Abstract CT212
Poster 12

Phase Ib/II, global, open-label, randomized evaluation of atezolizumab (atezo) + etrumadenant (etruma) + chemotherapy (chemo) vs chemo alone in MORPHEUS-PDAC

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INTRODUCTION

- Extracellular adenosine accumulation can occur in the tumor microenvironment in response to factors including hypoxia, cell turnover, and inflammation.[1-3] Adenosine signaling via the A2a and A2b receptors on immune cells suppresses the anti-tumor immune response and promotes tumor immunity in many cancers, including pancreatic ductal adenocarcinoma (PDAC)[2-4]
  - Combining adenosine signaling inhibition with immunotherapy may therefore enhance anti-tumor activity[5]
  - Etrumadenant is a small-molecule, dual-adenosine A2a/A2b receptor antagonist that has shown encouraging activity and a favorable safety profile in multiple tumor types, as monotherapy or in combination with chemotherapy/immunotherapy[6,7]
  - Atezolizumab is a monoclonal antibody targeting the immune checkpoint protein programmed death-ligand 1 (PD-L1) that binds and inhibits PD-L1 on tumor cells and/or tumor-infiltrating immune cells and restores the antitumor immune response[8,9]
- The MORPHEUS platform consists of multiple, global, open-label, randomized, umbrella Phase Ib/II trials designed to accelerate the development of combinations in several indications by identifying early signals and establishing proof-of-concept clinical data[10,11]
- Trials under the MORPHEUS platform are assessing the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumor infiltration and/or recognition of tumor cells for elimination
  - Using a randomized trial design, multiple combination arms are being compared with a single control arm, thereby reducing the number of patients receiving control treatment
- Here, we present the 108-week final analysis of the atezolizumab + etrumadenant + chemotherapy arm in MORPHEUS-PDAC Cohort 1 (patients with PDAC treated in the first-line [1L] setting)

METHODS

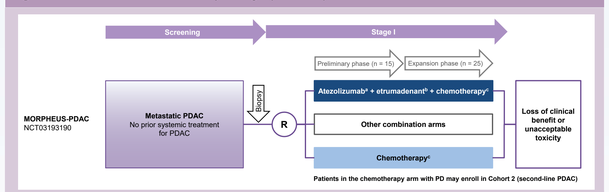
Study Design

- The MORPHEUS-PDAC study design is presented in Figure 1. Patients who had no prior systemic treatment for metastatic PDAC (Cohort 1, 1L PDAC) were randomized to receive atezolizumab + etrumadenant + chemotherapy or chemotherapy alone (control)
  - Key inclusion criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, age >18 years, baseline biopsy and measurable disease per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)
  - Key exclusion criteria included symptomatic, untreated, or actively progressing nervous system metastases, active or history of autoimmune disease or immune deficiency, and a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis or evidence of active pneumonitis
- Patients were treated until loss of clinical benefit or unacceptable toxicity. Additionally, patients in the chemotherapy arm who had disease progression (PD) had the option to enroll in Cohort 2 (second-line PDAC), provided that experimental treatment arms were open for enrollment and that patients met the eligibility criteria and signed the appropriate informed consent form

Biomarker Analysis

- Detection and quantification of biomarkers was performed by staining of formalin-fixed paraffin-embedded tumor tissue using immunofluorescence (IF) or immunohistochemistry (IHC):
  - Multiplex IF panel containing CD73 (clone D7F9A), TNAP (clone R034), PanCK (clone AE1/AE3/PCK26), CD8 (SP239) and PD-L1 (clone SP263) (atezolizumab + etrumadenant + chemotherapy arm; Ventana)
  - CD73 (clone D7F9A) IHC assay (atezolizumab + etrumadenant + chemotherapy arm; Cell Carta)
  - PD-L1 (clone SP263) IHC assay (chemotherapy arm; Cell Carta)
  - CD8 (clone SP239) and panCK (clone AE1/AE3/PCK26) duplex IHC assay (atezolizumab + etrumadenant + chemotherapy arm and chemotherapy arm; Cell Carta)

Figure 1. MORPHEUS-PDAC Study Design (Cohort 1)



IV, intravenous.
[a] Atezolizumab 840 mg IV on Days 1 and 15 of 28-day cycles.
[b] Etrumadenant 150 mg orally once daily.
[c] Nab-paclitaxel 125 mg/m² IV and gemcitabine 1000 mg/m² IV on Days 1, 8 and 15 of 28-day cycles.

Primary Efficacy Endpoint

- Objective response rate (ORR), determined by the investigator per RECIST 1.1

Key Secondary Efficacy Endpoints and Other Analyses

- Progression-free survival (PFS), overall survival (OS), duration of response (DOR), disease control rate (DCR)
- Long-term safety and exploratory biomarker analyses were also conducted

RESULTS

Patients

- As of the clinical cutoff date (January 12, 2023), 16 patients were enrolled in the atezolizumab + etrumadenant + chemotherapy arm and 21 in the chemotherapy arm (intention-to-treat population)
  - 15 and 20 patients received treatment in the atezolizumab + etrumadenant + chemotherapy arm and chemotherapy arm, respectively (efficacy- and safety-evaluable population)
- Baseline demographics were generally similar between treatment arms (Table 1), except there were fewer patients aged ≥ 65 years (31.3% vs 71.4%; Δ–40.2%) and more patients with liver metastases (87.5% vs 71.4%; Δ16.1%) in the atezolizumab + etrumadenant + chemotherapy arm vs chemotherapy arm, respectively

Table 1. Baseline Demographics and Disease Characteristics

Patients, n (%)	Atezo + etruma + chemo (n = 16)	Chemo (control) (n = 21)
Age ≥ 65 years	5 (31.3)	15 (71.4)
Male	8 (50.0)	11 (52.4)
Race		
Asian	8 (50.0)	10 (47.6)
Black or African American	1 (6.3)	0
White	7 (43.8)	9 (42.9)
Unknown	0	2 (9.5)
ECOG PS 1	7 (43.8)	11 (52.4)
Prior cancer surgery		
No	14 (87.5)	18 (85.7)
Prior cancer radiotherapy		
No	16 (100)	21 (100)
No. of metastatic sites at enrollment[a]		
Median	2.0	2.0
Range	1-4	1-5
Liver metastases		
Yes	14 (87.5)	15 (71.4)

Clinical cutoff: January 12, 2023.
[a] Taken from cancer history forms.

Efficacy

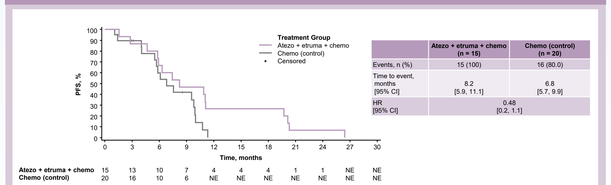
- The primary endpoint was not met: confirmed ORR was 26.7% (n = 4) in the atezolizumab + etrumadenant + chemotherapy arm vs 45.0% (n = 9) in the chemotherapy arm (Table 2)
  - There was 1 complete response (CR; 6.7%) and 3 partial responses (PRs; 20.0%) in the atezolizumab + etrumadenant + chemotherapy arm; all responses in the chemotherapy arm were PRs
- Median PFS was 8.2 months with atezolizumab + etrumadenant + chemotherapy vs 6.8 months with chemotherapy, with a hazard ratio (HR) of 0.48 (Figure 2)
- Median OS was 16.5 months with atezolizumab + etrumadenant + chemotherapy vs 12.1 months with chemotherapy, with an HR of 0.67 (Figure 3)
  - Median duration of survival follow-up was 16.5 vs 11.4 months

Table 2. Efficacy

	Atezo + etruma + chemo (n = 15)	Chemo (control) (n = 20)
Confirmed investigator-assessed ORR[a] per RECIST 1.1, n (%) [95% CI]	4 (26.7) [7.8, 55.1]	9 (45.0) [23.1, 68.5]
CR	1 (6.7) [0.2, 32.0]	0 [0.0, 16.8]
PR	3 (20.0) [4.3, 48.1]	9 (45.0) [23.1, 68.5]
SD, n (%) [95% CI]	9 (60.0) [32.3, 83.7]	9 (45.0) [23.1, 68.5]
PD, n (%) [95% CI]	1 (6.7) [0.2, 32.0]	1 (5.0) [0.1, 24.9]
NE, n (%)	0	0
Missing, n (%)	1 (6.7)	1 (5.0)
DCR, n (%) [95% CI]	10 (66.7) [38.4, 88.2]	16 (80.0) [56.3, 94.3]
DOR, months [95% CI]	4.9 [2.9, NE]	5.4 [2.8, 8.2]

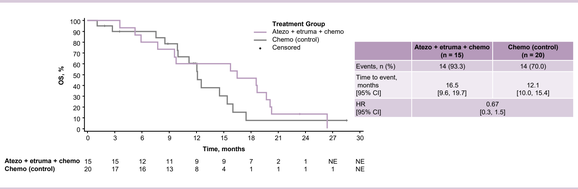
Patients were classified with 'SD' if assessment was at least 6 weeks from randomization. Patients were classified as 'missing' if no post-baseline response assessments were available. Patients were classified as 'unevaluable' if all post-baseline response assessments were unevaluable. Criteria for disease control was either response and/or SD or better for at least 12 weeks.
CI, confidence interval; SD, stable disease.
[a] One unconfirmed responder in the atezo + etruma + chemo arm; 2 unconfirmed responders in the chemo arm.

Figure 2. Kaplan-Meier Plot of PFS



	Atezo + etruma + chemo (n = 15)	Chemo (control) (n = 20)
Events, n (%)	15 (100)	16 (80.0)
Time to event, months [95% CI]	8.2 [5.9, 11.1]	6.8 [5.7, 9.9]
HR [95% CI]	0.48 [0.2, 1.1]	

Figure 3. Kaplan-Meier Plot of OS

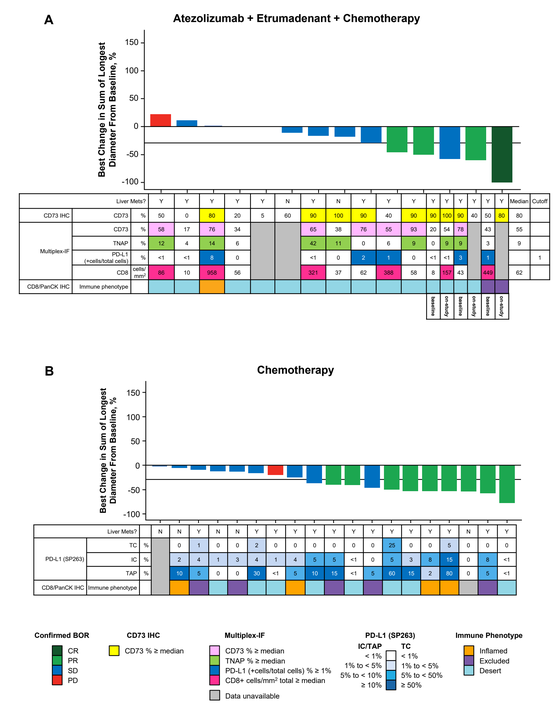


	Atezo + etruma + chemo (n = 15)	Chemo (control) (n = 20)
Events, n (%)	14 (93.3)	14 (70.0)
Time to event, months [95% CI]	16.5 [9.6, 19.7]	12.1 [10.0, 15.4]
HR [95% CI]	0.67 [0.3, 1.5]	

Biomarker Analysis

- Although based on limited data, there were no clear associations between baseline levels of CD73 or PD-L1 and clinical outcomes (Figure 4)

Figure 4. BOR and Percent Change in the Sum of Longest Diameter From Baseline According to Baseline Biomarkers in (A) the Atezolizumab + Etrumadenant + Chemotherapy arm and (B) the Chemotherapy Arm



BOR, best overall response; IC, immune cell; N, no; TAP, tumor area positivity; TC, tumor cell; Y, yes.

Safety

- Safety data are summarized in Table 3 and the most common adverse events (AEs; ≥30% incidence in either arm) are shown in Table 4
- The most frequent Grade 3/4 AEs (≥10% incidence) were neutrophil count decreased (26.7%), anemia (20.0%), white blood cell count decreased (20.0%), abdominal pain (13.3%), blood alkaline phosphatase increased (13.3%), hyponatremia (13.3%) and neurotoxicity (13.3%) in the atezolizumab + etrumadenant + chemotherapy arm, and neutropenia (30%), anemia (25%) and neutrophil count decreased (15%) in the chemotherapy arm
- All treated patients had ≥1 treatment-related adverse event (TRAE)

Table 3. Overall Safety Summary

Patients, n (%)	Atezo + etruma + chemo (n = 15)	Chemo (control) (n = 20)
Patients with ≥1 AE	15 (100)	20 (100)
TRAEs	15 (100)	20 (100)
Grade 3-5 AEs	12 (80.0)	16 (80.0)
Worst grade: 5	0	2 (10.0)[a]
Worst grade: 4	2 (13.3)	6 (30.0)
Worst grade: 3	10 (66.7)	8 (40.0)
Serious AEs	4 (26.7)	8 (40.0)
Treatment-related serious AEs	3 (20.0)	5 (25.0)
TRAEs leading to withdrawal from any treatment	3 (20.0)[b]	3 (15.0)[c]
TRAEs leading to dose modification/interruption	12 (80.0)	14 (70.0)

[a] Pneumonia (n = 1), septic shock (n = 1).
[b] Neurotoxicity (n = 1), peripheral sensory neuropathy (n = 1), pneumonitis (n = 1).
[c] Cardiac failure (n = 1), chest pain (n = 1), pneumonitis (n = 1).

Table 4. Most Common AEs (≥30% Incidence Rate in Either Arm)

Patients, n (%)	Atezo + etruma + chemo (n = 15)	Chemo (control) (n = 20)
Anemia	9 (60.0)	10 (50.0)
Nausea	7 (46.7)	12 (60.0)
Fatigue	3 (20.0)	11 (55.0)
Decreased appetite	7 (46.7)	8 (40.0)
Diarrhea	4 (26.7)	8 (40.0)
Alanine aminotransferase increased	6 (40.0)	4 (20.0)
Aspartate aminotransferase increased	6 (40.0)	4 (20.0)
Pruritus	6 (40.0)	3 (15.0)
Asthenia	6 (40.0)	2 (10.0)
Neutropenia	1 (6.7)	7 (35.0)
Dyspnea	1 (6.7)	7 (35.0)
Rash	5 (33.3)	5 (25.0)
Neutrophil count decreased	5 (33.3)	4 (20.0)
Constipation	4 (26.7)	6 (30.0)
Peripheral edema	4 (26.7)	6 (30.0)
Alopecia	4 (26.7)	6 (30.0)
Peripheral neuropathy	0	6 (30.0)

CONCLUSIONS

- With a small study population, the ORR primary endpoint was not met in MORPHEUS-PDAC, although both median PFS and OS were numerically improved with the combination therapy, suggesting that the addition of atezolizumab and etrumadenant to chemotherapy may confer a benefit
  - The OS findings are similar to those from the ARC-8 trial of quemliclustat, a small molecule inhibitor of CD73, a key enzyme involved in the production of extracellular adenosine[12]
- There were no clear associations between baseline levels of CD73 or PD-L1 and clinical outcomes, including response rates and long-term survival, although the biomarker subgroup analysis was based on limited data and sample size
- No new safety signals were observed with atezolizumab + etrumadenant + chemotherapy, and safety of the combination was consistent with the known risks of the individual treatments

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ACKNOWLEDGMENTS

- The patients and their families
- The investigators and clinical study sites
- This study is sponsored by F. Hoffmann-La Roche, Ltd
- Medical writing support for this poster was provided by Brian Law, PhD, of Nucleus Global, an Inizio company, and funded by F. Hoffmann-La Roche Ltd

DISCLOSURES

- Dr Kim reports research funding for third-party writing assistance for this poster, provided by Brian Law, PhD, of Nucleus Global, an Inizio company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland
- For all author disclosures, see the abstract

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