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STUDY TITLE:
A single arm, open-label multicenter phase II trial of temsirolimus in patients with relapsed/recurrent squamous cell cancer of the Head and Neck (HNSCC)

INFORMATION ABOUT STUDY PROTOCOL VERSION(S):
First submission: protocol version 1.7, date 19.11.2009
Subsequent substantial amendments: protocol version 1.8, date 28.07.2011

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STUDY CENTRE(S):
7 study centers in Germany enrolled patients.

FUNDING SOURCE: Wyeth Oncology Europe, Ltd. (Pfizer Limited, UK)

PUBLICATION(S): Not applicable

STUDY PERIOD:	**PHASE OF DEVELOPMENT:**
12 JUL 2010 – 09 MAY 2012 **INFORMATION ABOUT TEMPORARY HALT(S) AND PREMATURE TERMINATION OF THE TRIAL:** Not applicable	II

OBJECTIVES:
The objective of the study was to determine the efficacy and safety of 25 mg i.v. temsirolimus given once weekly in patients with relapsed or recurrent HNSCC after failure of platinum and cetuximab-based regimens.

METHODOLOGY:
This was an open-label, multicenter, single arm, non-randomized, single stage phase II study.
Screening phase: Baseline evaluations were performed within 2 weeks before the first dose of the study drug.
Treatment phase: All patients received temsirolimus 25 mg i.v. weekly until disease progression (by RECIST) or unacceptable toxicity or study discontinuation for other reasons. A treatment cycle consisted of 3 weeks. Dose reductions and dose interruptions for up to 2 weeks were allowed for intolerable toxicity.

NUMBER OF PATIENTS:
Planned Sample Size: 40 patients were planned to be included.
Actual Sample Size: Of 42 patients screened, 40 patients were eligible and followed up. At least 1 CT scan and status "progression or death" were available for 29 patients.

DIAGNOSIS AND MAIN INCLUSION/EXCLUSION CRITERIA:
Main Inclusion Criteria:

- Signed written informed consent had to be given prior to study inclusion
- Histological or cytological confirmed recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC)

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- Measurable progressive disease after platinum-based radiochemotherapy
  OR Recurrence or metastatic progressive disease after first-line platinum-based chemotherapy
- Patients with locoregional recurrence had to be progression-free for at least 6 months after platinum-based radiochemotherapy if locoregional recurrence was the only lesion
- Cetuximab must have been included in at least one prior line of therapy
- Prior exposure to a taxane was permitted
- Disease was not to be amenable to surgery, radiotherapy or platinum-based chemotherapy
- At least one measurable lesion according to Response Evaluation Criteria In Solid Tumors (RECIST, Version 1.0)
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Brain metastases required completion of local therapy with discontinuation of steroids prior to start of treatment
- If of childbearing potential, willingness to use effective contraceptive method (double barrier method) for the study duration and 2 months after last dose
- Willingness and ability to comply with the protocol
- Adequate bone marrow function, liver and renal function

Main Exclusion Criteria:

- Life expectancy less than 3 months
- Anticancer treatment during the last 30 days prior to start of treatment, including systemic therapy, radiotherapy or major surgery
- Participation in a clinical trial within the last 30 days prior to study treatment
- Serious illness or medical condition other than the disease under study
- Other malignancies within 3 years, with exception of HNSCC, history of a previous basal cell carcinoma of the skin or pre-invasive carcinoma of the cervix
- Inability to potentially complete follow up and treatment per protocol for psychological, familial, sociological or geographical reasons
- Pregnancy or breast feeding
- Known allergic/hypersensitivity reaction to any component of the treatment
- Concurrent treatment with oral anticoagulants
- Uncontrolled diabetes: fasting serum glucose > 2.0 upper limit of normal (ULN)
- Active or uncontrolled infection

TEST AND REFERENCE PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Temsirolimus was administered in 3-week cycles at 25 mg as i.v. infusions (30 minutes) once weekly. In the event of hematologic and other toxicities, the dose was reduced to 20 mg or 15 mg weekly or treatment was discontinued. The test drug was supplied by Wyeth Oncology Europe, Ltd. Batch numbers can be found in Appendix 16.1.6.

DURATION OF TREATMENT:

Total study duration including the follow-up period was estimated at 36 months; 12 patients (30.0%) completed treatment week 12.

CRITERIA FOR EVALUATION:

Primary Efficacy Endpoint

- Progression-free rate on treatment day 84 (12 weeks)

Secondary Efficacy Endpoints

- Time to progression
- Objective response rate (disease control rate [DCR]: complete response [CR] + partial response [PR] + stable disease [SD])

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- Overall survival
- Evaluation of predictive markers of tumor response in serum and tumor specimen

Secondary Safety Endpoints

- Physical and neurological examination
- Vital signs (pulse, blood pressure, temperature)
- Weight
- ECOG Performance Status
- Under suspicion of pulmonary toxicity concern pulmonary function analysis
- Common Terminology Criteria for Adverse Events (CTCAE) –Grading
- Adverse events and serious adverse events – continuously
- Complete Blood Count: leukocyte, neutrophil, and platelet counts, hemoglobin
- Serum Biochemistry: Sodium, potassium, calcium, phosphate, creatinine, triglycerides, cholesterol, fasting glucose, AST (SGOT), ALT (SGPT), total bilirubin, albumin, CK.
- Coagulation: aPTT, prothrombin time (PT)

STATISTICAL METHODS:

The primary endpoint was the progression-free rate after a treatment duration of 12 weeks, evaluated by RECIST. Temsirolimus was said to be of no interest if the true progression-free rate at 12 weeks was less than 5% and for sample-size calculation it was assumed that the true progression-free rate was 20% (albeit in a recent trial with cetuximab a response rate of 40% had been observed in an earlier stage of disease).

The null-hypothesis of this trial was, that the true probability for progression-free survival after 12 weeks would be less than or equal to 5%. For sample-size calculation it was assumed that the true progression-free rate at week 12 was 20 %. The type-1 error was set to 5% (two sided) and the study was planned to have 90% power to reject the null-hypothesis.

Under these assumptions and with a Fleming one-stage design 40 patients had to be included into the trial (the normal approximation to the binomial distribution was used here).

An interim analysis was planned and has been performed after 20 patients had been observed for 6 weeks. It was the aim to stop the trial for futility if amongst these 20 patients not at least one patient had achieved a progression-free survival of at least 6 weeks. If required, recruitment would have been stopped at that point in time until a decision could be made on whether the study should be continued, or not.

The type-1 error was not adjusted for this interim analysis as the sole purpose was to stop the trial for futility and definitely no positive conclusions could be taken from the trial at that point in time.

In the final analysis, a two-sided Wald 95% confidence interval (CI) was calculated for the progression-free survival rate after 12 weeks. The null-hypothesis had to be rejected if the lower boundary of this CI was larger than 0.05. This was equivalent to at least 7 of the 40 patients progression-free after 12 weeks. If 14 patients were progression-free after 12 weeks, the lower boundary of the CI would be larger than 20%.

The secondary endpoints were time to progression, objective response rate (by RECIST), overall survival and toxicity (evaluated by CTC 3.0). As for the primary endpoint, estimates and CIs were provided for the objective response rate.

Kaplan-Meier curves were used for the secondary endpoints time to progression and overall survival. The assessment of safety was based on the frequency of adverse events (AEs).

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SUMMARY – CONCLUSIONS

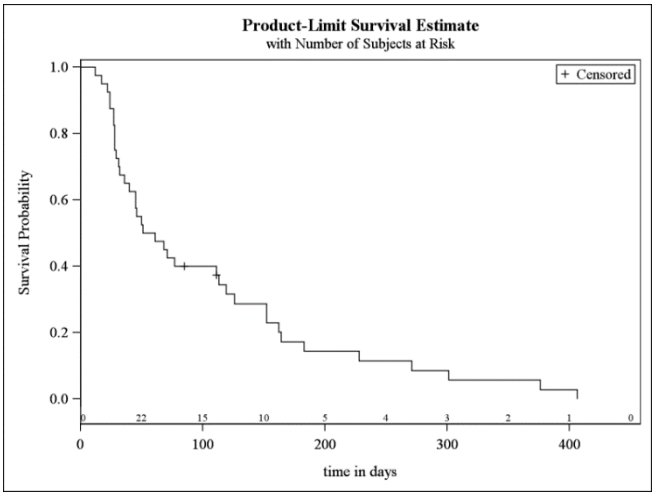
The study population consisted of 40 patients. All patients were Caucasian, most (31 patients, 77.5%) were men. The median age of the study population was 61.5 years, ranging from 42 to 79 years. At baseline, most (27) patients were assessed as ECOG Grade 1, 7 patients were Grade 0, 4 patients were Grade 2 (1 patient not assessed). The primary tumor was located in the oropharynx (15 patients), oral cavity (10), hypopharynx (5), larynx (5), and at other locations (5). Most patients had tumor T2 or T4, nodes N0, and M0 (no distant metastasis). Most (27) patients had 3 or more prior regimens of tumor therapy, 10 patients had 2 regimens, and 3 patients had 1 prior regimen.

Efficacy Results:

Primary and Key Secondary Efficacy Endpoints

Overall, 16 of 40 patients were at least stable, i.e. had no progression nor had died at week 12 (end of cycle 4); 10 patients were alive with progression, 3 patients died after progression, and 11 patients died before evaluation of progression. The progression-free rate estimated at week 12 was 40% (95% Wald CI: 25.0-54.6%; 95% CI using Greenwood's formula: 24.1-55.9%).

The median time to progression or death was 56 days (95% CI: 36-113 days). In a phase II trial of cetuximab administered to a similar population (Vermorken et al., 2007), the median time to progression on single-agent cetuximab was 70 days. Thus, temsirolimus showed clinical activity that was in the range of well established therapy of advanced HNSCC. The graph shows the Kaplan-Meier curve.



Secondary Efficacy Endpoints

The overall survival rate estimated at week 12 was 66% (95% Wald CI: 49.1-78.9%; 95% CI with a standard error using Greenwood's formula: 50.4-82.3%). The median survival time was 152 days (95% CI: 76-214 days).

No complete or partial response was achieved on treatment with temsirolimus. The DCR was 58% in cycle 2 (N=33) and increased to 77% in cycle 4 (N=17), which was solely due to stable disease as the best tumor response. The median change in tumor size was -4.2% in cycle 4. Thus, at the time of the primary endpoint, on average, the tumors tended to shrink.

Biomarkers analyzed failed to predict efficacy or prognosis.

Safety Results:

Of 40 patients treated with temsirolimus, treatment-emergent AEs were reported for all but one patient (97.5%). The most frequently reported AEs (all causality in >10% of patients) are given below:

	All grades	Grade 3	Grade 4

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Fatigue	19 (47.5%)	3 (7.5%)	1 (2.5%)
Anaemia	10 (25.0%)	6 (15.0%)	2 (5.0%)
Nausea	8 (20.0%)	0	0
Pneumonia	8 (20.0%)	3 (7.5%)	1 (2.5%)
Dyspnoea	7 (17.5%)	1 (2.5%)	0
Vomiting	7 (17.5%)	0	0
Infection	6 (15.0%)	2 (5.0%)	0
Weight loss	6 (15.0%)	0	0
Rash	6 (15.0%)	0	0
Pruritus	5 (12.5%)	0	0
Facial oedema	5 (12.5%)	0	0
Diarrhoea	5 (12.5%)	0	0
Stomatitis	5 (12.5%)	0	0

A total of 34 patients (85.0%) experienced AEs that were considered at least possibly related to study drug. The most common AEs assessed as at least possibly related were fatigue (37.5%), anaemia (22.5%), nausea (17.5%), and rash (15.0%).

The highest incidences of severe toxicity were anaemia (grade 3: 15.0% / grade 4: 5%), pneumonia (grade 3: 7.5% / grade 4: 2.5%), infection (grade 3: 7.5%), and fatigue (grade 3: 7.5%). The incidence of severe haematologic toxicity was rather low. Overall, the toxicity detected on treatment remained within expectations.

The most frequently reported serious adverse event (SAE) was pneumonia (5 patients, 12.0%), which is a known clinical problem in refractory HNSCC. The most frequently reported SAEs considered at least possibly related to study drug were pneumonia (3 patients, 7.5%) and anaemia (2 patients, 5.0%). None of the SAEs considered at least possibly related to study drug were unexpected.

A total of 11 patients died of SAEs. In 3 of these, a relationship between death and study drug could not be ruled out; the events with a fatal outcome were pneumonia (2 patients) and anaemia (1 patient).

There was no indication of clinically significant changes in laboratory parameters, and there were no clinically significant changes in vital signs or weight.

The safety profile observed in this study is consistent with the data presented in the current version of the Summary of Product Characteristics (SmPC).

Conclusions:

Patients with HNSCC who did not respond to platinum-based radiochemotherapy or first-line platinum-based chemotherapy were treated with temsirolimus in 3-week cycles at 25 mg i.v. The rate of progression-free patients at 12 weeks was 40% (95% CI: 25.0-54.6%); the median time to progression or death was 56 days (95% CI: 36-113 days). Temsirolimus showed clinical activity that was in the range of previously published data from a similar population treated with cetuximab (Vermorken et al., 2007), a current mainstay of therapy of advanced HNSCC.

Fatigue and anaemia were the most common AEs in this study, the incidence being 47.5% and 25%. The highest incidence of severe toxicity (grade 3 or 4) was observed for anaemia, pneumonia, infection, and fatigue. Pneumonia was reported as the most frequent SAE, which is a known clinical problem in refractory HNSCC. The toxicity observed in this study is consistent with the safety profile presented in the current SmPC. Temsirolimus 25 mg weekly thus continues to be a reasonably safe and tolerable therapeutic option in

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the treatment of HNSCC.

Date of the report:
05 AUG 2015