Abstract 2861

Prospective multicenter phase II study of the anti-EGFR (epidermal growth factor receptor) antibody panitumumab (P) in patients with platinum pre-treated, advanced head and neck squamous cell cancer (HNSCC)

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Background

Anti-EGFR-Antibodies and especially cetuximab (C) were able to show activity in HNSCC pts. So far a regimen containing a platinum compound with 5-FU and cetuximab was the only one showing an overall survival (OS) benefit in selected pts. with advanced HNSCC as first line therapy.[1]

A large phase III randomized clinical trial, in the meantime published, tested the same combination but with P, not showing a significant OS benefit.[2]

Until now, no prospective phase II clinical trial has been completed and reported with P as monotherapy in pretreated HNSCC.

- Therefore, we performed a multicenter phase II study with the fully human anti-EGFR-antibody P, administered as a single agent in platinum-pretreated HNSCC patients (pts.) to assess safety and efficacy. (***Clinical Research Objectives***)
- The second objective of our trial was to perform a translational analysis of different tumor biomarkers and to explore whether there is a potential pattern, predictive for response as shown in other tumor entities susceptible to anti-EGFR-antibody treatment. ***(Translational Research Objectives)***

Results from translational research will be presented separately during this meeting (Abstract 2807, poster P190).

Design and Methods

Phase II, multi-centre, open label study to evaluate response rate (RR) and safety profile of P in HNSCC pts. after at least one platinum-based chemotherapy.

Primary endpoint: Overall response rate (RR)

Secondary endpoints: Progression-free survival (PFS), Duration of response (DR), Overall survival (OS), Adverse Drug Reactions

Study planned according to the Simon's two stage optimal design, assuming an unacceptable response rate of ≦ 8% and an acceptable rate of ≧ 18%.

Step 1: 32 patients → if > 3/32 responding patients, go to step 2
Step 2: 50 patients → if > 10/82 responding patients, further investigation of the drug warranted

Recurrent or metastatic HNSCC pts. pre-treated with platinum-containing chemotherapy in three tertiary Swiss cancer centers were included.
Previous anti-EGFR-antibody (EAB) treatment was allowed if pts. had no progression during or within 3 months after therapy. The main eligibility criteria are presented in **Table 1**.

- P was administered iv. every two weeks at a dose of 6mg/kg, until progressive disease, unacceptable toxicity or patient's refusal.
- Tumor assessment according to RECIST V1.1 criteria every 2 cycles.
- Adverse events (AEs) were graded following the NCI Common Terminology Criteria (CTCAE V3.0).

Table 1. Main Eligibility Criteria

Inclusion	Exclusion
• Histologically/cytologically confirmed HNSCC, metastatic or recurrent, incurable by surgery or radiation	
• Progression or lack of response to platimum-containing treatment	• Progression during or ≤ 3 months after end of any EAB treatment
• Measurable disease (RECIST V 1.1)	• History of interstitial lung disease
• ECOG performance status 0-2	• Brain metastases
• Adequate hematological, hepatic and renal function	
• Magnesium ≥ 1.5 x lower limit of normal (LON); Calcium ≥ LON	

Results

33 pts. received in total 151 and a median of 4 (range1-16) cycles of P. Median age was 61 years (range: 43-87); 27/33 (81.8%) were males. Tumor characteristics and prior treatments are listed in **Table 2**.

Table 2. Tumor Characteristics and Prior Treatments

	Number of patients (%) n=33
Primary tumor site	
Oral cavity	12 (36.4%)
Oropharynx	6 (18.2%)
Hypopharynx	5 (15.2%)
Mesopharynx	2 (6.1%)
Epipharynx	1 (3.0%)
Larynx	4 (12.1%)
Other	3 (9.1%)
Stage at study entry	
Metastatic/Recurrent	33 (100%)
Prior local radiotherapy	28 (84.8%)
Number of prior systemic therapies*	
1	18 (54.5%)
2	12 (36.4%)
3	3 (9.1%)
Prior treatment with anti-EGFR	10 (30.3%)
Platinum-sensitivity**	
Sensitive	7 (21.2%)
Refractory/Resistant	26 (78.8%)

* *Including curative induction/chemo-radiotherapy*
** *Platinum-sensitive defined as PD ≥ 6 months after treatment end*

Efficacy

RR was 6.1% with two partial responses (PR) in platinum-refractory pts. **Table 3**. 14 pts. (42.4%) had stable disease (SD), lasting > 6 months in 4 cases, resulting in a clinical benefit rate of 18.2% **Table 4**.

The boundaries for proceeding to step 2 were not met. Therefore the study was stopped after step 1.

- Median PFS was 2.6 months (95% CI: 1.7 to 3.7) **Figure 2**.
- Pts. with PR were progression free for 8.5 and 9+ months **Table 4**.
- Median survival was 9.7 months (95% CI: 6.3 to 17.2) **Figure 3**.

Table 3. Best Tumor Response (RECIST V 1.1)

Response	Number of patients (%) N=33
CR	0
PR	**2 (6.1%)**
SD overall	14 (42.4%)
SD > 6 months	4 (12.1%)
Clinical Benefit (PR+SD > 6 months)	**6 (18.2%)**
PD	11 (33.3%)
NE	6 (18.2%)

Table 4. Responding Patients

Pt #	Sex	PS	# Cycles	Platinum Sensitivity	Prior Anti-EGFR	PFS (months)
71 007	F	1	10	Refractory	No	8.5
71 015	F	0	10	Refractory	No	9+

Figure 1. Best Change in Tumor Burden

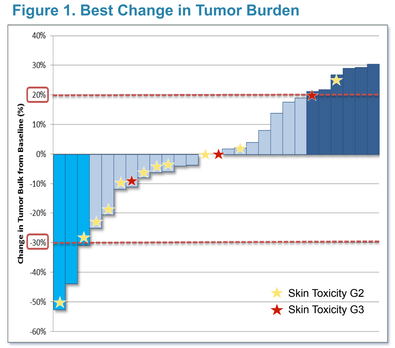

Figure 2. Progression-Free Survival (PFS)

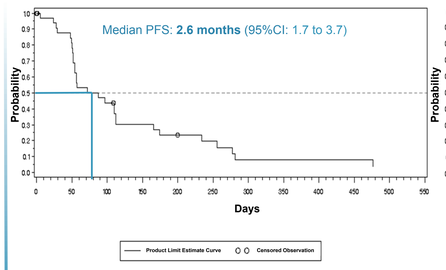

Figure 3. Overall Survival (OS)

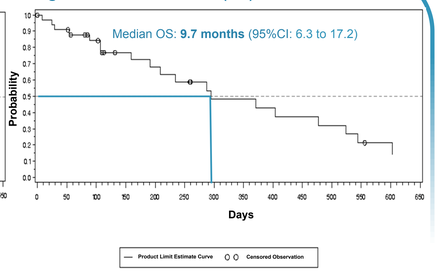

Table 5. Treatment-related AE's

AE Description	No. patients (%) Any Grade	G3-4
Rash	21 (63.6%)	1 (3.0%)
Hypomagnesaemia*	15 (45.5%)	4 (12.1%)
Blood potassium decreased*	7 (21.2%)	2 (6.1%)
Dry skin	5 (15.2%)	-
Dermatitis acneiform	4 (12.1%)	1 (3.0%)
Cheilitis	3 (9.1%)	1 (3.0%)
Paronychia	3 (9.1%)	-
Stomatitis	3 (9.1%)	1 (3.0%)
Fatigue	2 (6.1%)	-
Lymphocyte count decreased*	2 (6.1%)	-
Skin fissures	2 (6.1%)	-

* *Clinically significant according to Investigator*

Safety

Table 5 shows the most frequent adverse events (AE's). Ten pts. (30.3%) experienced ≥ G3 P-related AE's. Skin reactions (including rash, acneiform dermatitis, dry skin, nail disorders, skin fissures, cheilitis and erythema) were the most frequent in 29 out of 33 pts. (87.9%). Three pts. showing ≥ G3 skin toxicity (9.1%). Treatment withdrawal was required in one pt. Hypomagnesaemia was common in 19 out of 33 pts. (57.6%). One pt. died presumably due to a P-related severe alveolitis.
P was in general well tolerated, treatment compliance was excellent and no infusion-related reactions occurred.

Conclusions

- We present the first efficacy and safety results of P monotherapy in platinum pre-treated HNSCC pts.
- Toxicity profile and convenience was favorable making P a safe alternative for second line treatment in HNSCC.
- P showed antitumor activity with a RR of 6.1% and a remarkable duration of response and overall survival.
- Predefined boundaries for sufficient response to pursue the study and perform the second part in order to address secondary objectives were not met.

References
1. Vermorken et al. Platinum-based chemotherapy plus cetuximab in head&neck cancer. NEJM 2008;359:1116-27.
2. Vermorken et al. Cisplatin and fluorouracil with or without panitumumab in patients with r/mHNSCC of the head and neck: an open-label phase 3 randomised trial. Lancet Oncol 2013;14:697-710.

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