2. SYNOPSIS

Study centres

A total of 4 sites randomised at least one patient. The study was conducted in 3 countries (2 sites in the United States, one site in France, and one site in Taiwan).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives [a]	Endpoints [a]
Primary	
• To investigate prognosis-correlated immune activation due to DDR inhibition by monitoring the induction of immunologically relevant genes in tumours of patients treated with study investigational agent(s)	• Conversion of an immunologically based 25-gene signature from a prognostically unfavourable state to a prognostically favourable state
Secondary	
• To investigate the prevalence and localisation of TILs associated with prognosis	• Transition from a low TIL infiltrative state (poor prognosis) to a high TIL infiltrative state (favourable prognosis) shown by TIL enumeration and an increase in: ° CD8+ T-cells ° CD3+ T-cells
Safety	
• To monitor the safety and tolerability of each DDR agent	• AEs/SAEs • Vital signs • Collection of clinical chemistry/haematology parameters • ECGs
Exploratory [b]	
• CCI [redacted]	• CCI [redacted]
• CCI [redacted]	• CCI [redacted]

[a] Primary and secondary biomarker objectives and endpoints were updated at CSP Amendment 2.

[b] CCI [redacted]

[c] CCI [redacted]

Abbreviations: AE: adverse event; CD3+: cluster of differentiation 3; CD8+: cluster of differentiation 8; CSP: clinical study protocol; CSR: clinical study report; DDR: DNA (deoxyribonucleic acid) Damage Response; ECG: electrocardiogram; CCI [redacted]; CCI [redacted]; SAE: serious adverse event; SAP: statistical analysis plan; TIL: tumour infiltrating leukocyte.

Study design

This was an open-label, randomised, multi-centre, Phase Ib study to investigate biomarker effects of pre-surgical treatment with deoxyribonucleic acid (DNA) Damage Response (DDR) agents in patients with Head and Neck Squamous Cell Carcinoma (HNSCC) who were planned to undergo surgery that was likely to be followed by radiotherapy and/or chemotherapy.

This biomarker window basket study was designed with the intent of assessing the effects of different agents in both tumour tissue and peripheral samples to further inform optimal combinations of DDR agents with Immuno-Oncology (IO) therapies and the suitable sequencing and relative timing of these therapies. Two DDR agents were assessed as monotherapy (ceralasertib [AZD6738] and olaparib [AZD2281]). Additional arms could have been incorporated to evaluate other DDR agents and/or DDR and immunotherapy agents in combination or in series. However, the additional arms were not initiated.

Patients enrolled into the study were required to donate tissue taken before administration of investigational product (IP) in order to compare on-treatment versus pre-treatment (baseline) biomarker status.

Patients were randomised to either ceralasertib 160 mg twice daily or olaparib 300 mg twice daily and had to receive this treatment for at least 9 days, after which surgery or on-treatment biopsy could have been undertaken between Days 10 to 21 (+3 days). Surgery (or on-treatment biopsy) must have been performed within 24 hours immediately following 3 successive regularly scheduled days of administration of IP (olaparib or ceralasertib). It was permitted to dose on the Day of Surgery.

Safety was monitored weekly with collection of adverse events (AEs), safety laboratory tests (including full blood count, liver function tests, creatinine and serum urea [or blood urea nitrogen]), vital signs and electrocardiogram (ECG). Patients were withdrawn if they experienced any AEs that affected surgery or if their tumour progressed.

Target population and sample size

The key inclusion criteria were as follows: Male or female patients ≥ 18 years of age with Eastern Cooperative Oncology Group performance status 0, 1 or 2 with no deterioration over the previous 2 weeks and an estimated life expectancy of greater than 12 weeks; treatment naïve HNSCC either newly diagnosed, or with a second tumour at more than 2 years after successful treatment of the primary cancer, suitable for surgical resection that was likely to be

followed by radiotherapy and/or chemotherapy after surgery. Patients who were suitable for radical chemoradiation without surgery were eligible if they were willing to undergo an on-treatment biopsy.

A total of 20 patients were planned to be randomised to each arm (40 in total). An interim analysis was planned after 18 evaluable patients (ie, 9 per arm) had been enrolled and had an on-treatment biopsy. However, this did not occur due to insufficient number of evaluable patients. The study was terminated early on 19 January 2021 due to poor recruitment.

Investigational products: dosage, mode of administration and batch numbers

The IPs in this study were ceralasertib and olaparib.

Table S2 Study Treatments

	Investigational Products	
Investigational product name:	Ceralasertib (AZD6738)	Olaparib (AZD2281)
Dosage formulation:	Film-coated tablet	Film-coated tablet
Unit dose strength:	20 mg, 100 mg	100 mg, 150 mg
Route of administration:	Oral	Oral
Dosing instructions:	Twice daily (2 × 160 mg) continuous dosing for a minimum of 9 days [i] and a maximum of 21 days. Ceralasertib tablets were taken at the same time each day, approximately 12 hours apart (maximum ± 2-hour window) with one glass of water. No food was allowed from 2 hours prior to taking ceralasertib to one hour post-dose.	Twice daily (2 × 300 mg) continuous dosing for a minimum of 9 days and a maximum of 21 days. Olaparib tablets were taken at the same time each day, approximately 12 hours apart (maximum ± 2-hour window) with one glass of water.
Batch/Lot number(s)	Provided in Appendix 16.1.6 of the CSR	
Packaging and labelling:	Labels were prepared in accordance with GMP	
Provider:	AstraZeneca	

[a] Minimum treatment duration was indicated as 10 days in the CSP but, since dosing was allowed on the day of surgery, this was clarified as 9 days in a CSP clarification memo.

Abbreviations: CSP: clinical study protocol; CSR: clinical study report; GMP: Good Manufacturing Practice.

Duration of treatment

The minimum planned duration of treatment was 9 days and maximum duration of treatment was 21 days.

Statistical methods

No formal statistical analysis or between treatment comparisons were carried out for this study and the data were summarised for each treatment arm individually. Continuous data were reported using n (number of observations), mean, standard deviation, median, minimum, and maximum values. Categorical data were reported using number and percentage of patients.

For the primary pharmacodynamic (PD) analysis, the proportion of patients with a conversion of an immunologically based 25-gene signature from prognostically unfavourable to favourable state was summarised and 80% confidence intervals (CI) using the Clopper-Pearson interval provided. Assessment of the primary study objective was based on the percentage of patients in each treatment arm who showed conversion from a prognostically unfavourable state to a prognostically favourable state.

For the secondary PD analysis, the proportion of patients achieving a conversion of T-cells was summarised along with the 80% CI. The proportion of patients achieving a transition of immunoscore based on CD3CT and CD8CT T-cell counts from prognostically unfavourable to favourable state was summarised along with the 80% CI. Patients were considered to have achieved the secondary outcome measure when there was a tumour transition following drug treatment to an Immunoscore-determined more favourable prognostic category, ie, a transition from a pre-treatment Immunoscore in the lowest 10th percentile (≤ 10%) to > 10% or from a pre-treatment immunoscore at or below the 70th percentile (≤ 70%) to > 70%.

CCI [redacted]

CCI [redacted]

For the primary, secondary and CCI [redacted] endpoints, the analysis was based on all evaluable patients, where an evaluable patient was defined as a patient who had a baseline and on-treatment sample on Day 10 to 21, who received treatment for at least 9 days and 3 consecutive days prior to surgery or surgical biopsy, and who had no major protocol deviations that could impact the biomarker analysis.

CCI [redacted]

Safety outcome measures were analysed for all patients who received at least one dose of IP. Treatment-emergent AEs were summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term and by treatment arm, and were listed by individual patient and treatment arm. The number and percentage of patients with AEs in different categories (eg, worst Common Terminology Criteria for Adverse Events [CTCAE] grade, causally related, CTCAE grade ≥ 3, etc.), deaths, serious adverse events (SAEs), and other AEs (OAEs) were also summarised by MedDRA SOC and preferred term. Separate listings for deaths, SAEs, and OAEs were provided. Haematology, clinical chemistry, urinalysis, vital signs, and ECGs were listed and suitably summarised based on the safety analysis set. For all laboratory variables included in the current version of CTCAE, the CTCAE grade was calculated and summarised. Graphical presentations of safety data were presented as appropriate. This included, but was not restricted to, presentation of parameters against time, concentration or shift plots.

Decision to stop the study

After a review of the data outputs in an AstraZeneca Governance meeting held on 19 January 2021, it was decided to terminate the study early due to poor recruitment and the subsequent inability to evaluate the primary PD endpoint due to baseline immunoscore. The recommendation was that all screening activities and enrollment of new patients into the study were stopped and all ongoing patients followed the schedule of assessment as per protocol as needed.

Study population

- A total of 21 patients were randomised (12 and 9 in the ceralasertib and olaparib arms, respectively) out of 31 patients enrolled, and 20 out of 21 patients (95.2%) completed the study.
- One patient (in the olaparib arm) was lost to follow-up and withdrawn. One patient had an important protocol deviation that led to exclusion from the PD analysis set (patient had no record of receiving 9 or more days of treatment).
- There was a higher proportion of elderly patients PPD in the ceralasertib arm than in the olaparib arm (6 patients [50.0%] compared to 2 patients [22.2%]). No other notable differences regarding demographic and patient characteristics at baseline were reported between treatment arms.
- With regards to disease characteristics, more patients in the ceralasertib arm had a positive human papillomavirus status (3 patients [25.0%]) compared to the olaparib arm (one patient [11.1%]).

- All patients from both treatment arms were included in the CCI and safety analysis sets. Three patients in the ceralasertib arm and 2 patients in the olaparib arm were excluded from the CCI analysis set.

Summary of pharmacodynamic results

- For patients included in the primary PD endpoint analysis, zero of 2 patients in the ceralasertib arm and one of 4 patients in the olaparib arm had an immunological response to treatment (converting an immunologically based 25-gene signature "cold tumour" to an immunotherapeutically responsive or "immunologically hot tumour").
- In the secondary PD endpoint analysis, 2 of 4 patients in the ceralasertib arm and zero of 4 patients in the olaparib arm had immunoscore transitions from a low (poor prognosis) to a high (favourable prognosis) tumour infiltration leukocytes (TIL) infiltrative state.
- Due to the small number of patients included in the primary and secondary PD analyses, results should be interpreted with caution. CCI

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Summary of pharmacogenetic results

Exploratory tissue and blood biomarker and pharmacogenetic analyses will be reported separately from this clinical study report.

Summary of safety results

- Overall, the safety and tolerability profile was consistent with the known safety profile for ceralasertib and olaparib based on the limited data (low patient exposure) available. No unexpected safety findings were detected for either ceralasertib or olaparib.
- A similar percentage of patients had AEs in each treatment arm (91.7% and 88.9% in the ceralasertib and olaparib arms, respectively). Two patients in the ceralasertib arm and one patient in the olaparib arm had an AE of CTCAE grade 3 or higher. One patient, in the ceralasertib arm, had an AE that led to discontinuation of IP.
- The most commonly reported AEs (preferred terms) in the ceralasertib arm were tumour pain, constipation, nausea, and rash (3 patients [25.0%] each). The most commonly reported AEs (preferred terms) in the olaparib arm were anaemia, constipation, diarrhoea, and neck pain (2 patients [22.2%] each).
- One patient in each treatment arm experienced an SAE and there were no deaths during the study. There were no adverse events of special interest for olaparib.
- There were no potential Hy's Law events.
- Treatment-emergent AEs collected in the 30-day safety follow-up period after treatment discontinuation overlapped with the postoperative period and could be confounded by prior surgery.
- Eight patients (66.7%) in the ceralasertib arm and 2 patients (22.2%) in the olaparib arm had AEs causally related to IP. Causally related AEs in the ceralasertib arm were reported in various SOCs, with only 2 AEs (nausea and fatigue) reported for more than one patient (2 patients [16.7%] each).
- All causally related AEs were of CTCAE grade 1 or 2, with the exception of an AE of chest pain experienced by one patient in the ceralasertib arm, which was of CTCAE grade 3, considered to be serious, and led to discontinuation of IP.

Conclusion(s)

- There were no unexpected safety findings identified for either ceralasertib or olaparib in this study. While a higher number of causally related AEs were reported in the ceralasertib arm compared to the olaparib arm, these events were generally low grade and spread across various SOCs; additionally, the low exposure makes any meaningful interpretation of these data difficult.
- Interpretation of the planned primary and secondary PD endpoints is limited due to the very small sample size of evaluable patients (< 5 per treatment arm).
- In the primary PD endpoint analysis, zero of 2 patients in the ceralasertib arm and one of 4 patients in the olaparib arm had an immunological response to treatment (converting an immunologically based 25-gene signature "cold tumour" to an immunotherapeutically responsive or "immunologically hot tumour").
- In the secondary PD endpoint analysis, 2 of 4 patients in the ceralasertib arm and zero of 4 patients in the olaparib arm had immunoscore transitions from a low (poor prognosis) to a high (favourable prognosis) TIL infiltrative state.

- CCI [redacted]
- CCI [redacted]