# UPGRADE: Phase 1 Trial of the NaPi2b-Directed Dolaflexin Antibody-Drug Conjugate UpRi in Combination With Carboplatin in Patients With Platinum-Sensitive Ovarian Cancer (PSOC)

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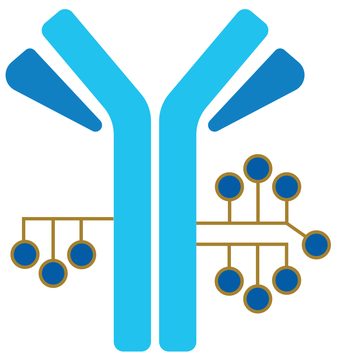
## BACKGROUND

- The standard of care for patients with recurrent ovarian cancer (OC) who are eligible for platinum-based therapy is platinum-containing combination regimens. Unfortunately, this approach has an effectiveness of only 45-59% response rates and ~10 months PFS, with frequent and high-grade toxicities (ie, neutropenia, neuropathy, alopecia).[1-5] Real-world data in the post-PARP setting suggest these response rates may be even lower[6-8]
- ADCs represent an important class of cancer therapies.[9] Data combining ADCs and chemotherapy suggest different targets and payloads could lead to complementary and enhanced efficacy. Unfortunately, this combination has historically been challenging owing to overlapping adverse events
- UpRi is a NaPi2b-directed ADC designed with a high DAR and a proprietary AF-HPA microtubule inhibitor payload with controlled bystander effect to minimize the common toxicities associated with other ADC platforms (ie, peripheral neuropathy, neutropenia, and ocular toxicity)[10]
- Based on a precedent study evaluating lifatuzumab vedotin, an MMAE NaPi2b ADC, in combination with carboplatin, which despite demonstrating clinical activity was associated with high-grade platform toxicities including neutropenia and peripheral neuropathy,[11] UPGRADE was a Phase 1 DES and EXP study to evaluate the combination of UpRi and carboplatin followed by UpRi maintenance in patients with recurrent PSOC
- Here we present the data from the UPGRADE DES (N=15; data cut: October 3, 2023)

### Rationale for Combination Therapy With Carboplatin

- To address the unmet need, novel platinum-based combinations must be developed that:
  - Offer a more favorable therapeutic index with no or limited overlapping toxicities
  - Replace paclitaxel to improve tolerability
  - Provide continued treatment with an anti-tubulin therapy
- ADCs may represent a promising strategy in combination with carboplatin to optimize therapeutic index for patients



**Antibody:** Humanized monoclonal anti-SLC34A2 (NaPi2b)

**Linker:** Polymer scaffold; stochastic cysteine conjugation

**Payload:** AF-HPA – controlled bystander effect; highly potent anti-tubulin inhibitor selectively toxic to rapidly dividing cells

**DAR:** Heterogeneous; ~10

## METHODS

### UPGRADE Trial Design

**Key Enrollment Criteria**

- Recurrent, high-grade serous PSOC[a]
- 1-3 prior platinum-based regimens or non–platinum-based chemotherapy regimens
- Tissue for retrospective assessment of NaPi2b expression (participants not selected by NaPi2b expression)
- RECIST measurable disease
- ECOG PS = 0-1

**Dose Escalation (BOIN design; N=15)**

**UpRi** 20 mg/m², 30 mg/m², and 36 mg/m² q4w until disease progression
**+ Carboplatin AUC 5**
q4w for six cycles

**Primary Endpoint**
- MTD for UpRi with carboplatin AUC 5

**Secondary Objectives**
- AEs, PK for UpRi, PK for carboplatin, immunogenicity for UpRi, ORR, PFS, OS

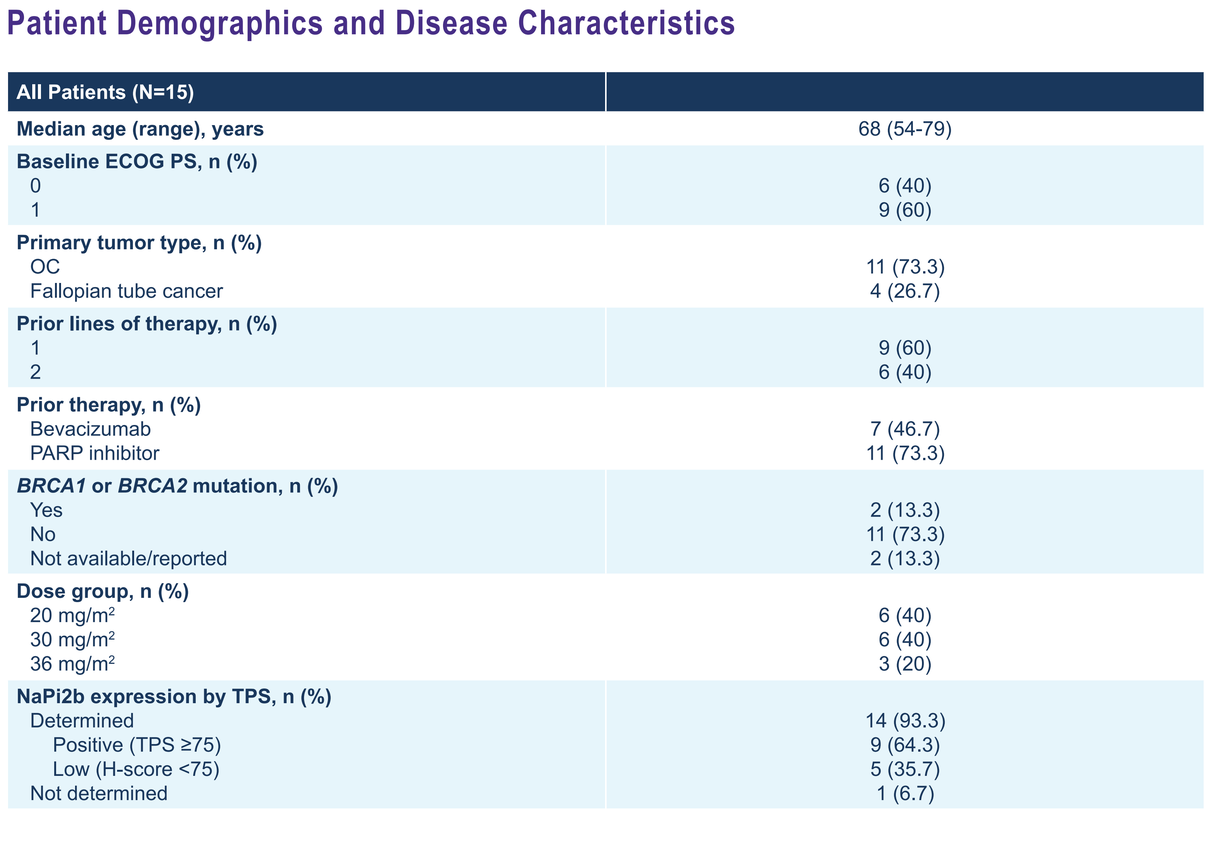
[a]PSOC is defined as having achieved either a partial or complete response to 4 or more cycles in their last platinum-containing regimen and their disease progressing more than 6 months after completion of the last dose of platinum-containing therapy.

## RESULTS

### Patient Demographics and Disease Characteristics

| All Patients (N=15) | |
|---|---|
| **Median age (range), years** | 68 (54-79) |
| **Baseline ECOG PS, n (%)** | |
| 0 | 6 (40) |
| 1 | 9 (60) |
| **Primary tumor type, n (%)** | |
| OC | 11 (73.3) |
| Fallopian tube cancer | 4 (26.7) |
| **Prior lines of therapy, n (%)** | |
| 1 | 9 (60) |
| 2 | 6 (40) |
| **Prior therapy, n (%)** | |
| Bevacizumab | 7 (46.7) |
| PARP inhibitor | 11 (73.3) |
| ***BRCA1* or *BRCA2* mutation, n (%)** | |
| Yes | 2 (13.3) |
| No | 11 (73.3) |
| Not available/reported | 2 (13.3) |
| **Dose group, n (%)** | |
| 20 mg/m² | 6 (40) |
| 30 mg/m² | 6 (40) |
| 36 mg/m² | 3 (20) |
| **NaPi2b expression by TPS, n (%)** | |
| Determined | 14 (93.3) |
| Positive (TPS ≥75) | 9 (64.3) |
| Low (H-score <75) | 5 (35.7) |
| Not determined | 1 (6.7) |

### TEAEs observed in ≥20% of patients (N=15)

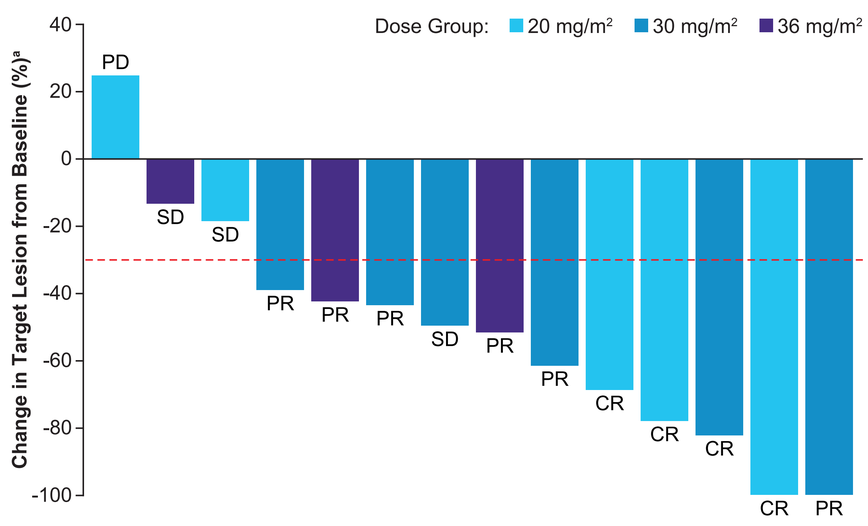



| | |
|---|---|
| UpRi treatment discontinuation due to TEAE, n/N (%)[c] | 3/15 (20.0%) |
| UpRi dose reduction due to TEAE, n/N (%)[d] | 3/15 (20.0%) |

Analysis with 15 patients. One DLT (AKI) observed at dose level 20 mg/m². No additional DLTs observed. No Grade 5 AE reported.
[a]Platelet counts transiently decreased at each cycle with a nadir at Day 8 of each cycle; most patients recovered to baseline or Grade 1 before the next scheduled dose.
[b]AST increase appears to be transient, consistent with UpRi monotherapy; peaking at Day 8 of each cycle with levels returning to baseline or Grade 1 by Day 28.
[c]Treatment discontinuation due to TEAE: proteinuria, pneumonitis, AKI. [d]Dose reduction due to TEAE: platelet count decrease, weight decrease, pneumonitis.

## RESULTS *(Continued)*

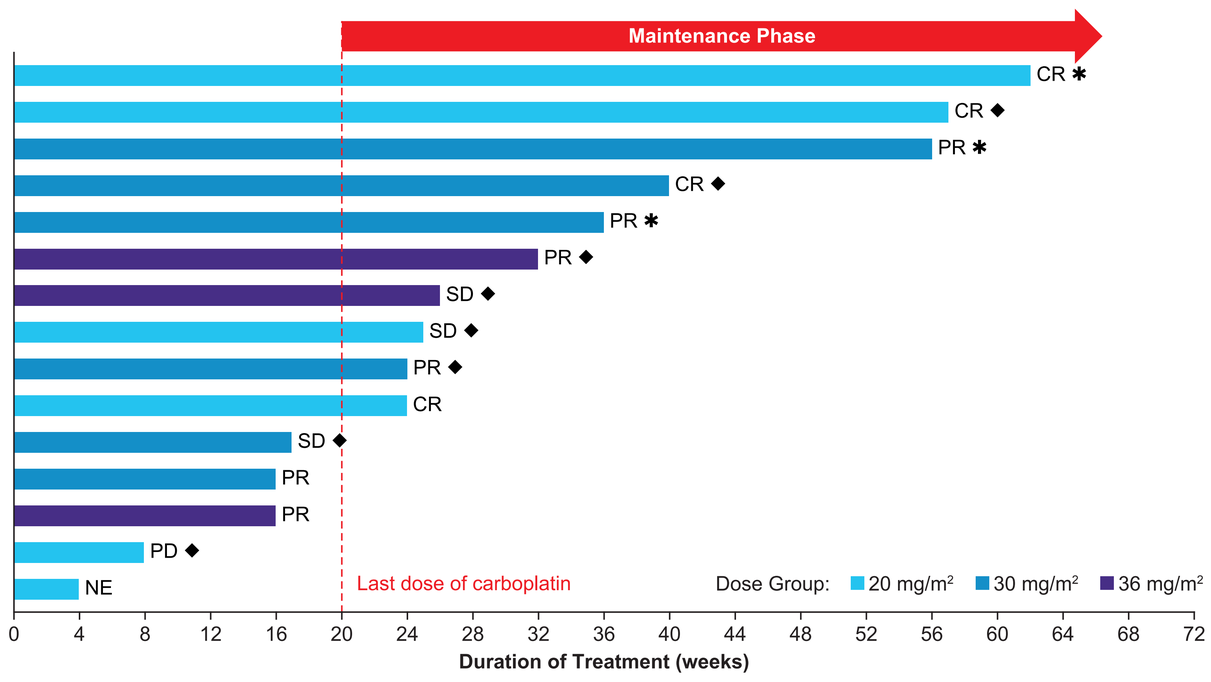
### Encouraging Activity in Evaluable Patients (n=14) – Best Overall Response




| Best Overall Response n (%) | All Patients (n=14)[b] |
|---|---|
| **ORR (CR+PR)** | **10 (71.4)** |
| CR | 4 (28.6) |
| PR | 6 (42.9) |
| SD | 3 (21.4) |
| **DCR** | **13 (92.9)** |

Following protocol amendment, patients on 36 mg/m² were down dosed to 30 mg/m².
[a]CR <100% indicates target lesion in lymph node reduced to 1 cm.
[b]One patient not evaluable: patient discontinued treatment (AKI DLT) following Cycle 1, before a RECIST assessment; patient started another anti-cancer treatment therefore had no follow-up.

### Duration on Treatment




Analysis with 15 patients. Following protocol amendment, patients on 36 mg/m² were down dosed to 30 mg/m².
Not evaluable (NE) patient: discontinued treatment (AKI DLT) following Cycle 1, before a RECIST assessment.
✱ Indicates patients who came off treatment for non-progression and non-AE reasons after the termination of the study. ◆ Indicates patients who discontinued due to PD.

## CONCLUSIONS

- UpRi is a NaPi2b-directed ADC designed with a high DAR and a proprietary AF-HPA microtubule inhibitor payload with controlled bystander effect
- UPGRADE was a Phase 1 DES and EXP study evaluating UpRi in combination with carboplatin in patients with recurrent PSOC (progressing >6 months after last dose of platinum) who have received 1-2 prior lines of therapy
- Data from the DES study (N=15) suggest the combination was well tolerated with TEAEs consistent with the profile of each individual agent, with no new safety signals reported. The safety profile improved over what has been previously reported with an investigational MMAE NaPi2b ADC carboplatin combination
  - Fatigue (86.7%), nausea (73.3%), platelet count decrease (66.7%; Grade 3/4, 33.3%), diarrhea (66.7%; Grade 3, 20%) and anemia (60%; Grade 3/4, 33.3%) were the most common TEAEs
  - The rate of treatment-emergent neutropenia (26.7%) was consistent with rates observed with carboplatin alone
  - Severe overlapping toxicities such as peripheral neuropathy, alopecia and mucositis were not observed in this limited DES dataset
- Fourteen patients were evaluable for response; confirmed ORR was 71.4% (n/N, 10/14) regardless of NaPi2b status, including 29% (4/14) CR
  - Clinical activity compared favorably with benchmark values of standard-of-care chemotherapy combinations (ORR, 45-59%)
- While development of UpRi has been discontinued by the sponsor, the reported UPGRADE data demonstrates the potential for ADCs utilizing the AF-HPA payload, to enable combinations with platinum with meaningful clinical activity and without significant overlapping toxicities

## ACKNOWLEDGMENTS

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## ADDITIONAL INFORMATION

Scan the Quick Response (QR) code for downloadable PDF copies of this poster and author disclosures.


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ADC, antibody-drug conjugate; AE, adverse event; AF-HPA, auristatin F hydroxypropyl amide; AKI, acute kidney injury; ALK, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; BRCA, breast cancer gene; BOIN, Bayesian optimal interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DAR, drug-to-antibody ratio; DCR, disease control rate; DES, dose escalation; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; EXP, dose expansion; FDA, US Food and Drug Administration; MMAE, monomethyl auristatin E; MTD, maximum tolerated dose; NaPi2b, sodium-dependent phosphate transporter 2b; NE, not evaluable; ORR, objective response rate; OS, overall survival; PARP, poly-ADP ribose polymerase; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; q4w, every 4 weeks; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; SD, stable disease; TEAE, treatment-emergent adverse event; TPS, tumor proportion score; UpRi, upifitamab rilsodotin.

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