2. SYNOPSIS

NAME OF SPONSOR/COMPANY: Genmab A/S	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: HuMax-EGFr NAME OF ACTIVE INGREDIENT(S): Zalutumumab	Volume: Page:	
Protocol No.: Hx-EGFr-C-207		
Title of Study: An Open-label, International, Multi-center, Phase I/II, Dose-escalation Trial Investigating the Safety of Zalutumumab, a Human Monoclonal Epidermal Growth Factor Receptor Antibody in Combination with Radiotherapy, in Patients with Stage III, IVa or IVb Locally Advanced Squamous Cell Carcinoma of the Head and Neck Ineligible for Platinum-based Chemotherapy.		
Investigators: Multicenter (5 principal investigators: 3 in France and 2 in the United Kingdom)		
Study Centre(s): Subjects were enrolled at 5 sites in 2 countries: 3 in France and 2 in the United Kingdom.		
Publication (Reference): Not applicable		
Studied Period (years): 16 September 2008 to 18 October 2010 (date of study termination)		**Phase of development:** I/II

Objectives:

The primary objective of this study was to evaluate the safety of repeat dosing and establish the maximum tolerated dose (MTD) of zalutumumab in combination with radiotherapy (RT) in subjects with stage III, IVa, or IVb locally advanced squamous cell carcinoma of the head and neck (SCCHN) ineligible for platinum-based chemotherapy.

The secondary objective was to evaluate the pharmacokinetic (PK) profile and the efficacy of repeat dosing of zalutumumab in combination with RT in subjects with stage III, IVa, or IVb locally advanced SCCHN ineligible for platinum-based chemotherapy.

Methodology:

This was an open-label, multicenter, Phase I/II, dose-escalation clinical study that investigated the safety of zalutumumab in combination with RT. The safety of zalutumumab doses in combination with RT was to be investigated by using 3 subject cohorts in a dose escalation/de-escalation design based on dose limiting toxicity (DLT). The following is a description of the planned study design:

- The dose escalation was to be initiated at 8 mg/kg zalutumumab in combination with RT.
- Initially, 3 subjects were to be treated at a dose level and observed for DLTs. If none of the 3 subjects experienced a DLT, the next cohort of 3 subjects was to be treated at the next higher dose of zalutumumab.
- If 1 of 3 subjects treated at a dose level experienced a DLT, then 3 more subjects were to be treated at the same dose level.
- If 2 or more of the 3 subjects in a cohort experienced DLTs, the next cohort of 3 subjects was to be treated at the next lower dose of zalutumumab unless at least 6 subjects on that dose had already been dosed.
- If 1 or fewer DLTs were observed among 6 subjects at a given dose level, then the next cohort of 3 subjects was to be treated at the next higher dose of zalutumumab.
- The MTD was to be decided by the sponsor based on the recommendations made by the Independent Data Monitoring Committee (IDMC) on the basis of their review of the aggregated safety data. The MTD was defined as the highest dose level at which no more than 1 DLT was observed in 6 subjects.
- If a dose level of 4 mg/kg was found to be intolerable, the study was to be terminated.

Zalutumumab was administered as a weekly infusion for 8 weeks. Subjects in the first cohort were administered a loading dose of [redacted] followed by 7 weekly maintenance doses of 8 mg/kg. The [redacted] dose level was to have included an initial loading dose of [redacted] followed by 7 weekly maintenance doses of [redacted]. Similarly, the 4 mg/kg dose level included an initial loading dose of [redacted] followed by 7 weekly maintenance doses of 4 mg/kg. The [redacted] dose level was to have consisted of 8 maintenance doses of [redacted] without a loading dose. Radiotherapy was given as 5 weekly fractions of 2 Gy for 7 weeks (ie, a total of 70 Gy) during Weeks 2 to 8 in the Treatment Period.

After completing the 8-week Treatment Period, all subjects entered a Follow-up Period of 4 weeks starting from the last

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dose of zalutumumab. Subsequently, subjects entered an Extended Follow-up Period that was to end for all subjects approximately 2 years after administration of the first dose of zalutumumab. During the Extended Follow-up Period, data were collected to evaluate serious adverse events (SAEs), subsequent anticancer treatment, late radiation toxicities, objective tumor response, and overall survival.

Number of Subjects (planned and analyzed): A maximum of 18 subjects was planned for enrollment in the dose-escalation/de-escalation part of the study. Once the MTD was established, an additional 12 subjects were planned to be enrolled and investigated at the MTD of zalutumumab in combination with RT. Therefore, a maximum of 30 subjects was planned for enrollment.

A total of 8 subjects was enrolled in the study: 5 subjects in the 8 mg/kg treatment cohort and 3 subjects in the 4 mg/kg treatment cohort.

Diagnosis and Main Criteria for Inclusion: Subjects aged 18 years or above who had histologically or cytologically confirmed diagnosis of locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx Stage III, IVa, or IVb were eligible for enrollment in the study. Subjects were ineligible for platinum-based chemotherapy and provided signed informed consent before any study-related activity was performed.

Test Product, Dose and Mode of Administration, Batch No.:

Zalutumumab (Batch number: PD07020) was administered weekly as an intravenous infusion at a dose of 4-[redacted] mg/kg during Weeks 0 to 7 (8 weeks total) during the Treatment Period.

Radiotherapy consisted of either 3-dimensional or Intensity Modulated Radiation Therapy administered as 1 fraction (2 Gy) per day, 5 days per week, for 7 weeks (ie, a total of 70 Gy in 35 fractions throughout Weeks 1-7) during the Treatment Period.

Duration of Treatment: Subjects were administered zalutumumab in combination with RT for 8 weeks (up to Visit 9) and then participated in a 4-week safety follow-up period (Visits 10 and 11). Subjects then entered an Extended Follow-up Period for 2 years from the time of allocation.

Reference Therapy, Dose and Mode of Administration, Batch No.: None

Criteria for Evaluation: All subjects who received at least 1 dose of study treatment were evaluable for safety, efficacy, and PK analysis.

Safety: The primary safety endpoint was the incidence of adverse events (AEs) upon administration of zalutumumab in combination with RT.

The secondary safety endpoints were:

- Skin rash (Common Terminology Criteria of Adverse Events [CTCAE] grading, onset, and duration)
- Incidence of acute and late radiation toxicities
- Host immune response: human anti-human antibodies (HAHA)

Efficacy: The efficacy endpoints were:

- Objective tumor response (according to Response Evaluation Criteria in Solid Tumors [RECIST])
- Progression free survival (PFS), defined as the time from treatment allocation until disease progression (based on tumor response evaluation according to RECIST) or death
- Overall survival, defined as the time from treatment allocation until the date of death from any cause

Pharmacokinetics: Pharmacokinetic endpoints evaluated were maximum concentration of zalutumumab in plasma (C_{max}), concentration of zalutumumab before infusion (C_{trough}), and time to maximum concentration (T_{max}).

Statistical Methods:

Analysis population: The full analysis population (FAS) comprised all subjects who were exposed to zalutumumab irrespective of the compliance to the planned course of treatment. The safety analysis population was identical to the FAS.

No per protocol analysis was defined because of the low number of subjects in each treatment cohort and because the

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primary objective of the study was to investigate the safety profile of zalutumumab.

Statistical analysis:

Analysis of primary safety endpoints:

- Adverse events were coded by using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 12.1. All AEs are included in listings. The number of events, number of subjects, and percentage of subjects reporting these events are summarized by treatment cohort, system organ class (SOC), and preferred term (PT) for:
  - Pretreatment AEs
  - Treatment-emergent AEs (TEAEs) and TEAEs related to zalutumumab
  - Serious TEAEs, serious TEAEs with an onset date within 30 days after the last infusion, and serious TEAEs related to zalutumumab
  - TEAEs with CTCAE grade 3, grade 4, and grade 3 or 4 and TEAEs with CTCAE grade 3, grade 4, and grade 3 or 4 related to zalutumumab
  - TEAEs related to RT
  - Serious TEAEs related to RT
  - Nonserious TEAEs with CTCAE grade 3 and nonserious TEAEs related to zalutumumab with CTCAE grade 3
  - TEAEs leading to withdrawal from treatment and TEAEs leading to skipped infusion
  - Fatal TEAEs and fatal TEAEs related to zalutumumab
  - Infusion-related TEAEs related to zalutumumab occurring on any infusion day
- Early radiation toxicity was defined as AEs with the following PTs: mucosal inflammation, stomatitis, laryngitis, pharyngitis, radiation mucositis, radiation skin injury, stomatitis radiation, dry mouth, dysphagia, and dermatitis.

Analysis of secondary endpoints:

- Blood and urine samples were taken for central laboratory evaluations of hematology, biochemistry, and urinalysis. Urine samples were obtained at Visits 1 and 11. Blood samples were drawn at Visits 1, 3, 5, 7, 9, and 11. All samples were shipped to a central laboratory for analysis.
- Skin rashes, graded according to the CTCAE, and duration of the skin rashes are listed and summarized by using appropriate descriptive statistics.
- Blood samples for HAHA assessment were drawn at Visits 2 and 11.

Analysis of PK endpoints: The following PK endpoints were calculated for each patient after the first infusion and the last infusion: C_{max}, C_{trough}, and T_{max}.

Analysis of efficacy endpoints:

- Objective tumor response, evaluated according to RECIST, is listed by treatment cohort, subjects, visit, and weeks since first dose. The number of subjects achieving complete response, partial response, stable disease and progressive disease based on best overall response (from screening until disease progression/recurrence), evaluated according to RECIST, are summarized by treatment cohort and overall.
- PFS was estimated by using Kaplan-Meier estimates.

Categorical data are presented as frequency counts. Continuous non-PK data are summarized by using the number of subjects (n), mean, standard deviation, median, and minimum and maximum values while continuous PK data are summarized by using the number of subjects (n), geometric mean, coefficient of variation, and minimum and maximum values. Demographics (gender, race, age, height, weight, and body mass index [BMI]) are summarized by treatment cohort and overall. Medical history, including disease-specific history, concomitant medications, and exposure to treatment are summarized by treatment cohort and overall. Abnormal findings in physical examination, clinical examinations, and vital sign measurements are listed. Vital sign measurements are displayed graphically. Laboratory safety (biochemistry and hematology) data are graded according to the CTCAE, version 3. A summary of the worst CTCAE grade below and above normal range is presented by treatment cohort and overall. A summary of change from baseline is provided. All analyses were performed by using SAS version 9.2 or higher.

SYNOPSIS (CONTINUED)

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SUMMARY - CONCLUSIONS

DISPOSITION OF STUDY POPULATION: A total of 9 subjects were screened for enrollment in this study. Of the 8 subjects who were enrolled, 6 subjects completed Visits 1 through 11. Two subjects were withdrawn from the Treatment or Follow-up Period for the following reasons: AE and death for 1 subject each in the 8 mg/kg treatment cohort. One of the subjects withdrawn from the Treatment or Follow-up Period returned to participate in the Extended Follow-up Period. Subjects did not complete the Extended Follow-up Period because of the following reasons: termination of the study (3 subjects each in the 4 and 8 mg/kg treatment cohorts) and deterioration of trial disease (1 subject in the 8 mg/kg treatment cohort). Three subjects in the 8 mg/kg treatment cohort were withdrawn from treatment: 2 subjects because of an AE and 1 subject for an "other" reason.

DEMOGRAPHICS OF STUDY POPULATION: Subjects were enrolled at 5 sites in 2 countries: 4 subjects at 3 sites in France and 4 subjects at 2 sites in the United Kingdom.

The majority of subjects was male (7/8 subjects) and all were white. The overall median age was 72.5 years (range: 43 to 81 years), and the median BMI was 25.35 kg/m^2 (range: 19.8 to 33.1 kg/m^2).

A diagnosis of SCCHN had recently been made for these subjects, with the primary tumor located in the oral cavity, oropharynx, or larynx for 2 subjects each. The majority of subjects (7/8 subjects) had Stage IVa cancer at the time of diagnosis.

SAFETY RESULTS: Over half of the subjects (5/8 subjects) received 8 infusions of zalutumumab as specified by the protocol. The median total dose of zalutumumab was 2796.0 mg and 3388.0 mg for the 4 mg/kg and 8 mg/kg treatment cohorts, respectively. All but 1 subject received RT as specified in the protocol: a total dose of 70.0 Gy delivered in 35 fractions of 2.0 Gy per fraction at a rate of 5.0 fractions per week.

Most of the 94 TEAEs reported were expected effects during treatment with zalutumumab and RT. Over one-third of the TEAEs were judged by the investigator to be related to zalutumumab and more than half were judged to be related to RT. A number of events were judged to be related to both zalutumumab and RT. The most common of these (2 events each) were skin infection in the 4 mg/kg treatment cohort and mucosal inflammation in the 8 mg/kg treatment cohort.

Most TEAEs were CTCAE grade 1 or 2. There was 1 CTCAE grade 5 (fatal) TEAE, 1 CTCAE grade 4 TEAE, and 34 CTCAE grade 3 TEAEs. The CTCAE grade 4 and 5 TEAEs were reported by subjects in the 8 mg/kg treatment cohort. A total of 24 CTCAE grade 3 TEAEs were reported by subjects in the 8 mg/kg treatment cohort.

During the study, there was 1 death, which resulted from an SAE of mucosal inflammation. This SAE was judged by the investigator to be related to zalutumumab, and the death occurred [redacted] days after the subject's last infusion with zalutumumab. Five subjects reported a total of 9 SAEs. Of these 9 SAEs, 7 events were reported by 3 subjects in the 8 mg/kg treatment cohort. Five SAEs, reported by 2 subjects in the 8 mg/kg treatment cohort, were judged by the investigator to be related to zalutumumab.

Overall, the incidence of radiation toxicity TEAEs was 100% across the 2 treatment cohorts. Higher doses of zalutumumab appear to potentiate the adverse effects of RT; this appearance was supported in this study by the observation that TEAEs of mucosal inflammation were seen in all 5 subjects in the 8 mg/kg treatment cohort and only 1 subject in the 4 mg/kg treatment cohort. Three radiation toxicity TEAEs were reported as SAEs: 2 events of stomatitis reported by 2 subjects in the 4 mg/kg treatment cohort and 1 event of mucosal inflammation reported by 1 subject in the 8 mg/kg treatment cohort. Dose-limiting toxicities (mucosal inflammation and confusional state) were reported only by subjects in the 8 mg/kg treatment cohort.

One CTCAE grade 5 acute toxicity of mucosal inflammation was reported. There were no CTCAE grade 4 acute toxicities reported during the study. CTCAE grade 3 acute toxicities were primarily seen for the organs of skin, mucous membranes, and pharynx. The most severe late toxicity was a CTCAE grade 4 toxicity of the mucous membranes seen in 1 subject in the 8 mg/kg treatment cohort. There were no CTCAE grade 3 late toxicities. CTCAE grade 2 late toxicities were primarily seen in the salivary glands and xerostomia.

No subjects developed positive HAHA titers during the study. Overall, there were no remarkable safety signals in clinical laboratory results, physical examination findings, and vital sign measurements.

Although the number of events per subject was slightly lower for subjects in the 8 mg/kg treatment cohort compared with that for subjects in the 4 mg/kg treatment cohort, the incidence of CTCAE grade 3 or higher TEAEs, SAEs, and DLTs

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increased for subjects in the 8 mg/kg treatment cohort. CTCAE grade 4 and 5 TEAEs (1 of each) were reported only in subjects in the 8 mg/kg treatment cohort and were considered to be DLTs. Based on these findings, the IDMC recommended enrolling 3 additional subjects at the 8 mg/kg dose level. However, the sponsor adopted a more conservative approach and enrolled 3 subjects at the reduced dose level of 4 mg/kg. No DLTs were observed at this dose level, thus the MTD was not established.

EFFICACY RESULTS: Efficacy of the combination of zalutumumab and RT was assessed in an exploratory fashion by evaluating objective tumor response, overall survival, and PFS. Overall, 7 out of the 8 subjects had a complete or partial response to treatment with zalutumumab and RT. Because of the small number of subjects in each treatment cohort, the majority of whom were censored, overall survival and PFS estimates were not very informative in this study.

PHARMACOKINETIC RESULTS: The PK profile of zalutumumab in plasma was evaluated in this study and was as expected. The C_{max} values show dose-proportionality at both Visits 2 and 9. The C_{trough} values for the 8 mg/kg treatment cohort show a marked increase over time through Week 4, which may indicate that achieving a steady state takes a longer time at this higher dose level compared with the 4 mg/kg dose level. This delay in achieving steady state is most likely because of a longer elimination half life at the higher dose level.

CONCLUSION: In subjects with late-stage or locally advanced SCCHN who were ineligible for platinum-based chemotherapy, administration of 8 mg/kg of zalutumumab in combination with RT resulted in the observation of 2 SAEs judged by the sponsor to be related to zalutumumab: 1 event of CTCAE grade 5 mucosal inflammation and 1 event of CTCAE grade 4 confusional state following a CTCAE grade 3 lung infection. Dose-limiting toxicities were defined for this study as any treatment-related AE assessed as CTCAE grade 4 or higher. The IDMC established for this study found that, although these SAEs were obviously also related to RT, the events fulfilled the criteria for being declared DLTs.

[redacted]

Overall, the safety data reveal that 8 mg/kg of zalutumumab in combination with RT in this population who are ineligible for platinum-based chemotherapy is more toxic than the 4 mg/kg dose level as evidenced by a higher incidence of CTCAE grade 3 TEAEs in the 8 mg/kg treatment cohort compared with that in the 4 mg/kg treatment cohort and the observation of CTCAE grade 4 and 5 TEAEs in the 8 mg/kg treatment cohort compared with none in the 4 mg/kg treatment cohort.

It can be concluded that the dose level of 4 mg/kg of zalutumumab in combination with RT in subjects with late-stage or locally advanced SCCHN who are ineligible for platinum-based chemotherapy (ie, a high-risk population) is well tolerated, the adverse effects reported during treatment with 4 mg/kg seem manageable, and the criteria for the stopping rules were not met at this dose level. The MTD, however, has not been established and the safety profile observed does not preclude the increase of the dose level to 6 mg/kg of zalutumumab. This study was terminated after 8 subjects were enrolled and treated in Cohorts 1 and 2 without testing the 6 mg/kg dose level. The sponsor has re-evaluated the indications of zalutumumab within SCCHN and decided not to pursue development of zalutumumab within this disease area.

Date of the report: 11 July 2011