[1]
- ➢ **Q2:** TLR Cohort 2 of ARTISTRY-6
- ➢ **1H:** PDR Cohort 3-mono of ARTISTRY-6 (Phase 2, CM)[2]
- ➢ **2H:** PDR Cohort 4-combo of ARTISTRY-6 (Phase 2, CM)[2]

## Preclinical Assets:

**4Q 2024:** Candidate nominations for IL-18 and IL-12
**4Q 2025:** IL-18 IND submission

## Cash Position:

**Cash runway into 4Q 2025**

## Commercial Opportunity:

Significant opportunity in 2 indications with **limited available therapies** and planned indication expansion

1. Subject to event accrual
2. Subject to patient enrollment



Abbrev.: **CM**: cutaneous melanoma; **IL-12:** interleukin-12; **IL-18:** interleukin-18; **MM**: mucosal melanoma; **OS**: overall survival; **PDR**: preliminary data readout; **PROC**: platinum resistant ovarian cancer; **RP2D**: recommended phase 2 dose; **TLR**: topline results



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# Nemvaleukin: Engineered to unlock the efficacy potential of High Dose IL-2 for more patients

**High dose (HD) IL-2 (PROLEUKIN©/aldesleukin) has proven curative potential in melanoma and RCC**

- Extremely durable complete responses
- However toxic AE profile requires administration in an acute care setting, and severely limits use to the fittest patients

**Nemvaleukin is a novel, stable, immediately active fusion protein**

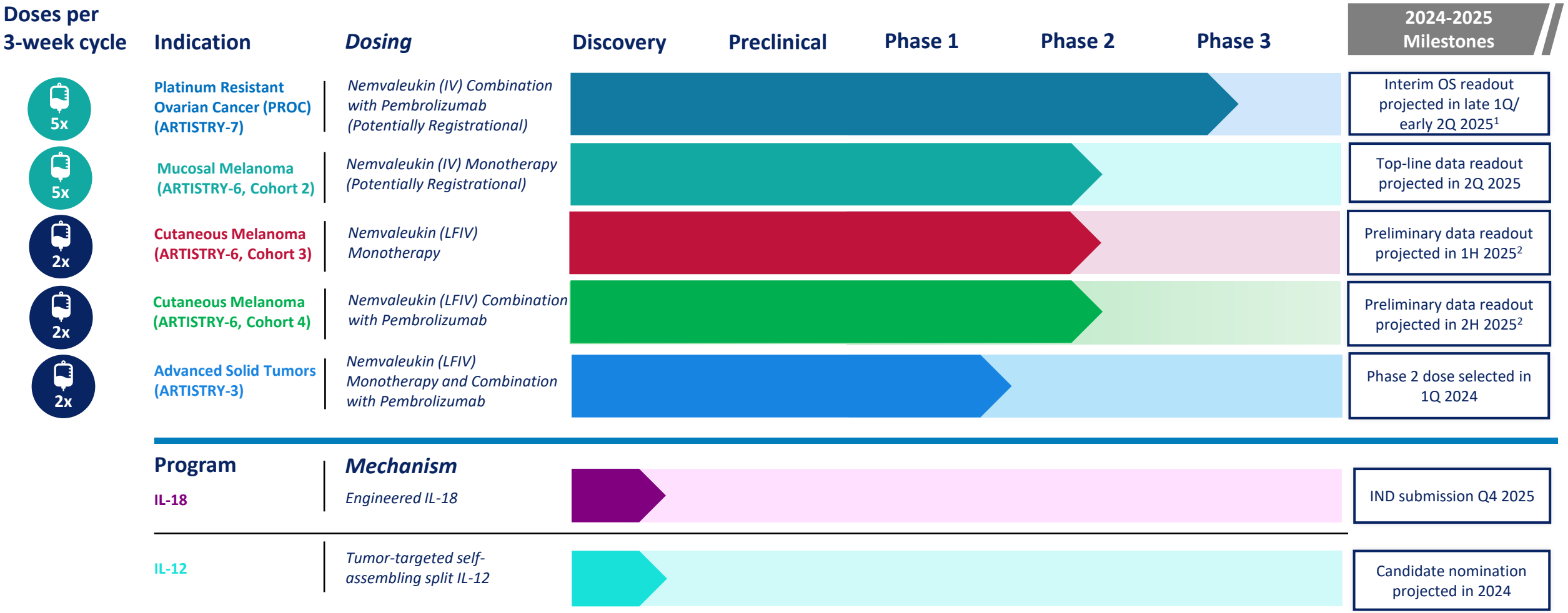
- Elegantly engineered with an 'alpha-non-alpha' structure to mitigate HD IL-2's toxicity
- Design also unlocks therapeutic effects through more selective expansion of cytotoxic $CD8^+$ T cells and NK cells

**Comprehensive clinical dataset from Ph1/2 trial (ARTISTRY 1), including deep and durable responses**

- Durable responses seen with monotherapy in post PD-1 cutaneous and mucosal melanoma
- Durable responses, including complete responses, seen in combination therapy with pembrolizumab in heavily pre-treated PROC patients[1]
- Manageable AE profile allows administration in outpatient setting. No capillary leak syndrome observed
- Currently in two registrational studies – mono and combination therapy

1. Data available on slide 15 of this presentation
2. ARTISTRY-7 (combination therapy), ARTISTRY-6, cohort 2 (monotherapy)

# Pipeline Overview: 2024-2025 Milestones




1. Subject to event accrual
2. Subject to patient enrollment



Abbrev.: **IL**: interleukin; **IV**: intravenous; **LFIV:** less frequent IV dosing; **OS**: overall survival; IND: Investigational New Drug



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# Today's Agenda

| | |
|---|---|
| **Nemvaleukin clinical proof of concept**<br>Monotherapy and combination therapy across broad range of solid tumors | **Ulka Vaishampayan, MD**<br>University of Michigan |
| **Unmet need in platinum-resistant ovarian cancer**<br>Current treatment options and gaps | **John Hays, MD, PhD**<br>The Ohio State University |
| **ARTISTRY-7 overview: PROC**<br>Trial design, powering assumptions, progress update | **Vicki Goodman, MD**<br>Mural's Chief Medical Officer |
| **Mucosal melanoma and the need for dedicated treatments**<br>Differences of disease and current standard of care | **Rich Carvajal, MD**<br>Northwell Health Cancer Institute |
| **ARTISTRY-6 overview: mucosal melanoma**<br>Trial design, powering assumptions, progress update | **Vicki Goodman, MD**<br>Mural's Chief Medical Officer |
| **Engineered IL-18 program**<br>Protein engineering and early data generation | **Jean Chamoun, PhD**<br>Mural's Vice President, Research |
| **Conclusion and Q&A** | **Caroline Loew, PhD and team** |

ULKA VAISHAMPAYAN, MD
UNIVERSITY OF MICHIGAN

# NEMVALEUKIN ALFA: CLINICAL PROOF OF CONCEPT

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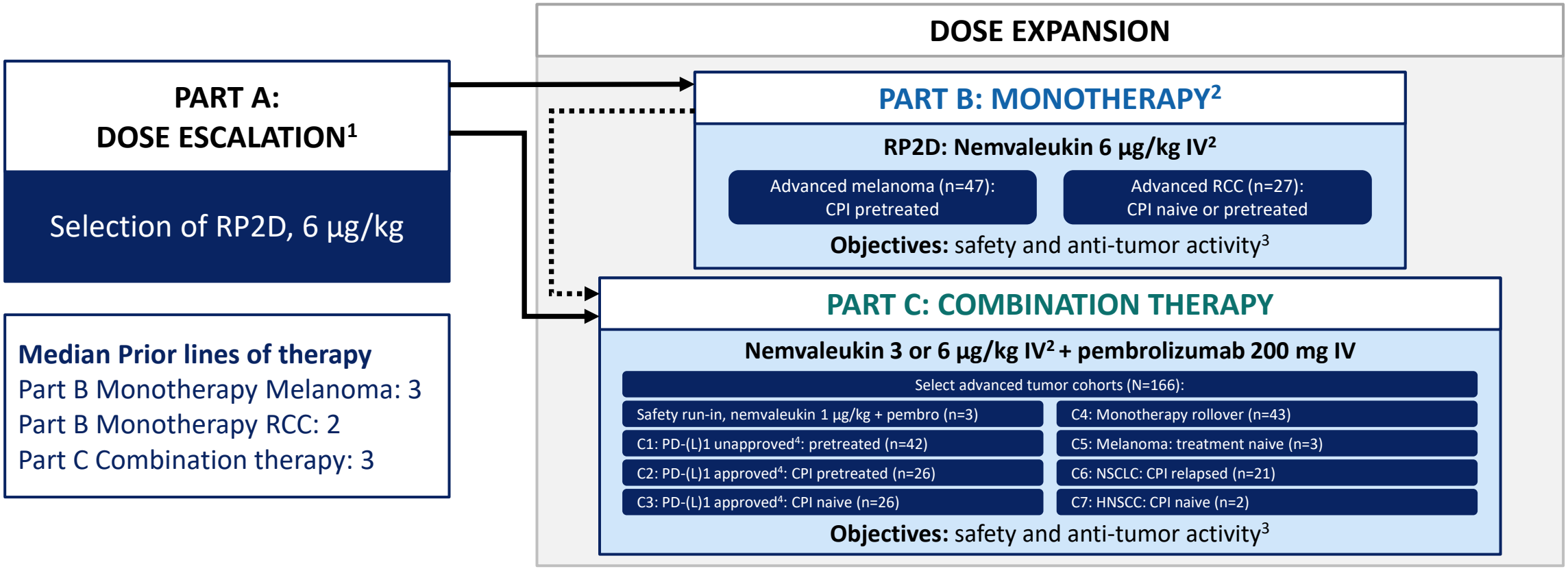
# ARTISTRY-1: First-In-Human Trial of IV Nemvaleukin
# Global, Multicenter, Open-Label Phase 1/2 Trial




NCTO2799095

1. Patients from Parts A and B could roll over to Part C upon progression or stable disease (after ≥ 4 cycles) on monotherapy
2. Nemvaleukin daily Q5D, then off treatment for 9 days (cycle 1) or 16 days (cycle 2+)
3. ORR assessed by investigator (RECIST v1.1)
4. Nemvaleukin 3 µg/kg/d in C1-C4, 6 µg/kg/d in C5-C7. PD-(L)1 approved/unapproved indication based on FDA prescribing information and may have changed over time

**Abbrev.: C1-7**: Cohorts 1-7; **CPI**: checkpoint inhibitor; **HNSCC**: head & neck squamous cell carcinoma; **IV**: intravenous; **NSCLC**: non-small cell lung cancer; **ORR**: overall response rate; **PD-(L)1**: programmed death (ligand) 1; **RCC**: renal cell carcinoma; **RECIST**: Response Evaluation Criteria In Solid Tumors; **RP2D**: recommended phase 2 dose





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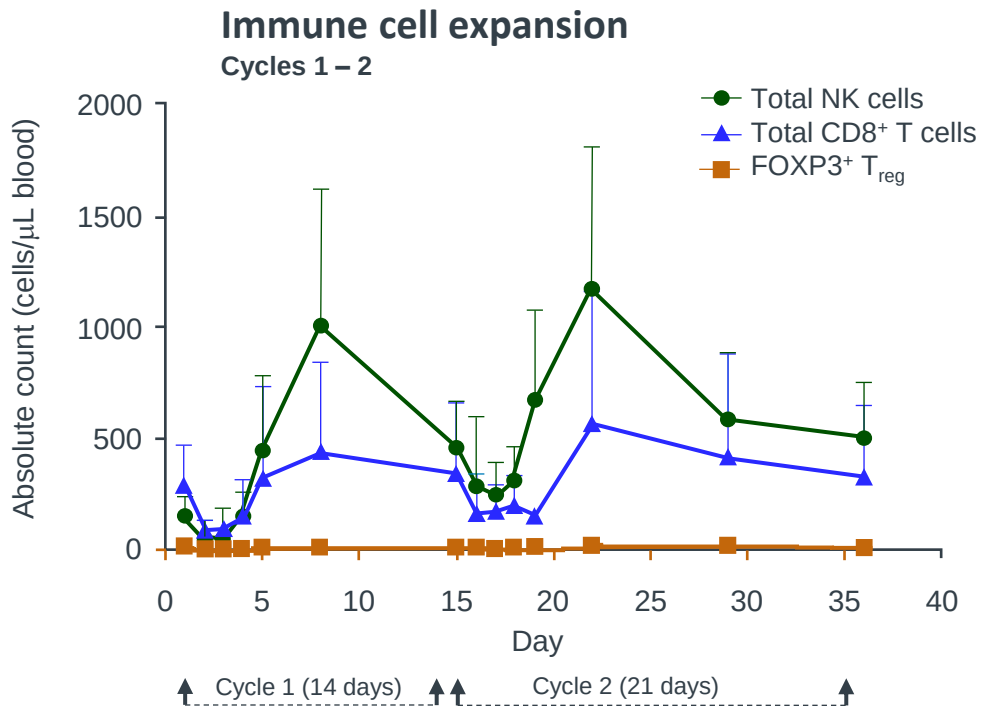
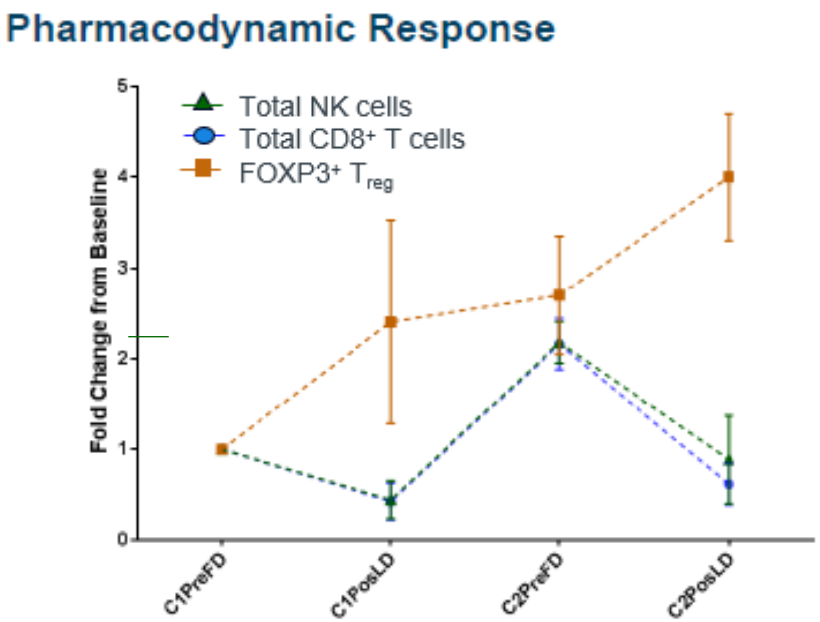
# Clinical Pharamacodynamic Effects of Nemvaleukin are Distinct from HD IL-2, Preferentially Expanding Only Cytotoxic CD8+ T Cells and NK Cells

## Nemvaleukin[1]




## High-Dose IL-2[2]




High-dose IL-2 33 µg/kg IV TIDx5

**Nemvaleukin: CD8+ T and NK cells preferentially expanded while $T_{regs}$ remained suppressed**



Nemvaleukin data are from the 6 µg/kg cohort in Part A of ARTISTRY-1. For fold change plots, data are mean + SE (N=10). For time course plot, data are mean + SD (N=12).
1. Vaishampayan et al. Oral Abstract 2500 presented at ASCO 2022. 2. Bhatt et al. Poster P123 presented at SITC 2018. Abbrev: **HD**: high-dose; **IL-2**: interleukin-2; **IV**: intravenous; **NK**: natural killer; **SD**: Standard deviation; **SE**: Standard Error; **TID**: 3 times daily; **Tregs**: regulatory T cells



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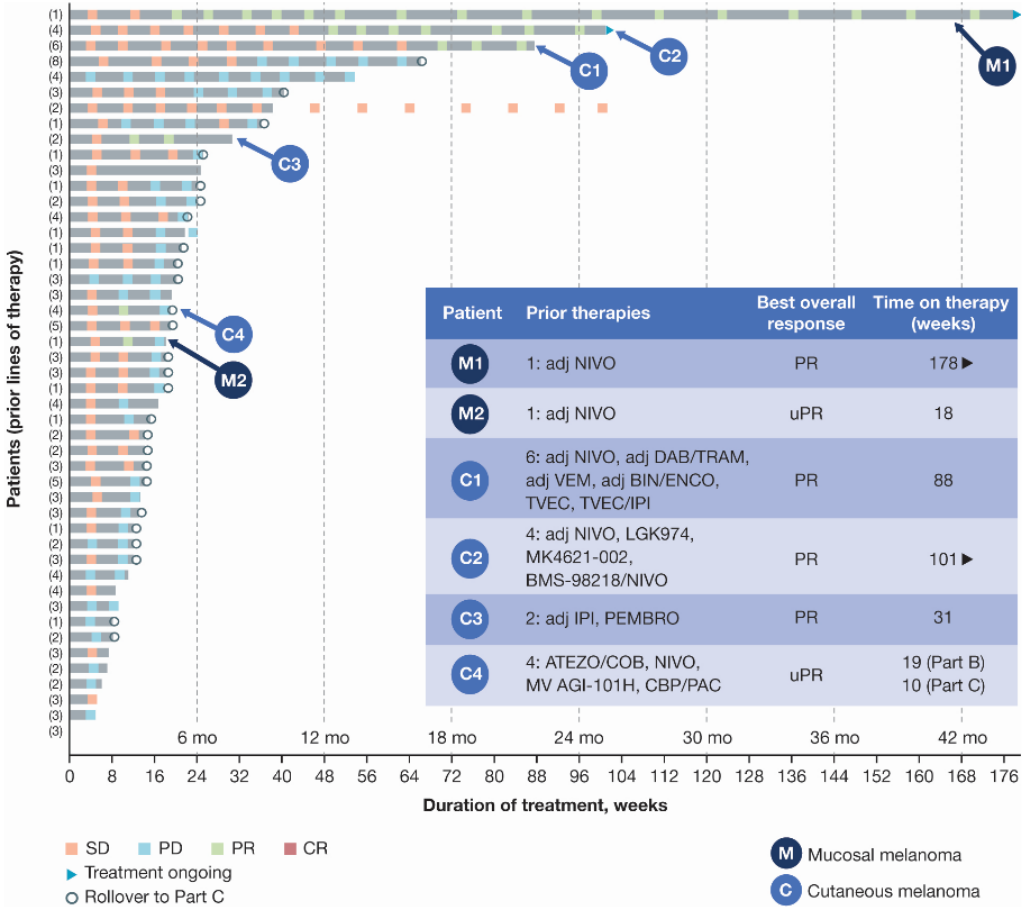
# ARTISTRY-1: Nemvaleukin Demonstrated Durable Monotherapy Responses in Melanoma (Part B)




Responses per RECIST v1.1

| | All[a,b] (n=46) | Mucosal (n=6) |
|---|---|---|
| Best overall response, n (%) | | |
| CR | 0 | 0 |
| PR | 6 (13.0)[c] | 2 (33.3)[d] |
| ORR, n (%) [95% CI] | 6 (13.0) [4.9-26.3][c] | 2 (33.3) [4.3-77.8][d] |
| DOR in weeks[d], Mean (SD)<br>Median (range) | 40.77 (55.6) [c]<br>16.75 (6.1-150.3) | 78.2 (101.9)[d]<br>78.2 (6.1-150.3) |

[a] Excludes 1 patient who did not meet tumor-evaluable criteria. [b] Patients with mucosal, cutaneous, uveal, acral included in 'All'. [C] Includes 4 confirmed PRs, 2 unconfirmed PRs, [d] 1 confirmed PR. [e] DOR for Part B only and does not include patients who rolled over to Part C; some patients may still be on treatment

- All responders had been on prior CPI therapy and progressed
- FDA Orphan Drug and Fast Track designations, as well as MHRA's ILAP Innovation Passport, granted in mucosal melanoma
- Data supported design of ARTISTRY-6 study

Data cut off Mar 27, 2023

Abbrev.: **adj**: adjuvant; **ATEZO**: atezolizumab; **BIN**: binimetinib; **CBP**: carboplatin; **CI**: confidence interval; **COB**: cobimetinib; **CPI**: checkpoint inhibitor; **CR**: complete response; **DAB**: dabrafenib; **DCR**: disease control rate (CR+PR+SD); **DOR**: duration of response; **ENCO**: encorafenib; **FDA**: US Food and Drug Administration; **IPI**: ipilimumab; **MHRA:** Medicines and Healthcare products Regulatory Agency; **MV**: melanoma vaccine; **NA**: not applicable; **NIVO**: nivolumab; **ORR**: overall response rate; **PAC**: paclitaxel; **PD**: progressive disease; **PEMBRO**: pembrolizumab; **PR**: partial response; **SD**: stable disease; **TRAM**: trametinib; **TVEC**: talimogene laherparepvec; **VEM**: vemurafenib. Data on file.

# Case Study: 66-Year-Old Female with Urethral Melanoma (1 of 2)

M1

## Dx

Melanoma

- Dx w primary urethral mucosal melanoma in Apr 2017
- Cystectomy & pelvic node dissection in Jun 2017

## Prior Treatment

- Adjuvant nivolumab (Sep 2017 – Sep 2018)
- Recurrence 8 months after treatment completion
- Most recent disease progression: Sep 2019

## Nemvaleukin Treatment

**Artistry 1: October 2019 – termination of study ( ~44 mo)**

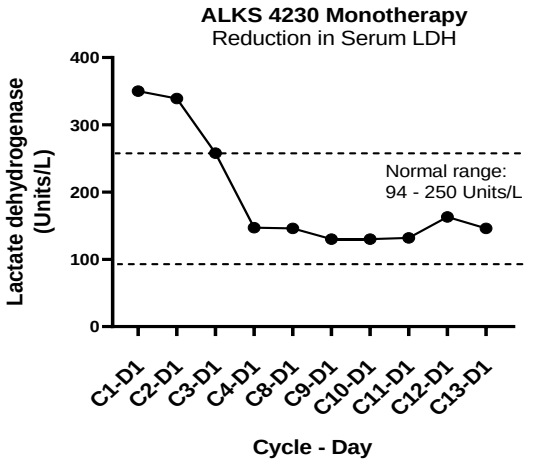
**Continuing treatment on EAP as of July 2024 (~57 months from Artistry-1 treatment start)**

- Nemvaleukin therapy
- 6 µg/kg IV Nemvaleukin

| Target Lesions (Axis mm) | | Non-Target Lesions | | |
|---|---|---|---|---|
| Lymph Node Retroperitoneal (31) | Lymph Node L iliac (18) | Lymph node iliac | Lymph node pelvic | Lymph node Retroperitoneal |

## On-Study Benefits

| Change in Target Lesions from Baseline+ | |
|---|---|
| Cycle 2 | Stable Disease (SD): 8% increase |
| Cycle 4 | SD: 17% reduction |
| Cycle 6-55 | **Partial Response (PR)+:** 54% reduction at the time of study completion |




Notable treatment-related AEs

- Immune-related SAE: Grade 2 iritis/vitritis treated w steroid eye drops
- Grade 3 transient hypotension managed w fluids (SAE)
- Grade 3/4 Neutropenia

+ per RECIST criteria

Artistry-1 Data cut off Aug 2, 2023, EAP cut-off July 2024





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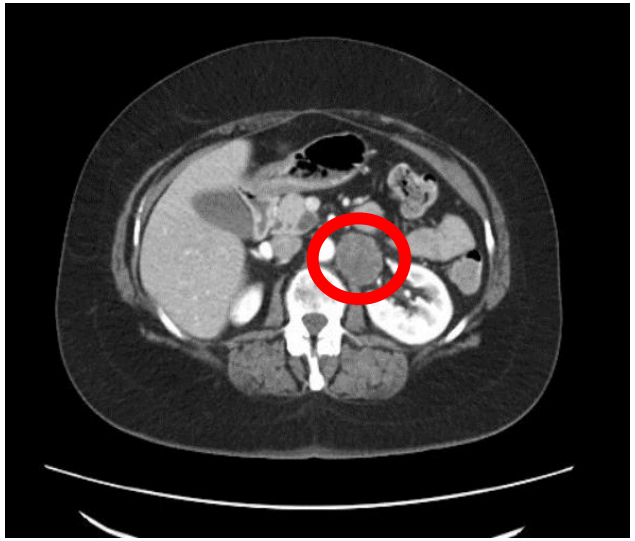
# Case Study: 66-Year-Old Female with Urethral Melanoma (2 of 2): Target Lesion Shrinkage

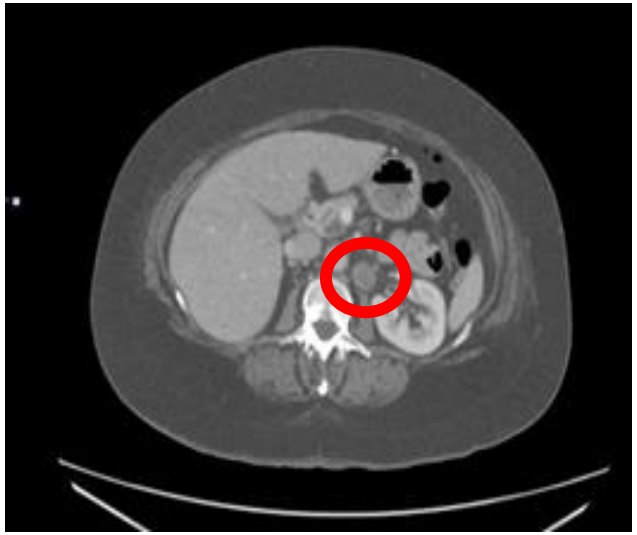
M1


***1 of 2 target lymph node lesions***

**SCREENING 10/9/2019**



**CYCLE 16 9/21/2021**



Artistry-1 Part B, melanoma cohort.
Data cutoff Aug 2, 2023

EAP study
Data cutoff July 2024





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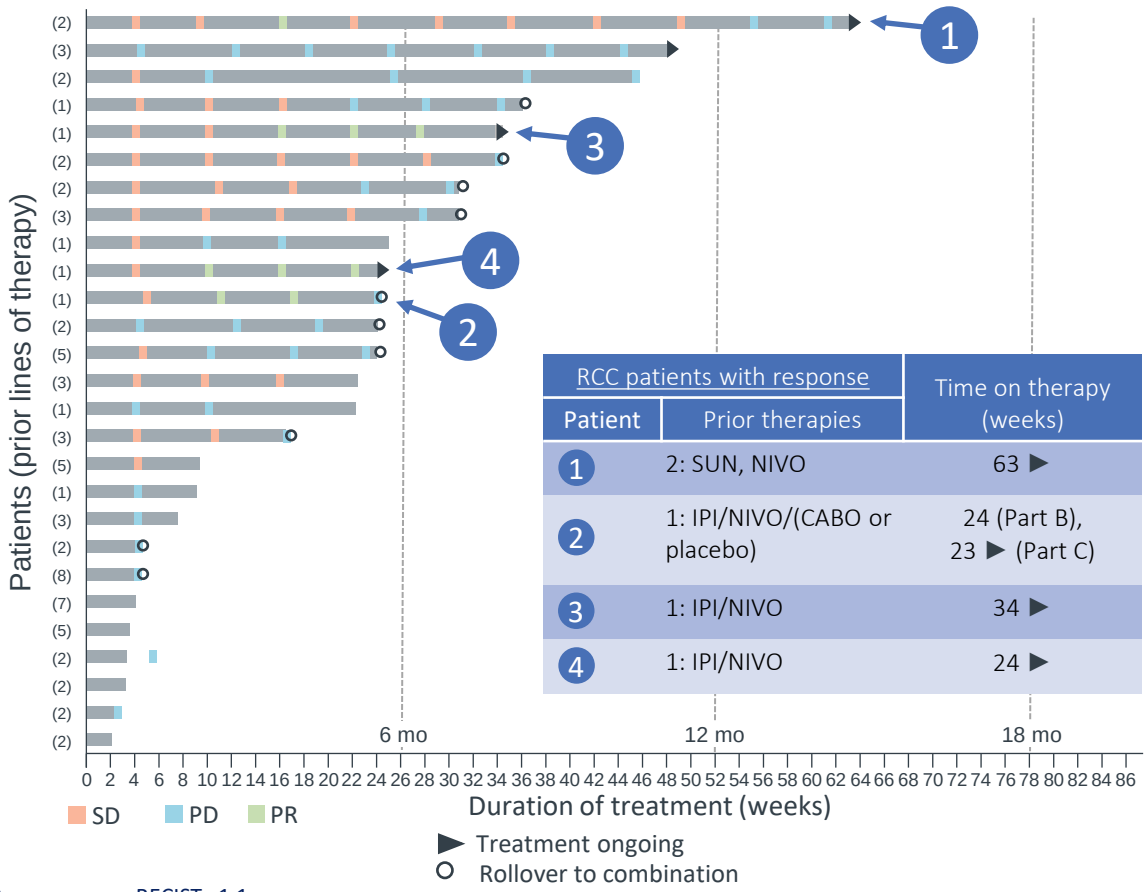
# ARTISTRY-1: Nemvaleukin Demonstrated Durable Monotherapy Responses in RCC (Part B)




| RCC patients with response | | Time on therapy (weeks) |
|---|---|---|
| Patient | Prior therapies | |
| 1 | 2: SUN, NIVO | 63 ▶ |
| 2 | 1: IPI/NIVO/(CABO or placebo) | 24 (Part B), 23 ▶ (Part C) |
| 3 | 1: IPI/NIVO | 34 ▶ |
| 4 | 1: IPI/NIVO | 24 ▶ |

| | RCC (n=22)[a] |
|---|---|
| Best overall response, n (%) | |
| CR | 0 |
| PR | 4 (18.2)[b] |
| ORR, n (%) [95% CI] | 4 (18.2) [5.2-40.3] |
| Median DOR,[c] weeks (range) | 15.6 (12.3-39.0) |

[a] N= 27 (56% received prior CPI), however 5 patients did not meet tumor-evaluable criteria [b]Includes 3 confirmed PRs and 1 unconfirmed PR. [c]DOR is for Part B only and does not include rollover to Part C; some patients may still be on treatment.

- Clinically meaningful responses observed
- All responders had been on prior CPI therapy and progressed

Data cut off Oct 29, 2021

Responses per RECIST v1.1.

CABO, cabozantinib; CPI, checkpoint inhibitor; CR, complete response; DCR, disease control rate (CR+PR+SD); DOR, duration of response; IPI, ipilimumab; mo, months; NIVO, nivolumab; ORR, overall response rate (CR+PR); PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; SD, stable disease; SUN, sunitinib.

1. Vaishampayan U et al. Poster presented at the ASCO Meeting, Chicago, IL, June 3 - 7, 2022





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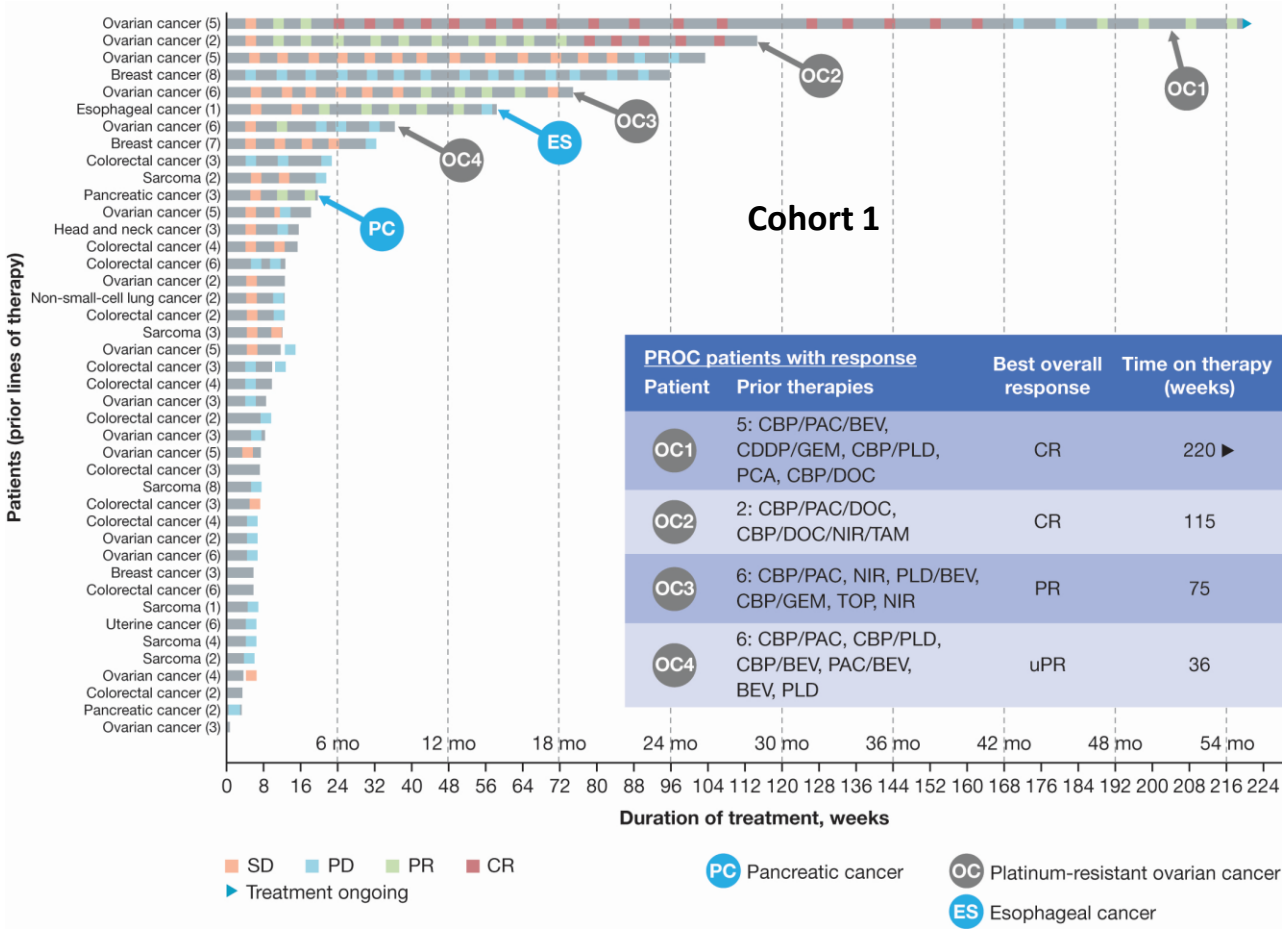
# ARTISTRY-1: Nemvaleukin Combination Treatment with Pembrolizumab Demonstrated Durable Responses




| Best overall response n (%) | PROC (n=14) |
|---|---|
| CR | 2 (14.3%) |
| PR | 2 (14.3)* |
| ORR, n (%) | 4 (28.6)* |
| DOR in weeks | 27.6-130.4[1] |

* Includes 1 confirmed PR, 1 unconfirmed PR

Of the 14 evaluable, investigator reported PROC patients, the median prior lines of ovarian cancer therapy was 5

Data cut off Mar 27, 2023
1. DOR data cut off Sept 27, 2023



Abbrev.: **BEV**: bevacizumab; **CBP**: carboplatin; **CDDP**: cisplatin; **CR:** complete response; **DOC**: docetaxel; **FDA**: Food and Drug Administration; **GEM**: gemcitabine; **mo**: month; **NIR**: niraparib; **PAC**: paclitaxel; **PCA**: paclitaxel albumin; **PD**: progressive disease; **PD-(L)1**: programmed death (ligand) 1; **PLD**: pegylated liposomal doxorubicin hydrochloride; **PR**: partial response; **PROC**: platinum-resistant ovarian cancer; **SD**: stable disease; **TAM**: tamoxifen; **TOP**: topotecan; **uPR**: unconfirmed PR. Data on file.



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# Case Study: 48-Year-Old Female with High-Grade Serous Ovarian Cancer

OC1

**Dx** in Aug 2014
High Grade Serous Ovarian Cancer

- PD-L1 status: TPS = 20%
- BRCA status: *wild-type*
- HRD status: Proficient
- TMB Intermediate
- MSS
- Platinum-Resistant

## Prior Treatment

| Line | Therapy | Duration (mos) | Best Response |
|---|---|---|---|
| 1 | CBP/TAXOL®/AVASTIN® | 5 | SD |
| 2 | CDDP/GEM | 4.6 | SD |
| 3 | CBP/DOXIL® | 4.6 | SD |
| 4 | ABRAXANE® | 3.8 | SD |
| 5 | CBP/TAXOTERE® | 4.6 | PR |

Last dose of prior treatment Feb 22, 2018

## ARTISTRY-1 Treatment

**Jan. 7, 2019 – termination of study** (On treatment ~52 months)*

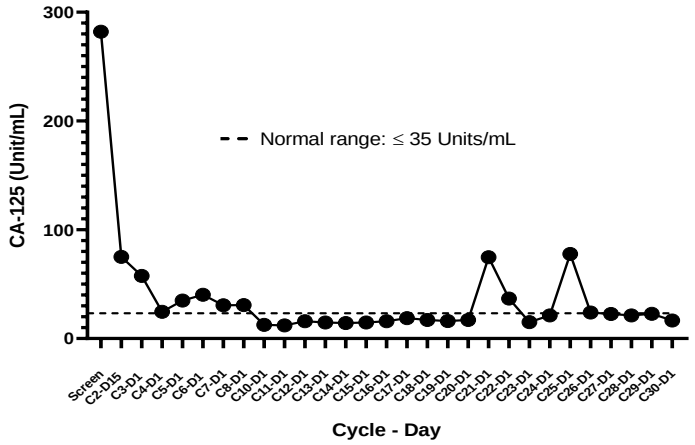
- Nemvaleukin + pembrolizumab therapy
- 3 µg/kg IV Nemvaleukin

| Target Lesions (Axis mm) | Non-Target Lesions |
|---|---|
| L common iliac lymph node (20) | Retroperitoneal lymph node |

## On-Study Benefits

| Change in Target Lesions from Baseline | |
|---|---|
| Cycle 2 | Stable Disease (SD) |
| Cycle 4 | Partial Response+ (PR): 60% reduction **Normalization of CA-125** |
| Cycle 6 | Confirmed PR+ |
| Cycle 8 | **Complete Response (CR)+†:** 60% reduction |
| Cycle 10-52 | **Confirmed (CR)+†:** 70% reduction |

**Nemvaleukin + Pembrolizumab** Normalization of CA-125 tumor marker




- Tolerated therapy well – no notable treatment-related AEs
- No SAEs reported

BEV=bevacizumab, CBP=carboplatin, CDDP=cisplatin, GEM=gemcitabine.

Data cut off Aug 2, 2023





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# Case Study: 83-Year-Old Female with High-Grade Serous Ovarian Cancer

OC2

**Dx** Oct 2008
High Grade Serous Ovarian Cancer

- PD-L1 status: *unknown*
- BRCA status: *wild-type*
- HRD status: unknown
- TMB status: unknown
- Micro-satellite unknown
- Platinum-Resistant

## Prior Treatment

| Line | Therapy | Duration (mos) | Best Response |
|---|---|---|---|
| 1 | CBP/TAXOL®/TAXOTERE® | 4 | Not Evaluable |
| 2 | CBP/ZJL/TAM/TAXOTERE® | 6 | CR |

Last dose of prior treatment Dec 7, 2018

## ARTISTRY-1 Treatment

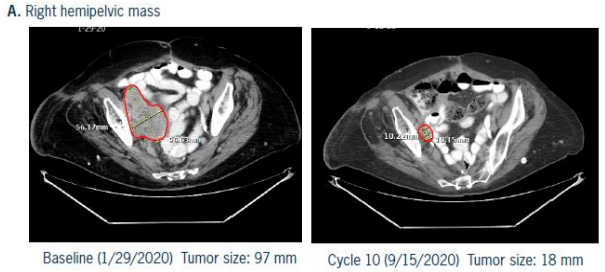
**Feb 2020 – April 2022 (On treatment ~26+ months)**

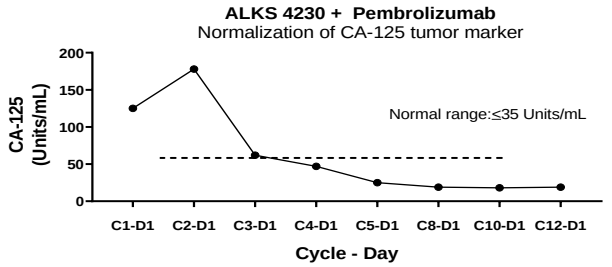
Nemvaleukin + pembrolizumab therapy

3 µg/kg IV Nemvaleukin

| Target Lesions (Axis mm) | | Non-Target Lesions |
|---|---|---|
| R hemi-pelvic mass (97) | R retroperitoneal nodule (34) | None |

> 80% decrease in target lesion in right pelvis




## On-Study Benefits

| Change in Target Lesions from Baseline | |
|---|---|
| Cycle 2 | Stable Disease (SD): 6% reduction |
| Cycle 4 | Partial Response (PR)+: 55% reduction |
| Cycle 6 | **Confirmed PR+**: 68% reduction |
| Cycle 8-22 | PR+: 76-95% reduction |
| Cycle 24-32 | Complete Response (CR): 100% reduction |

D/C study due to pt death (due to colonic perforation not related to study treatment)

Notable treatment-related AEs

- Grade 3 neutropenia

+per RECIST criteria.

Data cut off Aug 2, 2023





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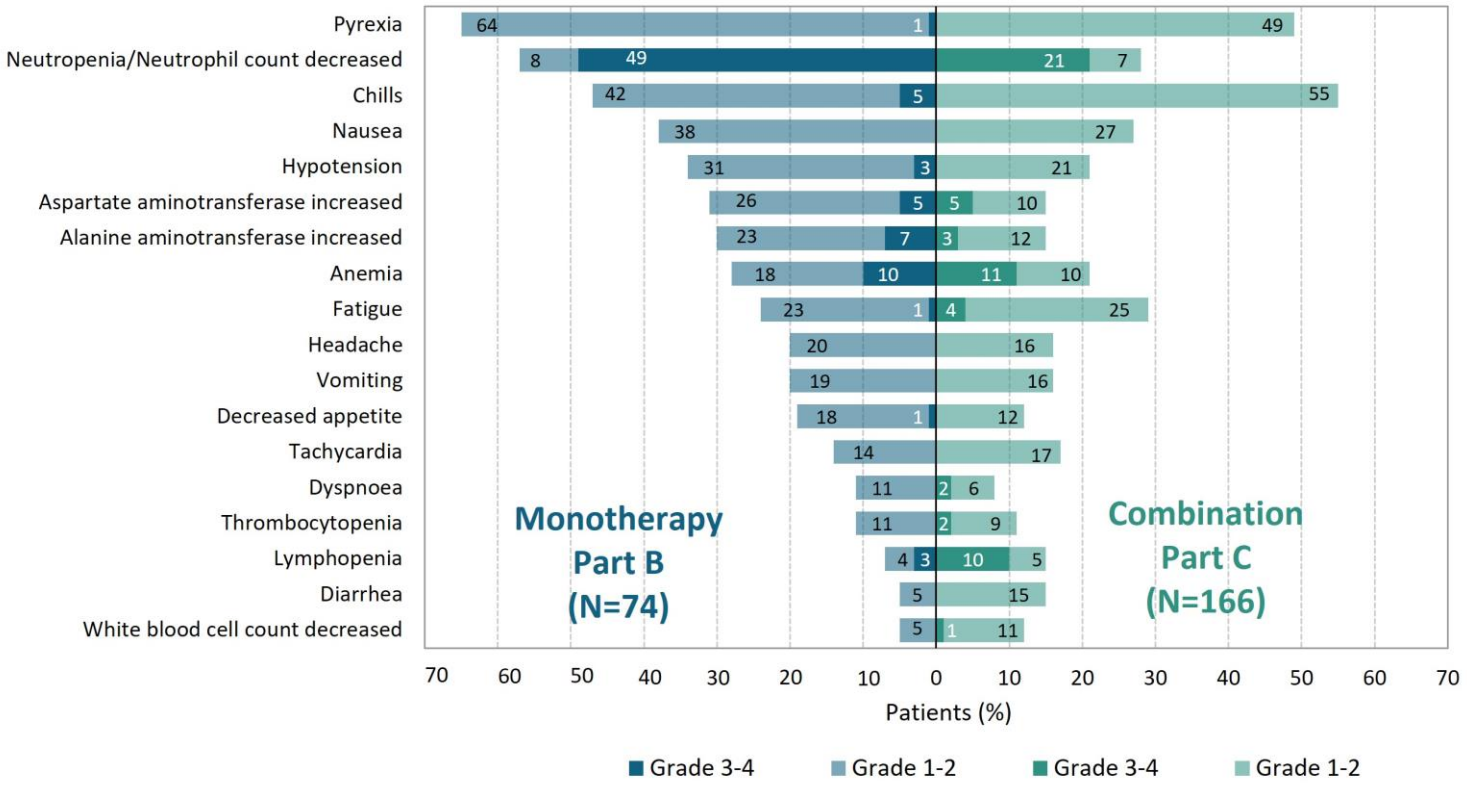
# Nemvaleukin's Adverse Event Profile in ARTISTRY-1 Was Consistent with Our Expectations Based on its Mechanism of Action

*Dose expansion: monotherapy (Part B) and combination therapy (Part C)*




Data as of March 27, 2023

- Administered on outpatient basis; most frequent AEs were manageable with supportive care
- AE profile consistent with nemvaleukin mechanism of action
- Monotherapy safety profile was similar to combination, with no additive toxicity
- Most frequently observed grade 3-4 TRAE: neutropenia[1]
  - Not associated with risk of serious infections or febrile neutropenia
- No capillary leak events reported in ART-1
- TRAEs leading to discontinuation: 4% (monotherapy)[2], 4% (combination)[3]

1. Includes neutropenia and neutrophil count decreased
2. TRAEs leading to discontinuation in monotherapy were Gr3 failure to thrive, Gr3 bronchospasm, Gr2 ECG T wave abnormal, and Gr1 cardiac troponin increase
3. TRAEs leading to discontinuation in combination were Gr5 starvation, Gr3 arthralgia, Gr3 fatigue, Gr3 pneumonia, and Gr2 cytokine release syndrome

Part C includes patients who received nemvaleukin at 1, 3, or 6 µg/kg IV in combination with pembrolizumab 200 mg IV. Data as of Mar 27, 2023 . Data on file.



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JOHN HAYS, MD, PHD
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

# UNMET NEED IN PLATINUM-RESISTANT OVARIAN CANCER

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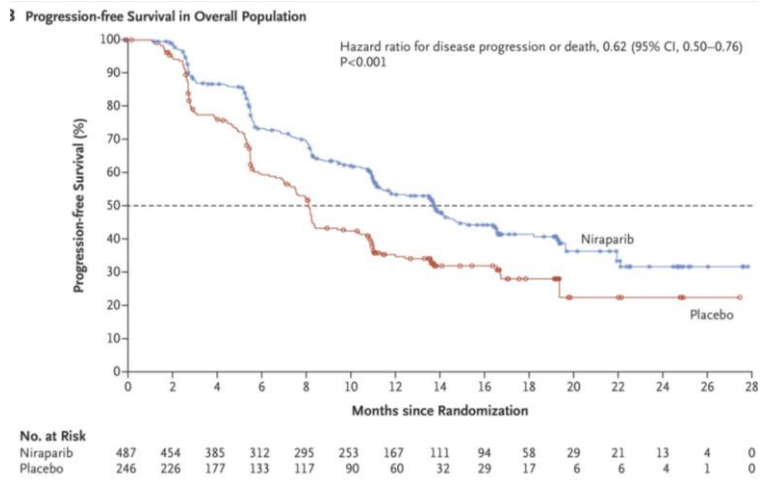
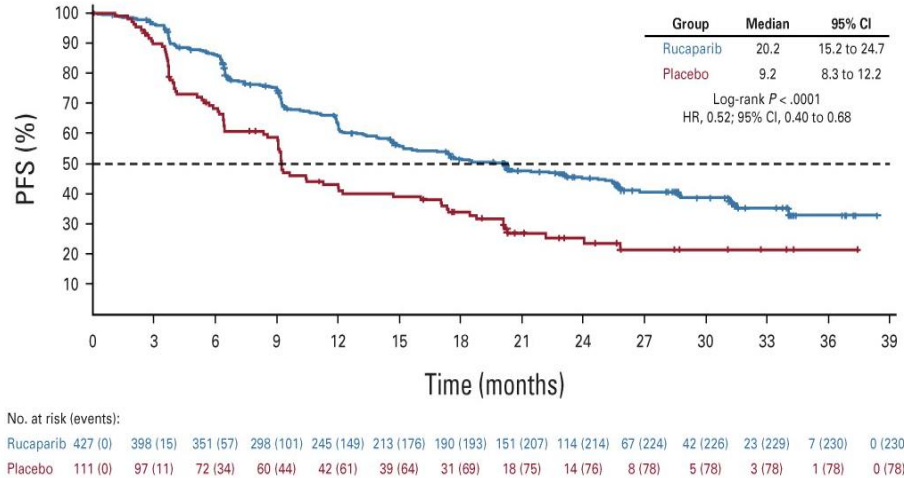
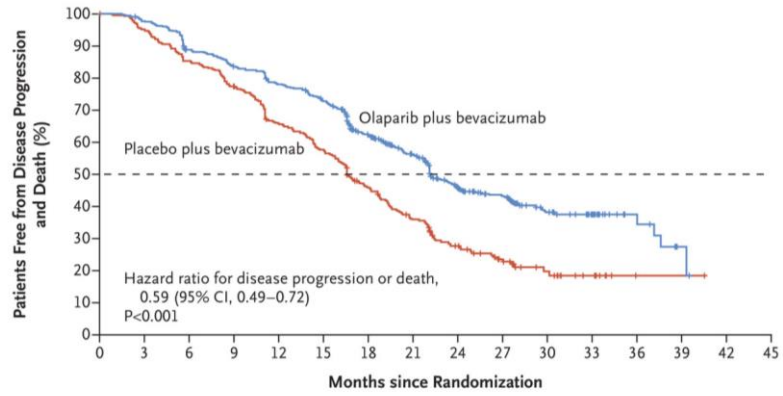
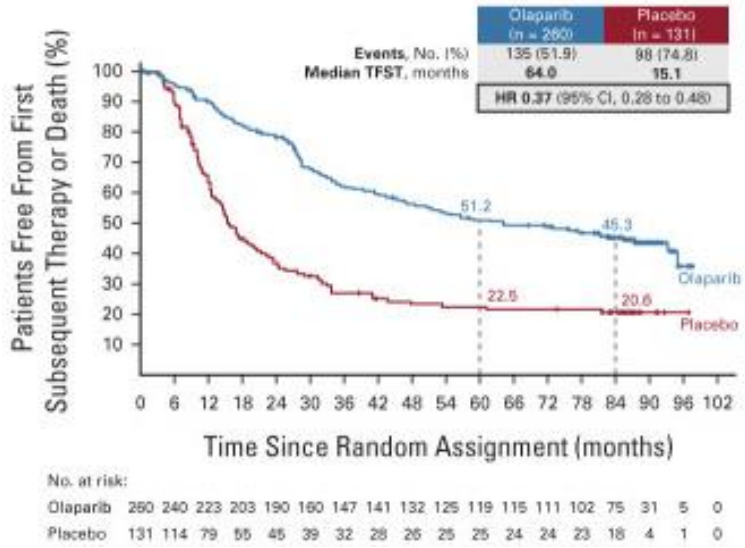
# Platinum Resistant Ovarian Cancer (PROC)

- Ovarian cancer is the second most common gynecologic malignancy but most common cause of gynecologic cancer death in US (~20-25K cases per year)
- No commonly agreed upon early detection test
- 75% of patients diagnosed at advanced stage (Stage III-IV)
  - Primary treatment is systemic chemotherapy/surgery ± maintenance therapy



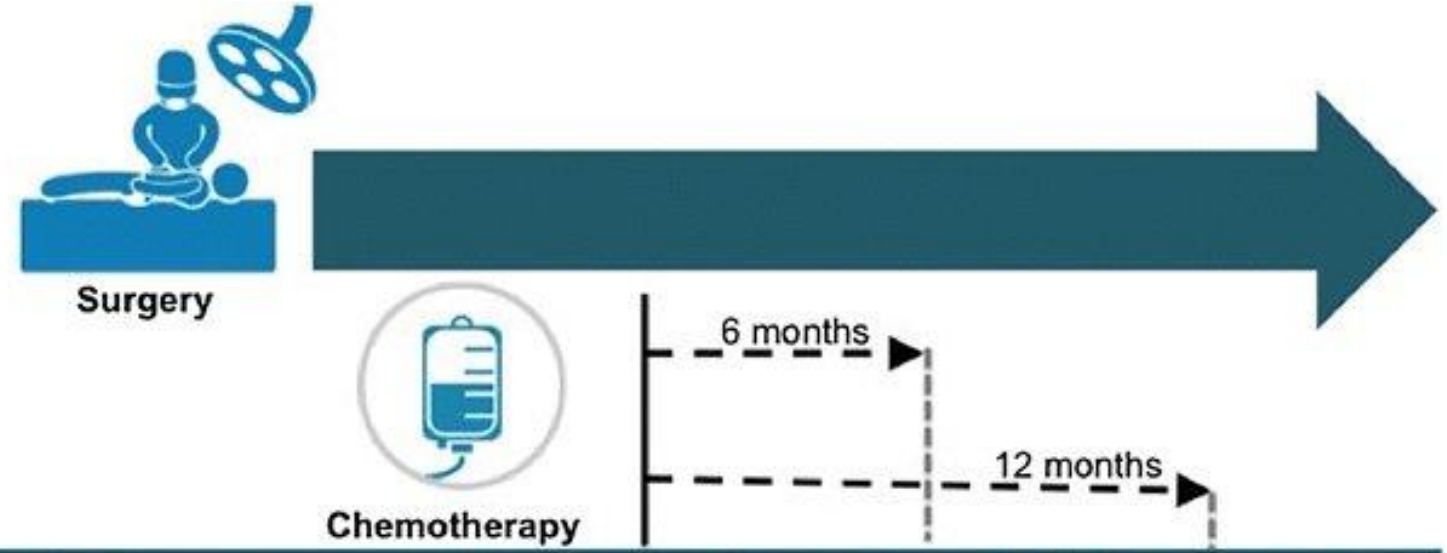




Clockwise from top left: Gonzales Martin et al N Engl J Med 2019;381:2391-2402; Monk et al JCO 2022; 40(34):3952-3964; Ray-Coquard et al N Engl J Med 2019;381:2416-2428; DiSilvestro et al JCO 2023 Jan 20;41(3):609-617

# What do we do when patients recur?




| Platinum sensitivity classification | Refractory | Resistant | Partially sensitive | Sensitive |
|---|---|---|---|---|
| Probability of second platinum response | 0% | <10% | 30% | >50% |

Oronsky et al Med Onc 2017 Med Oncol 2017 Jun;34(6):10

# Platinum Resistance

- Almost all patients who recur will become platinum resistant…
- Aurelia
  - Chemotherapy w/wo bevacizumab
  - Improved PFS but not OS

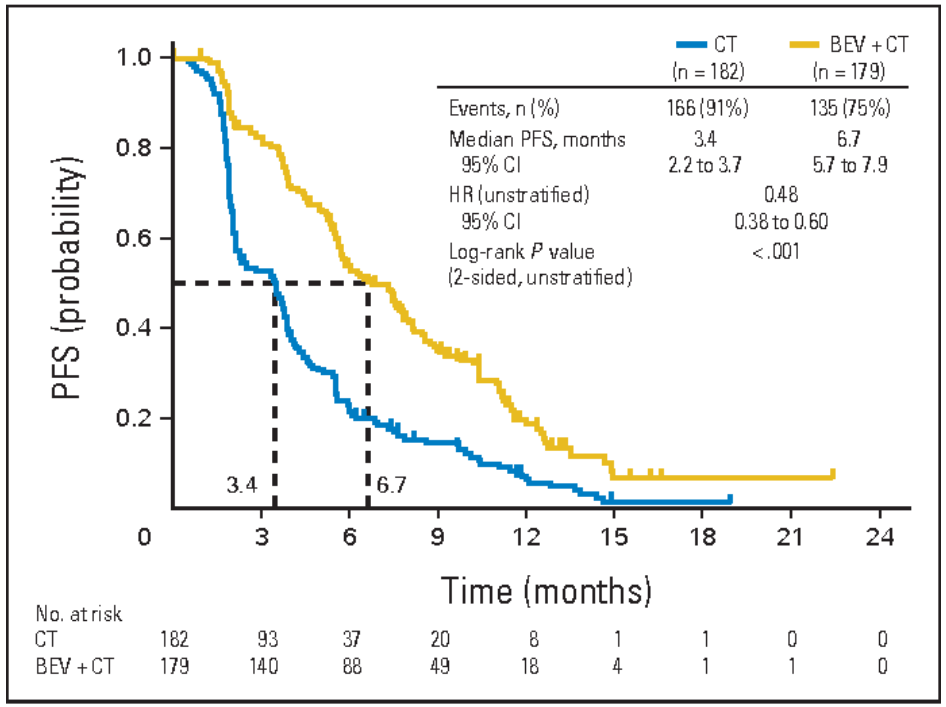



**Fig 2.** Progression-free survival (PFS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.

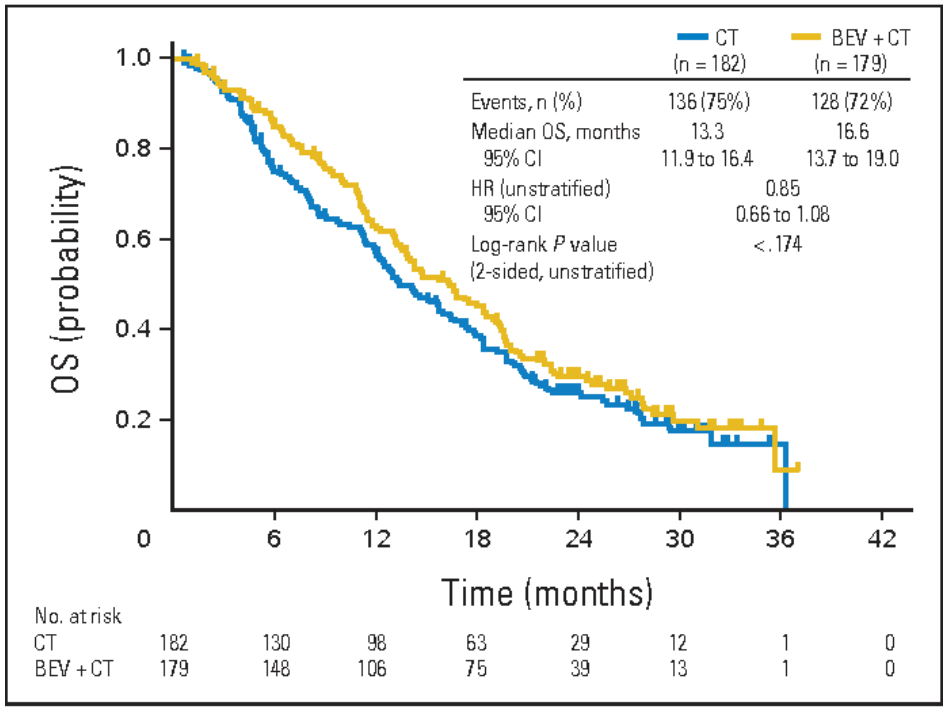


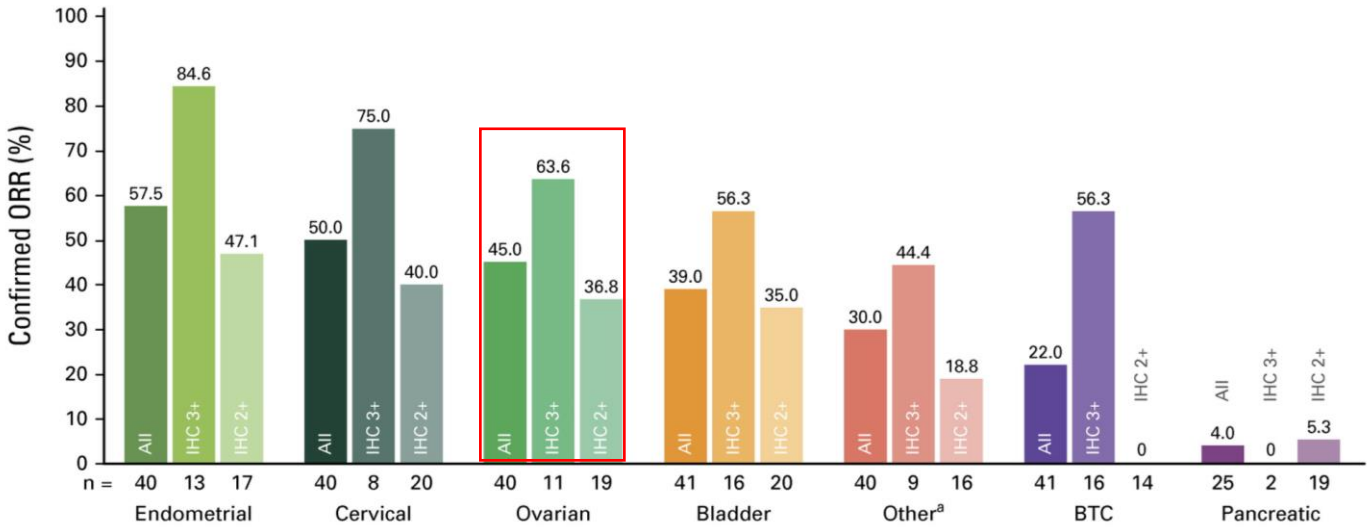

**Fig 3.** Overall survival (OS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.

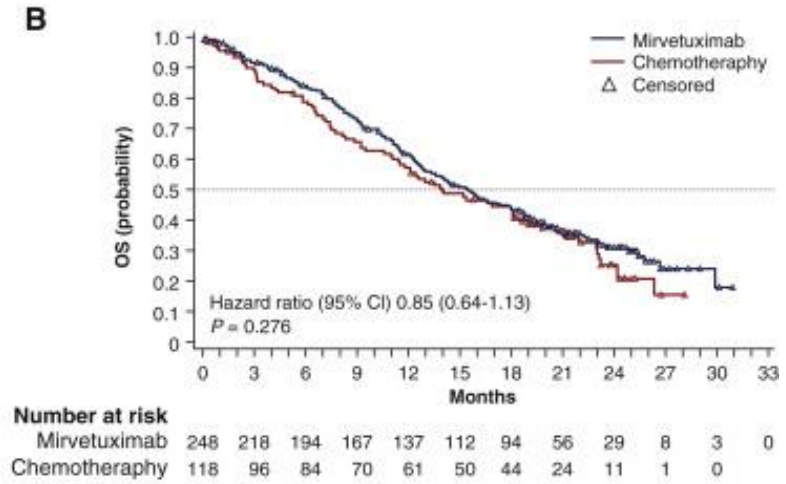
Pujade-Loraine JCO 2014 May 1;32(13):1302-8

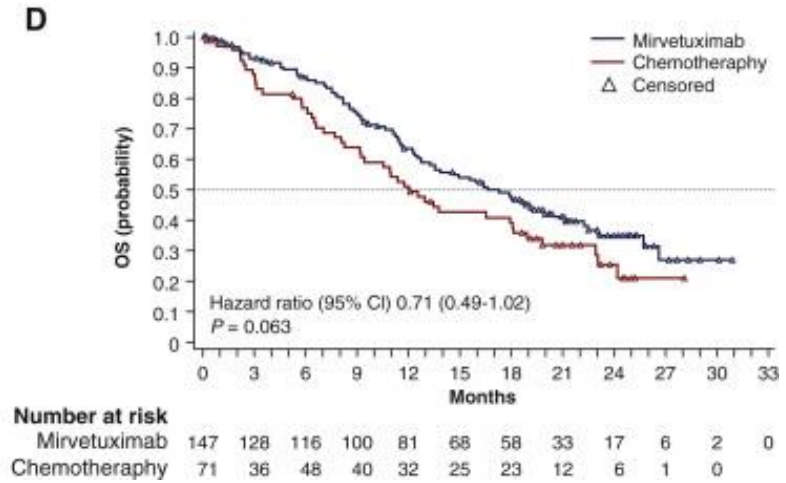
# What about the last 10 years?

## Antibody Drug Conjugates

- Two new approvals in last 2 years
  - Mirvetuximab Sorevtansine (FR$\alpha$)
  - Trastuzumab Deruxtecan (HER2)




Moore et al Annals of Oncology Volume 32, Issue 6, June 2021, Pages 757-765
Meric Burnstam et al JCO 2024 Jan 1;42(1):47-58.

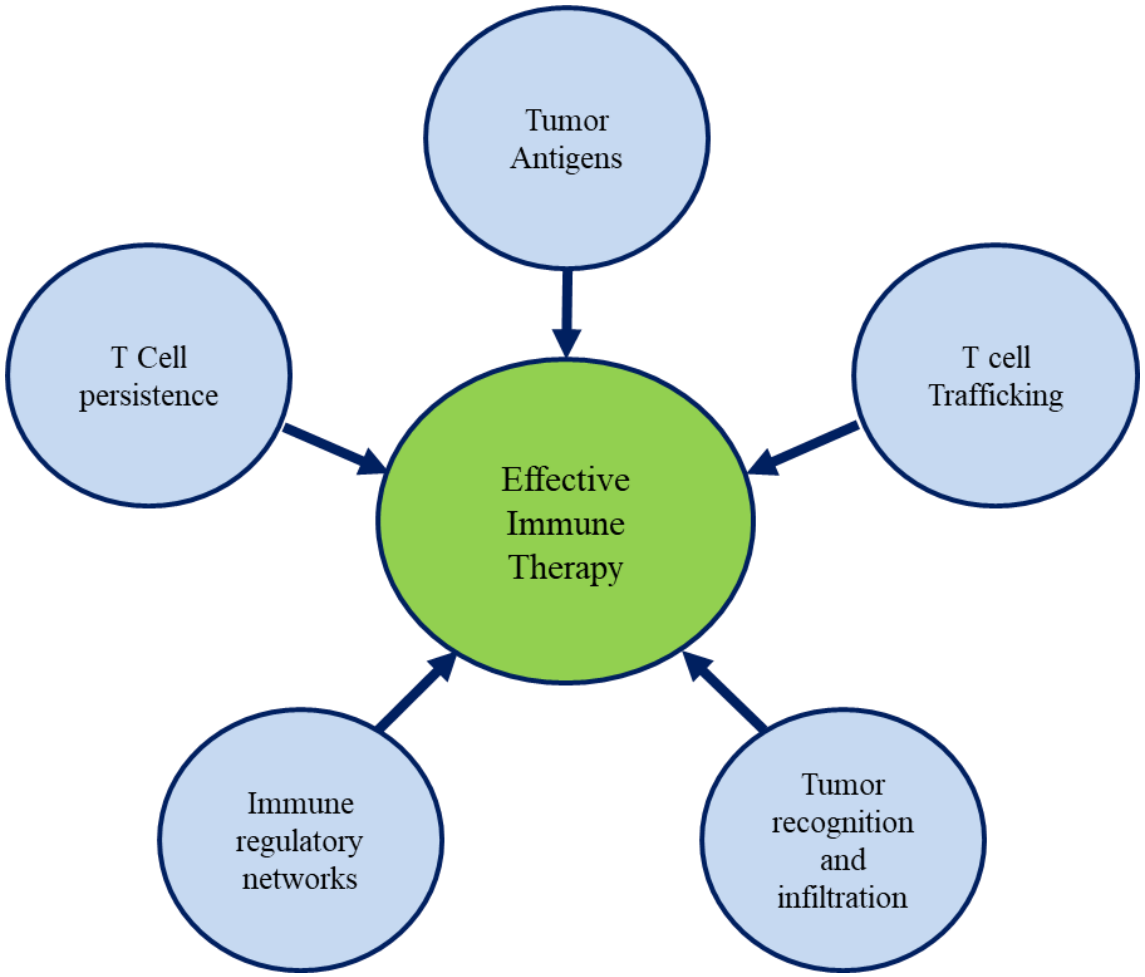
# What about the last 10 years?

Many agents tested:

- Immune therapy
    - Checkpoint inhibitors (PD1/PD-L1, CTLA4, TIGIT, etc…)
    - Novel antigen delivery/recognition (NY-ESO, CA125)
    - Bispecific T-Cell Engagers (BiTE)
    - CAR-T/TCR
- Underwhelming performance
    - 10-15% RR for single agents
    - Increased for combinations (e.g. PD-L1/CTLA4) but at increased toxicity cost

# What About the Future?

- ADCs are great, but…
  - Limited population with marker
    - FR$\alpha$ high – 30-60%
    - HER2 2/3+ – 30%
- IO therapy has promise but monotherapy has limitations
    - Smart combinations are the way forward



VICKI GOODMAN, MD
CHIEF MEDICAL OFFICER

# ARTISTRY-7 OVERVIEW

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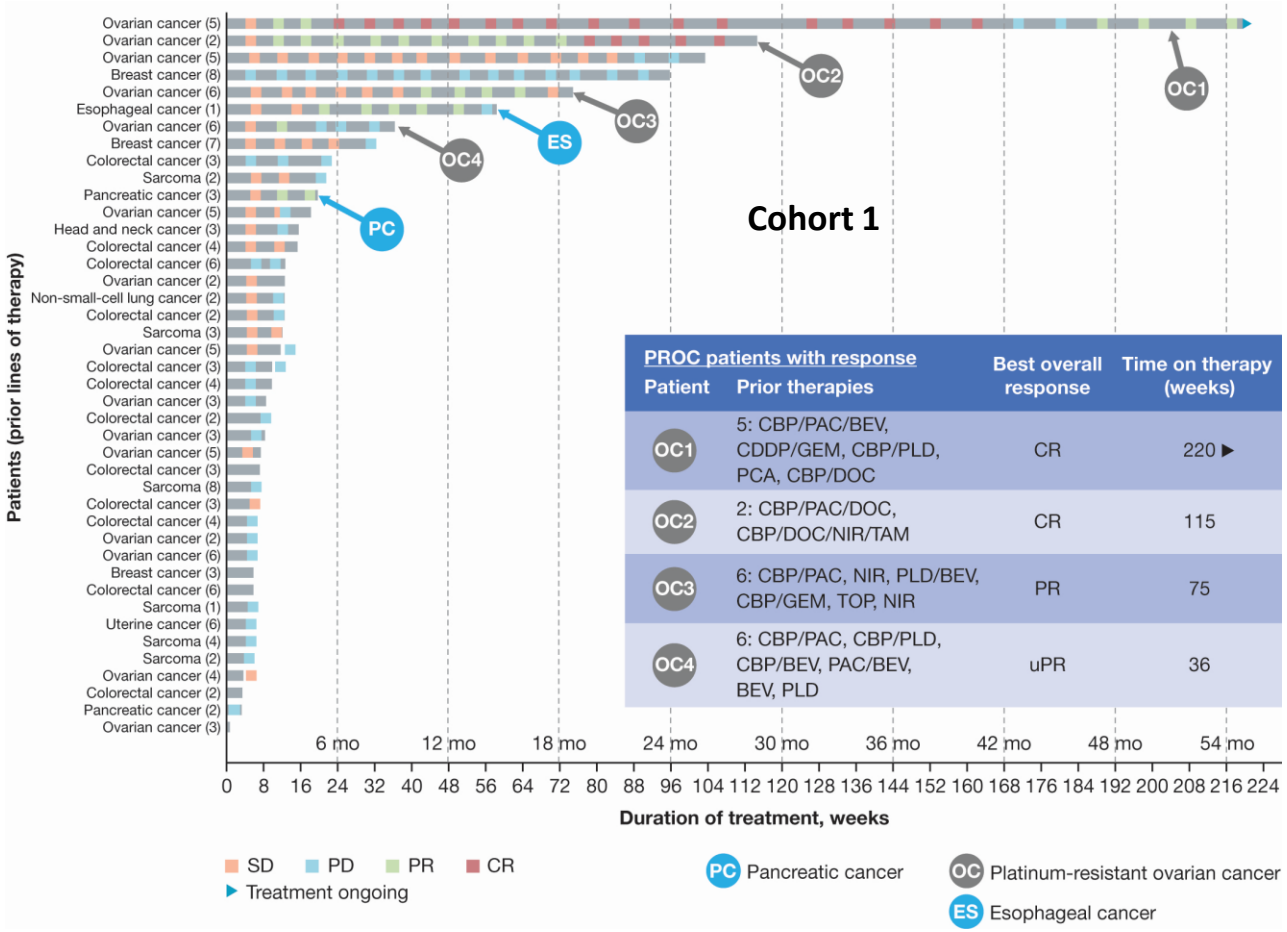
# ARTISTRY-1: Nemvaleukin Combination Treatment with Pembrolizumab Demonstrated Durable Responses




| Best overall response n (%) | PROC (n=14) |
|---|---|
| CR | 2 (14.3%) |
| PR | 2 (14.3)* |
| ORR, n (%) | 4 (28.6)* |
| DOR in weeks | 27.6-130.4[1] |

* Includes 1 confirmed PR, 1 unconfirmed PR

Of the 14 evaluable, investigator reported PROC patients, the median prior lines of ovarian cancer therapy was 5

Data cut off Mar 27, 2023
1. DOR data cut off Sept 27, 2023



Abbrev.: **BEV**: bevacizumab; **CBP**: carboplatin; **CDDP**: cisplatin; **CR:** complete response; **DOC**: docetaxel; **FDA**: Food and Drug Administration; **GEM**: gemcitabine; **mo**: month; **NIR**: niraparib; **PAC**: paclitaxel; **PCA**: paclitaxel albumin; **PD**: progressive disease; **PD-(L)1**: programmed death (ligand) 1; **PLD**: pegylated liposomal doxorubicin hydrochloride; **PR**: partial response; **PROC**: platinum-resistant ovarian cancer; **SD**: stable disease; **TAM**: tamoxifen; **TOP**: topotecan; **uPR**: unconfirmed PR. Data on file.



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# ARTISTRY-7: Phase 3 / Potentially Registrational Study for Platinum-Resistant Ovarian Cancer

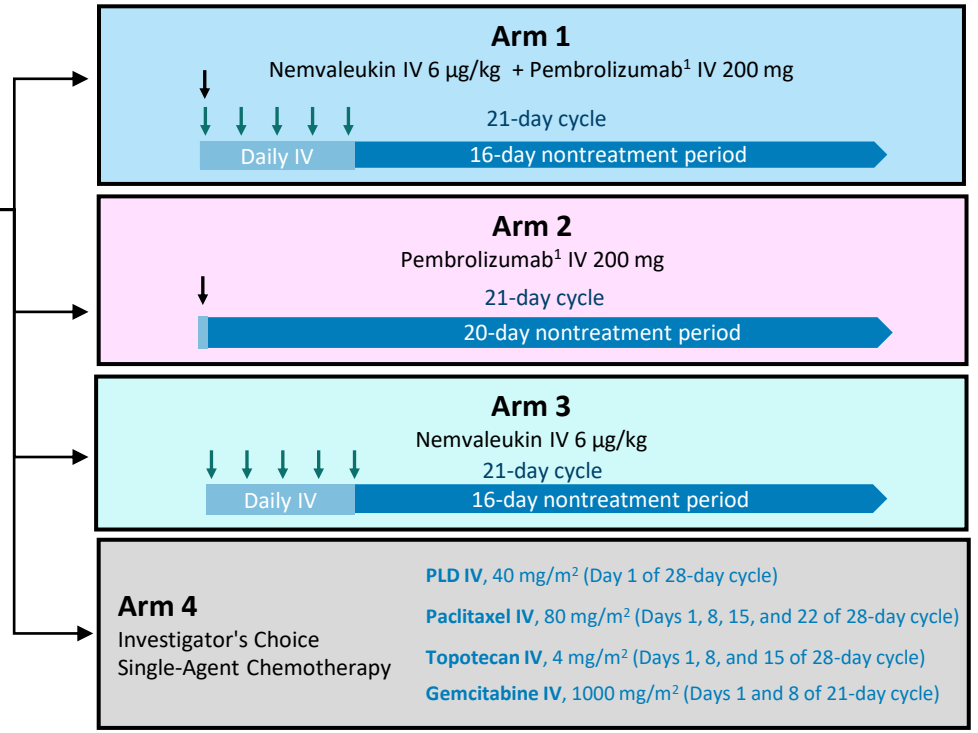
## Investigational Nemvaleukin IV + Pembrolizumab versus Chemotherapy

**Final Enrollment: 456 patients** (vs 448 planned)

Randomization
3:1:1:3
Futility analysis completed for monotherapy arms

### Key eligibility criteria

- Platinum-resistant/refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer
- At least 1L of systemic platinum therapy and ≤5L of systemic platinum-resistant therapy
- Prior bevacizumab treatment
- Measurable disease by RECIST v1.1




### Key Endpoints

**Primary outcome measure:**

- Overall survival (OS)

**Secondary outcome measures:**

- PFS, ORR, DCR, DOR, and TTR
- CA-125 response
- TEAEs

Clinical trial and supply agreement with MSD (a tradename of Merck & Co., Inc. Rahway, NJ, USA)

Conduct of trial is in association with The GOG Foundation, Inc. (GOG), the European Network of Gynaecological Oncological Trial groups (ENGOT), and the Asia-Pacific Gynecologic Oncology Trials Group (APGOT)

↓ Pembrolizumab dosing ↓ Nemvaleukin dosing

[a] Alternative topotecan regimen: 1.25 mg/m² on Days 1-5 of 21-d cycles
[b] Response per RECIST v1.1
[c] Response per GCIG

1. Pembrolizumab may be administered up to 35 cycles.

Abbrev.: **CA-125**: cancer antigen-125; **DCR**: disease control rate; **DOR**: duration of response; **GCIG**: Gynecologic Cancer InterGroup; **IV**: intravenous; **ORR**: objective response rate; **PFS**: progression-free survival; **PLD**: pegylated liposomal doxorubicin; **RECIST**: Response Evaluation Criteria in Solid Tumors; **TEAE**: treatment-emergent adverse event; **TTR**: time to response





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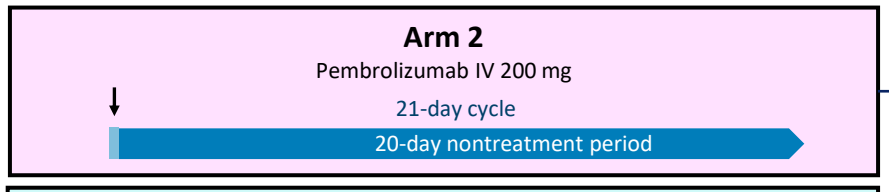
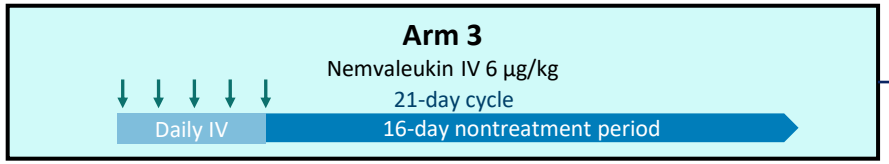
# ARTISTRY-7: Futility Criteria for Monotherapy Arms

## Smaller Single Agent Arms to Assess Contribution of Components


**Arm 4**
Investigator's Choice
Single-Agent Chemotherapy

**PLD IV**, 40 mg/m² (Day 1 of 28-day cycle)
**Paclitaxel IV**, 80 mg/m² (Days 1, 8, 15, and 22 of 28-day cycle)
**Topotecan IV**, 4 mg/m² (Days 1, 8, and 15 of 28-day cycle)
**Gemcitabine IV**, 1000 mg/m² (Days 1 and 8 of 21-day cycle)

**Futility criteria for Arm 2:**

- Based on Keynote-100 trial, where single agent pembro was evaluated in 376 patients with PROC with a response rate of 8%
- Futility in ARTISTRY-7 trial defined as <2 confirmed complete or partial responses in the first 12 patients enrolled
- **This arm was closed to further enrollment for futility in August 2023 after enrolling 27 patients**

**Futility criteria for Arm 3:**

- Based on two phase 2 trials using different doses and schedules of aldesleukin with consistent response rates of approx. 25%, including some patients with durable CRs[1]
- At least 1 patient among first 24 enrolled to achieve ORR or SD for at least 3 months needed to continue enrollment
- **Nemvaleukin single agent arm met the threshold to continue and enrolled a total of 55 patients**

1. Edwards et al. "Comparison of toxicity and survival following intraperitoneal recombinant interleukin-2 for persistent ovarian cancer after platinum: twenty-four-hour versus 7-day infusion." *Journal of Clinical Oncology*, November 1, 1997; Vlad et al. "A phase II trial of intraperitoneal interleukin-2 in patients with platinum-resistant or platinum-refractory ovarian cancer." *Cancer Immunology and Immunotherapy.* February 2010.



Abbrev.: **CA-125**: cancer antigen-125; **DCR**: disease control rate; **DOR**: duration of response; **GCIG**: Gynecologic Cancer InterGroup; **IV**: intravenous; **ORR**: objective response rate; **PFS**: progression-free survival; **PLD**: pegylated liposomal doxorubicin; **RECIST**: Response Evaluation Criteria in Solid Tumors; **TEAE**: treatment-emergent adverse event; **TTR**: time to response



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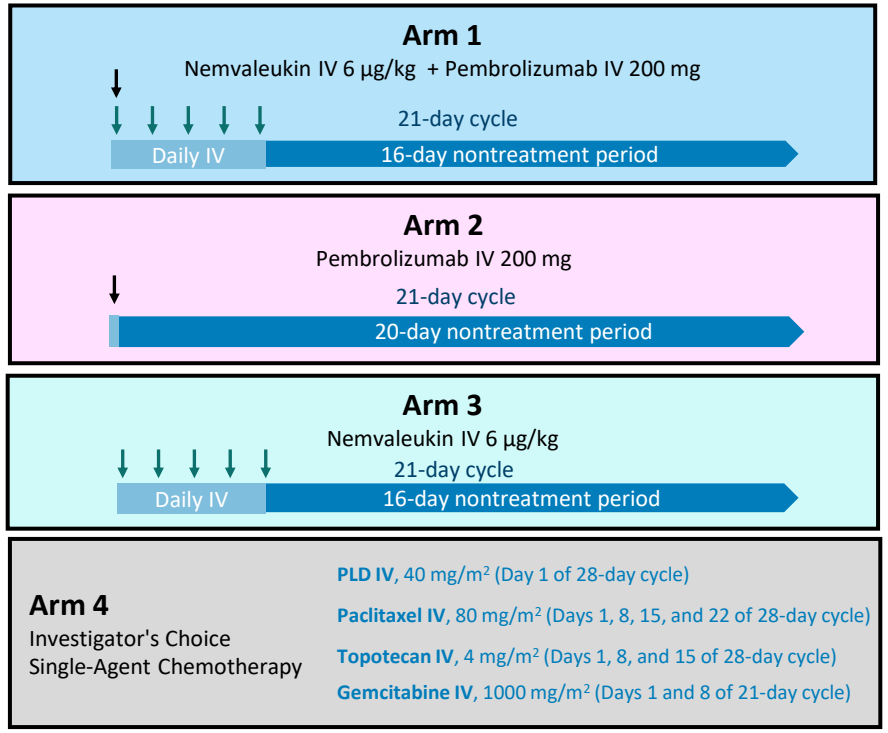
# ARTISTRY-7: Enrollment and Statistical Assumptions




**Final Enrollment**

~187

27

55

~187

456 patients

**Final Enrollment Across Experimental Arms:**

- 374 patients enrolled (approximately 187 per arm)
- Enrollment stratified by PD-L1 expression levels, histological subtype, and choice of chemotherapy

**Overall Survival Expectations and Rationale:**

- OS will be the only hypothesis tested endpoint, with alpha controlled at 2.5% (one sided)
- Expected OS benchmarked using several historical phase 3 trials:
  - Studies differed in eligibility, particularly concerning lines of prior therapy, and with respect to our study
  - Most allowed </= 3 prior lines of therapy and had median OS on chemo control arm between 8 and 13 months
- **Protocol assumptions are a median OS of 10 months for chemotherapy arm and median OS of 14.3 months for Arm 1 (nemvaleukin + pembrolizumab)**



Abbrev.: **CA-125**: cancer antigen-125; **DCR**: disease control rate; **DOR**: duration of response; **GCIG**: Gynecologic Cancer InterGroup; **IV**: intravenous; **ORR**: objective response rate; **PFS**: progression-free survival; **PLD**: pegylated liposomal doxorubicin; **RECIST**: Response Evaluation Criteria in Solid Tumors; **TEAE**: treatment-emergent adverse event; **TTR**: time to response



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# ARTISTRY-7 Interim Analysis Readout Expected Late Q1 or Early Q2 2025

## EVENTS AND STATISTICS

**# of Events:** Protocol specified interim analysis (IA) for overall survival (OS) will occur at 75% of events (~215 of 286 total events)

**Alpha Spend:** Cumulative alpha spend at interim analysis is 1-sided, 0.0096

**Hazard Ratio:** Maximum hazard ratio for success is 0.727 (a 27.3% reduction in the risk of death[1])

## TIMING

**Events:** ~215 events for interim analysis estimated by late Q4 2024 or early Q1 2025

**Data Readout: OS IA readout in late Q1 or early Q2 2025**

1. Assuming exactly 215 events





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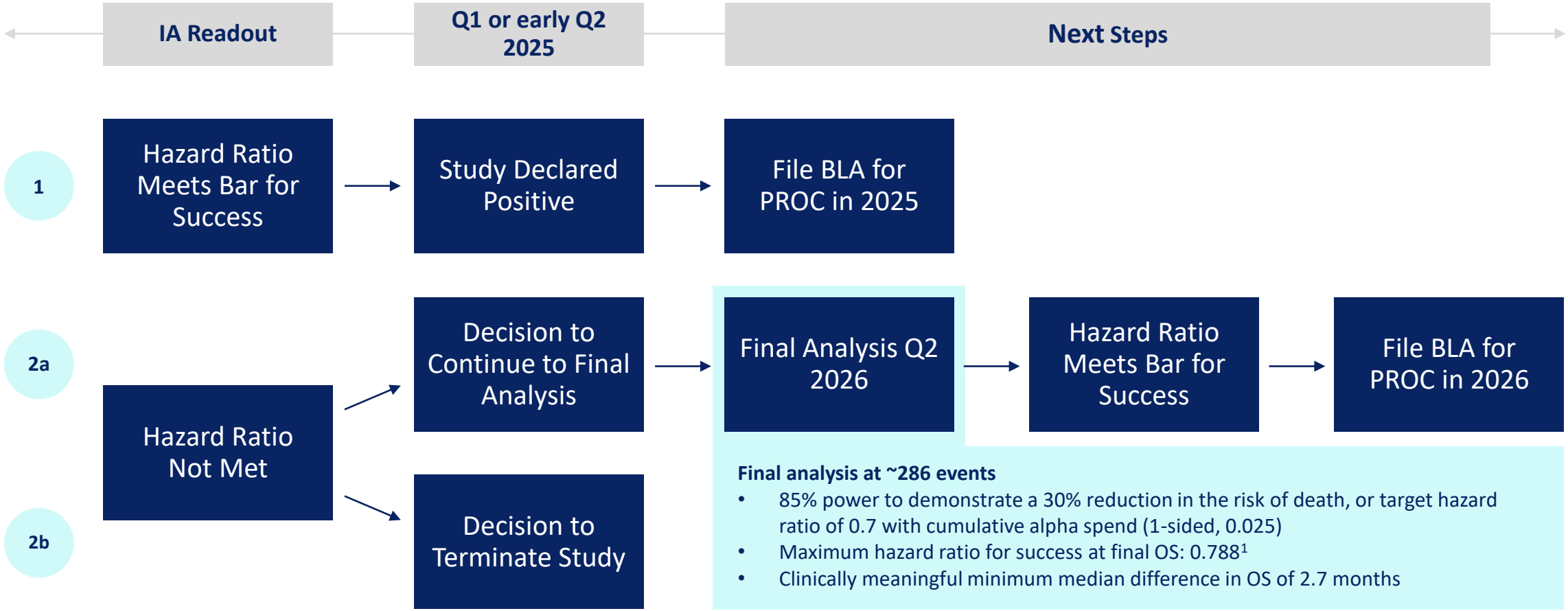
# ARTISTRY-7 Interim Analysis (IA): Potential Outcomes



RICH CARVAJAL, MD

NORTHWELL HEALTH CANCER INSTITUTE

# MUCOSAL MELANOMA & THE NEED FOR DEDICATED TREATMENTS

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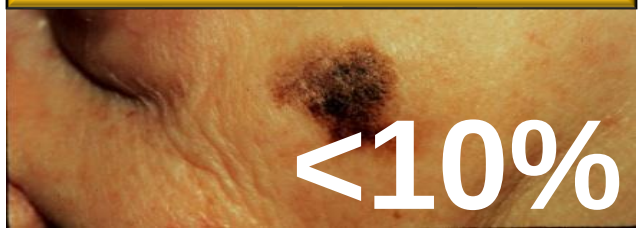
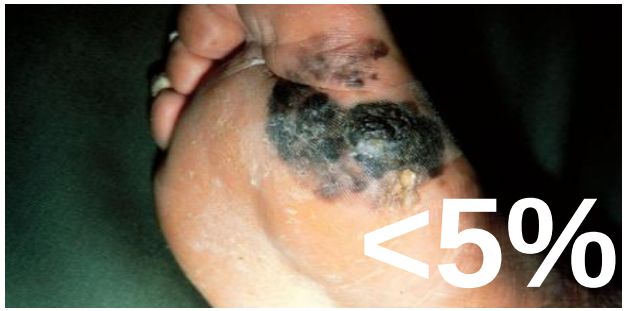
# Mucosal Melanoma: A Rare Melanoma Subtype

**Melanoma in Non-Sun Damaged Skin**

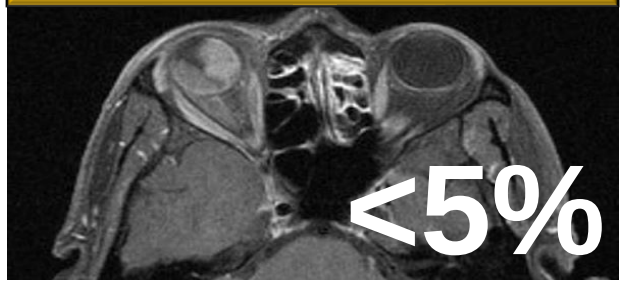

**Melanoma in Sun Damaged Skin**



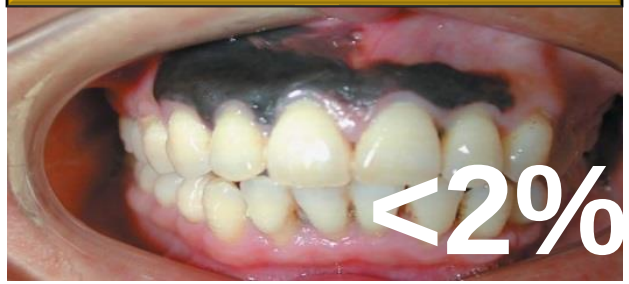

**Acral Melanoma**



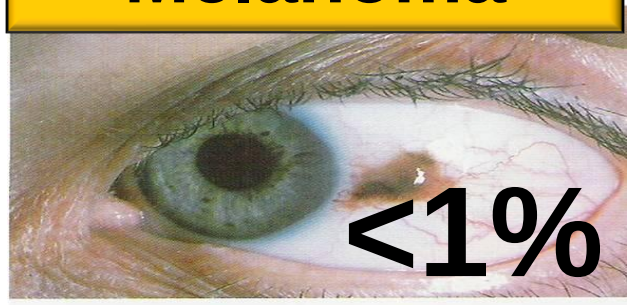

**Uveal Melanoma**




**Mucosal Melanoma**




**Conjunctival Melanoma**

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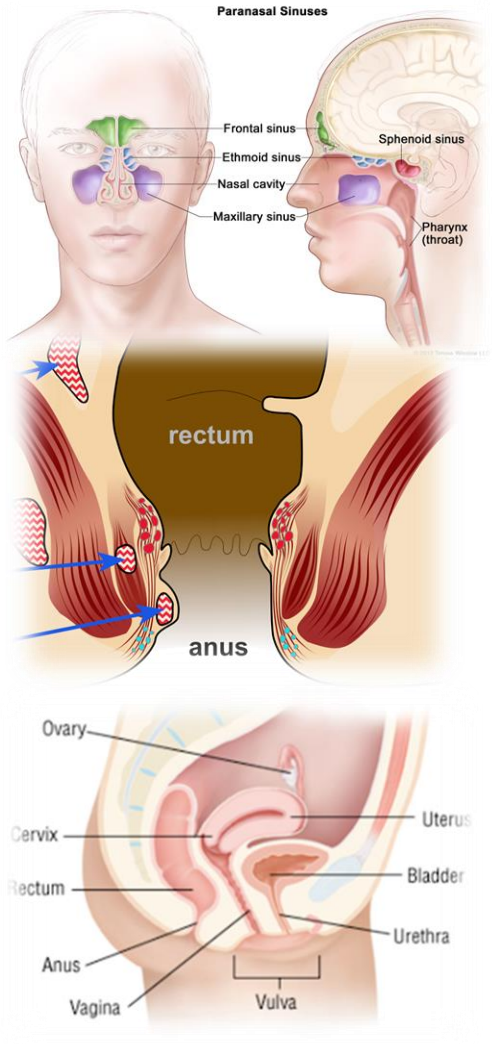
# The Clinical Heterogeneity of Mucosal Melanoma

## Head and Neck Mucosa (55%)

- **Location**
  - Nasal Cavity, 49%
    - Lateral nasal wall
    - Turbinates
  - Paranasal Sinuses, 10%
    - Maxillary sinus
    - Ethmoid sinus
  - Oral Cavity, 41%
    - Hard palate
    - Upper alveolus
- **Symptoms**
  - Sinonasal: Nasal obstruction, epistaxis, loss of smell, pain, proptosis, diplopia
  - Oral Cavity: Bleeding, ulceration, discoloration, ill-fitting dentures




## Anorectal Mucosa (24%)

- **Location**
  - Anal Canal, 33%
  - Anorectal, 25%
  - Rectal, 42%
- **Symptoms**
  - Rectal bleeding, painful defecation, anorectal masses, “hemmorrhoids”

## Vulvovaginal Mucosa (18%)

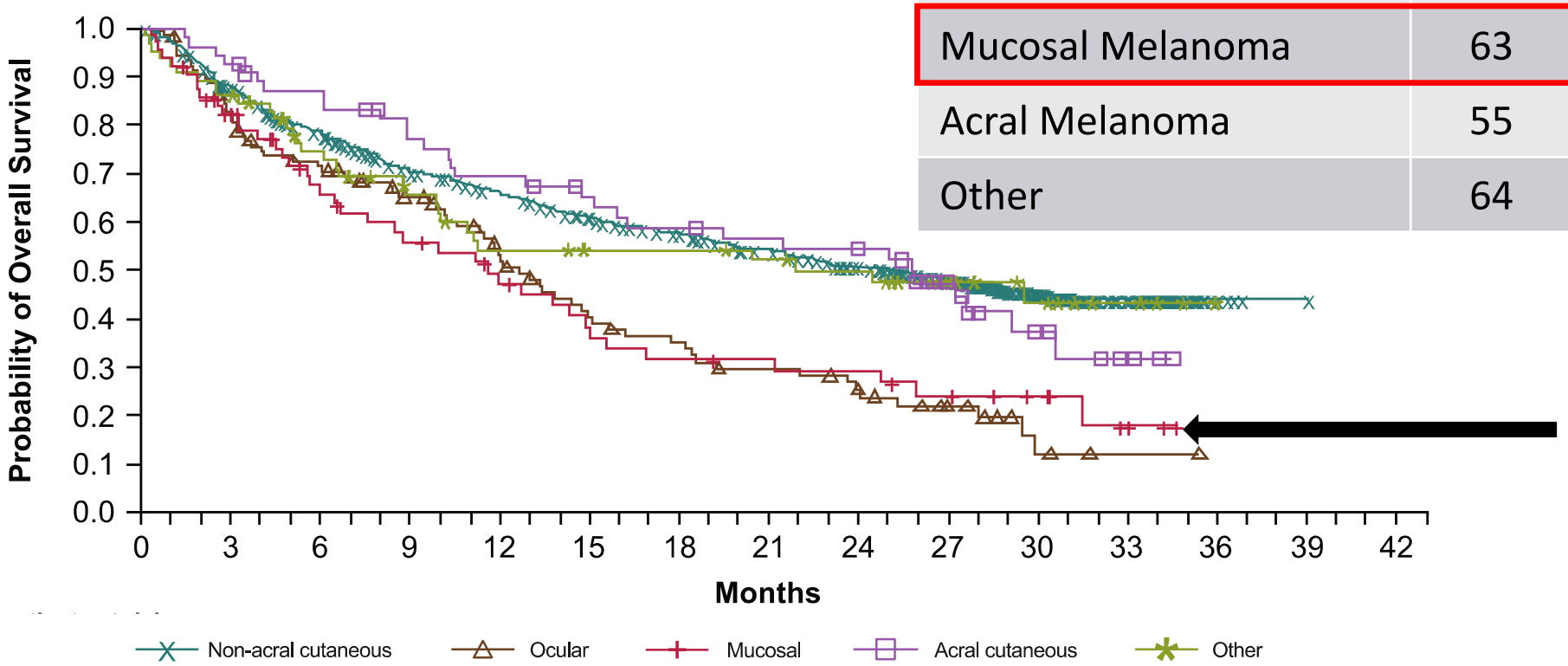
- **Location**
  - Vulvar, 90%
  - Vaginal, 10%
- **Symptoms**
  - Vulvar: Pruritis, bleeding, ulceration
  - Vaginal: Vaginal discharge, dysparenuria, vaginal mass

Northwell Health Cancer Institute

Carvajal RD et al. JNCCN 2012.
Prasad et al. Head and Neck 2006.

# CheckMate 172 (n=1008): OS with Nivolumab by Subtype

| Subtype | n | Median OS (mos) |
|---|---|---|
| Non-Acral Cut Melanoma | 723 | 25.3 (95% CI, 20.9 – 28.9) |
| Ocular Melanoma | 103 | 12.6 (95% CI, 10.2 – 15.1) |
| Mucosal Melanoma | 63 | 11.5 (95% CI, 6.4 – 15.0) |
| Acral Melanoma | 55 | 25.8 (95% CI, 15.1 – 30.6) |
| Other | 64 | 21.8 (95% CI, 9.8 – NR) |




Nathan et al, Eur J of Ca 2019.

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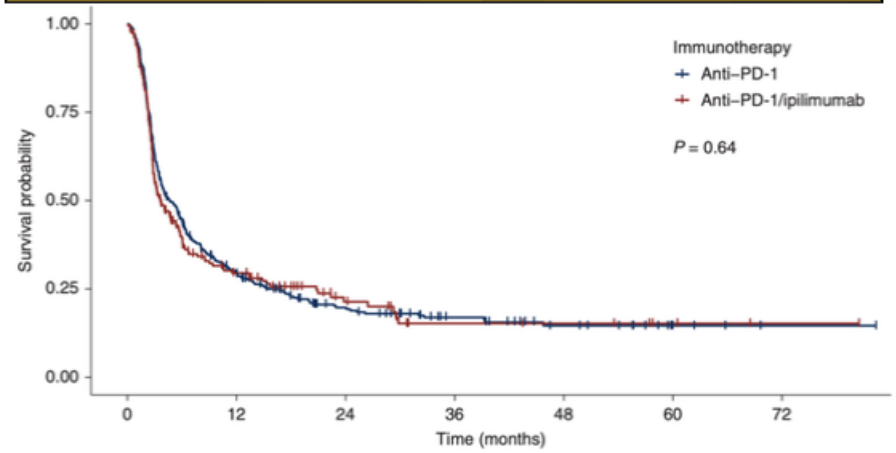
# International Real World Data Experience (n = 545)

- Data on patients from 25 centers in Australia, Europe, USA and Asia
- Median follow-up of 31 months (95% CI, 17-54)

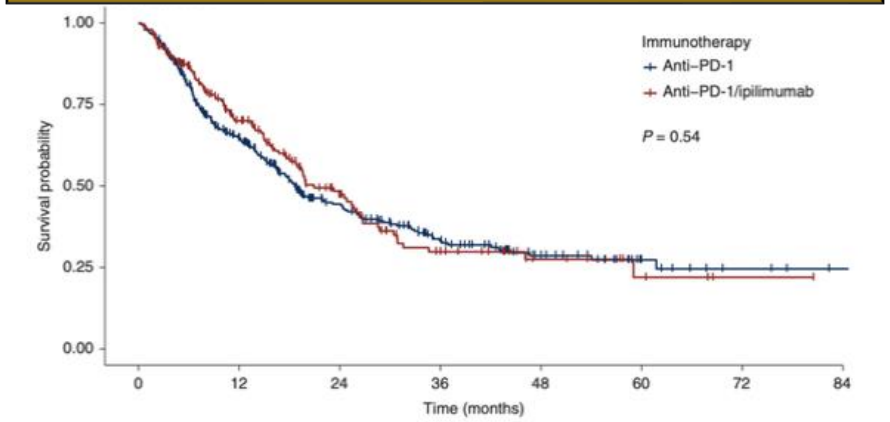
**Table 4.** ORR by primary site, Ethnicity/Race and systemic treatment.

| | | Overall n/N % | Ethnicity/Race | | Treatment | |
|---|---|---|---|---|---|---|
| | | | Caucasian | Asian | Anti-PD1 | AntiPD1/Ipilimumab |
| **Overall ORR n/N %** | | 162/545 (30) | 101/331 (31) | 47/176 (27) | 100/348 (29) | 62/197 (31) |
| **ORR by primary site n/N % (95% CI)** | Anorectal | 38/116 (33) | 27/81 (33) | 6/25 (24) | 22/70 (31) | 15/46 (33) |
| | Urogenital | 47/178 (26) | 34/124 (27) | 8/41 (20) | 31/104 (30) | 17/74 (24) |
| | Naso-oral | 66/206 (32) | 36/115 (31) | 26/79 (33) | 40/140 (29) | 26/66 (40) |
| | Other | 11/45 (24) | 4/11 (36) | 7/31 (23) | 7/34 (21) | 4/11 (36) |
| **ORR by race n/N % (95% CI)** | Caucasian | - | - | - | 58/191 (31) | 43/140 (32) |
| | Asian | - | - | - | 37/146 (26) | 10/30 (34) |
| **PFS** | Median, months (95% CI) | 4 (4 - 6) | 5 (4 - 6) | 4 (3 - 6) | 5 (4 - 6) | 4 (3 - 6) |
| | 3-year rate % (95% CI) | 17 (13 - 21) | 16 (12 - 21) | 18 (13 - 26) | 17 (13 - 22) | 16 (10 - 25) |
| **OS** | Median , months (95% CI) | 19 (18 - 24) | 21 (18 - 26) | 18 (15 - 27) | 19 (16 - 24) | 21 (19 - 27) |
| | 3-year rate % (95% CI) | 32 (27 - 37) | 33 (27 - 40) | 32 (24 - 43) | 33 (27 - 39) | 30 (22 - 40) |

**Progression-Free Survival**




**Overall Survival**




Dimitriou F et al. Ann Oncol, 2022.

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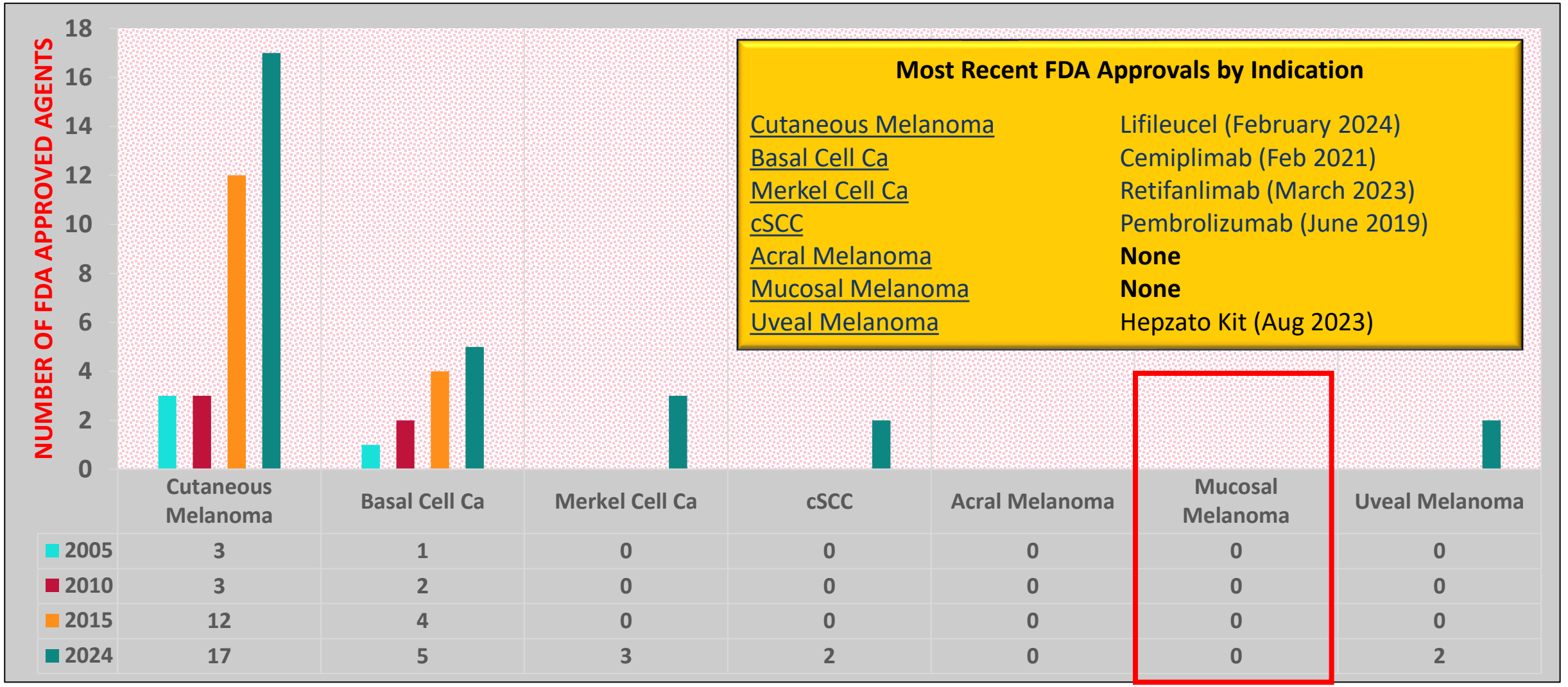
# FDA Approvals for Melanoma and Cutaneous Malignancies




| | Cutaneous Melanoma | Basal Cell Ca | Merkel Cell Ca | cSCC | Acral Melanoma | Mucosal Melanoma | Uveal Melanoma |
|---|---|---|---|---|---|---|---|
| 2005 | 3 | 1 | 0 | 0 | 0 | 0 | 0 |
| 2010 | 3 | 2 | 0 | 0 | 0 | 0 | 0 |
| 2015 | 12 | 4 | 0 | 0 | 0 | 0 | 0 |
| 2024 | 17 | 5 | 3 | 2 | 0 | 0 | 2 |

**Most Recent FDA Approvals by Indication**

| | |
|---|---|
| Cutaneous Melanoma | Lifileucel (February 2024) |
| Basal Cell Ca | Cemiplimab (Feb 2021) |
| Merkel Cell Ca | Retifanlimab (March 2023) |
| cSCC | Pembrolizumab (June 2019) |
| Acral Melanoma | **None** |
| Mucosal Melanoma | **None** |
| Uveal Melanoma | Hepzato Kit (Aug 2023) |

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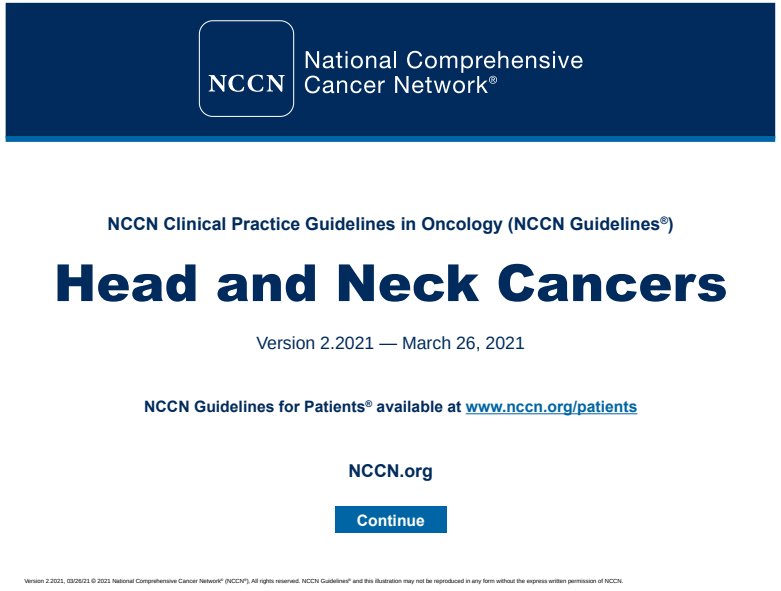
# Completed Clinical Trials in Mucosal Melanoma

| Setting | Study | Phase | n | Treatment Arm(s) | Results |
|---|---|---|---|---|---|
| Neoadjuvant | Mao et al, ASCO 2023 | 2 | 19 | Lenvatinib + Pembro | 32% path RR in resected population (n=15) |
| | Lian et al, Ann Oncol 2024 | 2 | 29 | Toripalimab + Axitinib | 33% path RR in resected population (n=24) |
| Adjuvant | **Lian et al, JCO 2013** | **2** | **189** | **Obs vs HDI vs Cis/TMZ** | **RFS and OS improved with Cis/TMZ vs Obs or HDI** |
| | **Lian et al, ASCO 2018** | **3** | **204** | **HDI vs Cis/TMZ** | **Primary Endpoint of RFS reached (15.5 vs 9.5 mos) in favor of chemo** |
| | **Lian et al, Ann Oncol 2022** | **2** | **145** | **Toripalimab vs HDI** | **Similar RFS (13.6 vs 13.9 mos) and more favorable safety profile in favor of toripalimab** |
| Metastatic | Sheng et al, JCO 2019; Li S, JITC 2022 | 1B | 33 | Toripalimab + Axitinib | 48% ORR in chemo-naive patients (n=29); PFS 7.5 mos |
| | Nomura et al, Int J Clin Onc 2020 | 2 | 20 | Nivolumab | ORR 23.5% (n=17); PFS 12 mos; 1 yr OS rate 50% |
| | **Yan et al, JCO 2021** | **2** | **114** | **Carbo/Taxol +/- Bev** | **Primary Endpoint of PFS reached in favor of bevacizumab (4.8 vs 3.0 mos); OS 13.6 vs 9 mos in favor of bev** |
| | Mao L, Clin Cancer Res 2022 | 2 | 43 | Atezolizumab + Bev | ORR 45%, median PFS 9.2 mos, median OS not reached |
| | Zhao L, JITC 2024 | 2 | 32 | Camrelizumab + Apatinib | ORR 43%, PSF 8 months |

# Limited Guidelines Available to Guide Management

## Sinonasal and Oral Cavity Melanoma


NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

**Head and Neck Cancers**

Version 2.2021 — March 26, 2021

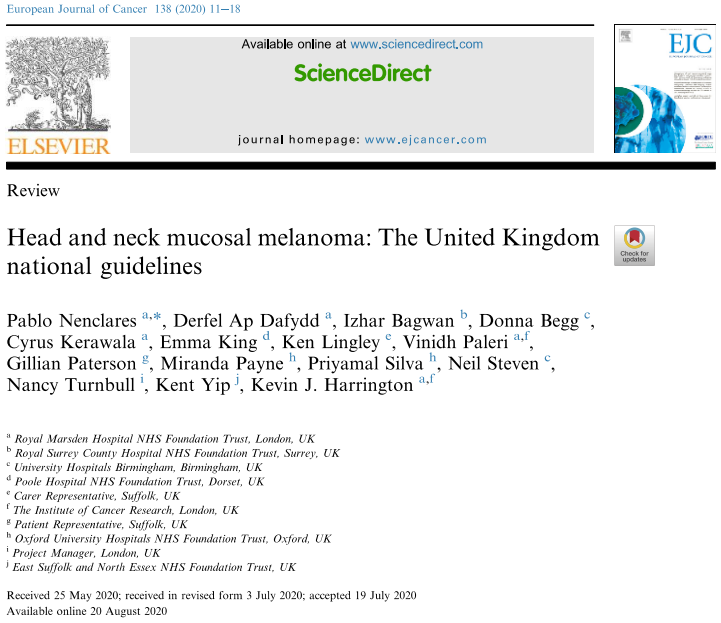
NCCN Guidelines for Patients® available at www.nccn.org/patients

NCCN.org

Continue



NCCN Guidelines, Head and Neck Cancers.


European Journal of Cancer 138 (2020) 11–18

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

Head and neck mucosal melanoma: The United Kingdom national guidelines

Pablo Nenclares [a,*], Derfel Ap Dafydd [a], Izhar Bagwan [b], Donna Begg [c], Cyrus Kerawala [a], Emma King [d], Ken Lingley [e], Vinidh Paleri [a,f], Gillian Paterson [g], Miranda Payne [h], Priyamal Silva [h], Neil Steven [c], Nancy Turnbull [i], Kent Yip [j], Kevin J. Harrington [a,f]

[a] Royal Marsden Hospital NHS Foundation Trust, London, UK
[b] Royal Surrey County Hospital NHS Foundation Trust, Surrey, UK
[c] University Hospitals Birmingham, Birmingham, UK
[d] Poole Hospital NHS Foundation Trust, Dorset, UK
[e] Carer Representative, Suffolk, UK
[f] The Institute of Cancer Research, London, UK
[g] Patient Representative, Suffolk, UK
[h] Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[i] Project Manager, London, UK
[j] East Suffolk and North Essex NHS Foundation Trust, UK

Received 25 May 2020; received in revised form 3 July 2020; accepted 19 July 2020
Available online 20 August 2020

Nenclares et al. Eur J Cancer, 2020.

## Anorectal and Vulvovaginal Melanoma


European Journal of Cancer 135 (2020) 22–30

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Ano-uro-genital mucosal melanoma UK national guidelines

Henry G. Smith [a], Izhar Bagwan [b], Ruth E. Board [c], Sharon Capper [d], Sarah E. Coupland [e], Jessica Glen [f], Susan Lalondrelle [a], Antonia Mayberry [g], Asif Muneer [h], Karen Nugent [i], Pubudu Pathiraja [j], Miranda Payne [j], Howard Peach [k], Jonathan Smith [k], Sarah Westwell [l], Ewan Wilson [m], Simon Rodwell [n], Martin Gore [a], Nancy Turnbull [n], Myles J.F. Smith [a,*]

Smith HG et al. Eur J Cancer, 2020.

Northwell Health® Cancer Institute

# How do we manage advanced disease?

1. Appropriate **clinical trial** if available

2. **CPI** as SOC front-line therapy

3. **Targeted therapy** as next line if actionable alteration present

4. **Carbo/Taxol/Bev**

5. Other **chemotherapy** regimens

# Summary

- Mucosal melanoma is a **rare melanoma subset** with a distinct biology and a **particularly poor prognosis**
- There is **no proven effective therapy** in the perioperative or metastatic settings
- Only **limited efforts** are ongoing that are focused on developing novel therapies specifically for mucosal melanoma
- This patient population represents a **significant unmet medical need**

VICKI GOODMAN, MD
CHIEF MEDICAL OFFICER

# ARTISTRY-6 OVERVIEW

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# Systematic Literature Review of Outcomes and Treatments in Post-Anti-PD-(L)1 Advanced Mucosal Melanoma

Systematic Literature Review (SLR) conducted to identify interventional and real-world (RW) studies assessing treatments and clinical outcomes in patients with advanced mucosal melanoma who have previously been treated with anti-PD-(L)1 therapy

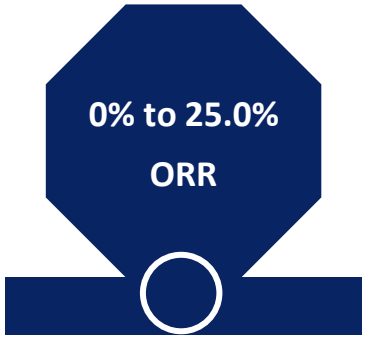
**11** RW studies

**1** interventional study

## TREATMENT OVERVIEW

- In the RW studies, post anti-PD-(L)1 treatments included checkpoint inhibitors (e.g., ipilimumab, and/or anti-PD-[L]1 rechallenge), cytotoxic agents, targeted therapies, radiation therapy, best supportive care, and treatments used off label such as tyrosine kinase inhibitors
- No cell therapy was reported in the RW studies
- In the interventional study, the reported post anti-PD-(L)1 treatment was lifileucel monotherapy, a tumor-infiltrating lymphocytes cell therapy

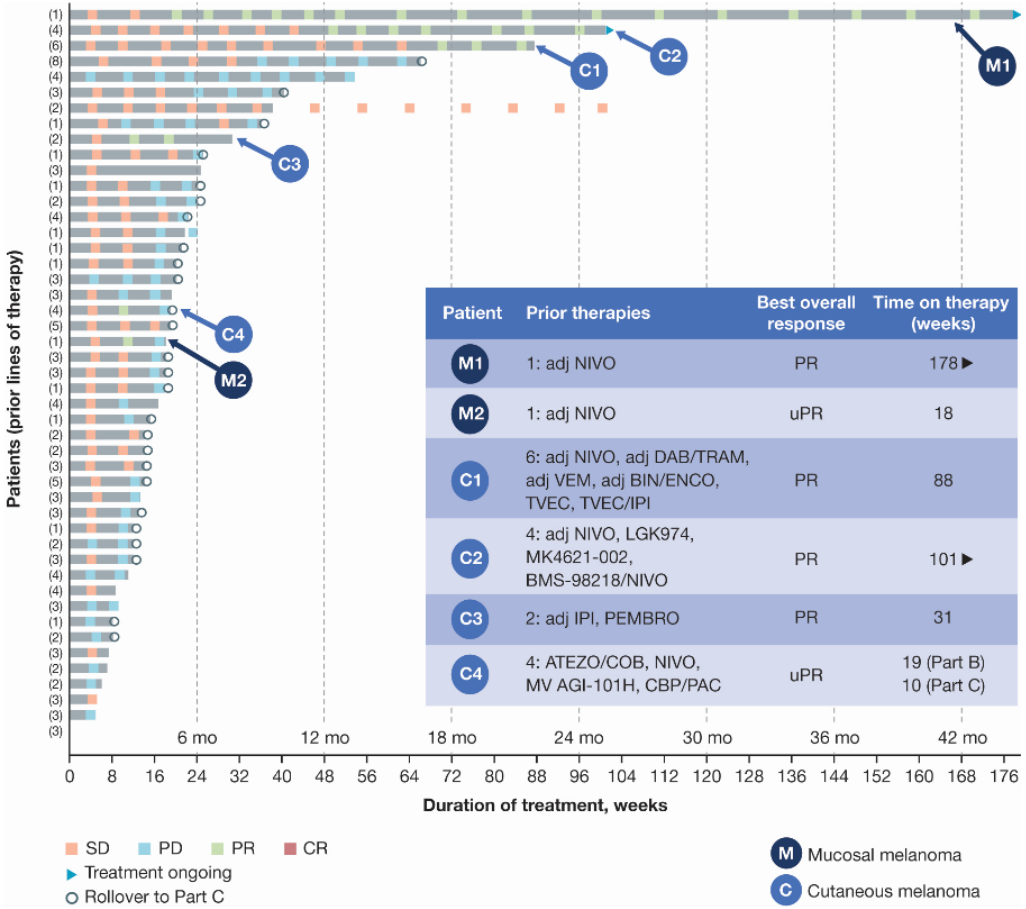
## RW ORR Outcomes in Patients with Mucosal Melanoma Post Anti-PD-(L)1




- Four of the 11 RW studies reported ORR
- Each study contained 4-16 patients
- Patients received a variety of agents, including single agent and combination CPIs, kinase inhibitors, and combo CPI/kinase inhibitors
- ORR ranged from 0-25%, the latter in a sample size of 4

**1 interventional study** included 12 patients treated with lifileucil, a treatment with severe limitations, with a response rate of 50%

# ARTISTRY-1: Nemvaleukin Demonstrated Durable Monotherapy Responses in Melanoma (Part B)




Responses per RECIST v1.1

| | All[a,b] (n=46) | Mucosal (n=6) |
|---|---|---|
| Best overall response, n (%) | | |
| CR | 0 | 0 |
| PR | 6 (13.0)[c] | 2 (33.3)[d] |
| ORR, n (%) [95% CI] | 6 (13.0) [4.9-26.3][c] | 2 (33.3) [4.3-77.8][d] |
| DOR in weeks[d], Mean (SD)<br>Median (range) | 40.77 (55.6) [c]<br>16.75 (6.1-150.3) | 78.2 (101.9)[d]<br>78.2 (6.1-150.3) |

[a] Excludes 1 patient who did not meet tumor-evaluable criteria. [b] Patients with mucosal, cutaneous, uveal, acral included in 'All'. [C] Includes 4 confirmed PRs, 2 unconfirmed PRs, [d] 1 confirmed PR. [e] DOR for Part B only and does not include patients who rolled over to Part C; some patients may still be on treatment

- All responders had been on prior CPI therapy and progressed
- FDA Orphan Drug and Fast Track designations, as well as MHRA's ILAP Innovation Passport, granted in mucosal melanoma
- Data supported design of ARTISTRY-6 study

Data cut off Mar 27, 2023

Abbrev.: **adj**: adjuvant; **ATEZO**: atezolizumab; **BIN**: binimetinib; **CBP**: carboplatin; **CI**: confidence interval; **COB**: cobimetinib; **CPI**: checkpoint inhibitor; **CR**: complete response; **DAB**: dabrafenib; **DCR**: disease control rate (CR+PR+SD); **DOR**: duration of response; **ENCO**: encorafenib; **FDA**: US Food and Drug Administration; **IPI**: ipilimumab; **MHRA**: Medicines and Healthcare products Regulatory Agency; **MV**: melanoma vaccine; **NA**: not applicable; **NIVO**: nivolumab; **ORR**: overall response rate; **PAC**: paclitaxel; **PD**: progressive disease; **PEMBRO**: pembrolizumab; **PR**: partial response; **SD**: stable disease; **TRAM**: trametinib; **TVEC**: talimogene laherparepvec; **VEM**: vemurafenib. Data on file.

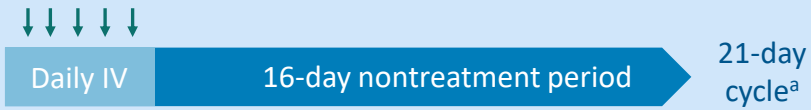
# Cohort 2 of ARTISTRY-6: Phase 2 - Potentially Registrational Trial of Nemvaleukin in Mucosal Melanoma

**Final Enrollment:** 92 patients

## Key eligibility criteria [1]

- Unresectable and/or metastatic mucosal melanoma
- Patient has received anti–PD(L)-1 ± anti–CTLA-4 therapy
- No more than 1 prior systemic therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1

**Cohort 2**
Mucosal melanoma (N=90)
Nemvaleukin IV 6 µg/kg QDx5 Monotherapy




## Key endpoints

- **Primary:** ORR per RECIST v1.1 (by independent central review)
- **Key secondary:** DOR, PFS, DCR, TTR per RECIST v1.1 (by independent central review)

[a] With the exception of Cycle 1, which is 14 days (daily IV for 5 days + 9 days nontreatment), all cycles are 21 days[3]

↓ Nemvaleukin dosing

- ARTISTRY-6 also includes Cohorts 1, 3, and 4 which are designed to explore alternative dosing regimens of nemvaleukin, both as a monotherapy and in combination with pembrolizumab, in cutaneous melanoma

1. https://clinicaltrials.gov, NCT04830124

Abbrev.: **CTLA-4:** cytotoxic T-lymphocyte–associated antigen 4; **DCR**: disease control rate; **DOR**: duration of response; **ECOG PS**: Eastern Cooperative Oncology Group performance status; **IV**: intravenous; **ORR**: objective response rate; **PD-(L)1**: programmed death (ligand) 1; **PFS**: progression-free survival; **RECIST**: Response Evaluation Criteria in Solid Tumors; **TTR**: time to response





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# ARTISTRY-6 Cohort 2: Assumptions on Final Data

- Cohort 2 of ARTISTRY-6 study expected to provide the most robust clinical dataset in advanced mucosal melanoma to date
- Primary analysis will occur when all patients have a minimum follow up of at least 6 months
- **Target response rate: 25%**
  - We believe a response rate of 20-25% would be meaningful for patients and would support discussion with FDA around Biologics License Application (BLA) submission
- Trial designed so that at 25% response rate, lower bound of 95% confidence interval will exceed a 15% response rate
- Intend to discuss data with FDA in advance of BLA submission
  - Potential accelerated approval with confirmatory evidence to be later submitted for conversion to regular approval
  - Regulatory filing may be deferred if ARTISTRY-7 study continues to final analysis, pending the final outcome

Abbrev.: BLA: Biologics License Application

JEAN CHAMOUN, PHD

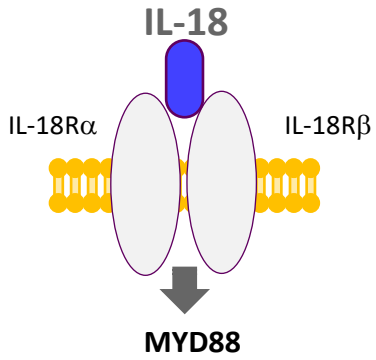
VICE PRESIDENT, RESEARCH

# ENGINEERED IL-18 PROGRAM

MURAL ONCOLOGY

# IL-18 is a Potent Stimulator of Innate and Adaptive Immunity, but with Key Limitations

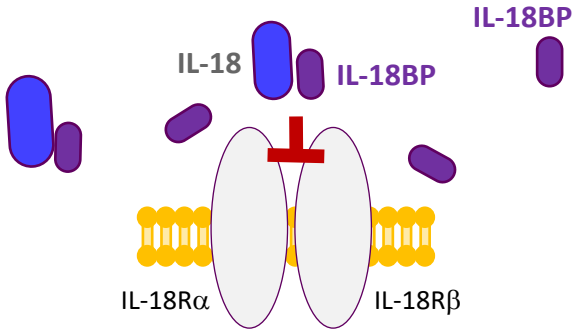
## *IL-18 Attractive Biology*




- **Activates NK cells and antigen-experienced CD8⁺ T cells**
- **Restores activity in dysfunctional T cells**
- **Matures dendritic cells (DCs)**

***Limited Application***

## *IL-18 Challenges*




- **IL-18BP overexpressed in the TME**
- **IL-18BP binds strongly to IL-18 minimizing it's signaling**
- **IL-18 rapidly cleared from circulation**

***Suppressed activity***



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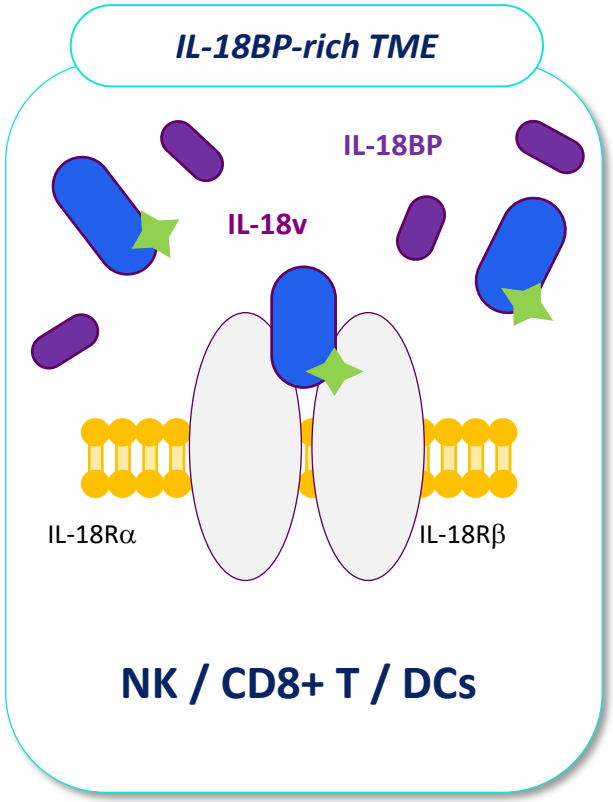
# Mural's Oncology IL-18: Engineered to Deliver a More Sustained Immune Response

## Mural Solution: Engineer an IL-18 with Optimized Characteristics

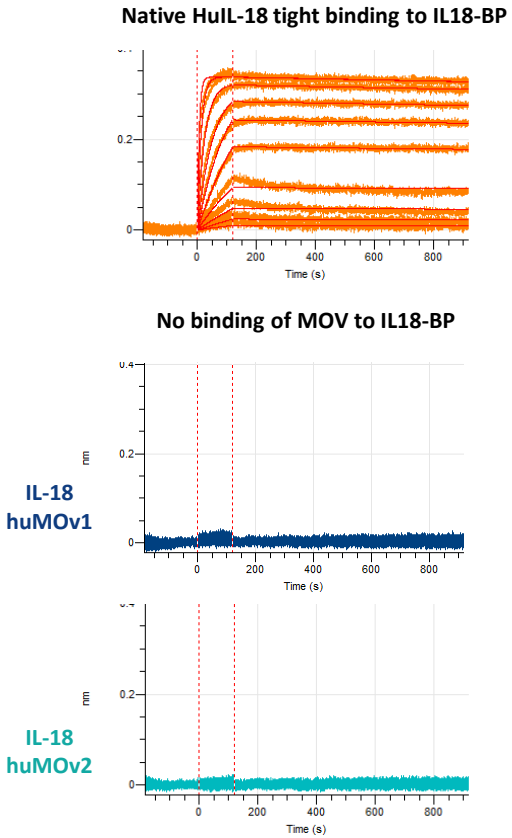



- **Engineer an active IL-18 molecule unaffected by IL-18BP presence**
- **Engineer an IL-18 with an extended half-life**
- **Optimize the IL-18 potency to fit its newly engineered profile**

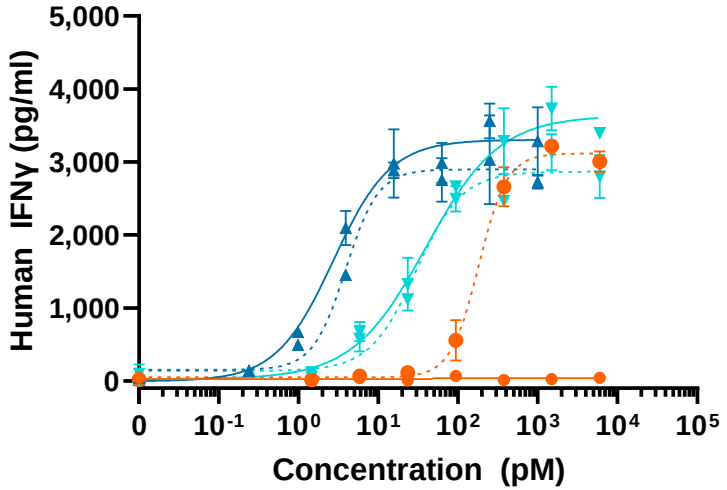
***Enhanced Anti-Tumor Activity***

# Preclinical Studies Demonstrated Enhanced Pharmacokinetics with an Optimized Potency and Maximal Resistance to IL-18BP Inhibition

## No Binding of Mural Oncology Variants to IL-18BP

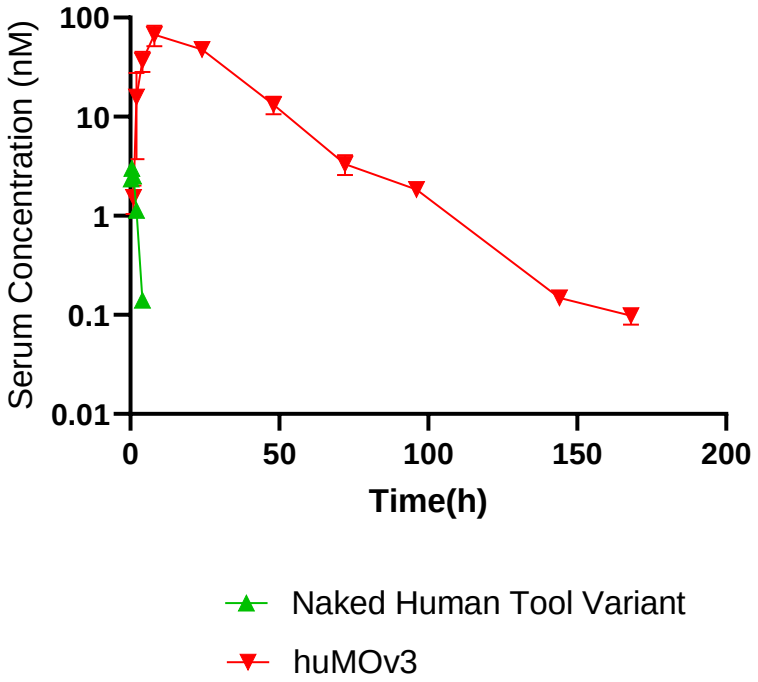



## Broad Range of Potency



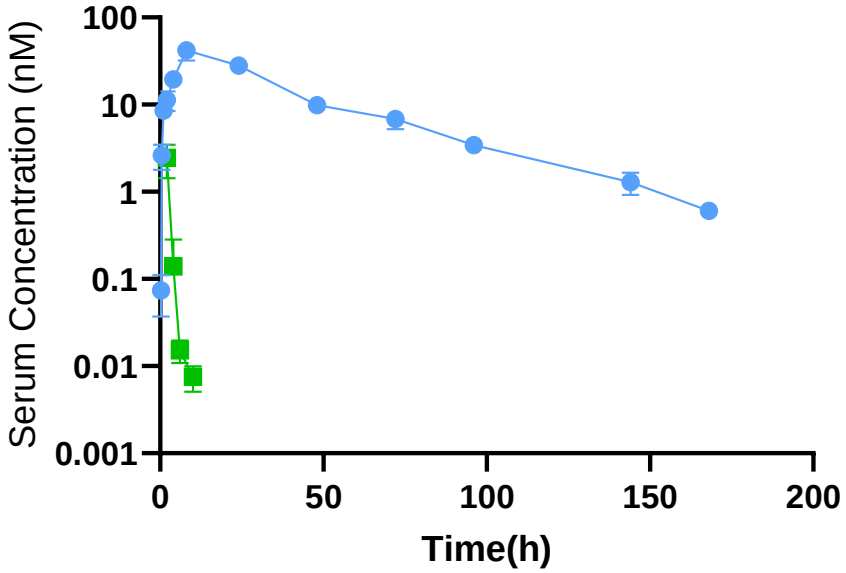

**huMOv1/2/3- human Mural Oncology variants**
IL18BP-resistant, half-life enhanced

## Enhanced Pharmacokinetics



# Mural's Approach Achieves Intended Half-Life and Associated Pharmacodynamics Effects

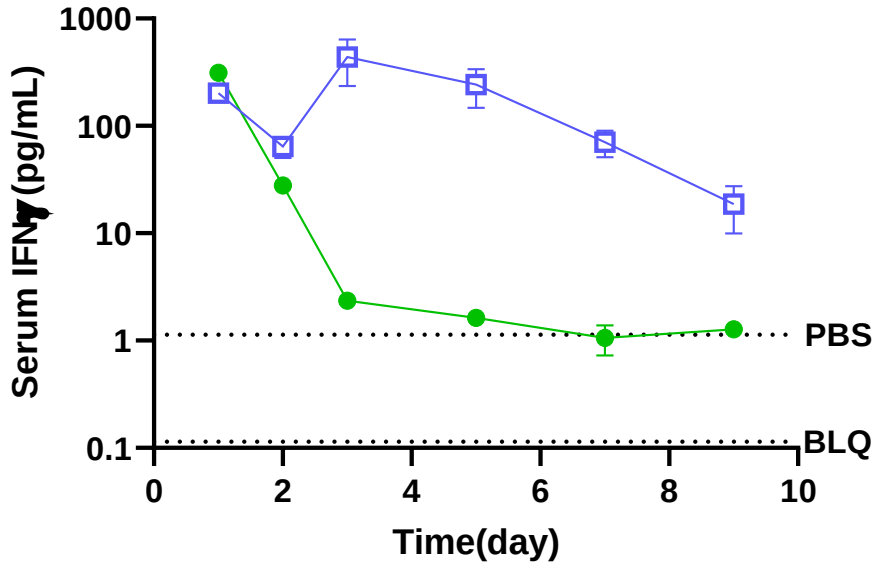
## Enhanced Pharmacokinetic




Naked mouse tool variant

muMOv1

## Extended Pharmacodynamic




Naked mouse tool variant

muMOv1

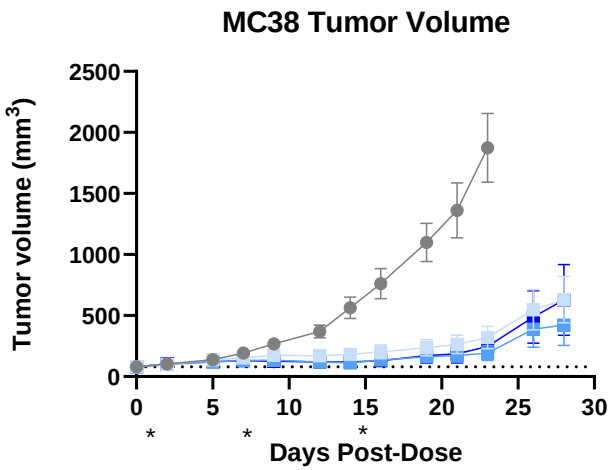
**muMOv1-mouse Mural Oncology variant**
IL18BP-resistant, half-life enhanced

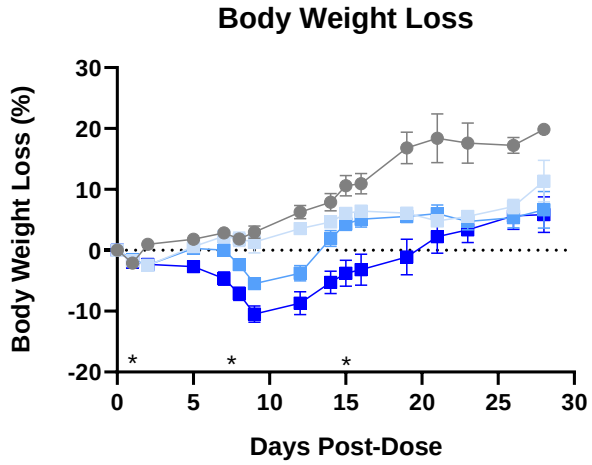


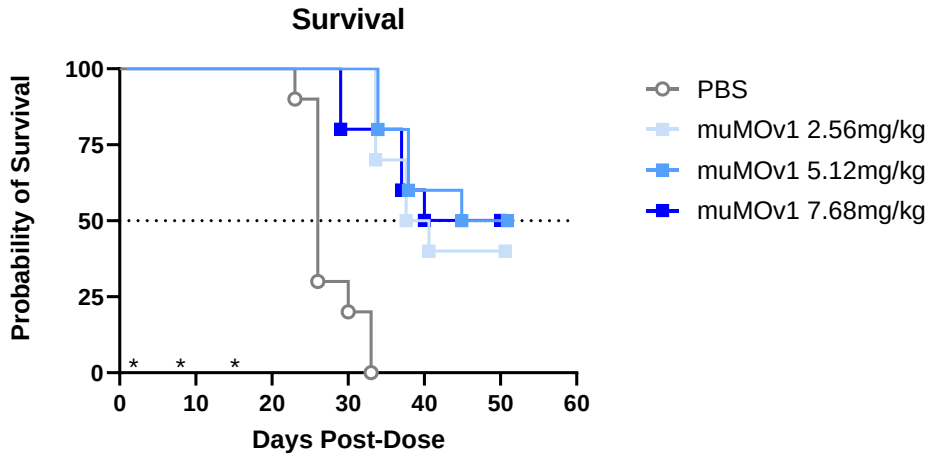


MURAL ONCOLOGY

# Complete Responses and Survival Improvement Seen in Mural's IL-18 Mouse Ortholog Variant




| Agent | Dose (mg/kg) | % TGI* Day 21 | Complete Response Day 50 | Probability of Survival Day 50 |
|---|---|---|---|---|
| muMOv1 | 2.56 | 86% | 2/10 | 40% |
| muMOv1 | 5.12 | 93% | 4/10 | 50% |
| muMOv1 | 7.68 | 92% | 5/10 | 50% |

**muMOv1-** IL18BP-resistant, half-life enhanced mouse ortholog of Mural human variant

***%TGI = % tumor growth inhibition, calculated before 1st animal in vehicle reached endpoint**

The combination of IL-18BP resistance and half-life enhancement achieved desired effect





MURAL ONCOLOGY

# Key Takeaways: IL-18

- Mural's **fit-for-purpose approach** successfully engineered an IL-18 molecule with the desired profile:
  - Maximal resistance to IL18-BP binding
  - Enhance half-life compared to native IL-18
  - Optimized potency

- Clearly demonstrated desired efficacy with mouse ortholog variant

- IND filing by Q4 of 2025

CAROLINE LOEW, PHD

# WHY MURAL & WHY NOW?

MURAL ONCOLOGY

# Mural at a Glance

Phase 2/3

## Late-Stage Trials:

- ✓ **Fully enrolled** for ARTISTRY-7 (Phase 3, PROC) and ARTISTRY-6 cohort 2 (Phase 2, mucosal melanoma)
- ✓ Ongoing discussions with FDA on ARTISTRY-6 potential **confirmatory evidence package**
- ✓ RP2D for **next generation dosing schedule** underway in ARTISTRY-6, cohorts 3 & 4 (phase 2, cutaneous melanoma )

**2025 CATALYSTS:**

- ➢ **Late Q1/Early Q2:** Interim OS for ARTISTRY-7[1]
- ➢ **Q2:** TLR Cohort 2 of ARTISTRY-6
- ➢ **1H:** PDR Cohort 3-mono of ARTISTRY-6 (Phase 2, CM)[2]
- ➢ **2H:** PDR Cohort 4-combo of ARTISTRY-6 (Phase 2, CM)[2]

## Preclinical Assets:

**4Q 2024:** Candidate nominations for IL-18 and IL-12
**4Q 2025:** IL-18 IND submission

## Cash Position:

**Cash runway into 4Q 2025**

## Commercial Opportunity:

Significant opportunity in 2 indications with **limited available therapies** and planned indication expansion

1. Subject to event accrual
2. Subject to patient enrollment



Abbrev.: **CM**: cutaneous melanoma; **IL-12:** interleukin-12; **IL-18:** interleukin-18; **MM**: mucosal melanoma; **OS**: overall survival; **PDR**: preliminary data readout; **PROC**: platinum resistant ovarian cancer; **RP2D**: recommended phase 2 dose; **TLR**: topline results



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# Key Takeaways: ARTISTRY-7 Trial Design Assumptions and Progress

- **Fully enrolled with 456 patients** (versus 448 planned), with approximately 187 patients per experimental arm

- **Futility analysis complete** for monotherapy arms:
  - Pembrolizumab monotherapy arm reached futility (defined as <2 confirmed CR or PR in the first 12 patients) in August 2023 after enrolling 27 patients
  - Nemvaleukin arm required at least 1 patient among the first 24 to achieve a response or SD for at least 3 months to continue; this arm continued to enroll a total of 55 patients

- **Design assumptions on overall survival endpoint**, with alpha controlled at 2.5% (one sided):
  - Chemo arm: estimated median OS of 10 months
  - Nemva + pembro arm: estimated median OS of 14.3 months

**Projected readout on 75% of events in late Q1 or early Q2 2025**

# Key Takeaways: ARTISTRY-6 Cohort 2 Trial Assumptions and Progress

- Cohort 2 or ARTISTRY-6 study expected to provide the **most robust clinical dataset in advanced mucosal melanoma to date**

- **Fully enrolled** with 92 patients

- **Target response rate: 25%**
  - Response rate of 20-25% would be meaningful for patients and would support discussion with FDA around Biologics License Application (BLA)

- Trial designed so that at 25% response rate, lower bound of 95% confidence interval will exceed a 15% response rate

- **Potential for accelerated approval, and discussions with FDA on potential confirmatory evidence package ongoing**
  - Regulatory filing may be deferred if ARTISTRY-7 study continues to final analysis, pending the final outcome of ARTISTRY-7

**Projected readout in Q2 2025**

# Q&A

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