


TEMHEAD: a single-arm multicentre phase II study of temsirolimus in platin- and cetuximab refractory recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) of the German SCCHN Group (AIO)†


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Background: Squamous cell carcinoma of the head and neck (SCCHN) is a common disease, which has a poor prognosis after failure of therapy. Activation of the PI3K–AKT–mTOR axis is commonly detected in recurrent or metastatic SCCHN, and provided the rationale for the clinical phase II trial in pretreated SCCHN.

Patients and methods: The primary end point was the progression-free survival rate (PFR) at 12 weeks. Forty eligible patients have been recruited after failure of platinum chemotherapy and cetuximab. A preplanned futility analysis was successfully passed after ≥ 1 success was detected in 20 patients. Secondary objectives consisted of progression-free survival (PFS), disease control rate (DCR), overall survival (OS), safety and tolerability, and predictive biomarkers for KRAS, BRAF, PIK3CA mutations, and HPV status. Archived tumor tissue was analyzed for DNA sequence.

Results: A total of 40 patients were eligible. The PFF at 12 weeks was 40% (95% CI 25.0–54.6). The median PFS and OS were 56 days (95% CI 36–113 days) and 152 days (76–256 days), respectively. In 33 assessable patients, disease stabilization occurred in 57.6%, with tumor shrinkage in 13 patients (39.4%). Overall, the treatment was well tolerated. Fatigue (47.5%), anemia (25.0%), nausea (20.0%), and pneumonia (20.0%) were the most common adverse events.
Neither PIK3CA mutations, nor HPV status were predictive for success with temsirolimus treatment. No mutations were found for KRAS or BRAF.

**Conclusion:** Tumor shrinkage and efficacy parameter indicate that inhibition of the PI3K–AKT–mTOR axis was a putative novel treatment paradigm for SCCHN. We could not identify parameters predictive for treatment success of temsirolimus, which underscores the need for refinement of the molecular analysis in future studies.

**Clinical trials number:** NCT01172769.

**Key words:** squamous cell carcinoma of the head and neck, mTOR, temsirolimus, PI3KCA

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**introduction**

Squamous cell carcinoma of the head and neck (SCCHN) is one of the most common cancers worldwide, affecting more than 500,000 incident cases annually, with an overall survival (OS) of 26%–47% after 5 years in localized disease [1]. Human papilloma virus (HPV)-associated SCCHN was recently identified as a positive prognostic factor in localized disease [2]. However, its predictive and prognostic value in palliative treatment remains unknown so far.

Overall, many patients will relapse and require subsequent palliative chemotherapy. Platin combined with fluorouracil and cetuximab is considered the current standard of care for palliative chemotherapy. Platin combined with fluorouracil and cetuximab is considered the current standard of care for palliative chemotherapy. However, most patients will face tumor progression and subsequent therapies may be offered with limited clinical activity.

Mutations of the AKT–mTOR pathway have been detected in various studies at different levels within the signaling cascade of SCCHN. PIK3CA mutations have been reported in 11%–17% in SCCHN [4, 5]. In addition, alterations of AKT–mTOR regulators, such as phosphatase and tensin homolog deleted on chromosome 10 (PTEN) or tuberous sclerosis complex (TSC) may be found in 23% and 36%, respectively [6, 7]. mTOR activity may also be found in clinical specimens, supporting the notion that the AKT–mTOR pathway is crucial in the development of SCCHN [8].

We therefore hypothesized that mTOR is a putative driver of resistant disease in SCCHN and explored the role of the mTOR inhibitor temsirolimus in refractory and/or metastatic (R/M) SCCHN.

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**patients and methods**

**study design and patient population**

The TEMHEAD study was an open-label, multicenter, single-arm, non-randomized, (Fleming) single-stage phase II study, which tested the safety and efficacy of temsirolimus in R/M SCCHN after the failure of platin- and cetuximab-based therapies. The primary end point was the progression-free survival rate (PFR) at 12 weeks. Secondary end points assessed progression-free survival (PFS, defined as time to progression or death), disease control rate (DCR: complete or partial response + stable disease), OS, safety and tolerability, and predictive markers. Key eligibility criteria are listed in supplementary Material S1, available at Annals of Oncology online.

The study was conducted in accordance with the Declaration of Helsinki and GCP/ICH. The protocol was approved by institutional review boards and all patients provided written informed consent before study procedures.

**study treatment**

All patients received temsirolimus 25 mg as a weekly 30 min i.v. infusion until disease progression or unacceptable toxicity or study discontinuation for other reasons. Premedication with diphenhydramine was mandated according to local standards. A treatment cycle consisted of 3 weeks. Dose reductions and dose interruptions for up to 2 weeks were allowed in case of toxicity. Non-polyvinylchloride bags and tubing, including in-line filter (≤0.5 μm) were used. Monitoring of vital signs during the first infusion was mandatory.

**clinical assessments**

Complete blood count and serum chemistry were assessed every cycle. Tumor evaluation consisted of computed tomography (CT) or magnetic resonance imaging scan of the primary region and CT scans of the thorax and abdomen, which were carried out within 2 weeks before start of treatment and every 6 weeks thereafter. Tumor response was evaluated according to RECIST 1.0 [9]. Serum biomarkers were collected at baseline and day 1 of every cycle, and available tumor specimens at time of study inclusion, either primary or metastatic site. The assessment of safety was based on the frequency of adverse events (AEs) according to CTCAE 3.0.

**molecular assessments**

Tumor specimens were collected from 25 patients. Either formalin-fixed paraffin-embedded (FFPE) tumor blocks or unstained slides were considered eligible at study entry and were collected for molecular analysis. KRAS, BRAF, and PIK3CA mutations were assessed in FFPE archived tumor tissue by DNA sequencing. In addition, tumor specimens have been collected before study entry from previous procedures. Details are provided in the supplementary Material S2, available at Annals of Oncology online.

**statistical methods**

The aim of the study was to show a PFR ≥5% at 12 weeks. The true PFR after 12 weeks was 20%. The type-1-error was 5% (two-sided) and the power to reject H0 90%. Under these assumptions, a total of 40 eligible patients had to be included. For futility, at least one of the first 20 patients had to achieve PFS of at least 6 weeks for trial continuation.

A two-sided 95% Wald confidence interval (CI) was calculated for the PFR at 12 weeks. At least 7 of the 40 patients had to be progression free after 12 weeks to meet the primary objective. The intention-to-treat population was used for the final analysis. Patients without tumor assessment at 12 weeks were counted as progress.

The key secondary end point OS and PFS were analyzed using Kaplan–Meier estimates with corresponding 95% Greenwood CI for the 12-week time point. As a sensitivity analysis, the primary analysis was repeated with this approach. All analyses were conducted in SAS 9.3. Predictive biomarkers were correlated with efficacy outcome.

**results**

**patient characteristics and treatment delivery**

From July 2010 to July 2011, a total of 40 eligible patients were enrolled at 7 German study sites. Twenty-nine patients received at least one post-baseline tumor evaluation. Ten patients died before...
the first tumor evaluation and one patient was lost to follow-up early and failed to receive study treatment. A possible relationship to temsirolimus was considered in three of these patients (pneumonia in two and anemia in one). Twelve patients (30%) completed the 12-week treatment interval. Specimens from 25 patients have been available for molecular assessment.

Table 1 provides patient and disease characteristics of eligible patients. The majority of patients had primaries of the oropharynx or oral cavity and favorable performance status.

**efficacy**

A total of 16 patients were alive without progression at 12 weeks (40%). The PFR at 12 weeks was 40% (95% CI 25.0–54.6), with a corresponding median PFS of 56 days (95% CI 36–113 days). The survival rate after 12 weeks was 66% (95% CI 48.76% to 78.72%) and the median OS 152 days (76–256 days). At the end of the study, a total of 33 patients (82.5%) had died, 1 patient remained lost to follow-up and 6 patients were alive at last follow-up. No difference for PFS and OS between smoker and nonsmoker was detected within the study (data not shown).

**tumor shrinkage**

No objective response was achieved with temsirolimus. Stable disease (SD) remained the main treatment effect in 19 patients (47.5%). Ten patients (25%) had progressive disease (PD) as best response. There was no RECIST evaluation available for 10 patients (25%) due to early death and 1 patient (2.5%) was non-assessable.

Figures 1 and 2 depict the waterfall plot for overall changes of target lesions of 29 assessable patients. A total of 13 patients (32.5%) achieved tumor shrinkage, whereas 2 patients (5.0%) remained without changes (middle of the plot) and, in 14 patients (35.0%), a tumor growth was noted as best response. Of 13 patients with tumor shrinkage, 10 (76.9%) have been detected at first evaluation at 6 weeks with a mean tumor shrinkage of 9.7% (range: 2.8–16.3% for 6 weeks).

**safety**

Thirty-nine patients (97.5%) had experienced at least one, and 35 patients (87.5%) at least two AEs. AEs occurring in ≥10% of patients have been depicted in Table 2. Fatigue (47.5%), anemia (25.0%), nausea (20.0%), and pneumonia (20.0%) remained the most common AEs. Respectively, one patient (2.5%) experienced pneumonitis grade 1, fungal infection grade 2, or aspergillosis grade 2.

A total of 38 severe AEs (SAEs) occurred in 25 (62.5%) patients, of whom 9 patients (22.5%) had at least 2 SAEs. The most common SAEs were pneumonia in seven patients (17.5%), and anemia in two patients (5.0%). Two patients with pneumonia and one patient with anemia experienced a fatal event, which were probably related to temsirolimus treatment. The remaining eight fatal events were not considered related to treatment.

All patients discontinued therapy. Causes for discontinuation were disease progression in 23 (57.5%), SAE in 3 (7.5%), tolerability in 1 (2.5%), withdrawal of consent in 3 (7.5%), 2 (5.0%) lost to follow-up, death in 3 (7.5%), and unknown reasons in 5 (12.5%) patients.

**mutational analyses**

Of 40 eligible patients, 25 had accessible archived tumor tissue for sequencing. A total of 14 patients had SD and 8 patients PD as best response. Three patients died early. KRAS and BRAF were analyzed in 25 patients each, and 23 patients for PI3KCA. None of the patients showed mutations of KRAS or BRAF. H1048Y and G1050S PIK3CA missense mutations were found in one patient each and were associated with a PFS of 46 and 27 days, respectively. OS were 46 and 55 days, respectively. Median values were 37 days for PFS and 51 days for OS (supplementary Table S1, available at *Annals of Oncology* online). Both patients were nonsmokers.

**HPV-status of tumors**

Twenty-four patients were assessable for HPV DNA testing from archived tumor tissues. A total of four patients were positive for HPV DNA, of which three were genotype 16 and 1 genotype 33. Three of these patients were nonsmokers. HPV+ tumors were located in the oropharynx (n = 3) or oral cavity (n = 1). One patient with HPV16-positive oropharynx carcinoma was also positive for G1050S PIK3CA missense mutation. Median PFS was 29 days and OS was not reached in HPV+ tumors. However, HPV− tumors achieved a PFS of 74 days and an OS of 152 days (supplementary Table S1, available at *Annals of Oncology* online).
Alterations of the PI3K–AKT–mTOR axis have been frequently found in SCCHN. Mutation of PI3KCA has been detected in SCCHN, as well as mutations of TSC and PTEN, all of which are known to regulate mTOR activity and provide the rational to test temsirolimus in SCCHN [4, 6, 7, 10].

Our data show that mTOR inhibition exerts some efficacy in SCCHN. Despite the lack of objective responses, tumor shrinkage has been detected in 32.5%. PFS of 56 days and the OS of 152 days remain within the range of previous studies in later lines of therapy. Single-agent cetuximab achieved 70 days of time to progression and an OS of 178 days in patients after platinum failure [11], and similar results were achieved with the epidermal growth factor receptor (EGFR) inhibitor zalutumumab or placebo (OS of 6.7 and 5.2 months, respectively) [12]. However, none of these studies included patients after failure of EGFR inhibition, making cross-trial comparison with our study intriguing. The inclusion of patients with failure of platinum and an EGFR inhibitor may select for a more aggressive stage of the disease and lacks a proper clinical benchmark from other trials.

Additional data support our findings. Ekshyyan et al. has reported tumor shrinkage in a pharmacodynamic study of temsirolimus in localized SCCHN [13]. Similar results were reported for the combination of erlotinib and temsirolimus in recurrent or metastatic SCCHN [14]. However, the trial was closed prematurely because of toxicity. Preclinical models indicated improved efficacy from combination of mTOR inhibition and chemotherapy [15, 16]. A recent
trial reported on induction chemotherapy consisting of everolimus, carboplatin, and paclitaxel. A total of 21 patients has been treated and achieved a promising objective response rate of 81% [17]. Anecdotal evidence suggests that the combination of bevacizumab and temsirolimus may increase efficacy, indicating that mTOR inhibitors may serve as combination partner in SCCHN treatment [18]. Current studies explore the role of mTOR inhibitors in SCCHN, including studies addressing the value of a chemotherapy combination as induction therapy, a placebo-controlled adjuvant trial, or a combination of temsirolimus and cetuximab in the palliative setting. Future strategies of mTOR inhibitors in SCCHN may include combination regimens in localized disease [19].

A major drawback of current mTOR inhibitors has been conceived as the ability to block mTOR bound in mTOR complex 1 (MTORC1) only [20]. However, clinical data may not suggest that these biological effects jeopardize clinical outcome. In a recent randomized clinical trial, the dual kinase inhibitor GDC-098 yielded inferior PFS and OS compared with everolimus in renal cell carcinoma (RCC) [21]. Novel agents targeting the PI3K–AKT–mTOR axis are currently in clinical development in SCCHN and may help to elucidate the role of such agents in this disease.

We further explored the role of the mutational status in order to predict clinical outcome. Surprisingly, the incidence of mutations remained lower than anticipated (PIK3CA 8.7%) and showed no association with clinical outcome. Similar results have been recently presented for the combination of erlotinib and temsirolimus [14].

The sample size of our study remains small and cannot assess the role of PIK3CA as a predictive marker in SCCHN. Patients with mutations of PIK3CA had an inferior outcome, suggesting a possible prognostic role of such mutations. Furthermore, such mutations may require agents directly targeting the mutated PIK3CA gene.
site. Such agents directly inhibit the kinases of PI3K or mTOR, and, hence, are distinct from the mechanism of action of temsirolimus. Preclinical evidence suggests that direct kinase inhibition of PI3K exerts efficacy exclusively in PIK3CA-mutated SCCHN xenografts, underscoring its potential role in SCCHN [22]. These results have spurred the development of clinical trials in SCCHN with PI3K inhibitors, such as BKM120 or BYL719.

Loss of PTEN has been associated with the activation of the AKT–mTOR axis [23]. However, the predictive value of the PTEN status for mTOR inhibitors remains controversial. Loss of PTEN or PIK3CA failed to predict outcome in some neoplasias [24, 25]. However, alterations of TSC1 and mTOR were associated with long-term response to mTOR inhibitors in RCC and loss of PTEN was prominent in SCCHN responding to bevacizumab and temsirolimus [18, 26]. The heterogeneity of cancer cells may draw a more complex pattern of genetic alterations, and, hence, may require more than a single marker to predict outcome of mTOR inhibitors in the clinic.

Overall, treatment with temsirolimus was well tolerated and met expectations. Fatigue has been reported as the predominant AE, whereas pneumonia remained one of the most frequent SAE. A similar incidence of pneumonia was detected in our previous study [27].

In conclusion, our study is the first to report on mTOR inhibition in recurrent or metastatic SCCHN after failure of platinum and EGFR inhibition. Despite the principle cytostatic nature of temsirolimus, tumor shrinkage indicates clinical relevance. The magnitude of clinical efficacy detected, is within the range of historical treatment strategies, such as cetuximab.

The clinical efficacy of mTOR inhibition is likely to be tied to the targets’ activity. Patient selection and adequate detection of activating mutations is a key ingredient in drug development of targeted agents and warrants future studies. In our series, activating mutations were lower than anticipated and showed no association with efficacy. Larger studies are needed to elucidate the role of activating mutations and its predictive nature to mTOR inhibitors. Clinical expectations have launched a battery of clinical trials with novel compounds inhibiting the PI3K–AKT–mTOR axis in SCCHN.

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references


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Background: To report the results of the first European prospective nonrandomized trial dedicated to pediatric synovial sarcoma.

Patients and methods: From August 2005 to August 2012, 138 patients <21 years old with nonmetastatic synovial sarcoma were registered in 9 different countries (and 60 centers). Patients were treated with a multimodal therapy including ifosfamide–doxorubicin chemotherapy and radiotherapy, according to a risk stratification based on surgical stage, tumor size and site, and nodal involvement.

Results: With a median follow-up of 52.1 months (range 13.8–104.4 months), event-free survival (EFS) was 81.9% and 80.7%, and overall survival (OS) was 97.2% and 90.7%, at 3 and 5 years, respectively. The only significant prognostic variable at univariate analysis was the risk group: 3-year EFS was 91.7% for low-risk, 91.2% for intermediate-risk, and 74.4% for high-risk cases. In 24 low-risk patients (completely resected tumor ≤5 cm in size) treated with surgery alone, there were two local relapses and no metastatic recurrences. Among 67 high-risk patients (unresected, or axial tumor or nodal involvement), 66 underwent surgery after neoadjuvant chemotherapy. Response to chemotherapy was 55.2%, including 22.4% cases with complete or major partial remissions, and 32.8% with minor partial remissions.

Conclusion: This study demonstrates that collaborative prospective studies on rare pediatric sarcomas are feasible even on a European scale, with excellent treatment compliance. The overall results of treatment were satisfactory, with