Phase Ib/II Open-Label, Randomised Evaluation of Second- or Third-Line Atezolizumab + Entinostat in MORPHEUS-HR+ Breast Cancer

Abstract 613
Poster 267P

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MORPHEUS PLATFORM AND COMBINATION THERAPY

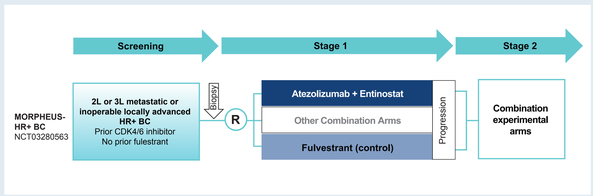
- The MORPHEUS platform consists of multiple, global, open-label, randomised, umbrella Phase Ib/II trials designed to accelerate the development of combinations in several indications by identifying early signals and establishing proof-of-concept clinical data[1,2]
- Trials under the MORPHEUS platform are assessing the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumour infiltration and/or recognition of tumour cells for elimination
  - Using a randomised trial design, multiple combination arms are being compared with a single control arm, thereby reducing the number of patients receiving control treatment
- Atezolizumab (anti–programmed death-ligand 1 [PD-L1]) is a checkpoint inhibitor that acts largely by re-invigorating pre-existing anti-tumour T-cell responses.[3] Combination atezolizumab regimens have been associated with greater clinical benefit than monotherapy in several cancers[4-6]
- Entinostat is a Class I specific histone deacetylase (HDAC) inhibitor that suppresses both myeloid-derived suppressor cells and regulatory T cells and increases antigen expression on tumour cells[6]
  - A Phase I study showed encouraging activity with the combination of entinostat and pembrolizumab (programmed death-1 inhibitor) in patients with hormone receptor positive (HR+) breast cancer (BC)[7]
- Given the ability of entinostat to reduce immune suppressive cells in the tumour microenvironment, we hypothesised that adding entinostat to atezolizumab could potentiate the anti-tumour responses in patients with metastatic or inoperable locally advanced HR+ BC

MORPHEUS-HR+BC (NCT03280563): 69-WEEK INTERIM ANALYSIS

Study Design

- Here, we report the results from patients receiving atezolizumab + entinostat in patients with HR+ BC (Figure 1)

Figure 1. Study Design of MORPHEUS-HR+ BC



2L, second line; 3L, third line; R, randomisation.

- Primary endpoint:
  - Investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST)
- Key secondary endpoints:
  - Investigator-assessed progression-free survival (PFS), disease control rate (DCR), clinical benefit rate (CBR) and duration of response (DOR) per RECIST 1.1
  - Overall survival (OS)
  - Pharmacokinetics (PK) and percentage of patients with anti-drug antibodies (ADAs) to atezolizumab
- Safety
  - Incidence, nature and severity of adverse events per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0
- Exploratory biomarker analyses were also conducted
  - PD-L1 and CD8/panCK immunohistochemistry (IHC) were evaluated in all tumour tissue samples

Inclusion Criteria and Treatment

- Key inclusion criteria were a histologically or cytologically confirmed diagnosis of metastatic or inoperable locally advanced HR+ HER2-negative BC that had progressed during or following a CDK4/6 inhibitor, age ≥ 18 years; ECOG PS score 0-1 and measurable disease per RECIST 1.1
- Eligible patients had to provide an entry biopsy before being randomised to receive either atezolizumab 1200 mg intravenously every 3 weeks + entinostat 5 mg orally on Days 1, 8 and 15 of each 21-day cycle or fulvestrant 500 mg intramuscularly on Days 1 and 15 (Cycle 1) followed by Day 1 of each 28-day cycle subsequently until they experienced unacceptable toxicity and/or loss of clinical benefit as determined by the investigator in the experimental arm or progressive disease (PD) per RECIST 1.1 (Figure 1)

Key Exclusion Criteria

- Key exclusion criteria included symptomatic, untreated or actively progressing central nervous system metastases; active or history of autoimmune disease or immune deficiency; and a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis or idiopathic pneumonitis, or evidence of active pneumonitis

Patient Demographics and Disposition

- Fifteen patients were randomised and treated with atezolizumab + entinostat in the experimental arm, and 14 patients with fulvestrant in the control arm
- An interim analysis of efficacy and safety was conducted at the 69-week cutoff on 9 June 2021
- Patient baseline characteristics and demographics are presented in Table 1

Table 1. Baseline Demographics and Disease Characteristics

n (%)	Atezolizumab + Entinostat (n = 15)	Fulvestrant (n = 14)
Age ≥ 65 years	3 (20.0)	4 (28.6)
Female	15 (100.0)	14 (100.0)
ECOG PS 1	7 (46.7)	6 (42.9)
Albumin level ≥ 35 g/L	15 (100.0)	13 (92.9)
CRP level > 12 mg/L	3 (20.0)	7 (50.0)
LDH level		
< 1.5 × ULN, 1.5 to < 2.5 ULN	14 (93.3), 1 (6.7)	10 (71.4), 4 (28.6)
Oestrogen receptor		
< 1%	0	1 (7.1)
≥ 1% to < 5%	0	3 (21.4)
≥ 10%	15 (100.0)	10 (71.4)
Progesterone receptor		
< 1%	7 (46.7)	6 (42.9)
≥ 1% to < 5%	1 (6.7)	2 (14.3)
≥ 5% to < 10%	0	1 (7.1)
≥10%	7 (46.7)	5 (35.7)
CDK4/6 inhibitor therapy duration, median (range), mo	14.8 (0.7-60.2)	11.4 (2.3-30.3)
Number of metastatic sites at enrolment		
0-3, ≥4	14 (93.3), 1 (6.7)	12 (85.7), 2 (14.3)
Metastatic sites at enrolment		
Liver	8 (53.3)	7 (50.0)
Bone	4 (26.7)	7 (50.0)
Breast	4 (26.7)	2 (14.3)
Lymph node	2 (13.3)	6 (42.9)
Lung	2 (13.3)	3 (21.4)

Clinical cutoff, 9 June 2021.
CRP, c-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase, ULN, upper limit of normal.

- Demographics and disease characteristics were generally similar between arms

Efficacy

- Efficacy data are summarized in Table 2

Table 2. Efficacy in MORPHEUS-HR+ BC

	Atezolizumab + Entinostat (n = 15)	Fulvestrant (n = 14)
Confirmed investigator-assessed ORR per RECIST 1.1, n (%) [95% CI]	1 (6.7) [0.2, 32.0]	0 [0.0, 23.2]
CR	0 [0.0, 21.8]	0 [0.0, 23.2]
PR	1 (6.7) [0.2, 32.0]	0 [0.0, 23.2]
SD, n (%) [95% CI]	5 (33.3) [11.8, 61.6]	4 (28.6) [8.4, 58.1]
PD, n (%) [95% CI]	8 (53.3) [26.6, 78.7]	8 (57.1) [28.9, 82.3]
Missing or NE, n (%)[a]	1 (6.7)	2 (14.3)
DCR, n (%) [95% CI][b]	3 (20.0) [4.3, 48.1]	2 (14.3) [1.8, 42.8]
DOR, mo [95% CI][c]	2.5 [NE, NE]	NA
CBR, n (%) [95% CI][d]	1 (6.7) [0.2, 32.0]	1 (7.1) [0.2, 33.9]
Median PFS per investigator–assessed RECIST 1.1, [95% CI], mo	1.8 [1.5, 3.8]	1.8 [1.5, 3.9]
Median OS, mo [95% CI][e]	24.9 [23.1, NE]	19.8 [5.3, NE]

Clinical cutoff, 9 June 2021.
CR, complete response; NA, not available; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Classified as "missing" if no post-baseline response assessments were available and NE if all post-baseline response assessments were unevaluable.
[b] Criteria for disease control are SD for ≥ 12 weeks or a CR or PR, as determined by the investigator per RECIST 1.1.
[c] Defined as the time from the first occurrence of a documented overall response to the first date of recorded disease progression or death from any cause (whichever occurs first), as determined by the investigator per RECIST 1.1.
[d] Criteria for clinical benefit are SD for ≥ 24 weeks or a CR or PR, as determined by the investigator per RECIST 1.1
[e] OS is mature for the fulvestrant arm and not yet mature for the atezolizumab + entinostat arm.

- 1 patient (6.7%) experienced PR while receiving atezolizumab + entinostat

Safety

- Safety data are summarized in Table 3

Table 3. Safety Summary

n (%)	Atezolizumab + Entinostat (n = 15)	Fulvestrant (n = 14)
Patients with ≥ 1 AE	15 (100.0)	12 (85.7)
Treatment-related AEs	12 (80.0)	5 (35.7)
Serious AEs	4 (26.7)	2 (14.3)
Related serious AEs	2 (13.3)	0
Grade 3-4 AEs	6 (40.0)	3 (21.4)
Grade 5 AEs	0	0
Related AEs leading to dose modification/ interruption[a]	8 (53.3)	0
Related AEs leading to withdrawal from treatment[a]	1 (6.7)	0

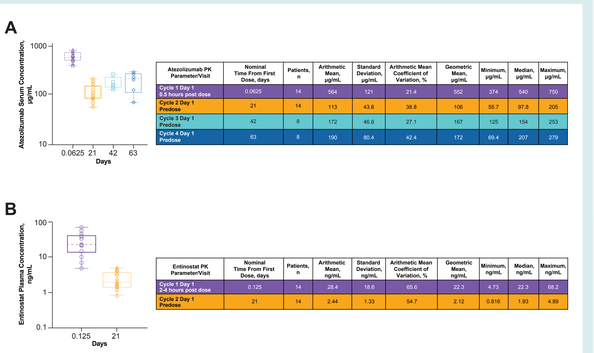
Clinical cutoff, 9 June 2021.
AE, adverse event.
[a] AE leading to withdrawal from treatment or dose modification/interruption for any drug.

- Treatment-related AEs occurring in ≥ 20% of patients in the atezolizumab + entinostat arm were nausea (33%), vomiting (27%), fatigue (27%), pyrexia (27%) and chills (20%)

Pharmacokinetic and Immunogenicity Analyses

- PK data are summarized in Figure 2

Figure 2. Concentrations of (A) Atezolizumab and (B) Entinostat



Atezolizumab PK Parameter/Visit	Nominal Time From First Dose, days	Patients, n	Arithmetic Mean, µg/mL	Standard Deviation, µg/mL	Arithmetic Mean Coefficient of Variation, %	Geometric Mean, µg/mL	Minimum, µg/mL	Median, µg/mL	Maximum, µg/mL
Cycle 1 Day 1 0.5 (hours) post dose	0.0625	14	164	121	74.4	130	374	540	750
Cycle 2 Day 1 Predose	21	14	113	43.8	38.8	106	55.7	97.8	205
Cycle 3 Day 1 Predose	42	8	172	46.8	27.1	167	125	154	253
Cycle 4 Day 1 Predose	63	8	190	80.4	42.4	172	69.4	207	279

Entinostat PK Parameter/Visit	Nominal Time From First Dose, days	Patients, n	Arithmetic Mean, ng/mL	Standard Deviation, ng/mL	Arithmetic Mean Coefficient of Variation, %	Geometric Mean, ng/mL	Minimum, ng/mL	Median, ng/mL	Maximum, ng/mL
Cycle 1 Day 1 2–4 (hours) post dose	0.125	14	28.4	14.8	51.9	22.3	4.73	22.3	68.2
Cycle 2 Day 1 Predose	21	14	2.44	1.33	54.7	2.12	0.816	1.93	4.89

- Peak and trough exposures of atezolizumab and entinostat were in line with expectations and clinical experience to date
- Mild accumulation in trough serum concentrations of atezolizumab was observed throughout the treatment with exposures above the target of 6 µg/mL for maximum receptor occupancy
- Peak exposure of serum concentrations of entinostat was expected to effectively inhibit HDAC
- Moderate inter-individual variability was observed with both atezolizumab (≈ 40%) and entinostat (≈ 65%)
- Treatment-emergent atezolizumab ADAs were seen in 5 of 14 patients (36%)

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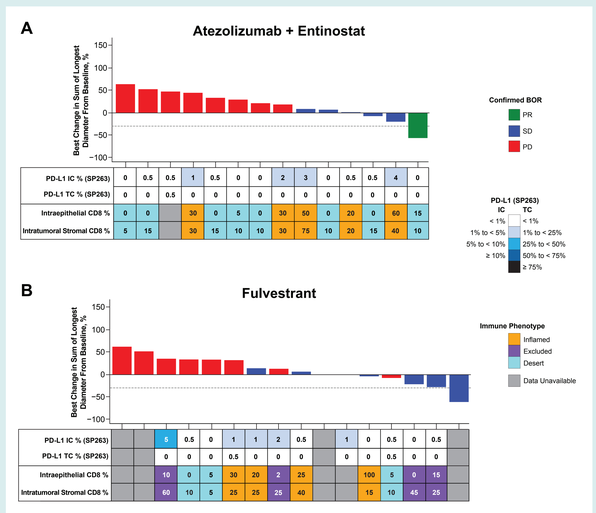
Biomarker Analysis

- Biomarker data are summarized according to best overall response to atezolizumab + entinostat and fulvestrant in Figure 3

Figure 3. Relationship Between PD-L1 Status, Tumour Immune Phenotype and Best Overall Response with (A) Atezolizumab + Entinostat and (B) Fulvestrant



IC, tumour-infiltrating immune cells; TC, tumour cells.
Immune phenotype calculated using CD8/panCK dual IHC (HistoGeneX) manual density proportion scores and the following algorithm: inflamed = IE2 + IE3 ≥ 20%; excluded = IE2 + IE3 < 20% and ITS2 + ITS3 ≥ 20%; desert = IE2 + IE3 < 20% and ITS2 + ITS3 < 20%. Two patients receiving atezolizumab + entinostat and one patient receiving fulvestrant are not included as they discontinued before their first tumour assessment.

- PD-L1 expression (SP263) was low or absent in most patients across both arms
- Neither PD-L1 expression nor CD8 immune phenotype correlated with stable disease or response with atezolizumab + entinostat

CONCLUSIONS

- Treatment with atezolizumab + entinostat led to limited responses in patients with HR+ BC
- The AEs observed were consistent with the known safety profiles of the individual study treatments. No new safety signals were identified with atezolizumab + entinostat
- Peak and trough exposures with atezolizumab and entinostat were in line with expectations and those observed in global studies for HR+ BC; peak exposure of entinostat should be sufficient to effectively inhibit HDAC
- Biomarker analyses did not identify any significant trends related to efficacy

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DISCLOSURES

- Dr Sonnenblick is an advisor to Novartis, Pfizer, Roche, Rhenium and Eli Lilly and provided expert testimony for AstraZeneca
- For coauthor disclosures, please refer to published abstract

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