- **Protocol number: D419QC00002**
- **Document title: A Phase II, Open-Label, Multi-Arm Study to Determine the Preliminary Efficacy of Novel Combinations of Treatment in Patients with Platinum Refractory Extensive-Stage Small-Cell Lung Cancer (BALTIC)**
- **NCT number: NCT02937818**
- **Version number: 1.0**
- **Date of the document: 23 February 2021**

SYNOPSIS

Study Centers

This study was conducted at 11 study centers in 5 countries (Germany, Hungary, Poland, Spain, and Ukraine).

Publications

There was one publication at the time of writing this report: Bondarenko I, Juan-Vidal O, Pajkos G, Kryzhanivska A, Székely ZP, Vicente D, et al. Preliminary efficacy of durvalumab plus tremelimumab in platinum-refractory/resistant extensive disease-small cell lung cancer from Cohort A of the Phase 2 BALTIC Study. Poster 1665PD, presented at the European Society for Medical Oncology congress; Munich, Germany; 19–23 October 2018.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To assess the preliminary efficacy of each treatment arm in terms of ORR	ORR using Investigator assessments according to RECIST 1.1
Secondary	Efficacy	To further assess the preliminary efficacy of each treatment arm in terms of DoR, DCR, TTR, PFS, and OS	DoR, DCR, TTR, and PFS using Investigator assessments according to RECIST 1.1, and OS
Secondary	PK	To assess the PK of novel combination treatments (Arm A, stages 1 and 2 only, Arm B and Arm C)	Concentration of novel combination treatments in blood Arm C: PK parameters of celarasertib and olaparib following single dose, eg, C_{max}, t_{max}, $AUC_{0-t,}$ AUC_{0-6}, as well as at steady state, eg, CL_{ss}/F, $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, AUC_{0-t}, and AUC_{0-6}
Secondary	Safety	To assess the safety and tolerability profile of each treatment arm	AEs, physical examinations, vital signs, including blood pressure and pulse, ECGs, and laboratory findings, including clinical chemistry, hematology, and urinalysis

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	CCI [redacted]	CCI [redacted]	CCI [redacted]
Exploratory	CCI [redacted]	CCI [redacted]	CCI [redacted]
Exploratory	CCI [redacted]	CCI [redacted]	CCI [redacted]
Exploratory	CCI [redacted]	CCI [redacted]	CCI [redacted]
Exploratory	CCI [redacted]	CCI [redacted]	CCI [redacted]

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	CCI	CCI	CCI
Exploratory	CCI	CCI	CCI
Exploratory	CCI	CCI	CCI
Exploratory	CCI	CCI	CCI
Exploratory	CCI	CCI	CCI
Exploratory	CCI	CCI	CCI

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Exploratory	CCI [redacted]	CCI [redacted]	CCI [redacted]
Exploratory	CCI [redacted]	CCI [redacted]	CCI [redacted]
Exploratory	CCI [redacted]	CCI [redacted]	CCI [redacted]
Exploratory	CCI [redacted]	CCI [redacted]	CCI [redacted]

Note: with exception to investigate the immunogenicity of novel combination treatments, all other exploratory objectives are reported separately from this Clinical Study Report.

Abbreviations: CCI [redacted]; CCI [redacted]
AE: Adverse event; AUC_{0-t}: Area under the concentration-time curve from time zero to the last measurable concentration; AUC_{0-6} : partial area under the concentration-time curve; CCI [redacted]; C_{max}: Maximum concentration; C_{min}: Minimum concentration; CL_{ss}/F: apparent clearance of drug at steady state; CCI [redacted]; ctDNA: Circulating tumor DNA; DCR: Disease control rate; DoR: Duration of response; ECG: Electrocardiogram; CCI [redacted] OS: Overall survival; ORR: Overall response rate; PD-L1: Programmed cell death ligand 1; PFS: Progression-free survival; PK: Pharmacokinetics; RECIST 1.1: Response Evaluation Criteria in Solid Tumors, version 1.1; ss: steady state; t_{max}: Time to C_{max}; CCI [redacted]; TTR: Time to response.

Study Design

This was a Phase II, open-label, multi-drug, multi-center, multi-arm umbrella study with primary endpoint of objective response rate (ORR) to determine the preliminary efficacy of novel combinations of treatment in patients with extensive-stage disease-small-cell lung cancer (ES-SCLC) who had refractory or resistant disease, defined as patients who progressed

during first line platinum-based chemotherapy or those who progressed within 90 days after completing first line platinum-based chemotherapy.

This multi-arm study initially opened with 2 arms (Arms A and B), and an additional arm (Arm C) was added in Clinical Study Protocol Version 3. Each arm was independent, and any signal observed in one arm did not have an impact on another arm in the study. The 3 experimental arms were:

- Arm A (durvalumab + tremelimumab followed by durvalumab monotherapy)
- Arm B (adavosertib + carboplatin)
- Arm C (ceralasertib + olaparib)

Enrollment into any given arm followed a sequential, 2-stage design. Each arm initially enrolled a minimum of 10 patients. An interim analysis was performed after the initial 10 eligible patients were treated on each arm, and assessed for a minimum of 12 weeks, to determine whether recruitment should develop to the second stage for that specific arm (an additional 10 patients for a total of 20 patients) or stop. Following review of data from stages 1 and 2, as applicable, the Review Committee could recommend an expansion cohort (an additional 20 patients, for a total of 40 eligible patients) to further explore findings.

Arm A: Durvalumab + Tremelimumab Study Design

For Arm A, a maximum of 40 eligible patients were to be enrolled; 10 in stage 1, 10 in stage 2, and 20 in the expansion phase. All patients received durvalumab 1500 mg + tremelimumab 75 mg via intravenous (IV) infusion every 4 weeks (q4w), starting on Week 0, for up to a total of 4 doses/cycles followed by durvalumab monotherapy 1500 mg via IV infusion q4w, starting on Week 16 until confirmed progressive disease (PD) and Investigator confirmation that the patient was no longer receiving clinical benefit from the treatment, or for other discontinuation criteria. If a patient's weight fell to 30 kg or below, the patient was to receive weight-based dosing after discussion between Investigator and Study Physician, until the weight improved to > 30 kg, at which point the patient was to receive the fixed dosing of durvalumab 1500 mg. The usual dose of tremelimumab (75 mg q4w) was to continue during the combination phase of treatment regardless of change in weight. The equivalent weight-based doses to the fixed doses were 20 mg/kg of durvalumab and 1 mg/kg tremelimumab q4w.

Following review of data from stages 1 and 2, the Review Committee recommended to open an expansion cohort in Arm A (an additional 20 patients, for a total of 40 eligible patients), to further explore findings. This recommendation was endorsed by the Clinical Project Team.

Arm B Study Design: Adavosertib + Carboplatin

For Arm B, a maximum of 40 eligible patients were to be enrolled; 10 in stage 1, 10 in stage 2, and 20 in the expansion phase. Patients were to receive adavosertib 225 mg twice daily (BID) by mouth (PO) for 2.5 days from Day 1 + carboplatin AUC 5 Day 1 IV, every 3 weeks (q3w).

Following review of initial 10 patients data in stage 1, a decision made not to move to stage 2 per protocol defined criteria, therefore Arm B was closed.

Arm C Study Design: Ceralasertib (AZD6738) + Olaparib

For Arm C, a maximum of 40 eligible patients were to be enrolled; 10 in stage 1, 10 in stage 2, and 20 in the expansion phase. Patients were to receive ceralasertib 160 mg once daily (QD) Days 1 to 7 + olaparib 300 mg BID Days 1 to 28, q4w.

Following review of stages 1 and 2 patient data, an expansion phase was not utilized for Arm C.

Target Patient Population and Sample Size

This study included patients with histologically or cytologically documented extensive disease American Joint Committee on Cancer Stage IV SCLC (T any, N any, M1 a/b) at initial diagnosis. Patients must have demonstrated PD either during first-line platinum-based chemotherapy (platinum refractory) or within 90 days of completing platinum-based chemotherapy (platinum resistant), and not received further treatment apart from first-line platinum-based chemotherapy.

This study was to enroll up to 40 eligible patients in each treatment arm.

Investigational Product and Comparator(s): Dosage, Mode of Administration, and Batch Numbers

Arm A

	Investigational product	**Investigational product**
Study treatment name:	Durvalumab	Tremelimumab
Dosage formulation:	500 mg/vial	20 mg/mL
Route of administration:	Intravenous	Intravenous
Dosing instructions:	Standard intravenous-time 60 min	Standard intravenous-time 60 min
Provider:	AstraZeneca	AstraZeneca
Batch numbers:	CCI CCI CCI CCI	CCI CCI

Arm B

	Investigational product	Investigational product
Study treatment name:	Adavosertib (AZD1775)	Carboplatin
Dosage formulation:	25 mg or 100 mg capsules	AUC 5, according to prescribing information
Route of administration:	Oral	Intravenous
Dosing instructions:	225 mg, taken in approximately 12-hour intervals, twice daily	Intravenous infusion according to prescribing information
Provider:	AstraZeneca	Sourced locally [a]
Batch numbers:	CCI, CCI	CCI, CCI

[a] Under certain circumstances when local sourcing was not feasible, standard of care treatment could be supplied centrally through AstraZeneca

Arm C

	Investigational product	Investigational product
Study treatment name:	Ceralasertib (AZD6738)	Olaparib
Dosage formulation:	20 mg or 100 mg tablets	100 mg or 150 mg film-coated tablets
Route of administration:	Oral	Oral
Dosing instructions:	160 mg once daily	300 mg twice daily
Provider:	AstraZeneca	AstraZeneca
Batch numbers:	CCI CCI CCI	CCI CCI

Duration of Treatment

The duration of treatment was dependent on whether a patient had confirmed PD or met other discontinuation criteria.

Statistical Methods

General principles:

- All analyses were descriptive, and no inferential analyses were performed based on statistical tests. All evaluations were exploratory in nature.
- All summaries were presented by treatment arm.
- Continuous variables were summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized by frequency counts and percentages for each category.

- Study Day 1 was defined as the date of first dose of study treatment.
- Baseline was defined as the last assessment of the variable under consideration prior to the intake of the first dose of study treatment, except for efficacy variables (the last visit prior to first dose of study treatment).

Analysis sets:

The Full Analysis Set (FAS) included all treated patients. Patients who were enrolled but did not subsequently go on to receive study treatment were not included in the FAS.

All patients who received at least 1 dose of study treatment per the protocol for whom any post-dose data were available and who did not violate or deviate from the protocol in ways that would significantly affect the pharmacokinetic (PK) analyses were included in the PK Analysis Set.

Statistical analyses:

- Efficacy analyses: Antitumor activity assessments included ORR (primary endpoint), and duration of response (DoR), disease control rate (DCR), time to response (TTR), progression-free survival (PFS), and overall survival (OS) (secondary endpoints). Tumor response was evaluated as per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1). ORR was estimated for each arm with corresponding 2-sided 95% confidence interval (CI). Summary tables for antitumor activity data were provided according to data type. Kaplan-Meier plots were presented for DoR, PFS, and OS.
- Safety and tolerability were assessed in terms of adverse events (AEs), laboratory data (clinical chemistry, hematology, thyroid function, and urinalysis), vital signs, electrocardiograms (ECGs), exposure, and Eastern Cooperative Oncology Group (ECOG) performance status using summary statistics. Shift tables were provided for laboratory variables, ECG data, and ECOG performance status. Duration of exposure and dose intensity were also calculated.
- PK concentration data were listed for each patient at each visit, and a summary was provided for PK concentration-time profiles by visit for the PK Analysis Set.
- Immunogenicity results (Arm A only) were listed for each patient at each visit and summary tables were provided.

Subject Population

A total of 72 patients who met the inclusion exclusion criteria were enrolled to the study. In Arm A, a total of 41 patients, 21 in the original cohort and 20 in the expansion cohort, were assigned to treatment with durvalumab and tremelimumab. In Arm B, 10 patients in total were assigned to treatment with adavosertib and carboplatin, and 21 patients were assigned to treatment with ceralasertib and olaparib in Arm C.

In all study arms, most patients discontinued study treatment, predominantly due to disease progression. At the time of data cut off, only 4 patients continued to receive treatment: 3 continued durvalumab only in Arm A, and 1 continued ceralasertib and olaparib in Arm C.

The patient demographics and disease characteristics were consistent with the study inclusion and exclusion criteria, and the target populations for the study treatments.

Summary of Efficacy Results

The primary objective of the study was to assess the preliminary efficacy of each treatment arm in terms of ORR according to RECIST v1.1. To further assess the preliminary efficacy, DoR, DCR, TTR, PFS, and OS were assessed as secondary objectives.

In Arm A, 3 (7.3%) patients (95% CI: 1.54, 19.92) in total had a confirmed objective response of complete response (CR) or partial response (PR) to treatment with durvalumab + tremelimumab. Median DoR was 3.0 months, DCR at 12 weeks was 26.8%, median TTR was 1.8 months, median PFS was 1.84 months (95% CI: 1.77, 1.91), and the median OS was 5.36 months (95% CI: 2.89, 7.23).

In Arm B, none of the 10 patients had a confirmed objective response of CR or PR to treatment with adavosertib + carboplatin. The DCR at 12 weeks was 30.0%, median PFS was 2.60 months (95% CI: 0.56, 4.83), and median OS was 4.67 months (95% CI: 0.56, 5.98).

In Arm C, there was 1 (4.8%) patient (95% CI: 0.12, 23.82) with a confirmed objective response of CR or PR to treatment with ceralasertib + olaparib; median DoR was 8.5 months and TTR was 1.7 months. The DCR at 12 weeks was 38.1%, median PFS was 2.92 months (95% CI: 1.81, 4.53) and median OS was 7.56 months (95% CI: 4.21, 12.58).

In a recent Phase III study, 96 patients with refractory SCLC treated with current standard of care, topotecan, showed ORR of 9.4%, PFS 2.6 months (95% CI: 1.8, 3.3), and OS 5.7 months (95% CI: 4.1, 7.0). In this patient population, ORR, PFS, and OS from durvalumab + tremelimumab (Arm A) were in line with historical data for topotecan. Additionally, despite the lack of responders, PFS and OS following adavosertib + carboplatin (Arm B) were also in line with historical data for topotecan. Furthermore, ORR, PFS, OS following ceralasertib + olaparib (Arm C) were likewise in line with historical data for topotecan.

Although anti-tumor activities were observed in all 3 arms, ORR was low, and all 3 treatment combinations failed to meet the pre-defined criteria to warrant further development in ES-SCLC as a result of this study.

Due to the small number of patients across the treatment arms, the interpretation of the efficacy parameters is limited.

Summary of Pharmacokinetic Results

Assessment of the PK of novel combination treatments was a secondary objective in this study. All patients assessed were exposed to the study treatments as demonstrated by serum concentrations for durvalumab and tremelimumab, and by plasma concentrations of adavosertib and carboplatin, and ceralasertib and olaparib.

In Arm A, the observed PK for both durvalumab and tremelimumab in this study was consistent with observed PK for similar doses. When administered as 20 mg/kg q4w, durvalumab has a geometric mean (geometric coefficient of variation [CV%]) maximum drug concentration (C_{max}) of 409 µg/mL (45.70%), which is consistent with the observed Cycle 1, Day 1 post-dose serum concentration for durvalumab (391.192 µg/mL [23.60%]). The geometric mean (geometric CV%) trough concentration (C_{trough}) and trough concentration at steady state ($C_{trough,ss}$) values for 20 mg/kg q4w durvalumab following administration of durvalumab and tremelimumab combination are 55.5 µg/mL (47.7%) and 119 µg/mL (32.4%), respectively, which again agrees with the observed pre-dose Cycle 2, Day 1 (55.590 µg/mL [53.07%]) and Cycle 5, Day 1 (116.846 µg/mL [51.00%]) durvalumab serum concentrations. Tremelimumab has a geometric mean (geometric CV%) C_{max} of 22.5 µg/mL (36.8%) after first dose of 1 mg/kg within durvalumab and tremelimumab q4w combination, which is consistent with that observed on Cycle 1, Day 1 post-dose (geometric mean [geometric CV%] 18.299 µg/mL [20.82%]) serum concentration for tremelimumab.

In Arm B, the geometric mean (geometric CV%) of adavosertib plasma concentrations at pre-dose and post-dose (at Cycle 1, Day 3) were 551.489 nM (41.58%) and 728.342 nM (62.40%), respectively. The plasma concentration of adavosertib in this study appeared to be similar as compared to other studies at a similar dose and was not affected by the co-administration of carboplatin. The geometric mean (geometric CV%) of carboplatin plasma concentrations at the end of infusion (at Cycle 1, Day 3) was 12834.615 ng/mL (27.55%). The end of infusion plasma level of carboplatin in this study was comparable to other studies at same dose and was not altered by the co-administration of adavosertib. Adavosertib is metabolized by cytochrome P450 (CYP) 3A4 and flavin-containing monooxygenase-3 (FMO3), whereas, carboplatin is cleared by non-CYP mediated ways. Mechanistically, a drug-drug interaction between these two compounds when co-administered is not expected, and the results from this study also indicate that there is no potential interaction between these compounds. In summary, the plasma levels for both adavosertib and carboplatin were within the expected range and there was no potential drug-drug interaction.

In Arm C, the geometric mean exposure parameters for olaparib based on C_{max} and partial area under the concentration-time curve (AUC_{0-6}) following multiple dose administration on Day 7 were approximately 1.4- and 1.6-fold higher than those on Day 1 (9.19 µg/mL vs 6.56 µg/mL for C_{max} and 42.0 µg*h/mL vs 26.4 µg*h/mL for AUC_{0-6}). These increases in exposure were consistent with those observed for olaparib monotherapy following multiple dosing (observed

mean accumulation ratio of 1.4 to 1.9 for the area under the concentration time-curve [AUC] following multiple doses). Olaparib is a time dependent inhibitor of CYP3A. As olaparib is a substrate of CYP3A, the observed increase in the exposure of olaparib following multiple doses is likely caused by the time dependent inhibition of CYP3A. At steady state, the geometric mean $C_{max,ss}$ for olaparib in this study (9.19 µg/mL) is in the same range as those reported in olaparib monotherapy at the same dose in other studies (CCI µg/mL, CCI µg/mL, and CCI µg/mL in Study CCI, Study CCI, and Study CCI, respectively). However, the geometric mean AUC_{ss} (AUC_{0-t}) in the study (67.9 µg*h/mL) is slightly higher compared to those in other monotherapy studies (CCI µg*h/mL, CCI µg*h/mL, and CCI µg*h/mL in Study CCI, Study CCI, and Study D081CC00001, respectively). Ceralasertib is not expected to affect the PK of olaparib based on its in vitro drug interaction profile. The slightly higher geometric mean AUC_{ss} value observed in this study may be reflective of a random variability between study. Geometric mean exposure parameters for ceralasertib based on C_{max} and AUC_{0-6} following multiple dose administration on Day 7 were approximately 1.2- and 1.3-fold higher than those on Day 1 (5.18 µg/mL vs 4.22 µg/mL for C_{max} and 23.7 µg*h/mL vs 18.3 µg*h/mL for AUC_{0-6}). There are no formal data for ceralasertib monotherapy at a similar dose to this study to compare PK parameters and to evaluate the potential effect of olaparib co-administration.

CCI

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Summary of Safety Results

An objective of this study was to assess the safety and tolerability profile of each treatment arm.

In Arm A, the median total treatment exposure was 84.0 days for both durvalumab and tremelimumab. The most frequently reported AEs (by at least 10% of patients) were cough, diarrhea, dyspnea, and fatigue. The most frequently reported AEs of Common Terminology Criteria for Adverse Event (CTCAE) Grade 3 or 4 were diarrhea (3 [7.3%] patients), febrile neutropenia, thrombocytopenia, hyponatremia, myasthenic syndrome, fatigue, and dyspnea (2 [4.9%] patients each). The most frequently reported AEs of special interest (AESIs) were diarrhea (7 [17.1%] patients), and hyperthyroidism and hypothyroidism (4 [9.8%] patients each). The vast majority of patient deaths in Arm A were due to the disease under investigation only. One patient had a fatal AE of hemorrhagic enterocolitis, considered by the Investigator to be causally related to both durvalumab and tremelimumab. Overall, durvalumab in combination with tremelimumab appeared to be well-tolerated and had a manageable safety profile. The type and severity of events were consistent with the established durvalumab + tremelimumab safety profiles to date. There were no new potential safety signals.

In Arm B, the median total treatment exposure was 69.0 days and 70.0 days for adavosertib and carboplatin, respectively. The most frequently reported AEs (at least 20% of patients) were diarrhea, thrombocytopenia, nausea, anemia, asthenia, fatigue, neutropenia, and vomiting. The most frequently reported AEs of CTCAE Grade 3 or 4 were neutropenia (3 [30.0%] patients), and diarrhea and thrombocytopenia (2 [20.0%] patients each). The vast majority of patient deaths in Arm B were due to the disease under investigation only. One patient had a fatal AE of pancytopenia, associated with disease progression, considered causally related to carboplatin only.

In Arm C, the median total treatment exposure was 84.0 days for both ceralasertib and olaparib. The most frequently reported AEs (at least 15% of patients) were anemia and pyrexia. The most frequently reported AE of CTCAE Grade 3 or 4 was anemia (6 [28.6%] patients). The vast majority of patient deaths in Arm C were due to the disease under investigation only. One patient had a fatal AE of pneumonia, associated with disease progression, and not considered to be causally related to study treatments.

Overall, each of the treatment combinations appeared to be well tolerated and the observed toxicities were generally manageable. The type and severity of AEs were generally consistent with the established safety profiles to date for each study treatment. No new safety concerns were identified.

Conclusions

- This BALTIC study was a multi-arm umbrella Phase II study with primary endpoint of ORR, adopting a 2-stage design. BALTIC enrolled a targeted patient population with refractory/resistant ES-SCLC following frontline treatment.
- Anti-tumor activities were observed in all 3 arms; however, ORR was low, and all three treatment combinations failed to meet the pre-defined criteria to warrant further development of the treatment in ES-SCLC.
- PK of each study treatment was generally consistent with that observed to date.
- Overall, each treatment combination appeared to be well-tolerated and had a manageable safety profile. The type and severity of events were consistent with the known safety profiles of the individual drugs and used combinations to date. There were no new potential safety signals.