Clinical Study Report Synopsis	
Drug Substance	AZD2811 + Durvalumab
Study Code	D6132C00001
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NCT Number	NCT04745689

A Phase II Multicenter, Open-Label, Single Arm Study to Determine the Efficacy, Safety and Tolerability of AZD2811 and Durvalumab Combination as Maintenance Therapy After Induction with Platinum-Based Chemotherapy Combined with Durvalumab, for the First-Line Treatment of Patients with Extensive Stage Small-Cell Lung Cancer

Study dates:
First subject enrolled: 23 February 2021
Date of early study termination: 17 December 2021
Reason for early study termination: Inadequate benefit-risk profile
Last subject last visit: 18 June 2022
The analyses presented in this report are based on a clinical data lock date of 18 June 2022

Phase of development:
Therapeutic exploratory (II)

International Co-ordinating Investigator:
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Rationale for Submitting an Abbreviated Clinical Study Report

On 17 December 2021, enrolment to Study D6132C00001 was terminated prior to completion of the study due to the evolving benefit-risk profile of AZD2811 not supporting further development for the first-line treatment of patients with extensive stage small-cell lung cancer (ES-SCLC). The fatal sepsis safety signal was a key component of a multifactorial decision to terminate future development of AZD2811 in this patient population. Due to the early termination of the study, only 9 participants (of the planned 80 participants) received maintenance treatment with AZD2811 in combination with durvalumab. Therefore, efficacy analyses were not performed and this study is reported as an abbreviated Clinical Study Report (aCSR).

Study Centers

Participants were screened and enrolled for this study at 12 sites in the United States of America, South Korea, Spain, and Poland.

Publications

None at the time of writing this report.

Objectives and Endpoints

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary [a]	
To evaluate the efficacy of AZD2811 + durvalumab by assessment of APF12 in participants who have not progressed during EP-durvalumab based induction therapy. [a]	APF12 will be defined as the Kaplan-Meier estimate of PFS per RECIST v1.1 as assessed by the investigator at local site at 12 months, in participants who enter the maintenance phase. [a]
Secondary [a, b]	
To evaluate efficacy of AZD2811 + durvalumab by assessment of OS12, OS15, and OS18, in participants who have not progressed during EP-durvalumab based induction therapy. [a]	OS12, OS15, and OS18 will be defined as the Kaplan-Meier estimate of OS at 12 months, 15 months, and 18 months, respectively, in participants who enter the maintenance phase. [a]
To evaluate efficacy of AZD2811 + durvalumab by assessment of APF6 and APF9 in participants who have not progressed during EP-durvalumab based induction therapy. [a]	APF6 and APF9 will be defined as the Kaplan-Meier estimate of PFS per RECIST v1.1 as assessed by the investigator at local site at 6 months and 9 months, respectively, in participants who enter the maintenance phase. [a]
To evaluate efficacy of EP-durvalumab by assessment of ORR in the induction phase. [a]	ORR is defined as the proportion of participants with measurable disease at baseline who have a confirmed CR or PR, by the investigator at local site per RECIST v1.1 in the induction phase (all participants). [a]
To evaluate efficacy of AZD2811 + durvalumab by assessment of ORR in the participants who had not progressed during EP-durvalumab based induction therapy. [a]	ORR is defined as the proportion of participants with measurable disease at baseline who have a confirmed CR or PR, by the investigator at local site per RECIST v1.1, in participants who enter the maintenance phase. [a]
To evaluate efficacy of AZD2811 + durvalumab by assessment of PFS in participants who had not progressed during EP-durvalumab based induction therapy. [a]	PFS is defined as time from date of first dose study intervention in the induction phase until progression per RECIST v1.1 or death due to any cause. The median Kaplan-Meier estimate in participants who enter the maintenance phase. [a]
To evaluate efficacy of AZD2811 + durvalumab by assessment of OS in participants who had not progressed during EP-durvalumab based induction therapy. [a]	OS is defined as time from date of first dose study intervention in the induction phase until the date of death due to any cause. The median Kaplan-Meier estimate in participants who enter the maintenance phase. [a]
To assess the safety and tolerability profile of study intervention in ES-SCLC.	Safety and tolerability will be evaluated in terms of AEs, vital signs, physical examination, clinical chemistry, TSH, PT/PTT/INR, hematology, ECG, and urinalysis, as well as treatment delays, dose reductions, and dose discontinuations.
To evaluate the PK of durvalumab and AZD2811.	Concentration of durvalumab, and AZD2811 and its metabolite in serum and whole blood, respectively.

To evaluate the effect of AZD2811 + durvalumab on ES-SCLC symptoms and health-related QoL using EORTC QLQ-C30 and QLQ-LC13. [b]	EORTC QLQ-C30: Symptoms (fatigue, pain, nausea/vomiting, dyspnea, loss of appetite, insomnia, constipation, and diarrhea). Health-related QoL/functioning (physical function, role function, emotional function, cognitive function, social function, and global health status/QoL). EORTC QLQ-LC13: Disease-related symptoms (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, and other pain). [b]

[a] Due to the early termination of the study, only 9 participants (of the planned 80 participants) received maintenance treatment with AZD2811 in combination with durvalumab. Therefore, efficacy analyses (excluding PK results) were not performed and reporting of efficacy results in this aCSR is reduced to individual participant listings.

[b] The secondary endpoint of QLQ-C30 and QLQ-LC13 questionnaire answers is not reported in this aCSR. CCI [redacted] are not reported in this aCSR. For the planned CCI [redacted] see Section 3 of the CSP v9.0.

aCSR = abbreviated Clinical Study Report; AE = adverse event; APF6 = proportion of participants alive and progression free at 6 months from first dose of study therapy in the induction phase (ie, PFS rate at 6 months); APF9 = proportion of participants alive and progression free at 9 months from the first dose of study therapy in the induction phase (ie, PFS rate at 9 months); APF12 = proportion of participants alive and progression free at 12 months from first dose of study therapy in the induction phase (ie, PFS rate at 12 months); CR = complete response; CCI [redacted]; DoR = duration of response; ECG = electrocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EP = etoposide and platinum-based chemotherapy; ES-SCLC = extensive stage small-cell lung cancer; CCI [redacted]; INR = international normalized ratio; ORR = objective response rate; OS = overall survival; OS12 = proportion of participants alive at 12 months (ie, OS rate at 12 months); OS15 = proportion of participants alive at 15 months (ie, OS rate at 15 months); OS18 = proportion of participants alive at 18 months (ie, OS rate at 18 months); PD = progressive disease; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival; PFS2 = progression-free survival after subsequent anticancer therapy; PK = pharmacokinetics; PR = partial response; PT = prothrombin time; PTT = partial prothrombin time; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; CCI [redacted]; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-LC13 = 13-item Lung Cancer Quality of Life Questionnaire; QoL = quality of life; CCI [redacted]; TSH = thyroid-stimulating hormone.

Study Design

This was a Phase II, open-label, multicenter, single arm, global study to determine the efficacy, safety, and tolerability of AZD2811 + durvalumab maintenance therapy in patients with ES-SCLC. Treatment was conducted in 2 phases:

- In the initial induction phase participants were treated with etoposide and platinum-based chemotherapy (EP) combined with durvalumab induction therapy as first-line treatment.
- In the maintenance phase, participants who had not progressed per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by the end of the induction phase and who met maintenance phase eligibility criteria were to continue into the maintenance phase of the trial and be treated with AZD2811 + durvalumab as maintenance therapy

(any participants who were in the induction phase at the time the fatal sepsis safety signal was identified, as well as participants still in the induction phase at the time the decision to terminate the study was made, received durvalumab monotherapy if they transitioned to maintenance).

Target Population and Sample Size

This study planned to assign treatment to approximately 100 eligible participants with ES-SCLC to achieve 80 evaluable participants having received maintenance therapy.

Investigational Product: Dosage and Mode of Administration

AZD2811 was initially administered at a dose of [redacted] via intravenous infusion. Following identification of a safety issue, the AZD2811 dose was reduced to [redacted] for participants already ongoing in the maintenance phase.

Duration of Treatment

Participants were to be treated until disease progression unless there was unacceptable toxicity or withdrawal of consent, or if another discontinuation criterion was met.

Statistical Methods

See Section 9 of the Clinical Study Protocol (CSP) version 9.0 in Appendix 16.1.1 of the aCSR and the Statistical Analysis Plan in Appendix 16.1.9 of the aCSR.

Study Population

A total of 42 participants were enrolled, of which 31 were assigned to study treatment and 11 were screen failures. All 31 participants who entered the induction phase received treatment with durvalumab, etoposide, and either carboplatin (28 [90.3%] participants) or cisplatin (3 [9.7%] participants).

Twenty-two participants entered the maintenance phase; 9 participants received AZD2811 in combination with durvalumab and 13 participants received durvalumab monotherapy.

At the time of final analysis (data cut-off [DCO]: 18 June 2022), 15 (48.4%) participants had died on study (11 [35.5%] due to underlying disease and 4 [12.9%] due to adverse events [AEs]), 2 (6.5%) participants had chosen to withdraw from the study, and 1 (3.2%) participant was lost to follow-up. The remaining 13 (41.9%) participants discontinued from the study due to the study being terminated by the Sponsor. Five (22.7%) participants were receiving durvalumab monotherapy at the time of DCO (note: as per the CSP [see Appendix 16.1.1], any participants gaining benefit from treatment in the maintenance phase could continue with durvalumab monotherapy at investigator's discretion as standard of care following the termination of the study but were not subject to further data collection [with the exception of

serious adverse event [SAE] reporting]. For further details, see Participant Narratives in Section 14.4 of the aCSR).

Summary of Efficacy Results

Due to the early termination of the study, only 9 participants (of the planned 80 participants) entered the maintenance phase and received treatment with AZD2811 in combination with durvalumab. Therefore, efficacy analyses were not performed and reporting of efficacy results in this aCSR is reduced to individual participant listings.

Summary of Pharmacokinetic Results

Whole blood total AZD2811 peak geomean concentration (C_{max}) was 99264.17 ng/mL (n = 4), after the end of the administration on CCI. Total AZD2811 geomean concentrations after the end of the administrations in CCI (86706.65 ng/mL [n = 6], 83625.22 ng/mL [n = 4], and 92287.23 ng/mL [n = 3], respectively) were comparable to C_{max} in CCI (99264.17 ng/mL). The decline in total AZD2811 concentration post-infusion appears to have multiple phases. Total AZD2811 geomean concentration slowly decreased to 66764.94 ng/mL (n = 5) on CCI then rapidly decreased to 11024.89 ng/mL (n = 5) on CCI Total AZD2811 geomean concentration decreased to 27.29 ng/mL (n = 5) at CCI, and remained at a similar level on CCI (18.87 ng/mL [n = 6]).

Following the administration of AZD2811 on CCI AZ12102238 (AZD2811 metabolite) geomean concentration peaked at 42.937 ng/mL (n = 5) on CCI then decreased to 8.345 ng/mL (n = 5) before the administration on CCI. AZ12102238 geomean concentrations on CCI 36.509 ng/mL [n = 6], 22.117 ng/mL [n = 3], and 28.195 ng/mL [n = 3], respectively) were comparable to C_{max} in CCI (42.937 ng/mL).

Summary of Safety Results

For the 9 participants who received maintenance treatment with AZD2811 and durvalumab, during maintenance the median (min, max) total AZD2811 treatment duration was 8.86 (5.6, 26.0) weeks, and the median (min, max) actual AZD2811 treatment duration was 7.86 (5.4, 20.9) weeks.

For the 22 participants who received maintenance treatment, during maintenance the median (min, max) total durvalumab treatment duration was 10.36 (3.0, 36.4) weeks, and the median (min, max) actual durvalumab treatment duration was 9.79 (2.9, 36.1) weeks.

Induction Phase (N = 31)

The number of participants who had any AEs in the induction phase was 31 (100%) in total. Twenty-four (77.4%) participants had any Grade ≥ 3 AEs, 2 (6.5%) participants had AEs with

outcome of death (preferred terms [PTs]: COVID-19 and pneumonia), and 9 (29.0%) participants had SAEs.

The number of participants who had treatment-related AEs was 29 (93.5%) in total. Twenty-nine (93.5%) participants had AEs related to etoposide, carboplatin, or cisplatin, and 11 (35.5%) participants had durvalumab-related AEs.

The most common (occurring in > 10% of all participants) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 AEs by PT were neutrophil count decreased (16 [51.6%]), anaemia (10 [32.3%] participants), neutropenia, and thrombocytopenia (5 [16.1%] participants each), and white blood cell count decreased, and pneumonia (4 [12.9%] participants each).

Three (9.7%) participants had SAEs of pneumonia and 2 (6.5%) participants had SAEs of pneumonia aspiration; all other SAEs by PT in this group were experienced by 1 (11.1%) participant each. Two (6.5%) participants in the induction phase experienced AEs with a fatal outcome (COVID-19 and pneumonia, 1 [3.2%] participant each); these events were considered unrelated to study treatment.

Maintenance Phase – AZD2811 + Durvalumab (N = 9)

The number of participants who had any AEs in the maintenance phase was 9 (100%) in the AZD2811 + durvalumab group. All (100%) participants had any CTCAE Grade ≥ 3 AEs, 2 (22.2%) participants had AEs with outcome of death, 6 (66.7%) participants had SAEs, and 4 (44.4%) participants had adverse events of special interest (AESIs) for durvalumab.

Eight (88.9%) participants had AZD2811-related AEs, 4 (44.4%) participants had durvalumab-related AEs, and 3 (33.3%) participants had AEs which either started or worsened (ie, the CTCAE grade increased) during the maintenance phase and were considered related to etoposide or cisplatin/carboplatin received during the induction phase.

Eight (88.9%) participants experienced AEs of CTCAE Grade ≥ 3 considered related to AZD2811 and 3 (33.3%) participants experienced AEs of CTCAE Grade ≥ 3 considered related to durvalumab. The most common (occurring in > 1 participant) CTCAE Grade ≥ 3 AEs by PT in the AZD2811 + durvalumab group were neutrophil count decreased (7 [77.8%] participants), and anaemia, febrile neutropenia, and white blood cell count decreased (2 [22.2%] participants each).

Two (22.2%) participants had SAEs of febrile neutropenia; all other SAEs by PT in this group were experienced by 1 (11.1%) participant each. Two (22.2%) participants experienced AEs with a fatal outcome (febrile neutropenia and neutropenic sepsis, 1 [11.1%] participant each); these events were both considered related to AZD2811 and unrelated to durvalumab (see Participant Narratives in Section 14.4 of the aCSR for further details).

Maintenance Phase –Durvalumab Monotherapy (N = 13)

The number of participants who had any AEs in the maintenance phase was 6 (46.2%) in the durvalumab monotherapy group. One (7.7%) participant had any CTCAE Grade ≥ 3 AEs, no participants had AEs with outcome of death or SAEs, and 2 (15.4%) participants had AESIs for durvalumab.

The number of participants who had treatment-related AEs was 4 (30.8%) in the durvalumab monotherapy group. Two (15.4%) participants had durvalumab-related AEs and 2 (15.4%) participants had AEs which either started or worsened (ie, the CTCAE grade increased) during the maintenance phase and were considered related to etoposide or cisplatin/carboplatin received during the induction phase.

One (7.7%) participant in the durvalumab monotherapy group experienced a CTCAE Grade 3 event of neutrophil count decreased which either started or worsened (ie, the CTCAE grade increased) during the maintenance phase and was considered related to etoposide or cisplatin/carboplatin received during the induction phase, but not related to durvalumab (see Table 14.3.2.10 and Listing 16.2.7.1). There were no other CTCAE Grade ≥ 3 events in the durvalumab monotherapy group during the maintenance phase.

Conclusion

The safety profile of AZD2811 in combination with durvalumab does not support further development of AZD2811 in first-line ES-SCLC at this time.