Initial results from a first-in-human study of AZD5335, a folate receptor α-targeted antibody-drug conjugate, in patients with platinum-resistant recurrent ovarian cancer

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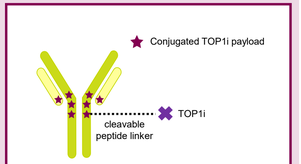
Background

- Folate receptor α (FRα) is a cell-surface protein that binds and internalises folate, a cofactor required for DNA synthesis, cell growth, and proliferation.[1–3]
- FRα is highly expressed in multiple epithelial tumours, including ovarian cancer (OC), but has a limited expression in normal tissues, highlighting FRα as a potential tumour target.[2,3]
- AZD5335 is an FRα-targeted antibody-drug conjugate (ADC) that specifically binds to FRα with high affinity and delivers a topoisomerase 1 inhibitor (TOP1i) payload (**Figure 1**).[4]
- Preclinical studies of AZD5335 in patient-derived xenograft (PDX) models of OC demonstrated that a single injection of AZD5335 (5 mg/kg) inhibited tumour growth, with a median best reduction in tumour volume of >30% in 18/23 (78%) PDXs.[4]
  - AZD5335 also demonstrated activity in a xenograft model of OC resistant to a surrogate of mirvetuximab soravtansine, an FRα ADC with a microtubule inhibitor payload.[4]

Figure 1. Schematic of AZD5335



The FRα monoclonal antibody is conjugated to the TOP1i using a cleavable peptide linker. AZD5335 has an average drug-antibody ratio of 8.

FRα, folate receptor α; TOP1i, topoisomerase 1 inhibitor
Figure adapted from Gymnopoulos M, et al. Presented at AACR 2023 (LB025).

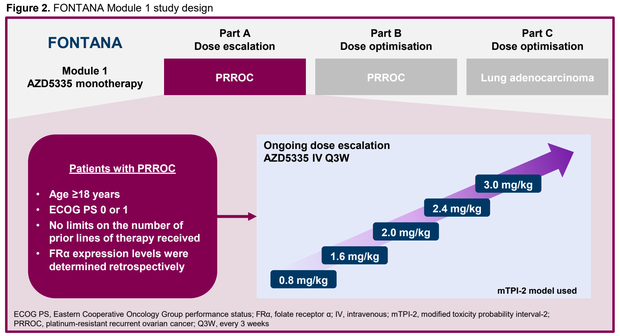
Study aims

- FONTANA (NCT05797168) is a phase 1/2a, first-in-human, modular, open-label study of AZD5335 in patients with advanced solid tumours.[5]
  - We report data from Module 1, the ongoing dose-escalation phase.

Methods

- Module 1 Part A of FONTANA evaluated AZD5335 monotherapy (0.8, 1.6, 2.0, 2.4, or 3.0 mg/kg intravenously) every 3 weeks (Q3W) in patients with platinum-resistant recurrent OC (PRROC; **Figure 2**).
  - Dose escalation is ongoing; patients may receive doses >3.0 mg/kg as dose escalation continues.
  - Study details, including inclusion/exclusion criteria, have been previously presented[5] and can also be found at https://www.clinicaltrials.gov/study/NCT05797168?term=NCT05797168&rank=1

Figure 2. FONTANA Module 1 study design



ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor α; IV, intravenous; mTPI-2, modified toxicity probability interval-2; PRROC, platinum-resistant recurrent ovarian cancer; Q3W, every 3 weeks

Primary objective

- To assess the safety and tolerability of AZD5335 monotherapy by evaluating adverse events (AEs), serious AEs, and dose-limiting toxicities (DLTs).

Secondary objectives

- To determine the preliminary antitumour activity of AZD5335 monotherapy in terms of the objective response rate (ORR) as assessed per Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 (evaluated every 6 weeks in all patients).
- To characterise the pharmacokinetics (PK) of AZD5335.

Results

Baseline characteristics and treatment received

- As of 5 August 2024, 39 patients who had received a median (range) of 4 (1–9) prior lines of therapy had been treated (**Table 1**).
- The median (range) duration of treatment was 4.5 (0–12) months.
- At data cutoff, 24 patients (61.5%) were still receiving treatment.

Table 1. Baseline patient and disease characteristics

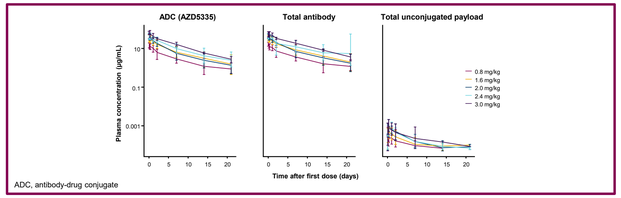
Baseline characteristic	0.8 mg/kg (n=9)	1.6 mg/kg (n=8)	2.0 mg/kg (n=9)	2.4 mg/kg (n=8)	3.0 mg/kg (n=5)	Total (N=39)
Age, median (range) years	61.5 (46–76)*	61.0 (55–75)	64.0 (48–71)	65.0 (57–71)	56.0 (51–64)†	62.0 (46–76)‡
Race, n (%)						
White	6 (66.7)	4 (50.0)	6 (66.7)	5 (62.5)	3 (60.0)	24 (61.5)
Asian	2 (22.2)	3 (37.5)	3 (33.3)	3 (37.5)	1 (20.0)	12 (30.8)
Black or African American	0	1 (12.5)	0	0	0	1 (2.6)
Missing	1 (11.1)	0	0	0	1 (20.0)	2 (5.1)
ECOG PS, n (%)						
0	5 (55.6)	3 (37.5)	4 (44.4)	4 (50.0)	3 (60.0)	19 (48.7)
1	4 (44.4)	5 (62.5)	5 (55.6)	4 (50.0)	2 (40.0)	20 (51.3)
Median number of prior lines of therapy (range)	4.0 (1–8)	4.5 (3–9)	7.0 (2–9)	3.5 (2–5)	3.0 (2–6)	4.0 (1–9)
Number of prior lines of therapy, n (%)						
≤2	2 (22.2)§	0	1 (11.1)	1 (12.5)	1 (20.0)	5 (12.8)
3	1 (11.1)	3 (37.5)	0	3 (37.5)	2 (40.0)	9 (23.1)
4	2 (22.2)	1 (12.5)	2 (22.2)	3 (37.5)	1 (20.0)	9 (23.1)
5	3 (33.3)	1 (12.5)	1 (11.1)	1 (12.5)	0	6 (15.4)
≥6	1 (11.1)	3 (37.5)	5 (55.6)	0	1 (20.0)	10 (25.6)
Prior therapy received, n (%)						
FRα-targeted therapy	0	1 (12.5)	1 (11.1)	0	1 (20.0)	3 (7.7)
TOP1 inhibitor	0	3 (37.5)	2 (22.2)	1 (12.5)	0	6 (15.4)¶
PARP inhibitor	7 (77.8)	5 (62.5)	5 (55.6)	4 (50.0)	3 (60.0)	24 (61.5)
Bevacizumab	7 (77.8)	6 (75.0)	6 (66.7)	5 (62.5)	3 (60.0)	27 (69.2)

*n=8; †n=4; ‡n=37; §one patient had received one prior line of therapy; ¶all patients had received systemic TOP1 inhibitor.
ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor α; PARP, poly-ADP ribose polymerase; TOP1, topoisomerase 1

Pharmacokinetics

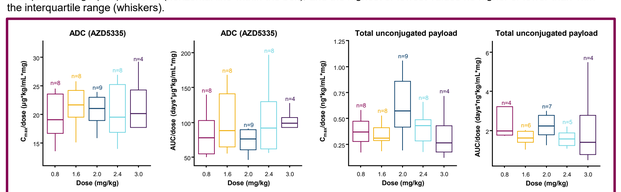
- The PK of AZD5335 and its payload were linear from 0.8 to 3.0 mg/kg (**Figures 3 and 4**).
- AZD5335 was stable in circulation with minimal accumulation prior to the second dose (half-life of 5.25–6 days); the overall PK profile supports dosing Q3W.

Figure 3. Cycle 1 plasma concentration of AZD5335, total antibody, and the total unconjugated payload. Data shown are geometric means and 95% confidence intervals.



ADC, antibody-drug conjugate

Figure 4. Cycle 1 dose-normalised C_{max} and AUC of AZD5335 and the total unconjugated payload. Data shown are interquartile range (box), median (horizontal line within the box), and the highest or lowest values no higher or lower than 1.5x the interquartile range (whiskers).

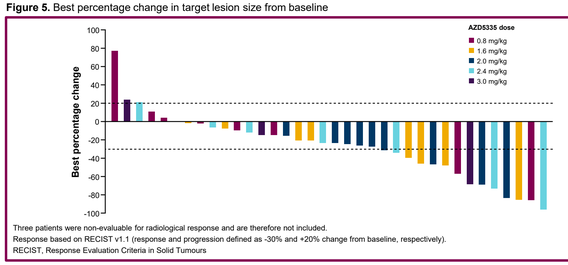


ADC, antibody-drug conjugate; AUC, area under curve; C_{max}, maximum serum concentration

Preliminary efficacy

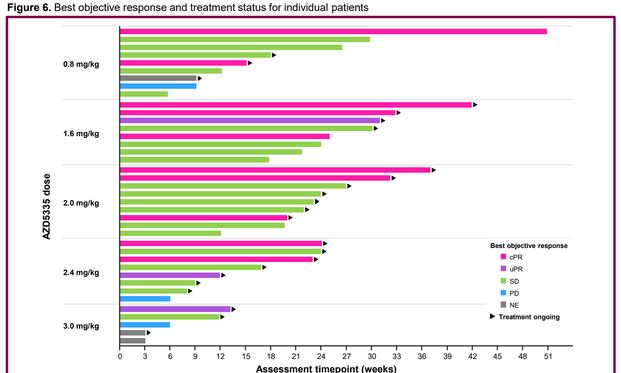
- Among dosed patients with an available on-treatment scan at data cutoff (n=38), the ORR (confirmed and unconfirmed) was 34.2% (95% confidence interval: 19.6, 51.4), with responses observed at all doses.
- Best percentage change in target lesion size is shown in **Figure 5** and best objective response and treatment status is shown in **Figure 6**.
- 46.2% of patients (6/13) with high FRα expression had a confirmed objective response (**Table 2**).
  - In patients with high FRα expression treated with AZD5335 at doses ≥1.6 mg/kg, confirmed ORR was 55.6% (5/9).
- 35.7% of patients (5/14) with low FRα expression had an objective response (**Table 2**; including unconfirmed responses).
  - In patients with low FRα expression treated with AZD5335 at doses ≥1.6 mg/kg, ORR was 41.7% (5/12; including unconfirmed responses).

Figure 5. Best percentage change in target lesion size from baseline



Three patients were non-evaluable for radiological response and are therefore not included.
Response based on RECIST v1.1 (response and progression defined as -30% and +20% change from baseline, respectively).
RECIST, Response Evaluation Criteria in Solid Tumours

Figure 6. Best objective response and treatment status for individual patients



cPR, confirmed partial response; NE, not evaluable; PD, progressive disease; SD, stable disease; uPR, unconfirmed partial response

Table 2. Summary of preliminary efficacy (radiological response per RECIST v1.1)

Parameter	0.8 mg/kg	1.6 mg/kg	2.0 mg/kg	2.4 mg/kg	3.0 mg/kg	Total	Total ≥1.6 mg/kg
All patients	(n=9)	(n=8)	(n=9)	(n=8)	(n=4)*	(N=38)*	(n=29)*
ORR,† n (%)	2 (22.2)	4 (50.0)	3 (33.3)	3 (37.5)	1 (25.0)	13 (34.2)	11 (37.9)
cORR,‡ n (%)	2 (22.2)	3 (37.5)	3 (33.3)	2 (25.0)	0	10 (26.3)	8 (27.6)
FRα-high patients	(n=4)	(n=3)	(n=3)	(n=2)	(n=1)	(n=13)	(n=9)
ORR,† n (%)	1 (25.0)	2 (66.7)	1 (50.0)	1 (50.0)	0	6 (46.2)	5 (55.6)
cORR,‡ n (%)	1 (25.0)	2 (66.7)	2 (66.7)	1 (50.0)	0	6 (46.2)	5 (55.6)
FRα-low patients	(n=2)	(n=4)	(n=3)	(n=4)	(n=1)	(n=14)	(n=12)
ORR,† n (%)	0	2 (50.0)	1 (33.3)	2 (50.0)	0	5 (35.7)	5 (41.7)
cORR,‡ n (%)	0	1 (25.0)	1 (33.3)	1 (25.0)	0	3 (21.4)	3 (25.0)

High FRα expression was defined as ≥75% of tumour cells staining at ≥2+ intensity per immunohistochemistry. Low FRα expression was defined as outside the high FRα definition but with ≥25% of tumour cells staining at ≥1+.
*One further patient was excluded from the 3.0 mg/kg cohort due to not having the opportunity to complete any on-treatment scan at data cutoff.
†Objective response rate (ORR) including both confirmed and unconfirmed responses with the potential to be confirmed. ‡Confirmed objective response rate (cORR)
FRα, folate receptor α; RECIST, Response Evaluation Criteria In Solid Tumours

Safety

- Safety results are summarised in **Table 3**.
- No DLTs or deaths due to treatment were reported.
- The maximum tolerated dose has not been defined.
- The most common treatment-related AEs (TRAEs) were nausea (61.5%), neutropenia (38.5%), and fatigue (30.8%; **Table 4**).
  - No cases of interstitial lung disease/pneumonitis were reported, irrespective of causality association.
- The most common grade ≥3 TRAEs were neutropenia (17.9%) and anaemia (15.4%).

Table 3. Safety summary

Parameter, n (%)	0.8 mg/kg (n=9)	1.6 mg/kg (n=8)	2.0 mg/kg (n=9)	2.4 mg/kg (n=8)	3.0 mg/kg (n=5)	Total (N=39)
Any TRAE	8 (88.9)	8 (100)	9 (100)	8 (100)	4 (80.0)	37 (94.9)
Grade 3/4	2 (22.2)	3 (37.5)	7 (77.8)	3 (37.5)	2 (40.0)	17 (43.6)
Any treatment-related SAE	0	2 (25.0)	2 (22.2)	0	2 (40.0)	6 (15.4)
TRAE leading to						
Discontinuation	1 (11.1)	1 (12.5)	0	0	1 (20.0)	3 (7.7)
Dose reduction	0	1 (12.5)	2 (22.2)	1 (12.5)	0	4 (10.3)

TRAEs were defined as reasonable possibility that the AE was caused by AZD5335, as assessed by the investigator. The table includes AEs with an onset date on or after the date of first dose of AZD5335 up to and including 30 days following the date of last dose but prior to subsequent cancer therapy. Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event

Table 4. TRAEs of any grade occurring in ≥15% of patients

TRAE, n (%)*	0.8 mg/kg (n=9)		1.6 mg/kg (n=8)		2.0 mg/kg (n=9)		2.4 mg/kg (n=8)		3.0 mg/kg (n=5)		Total (N=39)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Nausea	4 (44.4)	0	6 (75.0)	0	6 (66.7)	0	6 (75.0)	0	2 (40.0)	1 (20.0)	24 (61.5)	1 (2.6)
Neutropenia	1 (11.1)	0	3 (37.5)	1 (12.5)	4 (44.4)	4 (44.4)	6 (75.0)	2 (25.0)	1 (20.0)	0	15 (38.5)	7 (17.9)
Fatigue	2 (22.2)	0	1 (12.5)	0	3 (33.3)	0	4 (50.0)	0	2 (40.0)	0	12 (30.8)	0
Anaemia	1 (11.1)	1 (11.1)	3 (37.5)	2 (25.0)	3 (33.3)	2 (22.2)	4 (50.0)	1 (12.5)	0	0	11 (28.2)	6 (15.4)
Pyrexia	2 (22.2)	0	2 (25.0)	0	3 (33.3)	0	0	0	2 (40.0)	0	9 (23.1)	0
Alopecia	1 (11.1)	0	1 (12.5)	0	3 (33.3)	0	2 (25.0)	0	1 (20.0)	0	8 (20.5)	0
Diarrhoea	0	0	0	0	4 (44.4)	0	1 (12.5)	0	2 (40.0)	1 (20.0)	7 (17.9)	1 (2.6)
Vomiting	1 (11.1)	0	2 (25.0)	1 (12.5)	1 (11.1)	0	1 (12.5)	0	2 (40.0)	1 (20.0)	7 (17.9)	2 (5.1)
Decreased appetite	0	0	2 (25.0)	0	2 (22.2)	1 (11.1)	2 (25.0)	1 (12.5)	0	0	6 (15.4)	2 (5.1)
Infusion-related reaction	1 (11.1)	0	0	0	2 (22.2)	0	3 (37.5)	0	0	0	6 (15.4)	0

*Combined preferred terms: neutropenia, neutrophil count decreased + neutropenia; anaemia, haemoglobin decreased + anaemia; fatigue, asthenia + fatigue.
Treatment-related events were defined as reasonable possibility that the AE was caused by AZD5335, as assessed by the investigator. The table includes AEs with an onset date or that worsen on or after the date of first dose and up to and including 30 days following the date of last dose of treatment. Patients with multiple occurrences are counted once per preferred term regardless of the number of occurrences.
AE, adverse event; TRAE, treatment-related adverse event

Conclusions

- Promising efficacy data have been observed in a heavily pretreated population of patients with PRROC.
  - Radiological responses were observed at all doses of AZD5335 investigated.
  - 46.2% (6/13) of patients with high FRα expression had a confirmed objective response. The confirmed ORR in patients with high FRα expression who received AZD5335 ≥1.6 mg/kg was 55.6% (5/9).
- AZD5335 demonstrated a safety profile consistent with other TOP1i-based ADCs, with manageable levels of dose modification.
- The overall PK profile of AZD5335 demonstrated stability, supporting Q3W dosing.
- Dose escalation of AZD5335 monotherapy is ongoing in patients with PRROC.
  - AZD5335 monotherapy in patients with lung adenocarcinoma will open in the near future.
  - AZD5335 in combination with saruparib (AZD5305), a poly-ADP ribose polymerase 1 (PARP1)-specific inhibitor, in patients with PRROC is ongoing.[6]

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Disclosures

Ronnie Shapira-Frommer reports advisory board activity, acting as a steering committee member, and the receipt of research funding and research grant(s) from MSD; an advisory role for MSD and Novartis; and acting as a principal investigator for AstraZeneca, Bristol Myers Squibb, MSD, and Pfizer.

Co-author disclosures: Please refer to the abstract.

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