Abstract 2807

Phase II explorative trial to prospectively investigate predictive molecular biomarkers for efficacy of panitumumab (P) in platinum-pretreated 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 with P was also performed and in the meantime published in the same setting, 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. **(Primary objectives)**

Results from the phase II trial will be presented during this meeting
(Abstract 2861, poster P244).

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. **(Secondary objective)**

- o This secondary objective was chosen due to the fact that there is still no predictive biomarker available for efficacy of an anti-EGFR-antibody treatment in HNSCC pts.
- o Clinical experience showed presence of a subgroup of pts. with clear benefit and durable response with anti-EGFR-antibody treatment.[3] Identification of this pts. at treatment start would be of major importance.
- o It should be considered that both antibodies (C and P) have different properties and mechanism of action:

P is fully humanized whereas C is partly murine. C is not only active by inhibition of ligand-dependent activation of EGFR but also by marked ADCC (antibody-dependent cellular cytotoxicity) activity, which is much less the case with P treatment, **making P an ideal candidate for an exclusive assessment of EGFR-pathway activity and subsequent biomarker analysis for response.**

We present here results of the pre-specified biomarker analysis of the first part of a prospective phase II multicenter trial in platinum-pretreated pts. with HNSCC treated with P as second line therapy.

Material and Methods

Pts. with platinum-pretreated HNSCC included in a prospective phase II multicenter trial exploring P as 2nd line treatment consented for molecular biomarker analysis on available tumor tissue. Patient and Tumor Characteristics are shown in **Table 1**.
As P is less active through indirect mechanisms like ADCC (antibody dependent cellular cytotoxicity), it seems to be an ideal candidate to examine the pure effect on EGFR pathway.
To find a predictive marker pattern for response, a central laboratory investigated the following markers: KRAS, NRAS, HRAS, PI3KCA, BRAF gene mutations by Sanger sequencing; EGFR gene status by FISH; HPV genotyping by in-situ hybridization. **Figure 1 a) and b).**

Figure 1. EGFR dual color FISH assay (Abbott Molecular) on FFPE tissue sections from H&N patients

a) EGFR gene amplification (FISH+) **b) normal EGFR gene status (FISH-)**

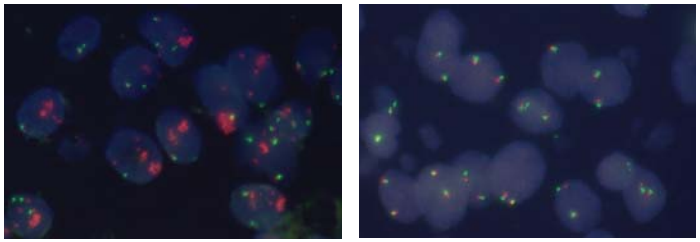
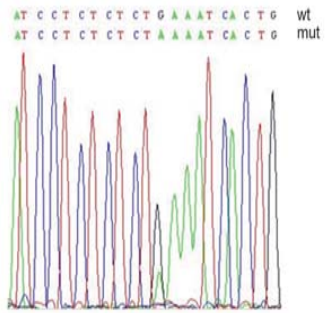


Figure 2 Figure 2 shows a common E545K mutation in the PIK3CA gene identified in three pts. of our cohort"

Figure 2. E545K mutation in the PIK3CA gene



- Median PFS was 79.5 days (95% CI: 52 to 112).
- Median OS was 295 days (95% CI: 191 to 524).

Table 1. Patient and Tumor Characteristics

	Number of patients (%) n=33
Median age	61
Range	43-87
Sex	
Male	27 (81.8%)
Female	6 (18.2%)
ECOG PS	
0	17 (51.5%)
1	15 (45.5%)
2	1 (3.0%)
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*

Results

All pts. consented for the biomarker sub-study. Tumor tissue was collected for all pts. One case was excluded for bad quality of DNA. Two patients never received planned treatment and can not be evaluated for response. Two uncommon KRAS mutations (G48E, T50I) and 3 canonical PIK3CA mutations (all E545K) were detected; all the other genes were wild-type. HPV high-risk 16 was found in 10 pts. and EGFR copy number gain (CNG) in 13 pts. No correlation between response and molecular alterations was observed. EGFR CNG seems to be more frequent in responding individuals with at least SD **Table 2**.
After our initial analysis showing no EGFR CNG in SD and PD pts., we performed post-hoc a central review of response, identifying three pts. with PD having EGFR CNG, qualifying our statement in our abstract.

Table 2. Biomarker Analysis

	Site	Pt No.	Best response	EGFR gene amplification	Chr7 polysomy	FISH	KRAS	NRAS	HRAS	BRAF	PIK3CA	HPV
1	IOSI	1	PD	no	no	FISH-	wt	wt	wt	wt	wt	HR16
2	KSSG	1	PD	no	no	FISH-	wt	wt	wt	wt	wt	HR16
3	KSSG	2	SD	no	yes	FISH+	wt	wt	wt	wt	wt	neg
4	KSSG	3	SD	no	no	FISH-	wt	wt	wt	wt	wt	neg
5	KSSG	4	SD	no	no	FISH-	wt	wt	wt	wt	wt	HR16
6	IOSI	2	SD	no	yes	FISH+	T50I	wt	wt	wt	wt	neg
7	KSSG	5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
8	KSSG	6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9	KSSG	7	PR	no	yes	FISH+	wt	wt	wt	wt	wt	neg
10	IOSI	3	NA	yes	yes	FISH+	G48E	wt	wt	wt	wt	HR16
11	KSSG	8	NA	NA	NA	NA	wt	wt	wt	wt	wt	neg
12	KSSG	9	PD	no	no	FISH-	wt	wt	wt	wt	wt	neg
13	IOSI	4	PD	no	no	FISH-	wt	wt	wt	wt	wt	HR16
14	HUG	1	SD	no	yes	FISH+	wt	wt	wt	wt	wt	HR16
15	IOSI	5	SD	no	yes	FISH+	wt	wt	wt	wt	wt	HR16
16	HUG	2	PD	no	yes	FISH+	wt	wt	wt	wt	wt	neg
17	IOSI	6	SD	no	no	FISH-	wt	wt	wt	wt	wt	neg
18	KSSG	10	SD	no	no	FISH-	wt	wt	wt	wt	wt	neg
19	KSSG	11	PD	no	no	FISH-	wt	wt	wt	wt	wt	neg
20	HUG	3	SD	yes	yes	FISH+	wt	wt	wt	wt	wt	neg
21	KSSG	12	PD	no	yes	FISH+	wt	wt	wt	wt	wt	HR16
22	KSSG	13	SD	yes	yes	FISH+	wt	wt	wt	wt	wt	neg
23	KSSG	14	SD	no	yes	FISH+	wt	wt	wt	wt	wt	neg
24	HUG	4	SD	yes	yes	FISH+	wt	wt	wt	wt	wt	neg
25	HUG	5	PD	yes	yes	FISH+	wt	wt	wt	wt	wt	neg
26	IOSI	7	SD	no	no	FISH-	wt	wt	wt	wt	E545K	neg
27	HUG	6	SD	no	yes	FISH+	wt	wt	wt	wt	wt	neg
28	IOSI	8	PD	no	no	FISH-	wt	wt	wt	wt	E545K	HR16
29	KSSG	15	PR	NA	NA	NA	NA	NA	NA	NA	NA	NA
30	KSSG	16	PD	NA	NA	NA	NA	NA	NA	NA	NA	NA
31	IOSI	9	NA	no	no	FISH-	wt	wt	wt	wt	E545K	HR16
32	HUG	7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
33	KSSG	17	PD	no	no	FISH-	wt	wt	wt	wt	wt	neg
34	ICSI	10	SD	NA	NA	NA	NA	NA	NA	NA	NA	NA
35	HUG	8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

NA: not assessable, wt: wild-type, SD: stable disease, PR: partial remission, PD: progressive disease

Conclusions

- EGFR CNG by FISH seems to be more frequent in HNSCC patients who benefit from P administration and could potentially be a marker to predict efficacy of P.
- The cascade of MAP kinases (RAS, BRAF), downstream to EGFR, was not predictive, at odds with colorectal cancer.
- This preliminary observation needs to be confirmed in a larger series.
- The role of PIK3CA mutations remains to be elucidated.

References

1. Vermorken et al. Platinum-based chemotherapy plus cetuximab in head&neck cancer. NEJM 2008;359:1116-27.
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3. Bossi et al. Identification of a gene expression profile associated with PFS r/mHNSCC pts. treated with first-line cetuximab and platinum therapy. J Clin Oncol 31, 2013 (suppl; abstr 6027)

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