INTRODUCTION

Ectonucleotidase activity is known to occur in the tumor microenvironment in response to factors including, tissue cell turnover, and inflammation.1 Adenosine signaling via the A2A and A2B receptors is a major immune checkpoint and promotes tumor immunity in many cancers, including pancreatic ductal adenocarcinoma (PDAC).2

Combining antitumor agents may therefore enhance antitumor activity.3 Etrumadenant is a small-molecule, dual adenosine A2A/A2B receptor antagonist that has shown encouraging activity and favorable safety profiles in multiple tumor types, as monotherapy or in combination with checkpoint inhibitors.4

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 promotes the antitumor immune response.

• The MORPHEUS-PDAC platform consists of multiple, global, open-label, randomized Phase Ib/II trials designed to accelerate the development of combinators in several indications by identifying early signals and establishing proof-of-concept clinical data.5 6

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 Atezolizumaba + etrumadenantb + chemotherapyc vs chemotherapy alone in MORPHEUS-PDAC Cohort 1 (patients with PDAC treated in the first-line [1L] setting).

RESULTS

Primary Efficacy Endpoints

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.

Efficacy

- The primary endpoint was not met: confirmed ORR was 26.7% (95% CI: 15.0%; 41.9%) in the atezolizumab + etrumadenant + chemotherapy arm vs 43.3% (95% CI: 23.1%; 63.5%) in the chemotherapy arm (Table 1).

- There was a complete response (CR) rate of 6.3% and a partial response (PR) rate of 20.0% in the atezolizumab + etrumadenant + chemotherapy arm; all responders in the chemotherapy arm were 17.5 and 20.0%, respectively; efficacy- and safety-evaluable population).

- There was 1 complete response (CR; 6.7%) and 3 partial responses (PRs; 20.0%) in the chemotherapy arm, respectively (efficacy- and safety-evaluable population).

- Safety

- Serious adverse events (SAEs) were recorded for 11 patients (50.0%) in the atezolizumab + etrumadenant + chemotherapy arm vs 14 patients (70.0%) in the chemotherapy arm. The most common SAEs were neutropenia (26.7%), anemia (20.0%), decreased appetite (20.0%), abdominal pain (13.3%), blood alkaline phosphatase increased (15.0%), hyponatremia (13.3%) and neurotoxicity (13.3%) in the chemotherapy arm.

- Four (26.7%) patients in the atezolizumab + etrumadenant + chemotherapy arm and three (15.0%) patients in the chemotherapy arm had grade 3 or 4 neutropenia.

- There were no significant differences in overall survival (OS) between the treatment arms (HR 0.48; 95% CI: 0.23; 1.0)

- Safety data are summarized in Table 2 and the most common adverse events (AEs) ≥30% incidence in either arm are shown in Table 3.

- The most frequent Grade 3/4 AEs (≥10% incidence) were neutropenia decreased (26.7%), anemia (20.0%), white blood cell count decreased (20.0%), decreased appetite (13.3%), neutrophil count decreased (13.3%), hyponatremia (13.3%) and neurotoxicity (13.3%) in the chemotherapy arm.

- All treated patients had at least one treatment-related adverse event (TRAE).

Biomarker Analysis

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

CONCLUSIONS

- Despite 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 etrumadenant to chemotherapy may confer a benefit.

- The OS findings are similar to those from the ASCO trial of atezolizumab, a small molecule inhibitor of CD73, a key enzyme involved in the production of adenosine.

- No new safety signals were observed with atezolizumab + etrumadenant + chemotherapy, and safety of this combination was consistent with the known rates of the individual treatments.

DISCLOSURES

The authors declare no conflicts of interest.

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REFERENCES

