2. STUDY SYNOPSIS

Name of Sponsor/Company: **Genmab A/S**	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product: **zalutumumab**		
Name of Active Ingredient: **zalutumumab**		

Title of study:

An Open-label Single-arm Trial Investigating Zalutumumab, a Human Monoclonal Anti-EGF-receptor Antibody, in Combination with Best Supportive Care, in Patients with Non-curable Squamous Cell Carcinoma of the Head and Neck who have Failed Standard Platinum-based Chemotherapy

Principal Investigator:

[redacted], MD
[redacted]
USA

Study centre(s):

A total of 57 centers were initiated in 12 countries in the USA, Europe and rest of the world.

Publication(s):

None.

Study period:	**Development Phase:**
03 Jan 2008 to 31 Aug 2011	Phase II

Objectives:

Primary Objective:

To investigate zalutumumab in combination with best supportive care (BSC) in terms of overall survival (OS) in non-curable patients with recurrent and/or metastatic disease who have failed after at least one course of standard-based chemotherapy.

Secondary Objectives:

To investigate zalutumumab in combination with BSC with respect to efficacy and safety, and to determine the pharmacokinetic (PK) profile of zalutumumab.

Methodology:

This was a phase II, open-label, single arm trial in patients with non-curable squamous cell carcinoma of the head and neck (SCCHN) who had failed standard platinum-based chemotherapy. No randomization was performed in this trial. However if patients were eligible for the study then they were assigned a patient number at Visit 2 and this was referred to as the 'randomization date' in some source outputs.

Following screening (Visit 1), eligible patients received weekly infusions of zalutumumab in combination with BSC on an outpatient basis. The treatment was initiated with a loading dose of [redacted] (Visit 2). Hereafter, the dose was [redacted] and individual dose titration based on skin rash evaluation was performed during the entire treatment period in increments of [redacted] up to a maximum of 16 mg/kg. To give guidance for the grading of the skin rash, a skin rash manual with photographs was provided to all study sites. The treatment period was continued until death, disease progression, other illness, or unacceptable toxicity prevented the patient from receiving further treatment (investigator decision), or until the patient's decision to withdraw from treatment.

Patients withdrawn from the treatment period entered a follow-up period and were subsequently seen within 2 weeks for tumor evaluation (if not performed within the last 4 weeks) and quality of life (QoL) assessment (where performed prior to removal in protocol Amendment 3 due to lack of a comparator arm). After completion of the follow-up visit, patients were included in the extended follow-up period and received

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observational contact every 4 weeks for survival, serious adverse events (SAEs), and concomitant anti-cancer treatment, including radiotherapy.

Tumor evaluation, with computerized tomography (CT) scan or magnetic resonance imaging (MRI), and QoL assessment (where performed prior to removal in protocol Amendment 3 due to lack of a comparator arm) was performed every 8 weeks. Response evaluation according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline was performed centrally by an independent review committee.

An independent data monitoring committee (IDMC) was established to assess patient safety and mortality at monthly intervals during the trial. The members were informed by corporate Drug Safety about any emergent safety signal at any time and as required throughout the trial.

Number of patients (planned and analyzed):

It was planned that 100 patients would be enrolled at approximately 70 sites. Inclusion of patients to the study was closed on 08 April 2011 when 90 of the planned 100 patients had been enrolled. The early termination of the study was due to reprioritization of the EGFr-project. Of the 90 patients enrolled, all received zalutumumab.

Diagnosis and main criteria for inclusion:

The patients must have been ≥18 years of age (except for in countries required to be ≥19 years of age for adult participation in a clinical trial) and have given informed consent. Patients had a histological or cytological confirmed diagnosis, initially or at relapse of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx, considered incurable with standard therapy.

The patients must have failed at least one course of standard platinum-based chemotherapy.

- One course of standard platinum-based chemotherapy was defined as at least two cycles of cisplatin (≥60 mg/m²/cycle) or carboplatin (≥250 mg/m²/cycle). The interval between the cycles should have been less than or equal to 4 weeks (dose-intensity ≥15 mg/m^2/week for cisplatin and ≥62 mg/m²/week for carboplatin).
- Platinum-based chemotherapy may have been given as monotherapy or in combination with other chemotherapy including fluorouracil (5-FU) and/or radiation.

Failure was defined as (a) refractory or (b) intolerant to standard platinum-based chemotherapy as follows:

a) Refractory is defined as disease progression according to RECIST during one course of standard platinum-based chemotherapy or within 6 months after completion of one course of standard platinum-based chemotherapy given as treatment of
   - non-metastatic disease -with curative intention
   - metastatic disease
   - relapsed disease not amenable for curative intervention
b) Intolerant was defined as discontinuation of one course of standard platinum-based chemotherapy due to side effects/toxicity irrespective of response

To be eligible for the trial, patients must have had disease progression according to RECIST documented from two CT scans or MRIs; one taken prior to and one taken within 6 months after standard platinum-based chemotherapy. The scan/image taken at the screening visit for this trial may have served as the post-treatment scan/image if this remained within 6 months following standard platinum-based chemotherapy.

- A CT scan/MRI taken as part of clinical practice and according to the defined standards up to 28 days before Visit 2 could be used as the screening scan/image.
- If more than 28 days passed until Visit 2, a new CT scan/MRI must have been taken before

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treatment was initiated to have the necessary baseline information.

A patient must have had measurable disease defined as one or more target lesions according to RECIST based on CT scan or MRI performed at screening. The patients must have had performance status ≤2 according to the World Health Organization (WHO) and an expected survival of >3 months.

The patients must not have been treated with more than two prior chemotherapy regimens (other than platinum-based chemotherapy). Prior exposure to epidermal growth factor receptor (EGFr) antibodies and/or EGFr small molecule inhibitors was not allowed unless given as first line treatment of locally or regionally advanced SCCHN in combination with chemotherapy and/or radiotherapy. Exposure to EGFr targeted therapy must have been completed ≥ 6 weeks prior to Visit 2.

Test product, dose and mode of administration, batch number:

Zalutumumab (batch numbers PD06179, PDO7020, GEHF01 and GEKC01) administered by weekly i.v. infusion through a 0.2 μm inline filter after dilution in pyrogen-free 0.9% sodium chloride. Zalutumumab was formulated at 20 mg/mL adjusted to pH 6.0 and supplied in 6 mL glass vials. Each vial contained 5 mL of zalutumumab (20 mg/mL), i.e. a total of 100 mg zalutumumab.

Duration of treatment:

The treatment period was continued until death, disease progression, other illness, or unacceptable toxicity prevented the patient from receiving further treatment (investigator decision), or until the patient's decision to withdraw from treatment. Patients already in the extended follow-up period were withdrawn on 08 April 2011 on termination of the study. Patients enrolled before 08 April 2011 continued with the treatment and follow-up period according to protocol.

Reference therapy, dose and duration of administration, batch number:

Not applicable.

Criteria for evaluation:

Efficacy:

Primary Endpoint

The primary endpoint was OS defined as the time from start of treatment (Visit 2) until date of death from any cause. For patients who were alive at the time of analysis, withdrew from the study, or who were lost to follow up, OS was censored with the date of censoring as the last date documenting survival status.

Secondary endpoints

- Objective tumor response (according to RECIST)
- Duration of response
- Time to progression (TTP) defined as the time from start of treatment until disease progression
- Progression free survival (PFS) defined as the time from start of treatment until disease progression or death.

Pharmacokinetics: Serum samples were drawn from all patients at all visits and 6 weeks following the last dose of zalutumumab, for analyses of zalutumumab concentrations. At Visit 2 and subsequently every fourth infusion, a more extended PK sampling was performed to include pre- and 1-hour post-infusion blood collections. The pharmacokinetic parameters to be measured were AUC, $AUC_{0\ 168h}$, CL, C_{max}, C_{min}, and $T_{½}$

Pharmacodynamics: Not applicable.

Safety: Adverse events **(**AEs), clinical laboratory parameters (biochemistry, hematology and urinalysis), physical examination, pregnancy test, electrocardiogram (ECG), vital signs, skin rash (morphology, common terminology for categorization of AEs [CTCAE] grading, duration), and host immune response (Human Anti-

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Human Antibodies [HAHA]) were evaluated. An IDMC was used to assess emergent safety signals occurring at any time throughout the trial and to monitor patient safety and mortality at monthly intervals.

Statistical methods:

The **Full Analysis Set (FAS)** was based on the intent-to-treat principle and thus comprised all patients. It was used for evaluation of all endpoints. It comprised all patients attending Visit 2 irrespective of their compliance to the planned course of treatment.

The **Per Protocol (PP**) analysis population was a subset of the FAS population. Patients were classified as PP patients or not, prior to the time when the data were declared clean and the database released. The PP population was used to evaluate the robustness of the primary endpoint of OS.

The **Safety Analysis** population was used for all safety endpoints and was identical to the FAS.

Primary Endpoint

OS was estimated using Kaplan-Meier estimates which were plotted with corresponding two-sided 95% confidence intervals (CIs) based on Greenwood estimates of variance. The number of deaths and number of censored observations (including a summary of reasons) was presented together with quartile and median survival times with corresponding two-sided 95% CIs based on the Kaplan-Meier estimates.

In addition, OS was estimated using the Kaplan-Meier approach for baseline WHO Performance status (PS) (0-1 or 2) and various other demographic and baseline characteristics as detailed in Section 6.6 of the statistical analysis plan (SAP). In addition, the influence of fluorescence in situ hybridization (FISH) EGFr positivity, HER-2 FISH positivity, and EGFr expression on OS was examined in exploratory analyses.

SUMMARY OF RESULTS

Demography

A total of 151 patients were screened for the study and 112 were eligible to receive open-label study medication. A total of 90 patients received zalutumumab and constituted the FAS population; 69 had a baseline WHO PS status of 0-1 and 21 had a baseline WHO PS status of 2. The majority of patients were white (81%), male (80%) and <65 years of age (78%), with a mean age of 59 years.

The most common location of the primary tumor was the oral cavity (38 patients, [42%]). The SCCHN staging of the patients showed that 7% of the patients had stage I disease, 4% stage II, 10% stage III and 78% stage IV; one patient having a missing stage. The most frequently occurring tumor, nodes, metastasis (TNM) classification was T4/N2/M0 (21% of patients). These characteristics were consistent with the population under study.

The majority of patients (61%) had duration of disease ≤24 months with a median duration of 19 months (range 6-180 months).

At baseline, 23% of patients had WHO PS 2 and 74% had distant relapse metastases. The median time since a recent recurrence or progression of SCCHN was 1.0 months and was 6.4 months since time of first recurrence/progression.

EFFICACY RESULTS:

Primary Endpoint

The results of the analysis of the primary endpoint of OS in the FAS (defined as the time from start of treatment [Visit 2] with zalutumumab + BSC until date of death from any cause) showed the median OS was 5.3 months (95% CI [4.1, 7.1]). There were 76 (84%) deaths in the study. Of the 14 (16%) censored patients, three patients were censored due to patient refusal, two patients were lost to follow-up, and nine patients were censored due to the early termination data cut-off on 08 April 2011 resulting in study end on 31 August 2011.

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The median OS time (95% CI), was shorter for patients with baseline WHO PS 2 compared with WHO PS 0-1 (2.5 months [2.2, 4.1] for WHO PS 2 compared with 6.3 months [5.0, 8.6] for WHO PS 0-1).

	WHO PS 0-1 N=69	WHO PS 2 N=21	Total N=90
Overall Survival, n (%)			
Censored	13 (19)	1 (5)	14 (16)
Death	56 (81)	20 (95)	76 (84)
Reason for Censoring, n (%)			
Data cut-off	8 (62)	1 (100)	9 (64)
Lost to follow-up	2 (15)	0	2 (14)
Patient refusal	3 (23)	0	3 (21)
Quartile, Months [95% CI]			
25%	3.1 [2.5, 5.0]	2.2 [1.3, 2.4]	2.5 [2.2, 3.3]
Median	6.3 [5.0, 8.6]	2.5 [2.2, 4.1]	5.3 [4.1, 7.1]
75%	11.2 [8.6, 13.0]	4.5 [2.8, 10.8]	10.4 [8.5, 12.0]

Descriptive statistics based on Kaplan-Meier estimation method

Secondary Endpoints

In the analysis of the best overall tumor response in the FAS, a complete response was observed in one (1%) patient and a partial response in four (5%) patients. The response rate was 5.7% (95% CI [1.9%, 12.8%]) and disease control rate was 39.8% (95% CI [29.5%, 50.8%]). Analyses by performance status at baseline showed generally similar results for complete and partial response and stable disease, as reflected in similar disease control rates between the two groups. A higher proportion of patients with baseline WHO PS 0-1 had progressive disease than those with WHO PS 2 (42% compared with 24%, respectively).

The median time to PFS was 8.6 weeks (95% CI [8.0, 10.4]) and was similar in all patients regardless of their baseline performance status; 8.3 weeks (95% CI [8.0, 11.6]) in those with a WHO PS of 0-1 and 9.6 weeks (95% CI [8.0, 11.0]) in those patients with a WHO PS of 2.

PHARMACOKINETIC RESULTS:

The patients had individual dosing regimens and correspondingly different PK-profiles. Accumulation of study drug was seen in most patients. The highest concentration of EGFr in serum was 1242 mg/L measured on infusion number 13 in a patient on 16 mg/kg.

PHARMACODYNAMIC RESULTS:

Not applicable

SAFETY RESULTS:

All 90 patients received at least one infusion of zalutumumab (median 9 infusions [range 1 to 87]) with a median duration of exposure of 8.1 weeks (range 0.1 to 89.3). In total, 69% of patients were escalated by one dose level (to 12 mg/kg). However, only half of the patients received the top dose of 16 mg/kg.

A summary of AEs is presented below. All 90 patients had at least one AE and experienced a total of 1006

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events. The incidence of AEs was largely attributable to rash (76%) and disease progression (64%). Hypomagnesemia, fatigue, dyspnea and pyrexia were also observed for ≥20% of patients (23%, 21%, 21%, and 20%, respectively). The most frequently occurring related AEs were rash (74%) and hypomagnesemia (23%) with skin fissures, pruritus, pyrexia, fatigue, mucosal inflammation, asthenia, vomiting, nausea, diarrhea, paronchia, folliculitis and headache all occurring in >5% of patients.

	Zalutumumab + BSC N = 90		
	n	(%)	E
AEs	90	100	1006
Related AEs	79	88	385
SAEs	83	92	152
Related SAEs	10	11	11
AEs grade ≥ 3	85	94	184
AE leading to withdrawal	33	37	37
Deaths	76	84	76

Abbreviations: BSC = best supportive care; E = number of AEs; N = number of patients in safety population; n = number of patients with AEs.

The majority of the 76 deaths during the study were due to disease progression (59%). Two deaths (cardiac arrest and respiratory acidosis) were deemed related to zalutumumab. One of these patients had a relevant medical history of myocardial infarction and was concurrently being treated for myocardial ischemia and dyslipidemia. The other patient had concurrent pleural effusion and hypomagnesemia and developed respiratory acidosis 13 days after the latest dose of zalutumumab.

In addition to the two patients who died following related AEs, a further eight patients had SAEs related to zalutumumab. Half of these SAEs were due to hypomagnesemia with the remaining four SAEs due to infusion-related reaction, rash, hypokalemia and renal tubular disorder.

The majority of AEs leading to withdrawal (17/33 [52%]) were due to disease progression.

Skin rash grade 2 or 3 as clinical biomarker of EGFr activity was achieved in 45% of patients. One patient experienced a related skin rash grade 4 that led to a skipped infusion and resolved in 16 days.

A total of five patients had grade 3 or 4 laboratory values of hypomagnesemia of which none had additional cardiac SAEs. Low sodium and potassium levels (grade 3 or 4) were reported for seven patients (8%) and four patients (4%), respectively. A total of 31 patients (34%) and five patients (6%) had low (grade 3 or 4) lymphocyte and hemaglobin values, respectively. No other significant changes were observed for laboratory parameters or vital signs.

There were no positive confirmations of HAHA.

CONCLUSIONS:

- The median (95% CI) OS was 5.3 months (4.1, 7.1). A longer median (95% CI) OS was observed for patients with a baseline WHO PS 0-1 compared with those patients with a poorer baseline prognosis of WHO PS 2 (6.3 months [5.0, 8.6] versus 2.5 months [2.2, 4.1], respectively).
- Secondary endpoints showed consistent results across both subgroups of patients based on baseline WHO PS.
- The EGFr concentrations in serum were consistent with the variable dosing regimen. The highest

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concentration seen was 1242 mg/L.

- The safety profile observed for zalutumumab, individually dose-titrated to rash, was as expected within the drug class.
- A total of five patients had grade 3 or 4 laboratory values of hypomagnesemia of which none had additional cardiac SAEs. Low potassium levels (grade 3 or 4) were reported in four patients (4%).
- The applied dosing regimen was feasible with 69% of patients being escalated. The finding of only one grade 4 rash indicates that the pausing procedures in case of grade 3 rash are generally effective in preventing progression to more severe reactions.

Date of the report: 07 February 2012