Clinical Study Report Synopsis	
Drug Substance	Monalizumab and cetuximab
Study Code	D7310C00001
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A Phase 3 Randomized, Double-blind, Multicenter, Global Study of Monalizumab or Placebo in Combination With Cetuximab in Participants With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Previously Treated With an Immune Checkpoint Inhibitor

Study dates:
First subject enrolled: 02 October 2020
Last subject last visit: 01 August 2022
The analyses presented in this report are based on a clinical efficacy data cut-off date of 11 May 2022, and clinical safety data cut-off date of 01 September 2022.

Phase of development:
Therapeutic confirmatory (III)

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

Study Centre(s)

Participants were enrolled at 126 sites in 23 countries: Argentina (3 sites), Australia (4), Austria (1), Belgium (4), Brazil (7), Bulgaria (3), Canada (5), France (8), Germany (7), Greece (3), Italy (8), Japan (12), Netherlands (3), Philippines (3), Poland (3), Portugal (5), Republic of Korea (7), Russia (5), Spain (5), Switzerland (3), Taiwan (6), United Kingdom (4), and United States of America (17).

Publications

There are no publications containing study data at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objective	Estimand [a] Description/Endpoint	Reported in the aCSR
Primary		
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in HPV-unrelated participants [b]	• Population: The HPV-unrelated Analysis Set, which will include all randomized participants who are either OPC HPV negative or non-OPC regardless of HPV status • Endpoint: OS, which is defined as time from randomization until the date of death due to any cause • Intercurrent events: If a participant is lost to follow-up or withdraws consent, OS will be censored based on the last recorded date on which the participant was known to be alive • Summary measure: p-value of treatment comparison using a stratified log-rank test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model	Yes, with simplification
Secondary		
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of OS in all randomized participants	• Population: The FAS which will include all randomized participants • Endpoint: OS, which is defined as time from randomization until the date of death due to any cause • Intercurrent events: If a participant is lost to follow-up or withdraws consent, OS will be censored based on the last recorded date on which the participant was known to be alive • Summary measure: p-value of treatment comparison using a stratified log-rank test and hazard ratio of Arm A relative to Arm B with its confidence interval using a stratified Cox Proportional Hazards model	Yes, with simplification

Objective	Estimand [a] Description/Endpoint	Reported in the aCSR
To compare the effect of monalizumab and cetuximab (Arm A) relative to placebo and cetuximab (Arm B) by assessment of PFS, ORR [c], and DoR [c] in participants who are HPV-unrelated and in all randomized participants	• PFS is defined as time from randomization until disease progression, per RECIST 1.1 as assessed by the investigator at local site or death due to any cause, whichever occurs first. • ORR [c] is defined as the proportion of participants with measurable disease who have a confirmed CR or PR, as determined by the investigator at local site per RECIST 1.1. • DoR [c] is defined as the time from the date of first documented response until date of documented disease progression or death in the absence of disease progression.	Yes, with simplification
To assess disease-related symptoms, functioning, and HRQoL [d] in participants treated with monalizumab and cetuximab (Arm A) compared to placebo and cetuximab (Arm B) using the EORTC QLQ-C30 and the EORTC QLQ-H&N35 questionnaires in participants who are HPV-unrelated and in all randomized participants	Symptoms, functioning, and global health status/QoL scale/item scores of the EORTC QLQ-C30 and EORTC QLQ-H&N35 • Change from baseline scores across visits • Time to clinically meaningful deterioration in scores	No, analyses not conducted
To assess the PK [d] of monalizumab	Concentration of monalizumab in blood and PK parameters (such as C_{max}, C_{trough}, as data allow; sparse sampling)	No, analyses not conducted
To investigate the immunogenicity [d] of monalizumab	Presence of ADAs for monalizumab (confirmatory results: positive or negative, titers)	No, analyses not conducted
To characterize the association between clinical outcome and protein expression [d] in the tumor microenvironment in participants treated with monalizumab and cetuximab (Arm A) or placebo and cetuximab (Arm B) in participants who are HPV-unrelated and in all randomized participants	HLA-E and NKp46+ expression in pre-treatment and post-treatment tumor biopsies	No, analyses not conducted
Secondary safety [e]		
To assess the safety and tolerability of monalizumab and cetuximab (Arm A) compared to placebo and cetuximab (Arm B) in participants with R/M SCCHN previously treated with ICI	AEs, vital signs, clinical laboratory results, ECGs	Yes, in full

[a] Estimand is the target of estimation to address the scientific question of interest posed by the primary objective. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable.

[b] The primary population was changed from FAS (all randomized participants) to HPV-unrelated (OPC HPV negative or non-OPC regardless of HPV status) in CSP amendment 1.

[c] BOR was assessed alongside ORR and DoR secondary endpoints. BOR is defined as the best response a participant has had following randomization but prior to starting any subsequent anti-cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression.

[d] Following futility IA1, assessment of disease-related symptoms, functioning, and HRQoL, PK and immunogenicity of monalizumab, and association between clinical outcome and protein marker expression were removed.

[e] Safety analyses were performed on SAF, defined as all participants who received any amount of study treatment. Safety data were summarized descriptively according to the treatment actually received.

Exploratory objectives and outcome measures are not reported in the abbreviated CSR.

aCSR = abbreviated clinical study report; ADA = antidrug antibodies; AE = adverse event; BOR = best objective response; C_{max} = maximum serum concentration; CR = complete response; CSP = clinical study protocol; CSR = clinical study report; C_{trough} = trough serum concentration; DoR = duration of response; ECG = electrocardiogram; EORTC = European Organization for Research and Treatment of Cancer; FAS = full analysis set; HLA-E = human leukocyte antigen E; HPV = human papillomavirus; HRQoL = health-related quality of life; ICI = immune checkpoint inhibitor; NK = natural killer; OPC = oropharyngeal cancer ; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; QLQ-C30 = 30-item Core Quality of Life Questionnaire; QLQ-H&N35 = Quality of Life Questionnaire Head and Neck Module; QoL = quality of life; RECIST 1.1 = Response Evaluation Criteria for Solid Tumors version 1.1; R/M = recurrent or metastatic; SAF = safety analysis set; SCCHN = squamous cell carcinoma of the head and neck.

Study Design

This was a Phase 3 randomized, double-blind, multicenter, global study designed to assess the efficacy and safety of monalizumab in combination with cetuximab, compared with placebo and cetuximab in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) who have progressed on or after prior systemic programmed cell death 1/programmed cell death ligand-1(PD-1/PD-L1) inhibitor (in any setting) and platinum-based therapies.

The study planned to randomize approximately 624 eligible participants in a 2:1 ratio to one of the following treatment arms using an interactive response technology.

- Arm A (number = 416): monalizumab and cetuximab (M+C)
  Monalizumab CCI intravenous (IV) every 2 weeks (Q2W) and cetuximab 400 mg/m^2 IV initial dose followed by 250 mg/m^2 IV once weekly (Q1W), as per label
- Arm B (number = 208): placebo and cetuximab (P+C)
  Placebo IV Q2W and cetuximab 400 mg/m^2 IV initial dose followed by 250 mg/m^2 IV Q1W, as per label

Participants were stratified by the following:

- Human papillomavirus (HPV) status (oropharyngeal cancer [OPC] HPV-positive or randomized participants who are either OPC HPV negative or non-OPC [HPV-unrelated]),
  - The number of OPC HPV-positive participants was closely monitored throughout the study and was planned to be capped at approximately 20% of the total sample size (this cap was introduced in CSP amendment 1).

- World Health Organization/Eastern Cooperative Oncology Group performance status (WHO/ECOG PS) (0 or 1), and
- Number of prior lines of therapy in the R/M setting (1 or 2)
  - The number of participants in each stratum (1 or 2 prior lines of therapy in the R/M setting) was closely monitored throughout the study. If a disproportionate number of participants were enrolled in a single stratum (eg, > 75% of the total sample size), the Sponsor might elect to close further recruitment into that stratum.

An Independent Data Monitoring Committee (IDMC) reviewed safety data regularly and made recommendations regarding further study conduct. There were two planned interim analyses (IA) and one final analysis. The first interim analysis (IA1) was for futility. For the two IAs, the IDMC were to review unblinded interim efficacy data and to inform the Sponsor whether the pre-specified interim boundaries were met. The study was declared futile on 01 August 2022 following futility IA1 that showed a lack of benefit in the primary endpoint of overall survival (OS) in the primary HPV-unrelated population, hence the second interim analysis (IA2) was not performed.

This abbreviated clinical study report presents final analysis based on:

- Efficacy data cut-off (DCO) date of 11 May 2022, the DCO date of the futility IA1. The efficacy results presented reflect the results of the futility IA1, which was the basis of study enrollment discontinuation. Data collected at this DCO date was sufficient to characterize the lack of efficacy for monalizumab in this clinical setting.
- Safety DCO date of 01 September 2022. This DCO date allowed longer cumulative follow-up for safety assessment following study enrollment discontinuation.

Target Population and Sample Size

The target population was adult patients (aged ≥ 18 years) with histologically or cytologically confirmed R/M SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx who had progressed on or after previous systemic cancer therapy and were not amenable to curative therapy. Participants must have received prior treatment with a systemic programmed cell death-1 or programmed cell death ligand-1 inhibitor (in any setting) and received one or two prior systemic regimes for R/M SCCHN.

The study planned to randomize 624 eligible participants in a 2:1 ratio to one of two treatment arms (M+C or P+C). The study was powered to demonstrate superiority in the OS benefit of M+C vs P+C in HPV-unrelated participants. HPV-positive participants were capped at 20% of the total sample size.

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

Table S2 Investigational Medicinal Products

Investigational Medicinal Product (Current/Former Name or Alias)	Dosage Form and Strength	Manufacturer	Batch Numbers
Monalizumab (IPH2201)	CCI [redacted]	CCI [redacted]	CCI [redacted]
Cetuximab (Erbitux®)	Initial dose: 400 mg/m^2 Subsequent doses: 250 mg/m^2 Q1W IV infusion	AstraZeneca or sourced locally for USA and Canada	G00BKM, G00VF2, G017AL [a]
Placebo	Saline or dextrose for injection Q2W IV infusion	Sourced locally by site	N/A

[a] Cetuximab batch numbers used in countries excluding USA and Canada.

IV = intravenous; N/A = not applicable; Q1W = once weekly; Q2W = every 2 weeks.

Duration of Treatment

Randomized study treatment was planned to continue until Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST 1.1)-defined radiological disease progression per investigator, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Statistical Methods

The study was powered to demonstrate superiority in the OS benefit of M+C vs P+C in HPV-unrelated participants. The formal statistical analysis of primary OS endpoint was performed using a stratified log-rank test adjusting for WHO/ECOG PS (0 or 1) and number of lines of prior therapy in the R/M setting (1 or 2). The hazard ratio (HR) and confidence interval (CI) were estimated from a stratified Cox Proportional Hazards model. The effect in treatment arm was estimated by the HR together with its corresponding CI and p-value (from stratified log-rank test). The stratification variables in the statistical test and modeling were based on the values entered into the interactive voice response system at randomization.

Analysis of OS in the full analysis set (FAS) were similar except that the stratified log-rank test was adjusted for HPV status (OPC HPV-positive or HPV-unrelated), WHO/ECOG PS (0 or 1), and number of lines of prior therapy in the R/M setting (1 or 2).

There were two planned IAs and one final analysis for the study.

- IA1 was a futility IA to evaluate OS in the HPV-unrelated population when approximately 99 OS events had occurred across both treatment arms in HPV-unrelated

participants (25% information fraction) who had been randomized at least 2 months before the DCO. Futility criteria was set at HR of > 0.874.

- IA2 was planned as part of a hierarchical multiple testing procedure but was not performed as futility criteria was met in IA1.
- Final efficacy analysis was performed with simplification. Safety data were summarized descriptively using the safety analysis set (SAF) which consisted of all participants who received any amount of study treatment.

Study Population

In total, 504 participants were enrolled in 126 study sites across 23 countries. Disposition, protocol deviations, demographic and baseline disease characteristics were balanced across the M+C arm and the P+C arm in the FAS, HPV-unrelated analysis set and SAF. There were no concerns regarding the overall conduct or quality of the study.

Efficacy Analysis

Efficacy analyses were performed on HPV-unrelated analysis set (OPC HPV negative or non-OPC regardless of the HPV status randomized at least 2 months before the 11 May 2022 efficacy DCO date) and FAS (all participants randomized at least 2 months before the efficacy DCO date).

Table S3 Subject Disposition (All Subjects) - Efficacy Analysis DCO (11 May 2022)

	Number (%) of subjects		
	Monalizumab + Cetuximab	**Placebo + Cetuximab**	**Total**
Subjects enrolled [a]			421
Subjects randomized	203 (100.0)	103 (100.0)	306 (100.0)
Full analysis set [b]	175 (86.2)	89 (86.4)	264 (86.3)
HPV-unrelated analysis set [b]	145 (71.4)	71 (68.9)	216 (70.6)
Subjects who discontinued monalizumab/placebo treatment [c]	145 (82.9)	67 (76.1)	212 (80.6)
Subjects who discontinued cetuximab treatment [d]	145 (82.9)	67 (77.0)	212 (80.9)
Subjects who terminated study [b]	92 (45.3)	47 (45.6)	139 (45.4)

[a] Informed consent received.

[b] Percentages are calculated from number of subjects randomized.

[c] Percentages are calculated from number of subjects who received monalizumab/placebo and are in the full analysis set.

[d] Percentages are calculated from number of subjects who received cetuximab and are in the full analysis set.

Full analysis set - all subjects randomized at least 2 months before the 11 May 2022 DCO (ie, on or before 11 Mar 2022).

Human papillomavirus-unrelated (HPV-unrelated) analysis set - all subjects randomized at least 2 months before the 11 May 2022 DCO (ie, on or before 11 March 2022) who are either OPC HPV negative or non-OPC regardless of the HPV status.

COVID-19 = coronavirus disease 2019; DCO = data cut-off; HPV = Human papillomavirus; OPC = Oropharyngeal cancer.

Safety Analysis

Safety analyses were performed using the SAF, which included all participants who received at least one dose of study treatment by the safety DCO date of 01 September 2022.

Table S4 Subject Disposition (All Subjects) - Safety Analysis DCO (01 September 2022)

	Number (%) of subjects		
	Monalizumab + Cetuximab	**Placebo + Cetuximab**	**Total**
Subjects enrolled [a]			504
Subjects randomized	247 (100.0)	123 (100.0)	370 (100.0)
Safety analysis set [b]	246 (99.6)	122 (99.2)	368 (99.5)
Subjects who discontinued monalizumab/placebo treatment [c]	211 (87.6)	117 (95.9)	328 (90.4)
Subjects who discontinued cetuximab treatment [d]	200 (81.3)	98 (81.7)	298 (81.4)
Subjects who terminated study [b]	238 (96.4)	119 (96.7)	357 (96.5)

[a] Informed consent received.

[b] Percentages are calculated from number of subjects randomized.

[c] Percentages are calculated from number of randomized subjects who received monalizumab/placebo.

[d] Percentages are calculated from number of randomized subjects who received cetuximab.

Safety analysis set - all subjects who received at least one dose of monalizumab/placebo or cetuximab by the time of 01 Sep 2022 DCO.

COVID-19 = coronavirus disease 2019; DCO = data cut-off; OPC = oropharyngeal cancer.

Summary of Efficacy Results

Based on efficacy DCO for IA1, treatment with M+C did not demonstrate a clinical benefit compared with P+C in HPV-unrelated analysis set and FAS for all the endpoints analyzed. The HR, adjusted for stratification factors (WHO/ECOG PS = 0 or 1, number of lines of prior therapy in the R/M setting = 1 or 2) was 1.00 (95 % CI: 0.660, 1.537; stratified log-rank test 2-sided p = 0.989).

Study enrollment was discontinued following the review of the IA1 results due to unlikelihood of achieving statistical significance for the primary endpoint OS in the HPV-unrelated population.

Summary of Safety Results

Overall, the combination monalizumab with cetuximab was well tolerated. There were no new safety findings in this study that preclude further development of monalizumab in combination with cetuximab.

In the M+C arm the median total duration of exposure for monalizumab was 2.33 months and 2.32 months for cetuximab. In the P+C arm the median total duration of exposure for placebo and cetuximab was 3.22 months. Dose interruptions and delays did not meaningfully affect the actual treatment duration of exposure.

The incidence of adverse events (AE) was similar across treatment arms with most of the participants in each treatment arm experiencing at least one AE. The most frequently reported AEs in both treatment arms were dermatitis acneiform, rash, fatigue, and hypomagnesemia. A higher incidence of AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 was reported in the M+C arm compared to P+C arm with majority of these events assessed as possibly related to cetuximab in both treatment arms with no specific trends identified. The incidence of AEs leading to discontinuation of study treatment was higher in the M+C treatment arm compared with the P+C arm with majority assessed as possibly related to cetuximab in both treatment arms, however no specific trends were identified.

Adverse events of special interest were reported by a similar proportion of participants in both treatment arms. Most events were CTCAE Grade 1 or 2 with the reported preferred terms (PT) in each system organ class (SOC) low in frequency and no trends identified. The majority of adverse events of special interest that led to steroid treatment were non-serious and recovered at the time of DCO. Immune-mediated AEs were reported by a similar proportion of participants in both treatment arms. The reported events in each SOC were low in frequency with no trends identified. Most events were CTCAE Grade 1 or 2 and non-serious.

A higher incidence of AEs with outcome of death was observed the M+C treatment arm. The most common SOC of AE with the outcome of death was Infections and infestations however, no AE PT trends were observed across any of the SOCs [redacted]

Serious adverse events (SAEs) were experienced by a higher proportion of participants in the M+C arm compared with the P+C arm. A higher incidence of SAEs assessed as possibly related to cetuximab compared with monalizumab was observed in both treatment arms. Pneumonia was the most frequently reported Grade 3 or 4 event in both treatment arms, however, was not assessed as related to study treatment. The percentage of participants that discontinued treatment due to an SAE was < 5% in both treatment arms.

The incidence of events within the hemorrhage standardized MedDRA (Medical Dictionary for Regulatory Activities) query (SMQ) was similar in both treatment arms.

There was one incident of potential Hy's Law that was assessed to have been due to disease progression and not confirmed as Hy's Law.

There were no clinically important trends or changes over time from baseline in hematology or clinical chemistry parameters.

There were no meaningful trends in ECGs and vital signs in the study.

Conclusion(s)

- Treatment with monalizumab in combination with cetuximab did not demonstrate a clinical benefit compared with placebo and cetuximab in the HPV-unrelated analysis set and FAS for all the endpoints analyzed.
- The combination of monalizumab and cetuximab demonstrated an acceptable safety and tolerability profile and there were no new safety concerns that preclude further clinical development.