Clinical Study Report Synopsis	
Drug Substance	AZD4635
Study Code	D8731C00001
Edition Number	1.0
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An Open-label, Multi-drug, Multi-center Phase II Combination Study of AZD4635 in Patients with Prostate Cancer

Study dates:
First patient enrolled: 05 September 2019
Last patient last visit: 16 June 2021
The analyses presented in this report are based on a clinical data lock date of 18 November 2021

Phase of development:
Therapeutic exploratory (II)

Sponsor's Responsible Medical Officer:
PPD
AstraZeneca
35 Gatehouse Drive
Waltham, MA, 02451, USA

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centers

Patients were enrolled in 9 centers in the United States of America.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints/Variables
Primary	
To evaluate efficacy of each combination therapy on objective response rate (ORR) for patients with measurable disease	Proportion of patients with measurable disease at baseline who have a confirmed ORR per Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
To evaluate efficacy of each combination therapy on prostate-specific antigen (PSA) response rate	Prostate-specific antigen confirmed response is defined as the proportion of participants with a reduction in the PSA level of ≥ 50% from baseline to the lowest post-baseline PSA results, measured twice, at least 3 weeks apart by the Prostate Cancer Working Group 3 criteria (PCWG3)
Secondary	
To evaluate the efficacy of each combination therapy on the proportion of patients alive and progression free at 6 months	Summaries of the Kaplan-Meier curve for radiological progression-free survival including the proportion of patients alive and radiological progression free at 6 months using RECIST 1.1 (soft tissue lesions) and PCWG3 (bone lesions)
To evaluate efficacy of each combination therapy on duration of response	Duration of response is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression
To evaluate efficacy of each combination therapy on overall survival	Overall survival is length of time from date of first dose until the date of death due to any cause
To evaluate the pharmacokinetics of AZD4635 and its metabolites and other combination agent(s)	Steady state trough
To evaluate the immunogenicity of the mAb study drug(s) in combination with AZD4635	Patients with the presence or absence of anti-drug antibody
Safety	
To assess the safety and tolerability of each treatment regimen	Adverse events/Serious adverse events Physical exam and vital signs Collection of clinical chemistry/hematology parameters

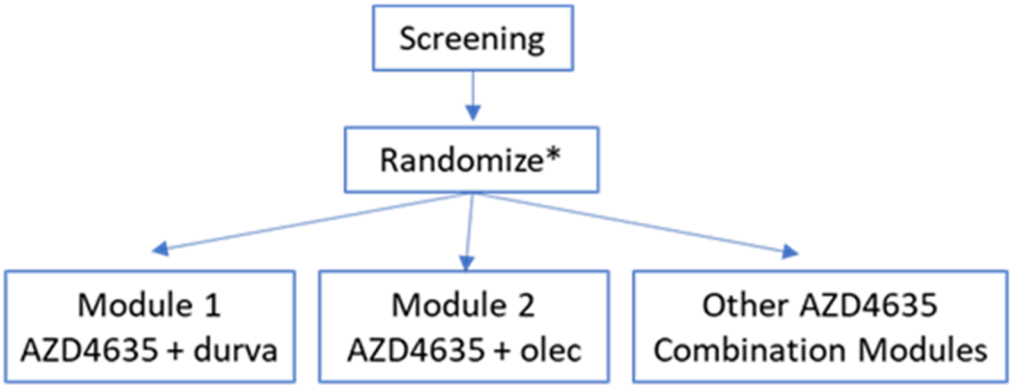
Results of the secondary and exploratory objectives are not included in the clinical study report.

Study design

This was an open-label, randomized, Phase IIa modular study in patients with prostate cancer to assess safety, efficacy, and tolerability of AZD4635 in combination with other therapeutic agents in different treatment modules.

The study had a modular design: Module 1 (AZD4635 in combination with durvalumab) and Module 2 (AZD4635 in combination with oleclumab).

Figure S1 Flow chart of study design



*if only eligible for one module, then patient was allocated to that module rather than randomized

Note: The decision was made by the Sponsor not to open other modules to recruitment after a comprehensive strategy review of the AZD4635 program and not due to new dose-limiting toxicities or concerning safety signals observed with AZD4635.

durva = durvalumab; olec = oleclumab

An Interactive Web Response System was used to allocate patients to a module. Randomization occurred when patients met eligibility criteria for both modules that were currently recruiting. All patients allocated or randomized were stratified by patients with either bone only metastasis or measurable soft tissue metastasis to ensure there was a sufficient number of patients in each group as specified in the sample size.

Target population and sample size

Patients were adults with prostate cancer.

Approximately 30 PSA evaluable patients were planned in each module. Twenty-nine patients were analyzed in Module 1 and 30 patients in Module 2.

Investigational product and comparator(s): dosage, and mode of administration

AZD4635 50 mg or 75 mg orally once daily.

For Module 2, the first 25 patients had the starting dose of AZD4635 50 mg. Following review by the safety review committee and clinical study protocol amendment, the starting dose for the remaining patients was 75 mg.

Durvalumab 1500 mg intravenously (IV) every 4 weeks (Q4W) from Cycle 1.

Oleclumab 1500 mg IV on Day 1, and on Day 1 and Day 15 of each 28-day cycle every 2 weeks × 4 doses followed by Q4W.

Duration of treatment

Patients could continue to receive AZD4635 and/or other combination therapeutic agent as long as they were continuing to show clinical benefit, as judged by the Investigator, and in the absence of discontinuation criteria.

Statistical methods

Prostate-specific antigen response was defined as the proportion of patients achieving a ≥ 50% decline from baseline to the lowest post-baseline PSA results, confirmed by a second consecutive PSA assessment at least 3 weeks later. PSA progression was defined as the date of the first PSA increase that is both ≥ 25% and ≥ 2 ng/mL above the nadir and which was confirmed by a second value ≥ 3 weeks later, including those progressions that occur after 12 weeks.

For all patients, the RECIST tumor response data were used to determine each patient's visit response (complete response, partial response, stable disease, disease progression, or not evaluable) according to RECIST version 1.1. It was also used to determine best objective response (BOR).

Best objective response, objective response rate, target lesion size, radiological progression-free survival, duration of response, overall survival, and PSA responses were summarized.

Adverse events (AEs), serious adverse events (SAEs), deaths, and discontinuations due to AEs were summarized. Treatment-emergent AEs were summarized by Medical Dictionary for Regulatory Activities (version 24) system organ class and preferred term, with further splits by maximum Common Terminology Criteria for Adverse Events (CTCAE) grade, causal relationship to any study medication, dose interruption or modification, and AEs classed as CTCAE Grade 3 or higher. Adverse events of special interest for durvalumab were summarized. Hematology, blood chemistry, urinalysis, vital signs, and electrocardiogram parameters were summarized.

Table S2 Study population

	Number of patients		
	Module 1 AZD4635 75 mg QD + durvalumab 1500 mg Q4W	**Module 2 AZD4635 50 / 75 mg QD + oleclumab 1500 mg Q2W**	**Total**
Patients enrolled [a]			83
Patients assigned to treatment [b]	29	30	59
Patients who received treatment (Safety Analysis Set)	29	30	59
Patients ongoing study treatment at data cut-off date [c]	3	2	5
Patients who discontinued AZD4635	26	28	54
Patients who discontinued durvalumab/oleclumab [d]	26	28	54

[a] Informed consent received by data cut-off date.

[b] Includes all patients, randomized or assigned to a specific module.

[c] Patients who did not discontinued at data cut-off are still receiving treatment for beneficial effect.

[d] Patients who started receiving treatment but did not discontinue at the data cut-off have not collected the end of treatment date and End-of-Treatment reason.

Note: For Module 2, the first 25 patients had the starting dose of AZD4635 50 mg. Following review by the SRC and protocol amendment, the starting dose for the remaining patients was 75 mg. Oleclumab was administered IV Q2W for the first 4 doses and Q4W thereafter.

Summary of efficacy results

- Twenty patients in Module 1 and 21 patients in Module 2 had a baseline tumor assessment and measurable disease at baseline. Of these, objective response was observed in one (5.0%) patient in Module 1 and no patients in Module 2. Seven (35.0%) patients in Module 1 and 8 (38.1%) patients in Module 2 had stable disease for ≥ 35 days. There were 10 (50.0%) patients in Module 1 with progression; one (5.0%) patient died and the rest had RECIST progression. For Module 2, 11 (52.4%) patients had progression; one (4.8%) patient died and the rest had RECIST progression.
- There were a total of 5 patients with a PSA response: 2 in Module 1 and 3 in Module 2. One patient in each module had a confirmed response. The majority of patients' best percentage change from baseline was an increase.

Summary of safety results

- The mean total treatment duration for AZD4635 was 3 months in both modules.
- Treatment interruptions were minimal and did not meaningfully affect the actual treatment duration.
- AZD4635 was well tolerated in combination with durvalumab or oleclumab.
- The most frequently reported AEs overall in both modules were nausea, fatigue, and decreased appetite (in 49%, 34%, and 24% patients, respectively); these AEs were also the most frequently reported AEs possibly related to AZD4635 in Module 1 (in 38%, 21%, and 17% patients, respectively). Nausea, fatigue, and vomiting were the most

frequently reported AEs possibly related to AZD4635 in Module 2 (in 50%, 30%, and 23% patients, respectively).

- No patients had SAEs related to AZD4635, durvalumab, or oleclumab and only one AE which led to discontinuation of AZD4635 was considered to be causally related to AZD4635.
- Three (10.3%) patients in Module 1 and 2 (6.7%) in Module 2 reported at least one AE of CTCAE ≥ Grade 3 considered possibly related to AZD4635.
- There were no dose limiting toxicities.
- There were no significant safety concerns that preclude further development of AZD4635 in combination with durvalumab or oleclumab.

Conclusion(s)

- Limited efficacy was observed. An objective response was observed in only one patient in Module 1 and no patients in Module 2, and one patient in each module had a confirmed PSA response.
- AZD4635 was well tolerated. The most frequently reported AEs overall were nausea, fatigue, and decreased appetite (in 49%, 34%, and 24% patients, respectively). These AEs were also among the most frequently reported AEs possibly related to AZD4635 in Module 1 (in 38%, 21%, and 17% patients, respectively). AEs most frequently reported as possibly related to AZD4635 in Module 2 were nausea, fatigue, and vomiting (in 50%, 30%, and 23% patients, respectively). There were no significant safety concerns that preclude further development of AZD4635 in combination with oleclumab or durvalumab.