Phase Ib/II Umbrella Trial to Evaluate the Safety and Efficacy of Multiple 2L Cancer Immunotherapy Combinations in Advanced/Metastatic Urothelial Carcinoma: MORPHEUS-mUC

Abstract # TPS591
Poster # N9

Alexandra Drakaki,[1] Arash Rezazadeh Kalebasty,[2] Jae-Lyun Lee,[3] Juan Martin-Liberal,[4] Miso Kim,[5] Sang Joon Shin,[6] Jane Shi,[7] Sanjeev Mariathasan,[8] Bo Ci,[8] Viraj Degaonkar,[8] Patrick Williams,[8] Edward Cha,[8] Julia Maltzman,[8] Thomas Powles[9]

[1]*University of California, Los Angeles, Los Angeles, CA;* [2]*Norton Cancer Institute, Louisville, KY;* [3]*Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea;* [4]*Catalan Institute of Oncology (ICO) L'Hospitalet, Barcelona, Spain;* [5]*Seoul National University Hospital, Seoul, Republic of Korea;* [6]*Yonsei University College of Medicine, Seoul, Republic of Korea;* [7]*Roche Product Development, Shanghai, China;* [8]*Genentech, Inc., South San Francisco, USA;* [9]*Barts Cancer Institute, Queen Mary University of London, Barts Experimental Cancer Medicine Centre, London, UK*

BACKGROUND

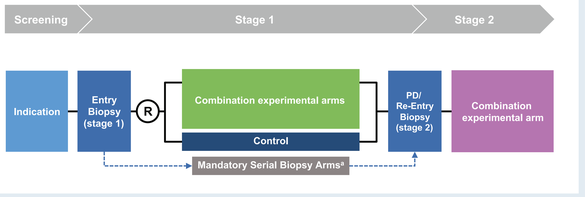
Cancer Immunotherapy

- Cancer immunotherapy (CIT) aims to enable pre-existing immunity to mount effective anti-cancer immune responses[1,2]
- The use of immune checkpoint inhibitors that target the programmed death-ligand 1/programmed death-1 (PD-L1/PD-1) axis has improved survival for patients with an array of advanced malignancies, including metastatic urothelial carcinoma (mUC)[3-6]
  - Although significant survival benefits have been seen in response to CIT monotherapy, durable clinical benefit has been observed only in a subset of these patients
- Combining CIT with different targeted or chemotherapeutic options may help to improve clinical outcomes by simultaneously addressing the multiple mechanisms of cancer immune evasion that can be present along the cancer-immunity cycle, to generate durable anti-tumor responses[1,7]
  - Identification of effective CIT combinations may require a large number of clinical trials, each evaluating a different combination regimen
- The MORPHEUS platform aims to evaluate CIT combination more efficiently than conventional trial designs

THE MORPHEUS PLATFORM

- Trials under the MORPHEUS platform assess the importance of simultaneously targeting mechanisms of immune escape, including immune cell priming and activation, tumor infiltration and/or recognition of tumor cells for elimination
- The MORPHEUS platform is composed of multiple global, open-label, randomized Phase Ib/II trials designed to capture early efficacy signals and evaluate the safety of treatment combinations in patients with different cancers
- The general design of trials based on the MORPHEUS platform is shown in Figure 1
- Trials under the MORPHEUS platform are designed to include multiple experimental arms and one shared standard-of-care control arm for each cohort, thereby reducing the number of patients receiving control treatment
  - New cohorts and treatment arms can be opened as novel combinations become available
  - Existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity can be closed
  - The CIT combinations currently planned for MORPHEUS-mUC include atezolizumab (anti–PD-L1) as the backbone
    - Atezolizumab is an engineered monoclonal antibody that inhibits the binding of PD-L1 to its receptors PD-1 and B7.1, thus restoring tumor-specific immunity[8]
    - Atezolizumab monotherapy has been approved globally and by the US Food and Drug Administration and European Commission for patients with locally advanced or metastatic UC after prior platinum-containing chemotherapy or who are considered cisplatin ineligible and whose tumors have PD-L1 expression ≥ 5%[9-10]
- Here we describe the mUC study under the MORPHEUS platform:
  - MORPHEUS-mUC is a randomized study of 6 CIT combinations compared with a single CIT control in patients with locally advanced UC/mUC who progressed during or after a platinum-containing regimen. The PD-L1 inhibitor atezolizumab will be combined with agents targeting different mechanisms (via nectin-4, PARP, CD47, CD38, DPP-4 and IL-6R) to enhance immune-cell priming and activation, tumor infiltration and/or recognition of tumor cells.

Figure 1. Overview of the MORPHEUS Platform



[a] Mandatory serial biopsy arms currently only applicable to treatment arms with clinical activity in the cohort.
R, randomization; PD, progressive disease.

MORPHEUS-MUC (NCT03869190)

Standard of Care and Unmet Need in Patients With mUC

- mUC is the thirteenth leading cause of cancer-related deaths globally, accounting for 199,922 deaths in 2018[11]
- mUC is typically treated initially with either platinum-based chemotherapy or checkpoint inhibitors depending on patient eligibility factors[12]
- Among patients with mUC, 40% to 50% are ineligible for cisplatin due to poor performance status, comorbidities, or impaired renal options; thereby highlighting the unmet medical need in this patient population[13]

Patient Population

- MORPHEUS-mUC enrollment requires histologically documented mUC
- In Stage 1, approximately 130-305 patients with histologically documented mUC will be randomized to atezolizumab monotherapy (control) or experimental arms: atezolizumab + enfortumab vedotin, niraparib, Hu5F9-G4, isatuximab, linagliptin or tocilizumab. Safety will be monitored for potential overlapping toxicities
- In Stage 2, arms will be atezolizumab + either enfortumab vedotin or linagliptin unless these combinations show no activity in Stage 1
- Eligible patients who experience unacceptable toxicity or loss of clinical benefit in Stage 1 may enroll in Stage 2 within 3 months

Key Inclusion and Exclusion Criteria

- General inclusion and exclusion criteria for MORPHEUS-mUC are listed in Table 1

Table 1. Key Inclusion and Exclusion Criteria for MORPHEUS-mUC

Inclusion Criteria	Exclusion Criteria
Age ≥ 18 years	Symptomatic or untreated CNS metastases
ECOG PS 0-1 (trial stage 1) and PS 0-2 (trial stage 2)	Prior treatment with any of the protocol-specified study treatments, with the exception of chemotherapy
Measurable disease per RECIST 1.1	Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies
Representative tumor specimen for PD-L1 and/or biomarker status	Treatment with investigational therapy ≤ 28 days prior to study treatment initiation
Tumor accessible for biopsy	Systemic treatments within 4 weeks or 5 half-lives of the drug before study treatment initiation

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; PS, performance status; RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1.

- The CIT combinations being studied in MORPHEUS-mUC are listed in Table 2

Table 2. Treatments Evaluated in MORPHEUS-mUC

Treatment	Target	Proposed Mechanism-of-Action Classification
Atezolizumab	PD-L1	Checkpoint inhibitor; reactivation of anti-tumor immune response[14]
Enfortumab vedotin	Nectin-4	Antibody-drug conjugate with anti–nectin-4 monoclonal antibody linked to MMAE[15]
Niraparib	PARP	PARP inhibitor; increases PD-L1 expression and immune activation[16]
Hu5F9-G4	CD47	Stimulation of macrophage phagocytosis with subsequent cross-presentation of tumor antigens and immune activation[17]
Isatuximab	CD38	Anti-CD38 monoclonal antibody; decreases T-regulatory cells and restores T-cell function[18]
Linagliptin	DPP-4	DPP-4 inhibitor; restores intra-tumoral chemotactic gradient and immune-cell recruitment[19]
Tocilizumab	IL-6R	IL-6R inhibitor; may decrease tumor-associated macrophages, T-regulatory cells, and myeloid-derived suppressor cells[20]

ADP, adenosine diphosphate; DPP-4, dipeptidyl peptidase-4;IL-6R, interleukin-6 receptor; IMP, investigational medicinal product; MMAE, monomethyl auristatin; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death ligand 1.

Table 3. CIT Combinations in MORPHEUS-mUC

	Arms	MORPHEUS-mUC
Stage 1	Control	Atezolizumab
	A	Atezolizumab + enfortumab vedotin
	B	Atezolizumab + niraparib
	C	Atezolizumab + Hu5F9-G4
	D	Atezolizumab + isatuximab
	E	Atezolizumab + linagliptin
	F	Atezolizumab + tocilizumab
Stage 2[a]		Atezolizumab + enfortumab vedotin *or* Atezolizumab + linagliptin[b]

[a] During stage 1, patients who experience loss of clinical benefit, as determined by the investigator, or unacceptable toxicity may be eligible to receive a different treatment combination during stage 2, provided they meet eligibility criteria.
[b] Patients who received enfortumab vedotin in stage 1 will not receive enfortumab vedotin in stage 2, and patients who received linagliptin in stage 1 will not receive linagliptin in stage 2. Other patients who are eligible for > 1 treatment arm will be assigned a treatment arm by the investigator.

Key Study Objectives

Efficacy

- Primary endpoint
  - Investigator-assessed objective response rate per RECIST 1.1 during Stage 1
- Secondary endpoints
  - Investigator-assessed progression-free survival (PFS) per RECIST 1.1 during Stage 1
  - OS
  - OS at specific timepoints (e.g., 12 months)
  - Investigator-assessed duration of response (DOR) per RECIST 1.1 during Stage 1
  - Investigator-assessed disease control rate (DCR) per RECIST 1.1 during Stage 1

Safety

- Incidence, nature and severity of adverse events and laboratory abnormalities
- Occurrence and severity of study treatment-related adverse events

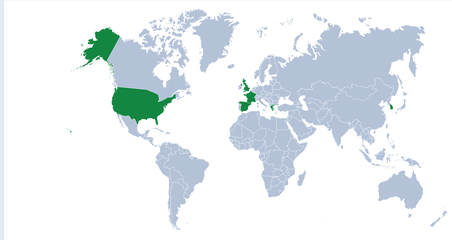
Exploratory

- Investigator-assessed ORR, DCR, DOR and PFS per immune-modified RECIST 1.1 during Stage 1
- Investigator-assessed ORR, DCR, DOR and PFS per RECIST 1.1 and immune-modified RECIST during Stage 2
- Pharmacokinetics
- Biomarker analyses of genes or gene signatures associated with tumor immunobiology, PD-L1, cytokines associated with T-cell activation, T-cell receptor repertoire and activation status of immune cells and their subsets
- Immunogenicity studies

Enrollment

- Patients will be randomized to one of the CIT combination arms or the standard-of-care control arm
- Approximately 15 to 40 patients will be enrolled per treatment arm in the stage 1 preliminary phase
  - Treatment arms demonstrating clinical activity will enroll 25 additional patients in the expansion phase
- Patients who experience disease progression, loss of clinical benefit or unacceptable toxicity with the initial treatment regimen (stage 1) may be eligible to continue treatment with a different CIT combination treatment (stage 2)
- Countries with clinical sites enrolling patients for the MORPHEUS-mUC cancer studies are shown in Figure 2
- MORPHEUS-mUC
  - 24 study sites in 6 countries (Figure 2)

Figure 2. Enrollment Sites for Patients With mUC



Countries involved:
- United States
- France
- Greece
- Republic of Korea
- Spain
- United Kingdom

FURTHER INFORMATION

- MORPHEUS-mUC: https://clinicaltrials.gov/ct2/show/NCT03869190

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ACKNOWLEDGMENTS

- The patients and their families
- The investigators and clinical study sites
- Industry partners Forty Seven Inc., Sanofi, Seattle Genetics and Astellas, Tesaro Inc. and Sanofi
- This study is sponsored by F. Hoffmann-La Roche, Ltd
- Medical writing assistance for this poster was provided by Priscilla Hong, PharmD, of Health Interactions and funded by F. Hoffmann-La Roche, Ltd

DISCLOSURES

- AD (presenting author) is employed by and part of the leadership of UCLA; has stock, equity and other ownership interest in Allogene, Athos Pharma, MedicusData.AI, and UroGen Pharma; has held consulting and advisory roles for AstraZeneca, Astellas/Seattle Genetics, Janssen, Nektar and RadMetrix; has patents, royalties and other intellectual property from UCLA; received travel, accommodations and expenses from AstraZeneca and Astellas/Seattle Genetics. For disclosures of co-authors, please see abstract, QR CODE and hyperlinks.