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ORIGINAL ARTICLE

Activity and safety of afatinib in a window preoperative EORTC study in patients with squamous cell carcinoma of the head and neck (SCCHN)

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Background: To investigate the activity and safety of afatinib in the preoperative treatment of squamous cell carcinoma of the head and neck (SCCHN).

Patients and methods: This study was an open-label, randomized, multicenter, phase II window of opportunity trial. Treatment-naïve SCCHN patients selected for primary curative surgery were randomized (5 : 1 ratio) to receive afatinib during 14 days (day −15 until day −1) before surgery (day 0) or no treatment. Tumor biopsies, 2-[fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET), and magnetic resonance imaging (MRI) were carried out at diagnosis and just before surgery. The primary end point was metabolic FDG-PET response (according to EORTC guidelines). Other end points included response assessment based on the Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, dynamic contrast-enhanced (DCE)-MRI, diffusion weighted (DW)-MRI, safety, and translational research (TR).

Results: Thirty patients were randomized: 25 to afatinib and 5 to control arm. Of the 23 eligible patients randomized to afatinib, 16 (70%; 95% CI: 47% to 87%) patients had a partial metabolic FDG-PET response (PMR). Five patients (22%; 95% CI: 8% to 44%) showed a partial response by RECISTv1.1. Responses assessed via DCE-MRI and DWI-MRI did not show a strong association with PMR or RECIST. One patient discontinued afatinib after 11 days for grade 3 diarrhea with subsequent renal failure and 24 days delay in surgery. No grade 4 toxicities or surgical comorbidities related to afatinib were reported. TR results indicated that PMR was more frequent in the tumors with high Cluster3-hypoxia score expression and with *TP53* wild type.

Conclusion: Afatinib given for 2 weeks to newly diagnosed SCCHN patients induces a high rate of FDG-PET partial metabolic response and partial response according to RECISTv1.1. Afatinib can be safely administered before surgery. Although exploratory, the hypoxic gene signature needs further investigations as a predictive biomarker of afatinib activity.

Clinical trial registration: ClinicalTrials.gov: NCT01538381

Key words: afatinib, window of opportunity, squamous cell carcinoma, head and neck cancer

Introduction

Cetuximab improves overall survival when associated with radiation therapy in locally advanced squamous cell carcinoma of the head and neck (SCCHN), or with platinum-based chemotherapy in incurable disease [1, 2]. However, only a minority of patients benefit from anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs). To tackle potential EGFR inhibitor resistance mechanisms, clinical studies have evaluated afatinib, an irreversible second generation ErbB family blocker, that inhibits signaling from all the homodimers and heterodimers formed by the ErbB family members. Afatinib modestly improved progression-free survival (PFS) versus methotrexate as second-line treatment of recurrent and/or metastatic (R/M) SCCHN [3]. Therefore, the identification of predictive biomarkers is of utmost importance.

Recently, we obtained preliminary results suggesting that the patients who derived a long-term benefit from cetuximab had tumors characterized by a gene expression defining the SCCHN cluster 3 with basal subtype traits such as strong EGFR signaling phenotype and hypoxic differentiation [4]. The same profile predicted afatinib sensitivity in CGP cell-lines [4].

Evaluation of compounds in the preoperative window setting maximizes the chance of observing tumor response in this treatment-naive population and allows the collection of biological materials as well as testing functional imaging for early response detection. In this study, we investigated the activity and safety of afatinib when administered preoperatively to SCCHN patients.

Materials and methods

This study was an open-label, randomized, multicenter, phase II window of opportunity trial. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice standards and the Declaration of Helsinki.

Study objectives and end points

The general objectives were to evaluate the activity and safety of afatinib administered for 2 weeks to untreated SCCHN patients and to perform translational research (TR). The primary end point was 2-[fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) response assessed by central imaging review according to EORTC guidelines (minimum 25% decrease in the SUVmax) at the end of the 2-week treatment period [5]. Secondary end points included response by Response Evaluation Criteria In Solid Tumors (RECIST)v1.1 [conventional magnetic resonance imaging (MRI)] [6], dynamic contrast-enhanced (DCE)-MRI and diffusion weighted (DW)-MRI, as well as toxicity evaluated during the 2-week period between randomization and surgery, surgical comorbidities evaluated up to 4 weeks after surgery and TR.

Patients

Eligible criteria: untreated histologically proven SCCHN (oral cavity, oropharynx, hypopharynx or larynx) selected for primary curative surgery; Primary tumor ≥2 cm in its largest diameter.

Treatment and procedures

The study design is depicted in Figure 1. Patients were randomized (5 : 1 ratio) to receive afatinib (arm A) for 14 days (day −15 until day −1) before surgery (day 0) or no treatment (arm B).

Treatment was stopped in case of unacceptable toxicity, patient's refusal or investigator decision.

Pretreatment biopsies of the tumor were harvested during the regular diagnosis staging procedure and at the time of surgery (day 0). Biopsies were fixed in 4% formalin and embedded in paraffin (FFPE).

FDG-PET/CT-scan, conventional MRI and DCE-MRI and DW-MRI were performed before randomization and the day before surgery (day −1).

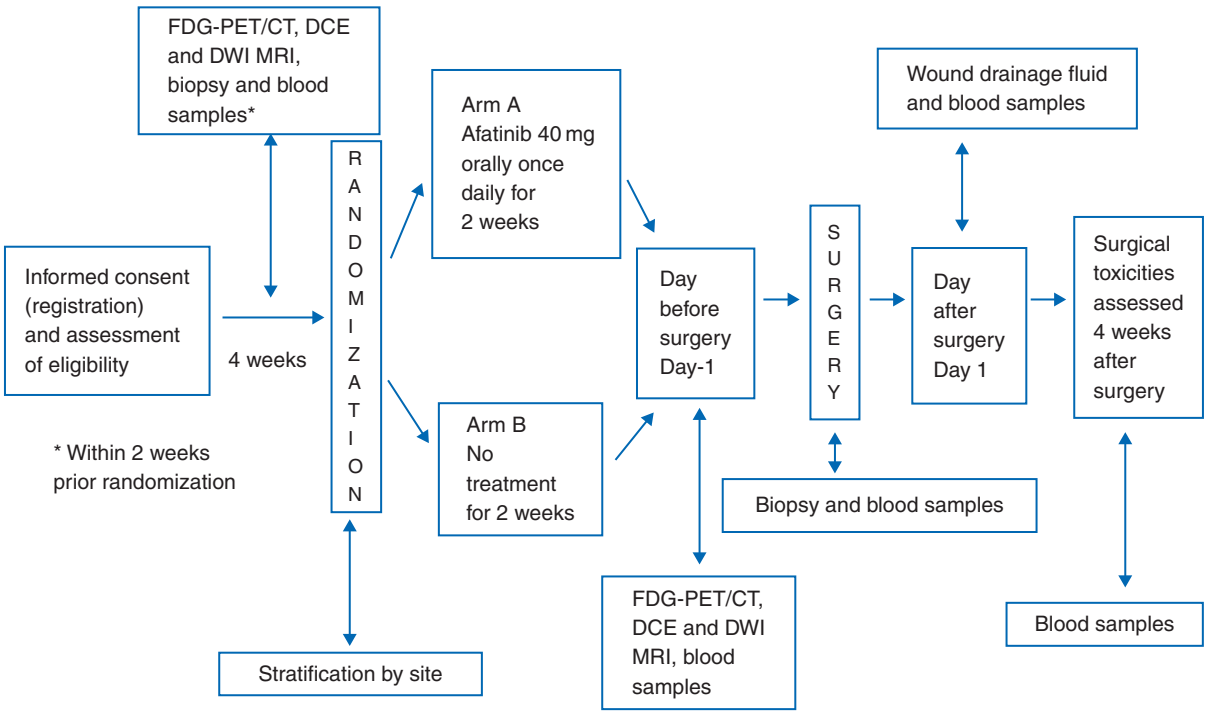

Figure 1. Study design.

The last dose of afatinib (day –1) was given strictly 2 h before the FDG-PET/CT before surgery.

In arm B, no treatment was provided and patients followed the same schedule of examinations of arm A.

Imaging techniques: standardization, quality control and central review

The imaging guidelines were released at the study set up to ensure the standard imaging acquisition and a proper data transfer [7]. FDG-PET/CT scanners were required to have EANM Research Ltd (EARL) accreditation. Sites had to submit a dummy run scan following the study imaging requirements. The quality control (QC) evaluated image visual quality and acquisition parameters compliance (injected activity, field of view, FDG uptake time, anatomy coverage). Patients were randomized only after the approval of baseline FDG-PET/CT QC acceptance. The QC on MRI was conducted in a retrospective manner (supplementary Material S1, available at *Annals of Oncology* online). Imaging central review was performed at the end of the trial in a blinded manner (supplementary Material S2, available at *Annals of Oncology* online).

Immunohistochemistry and TP53 mutational assessment

p16, HER3, PTEN, EGFR amplification and *TP53* mutational status were assessed as described [8, 9] (supplementary Material S3, available at *Annals of Oncology* online).

RNA extraction and gene-expression profiling

RNAs were retrieved from FFPE of pretreatment tumor biopsies of the patients included in arm A. The samples were processed for gene-expression profiling using DASL microarrays (Illumina) as previously described [4]. Microarray data were deposited and are available on GEO repository (http://www.ncbi.nlm.nih.gov/geo/) with the accession number GSE101491.

Statistical methods

Thirty patients were planned to be randomized (5 : 1 ratio) to receive afatinib or no treatment. Randomization was stratified according to the patient institution. Patients allocated to the 'no treatment' arm will mainly serve as a reference to interpret TR.

A one-stage A'Hern design was used for the afatinib arm, with 90% power to show that metabolic response (FDG-PET) rate after 2 weeks of afatinib and before surgery was higher than 10%, if the true response rate was 30% or higher, with a type I error of 10% one-sided.

The first six patients randomized to afatinib treatment arm were evaluated in two subsequent cohorts of three patients each, for surgical toxicities graded according to Common Terminology Criteria for Adverse Events (CTCAE)v4.0 and documented over the 4-week period following surgery to determine if preoperative afatinib intake was safe. The stopping rule was: if two or more patients out of six experienced grade $\geq$3 surgical toxicities related to afatinib, accrual should be stopped. Once the safety was established total planned enrollment was completed.

The pretreatment predictive value of PTEN, HER3, p16 expression, EGFR amplification and *TP53* mutation status on FDG-PET and RECISTv1.1 response was evaluated; in this exploratory analysis, both raw *P*-values and *P*-values adjusted using Benjamini and Hochberg method to control false discovery rate at 5% are provided.

Bioinformatics analyses

A score was determined according to the Pearson correlation between the gene expression profile of each sample and the centroids for Cluster3-hypoxia of De Cecco subtype classification [4]. Statistical and boxplot analyses were carried out using R (version 3.3.2), and data processing was carried out using BrB-ArrayTool developed by Dr Richard Simon and the Development Team (v4.2.0; National Cancer Institute, USA). The accuracy of cluster 3-hypoxia prediction was evaluated by ROC curve through ROCR.

Results

Study population

Between October 2012 and June 2015, 30 patients from 4 study sites in Belgium and Italy were randomly assigned to afatinib (arm A) ($n = 25$) and no treatment (arm B) ($n = 5$). Baseline demographics and disease characteristics are reported in Table 1. Figure 2 describes the study flow according to Consort diagram. Of the 25 and 5 patients randomized to A and B, 2 and 1, respectively, were later found to not meet the eligibility criteria. One of the four patients in Arm B was lost to follow-up before the second FDG-PET. Therefore, the number of patients evaluable for the primary end point was 23 in Arm A and 3 in Arm B.

Imaging end points

Of the 23 eligible patients in Arm A, 16 (70%, 95% CI: 47% to 87%) had a partial metabolic FDG-PET response (PMR); there were no complete responses and the remaining 7 patients had stable metabolic disease (SMD). The proportion of responders to afatinib was significantly higher than 10% ($P < 0.001$). The three evaluable patients in the no-treatment arm had a SMD.

A total of 5 of 23 patients in Arm A showed a partial response (PR) by RECISTv1.1 (22%; 95% CI: 8-44%); there were no complete responses. Responses assessed via DCE-MRI and DWI-MRI did not show a strong association with PMR or RECIST (supplementary Results S1, available at *Annals of Oncology* online).

Safety

Criteria for stopping accrual prematurely for safety reasons were not met. There were no grade 4 or 5 adverse events related to afatinib (supplementary Table S1, available at *Annals of Oncology* online). One patient had grade 3 acneiform rash and another grade 3 hypokalemia considered related to afatinib. Another patient discontinued afatinib after 11 days for grade 3 diarrhea with subsequent renal failure, causing delayed surgery by 24 days. This patient had grade 3 abdominal pain and acute pancreatitis, also considered to be possibly related to afatinib. The remaining 24 patients completed the planned treatment but 2 had delayed surgery by 4 and 2 days for grade 2 colitis and organizational issues, respectively. No surgical comorbidities were considered to be possibly related to afatinib (supplementary Table S2, available at *Annals of Oncology* online).

One patient in the control arm with an oral cavity cancer having borderline indication for surgery was not operated after the second MRI evaluation because surgery was not considered to be feasible with a curative intent.

Long-term follow-up

Two-year PFS and overall survival rates in the afatinib arm were 64.2% (95% CI: 40.8% to 80.4%) and 72.7% (95% CI: 48.7% to 86.8%).

Table 1. Patient characteristics

Baseline characteristics—evaluable population

	Randomized treatment		
	Afatinib (*N* = 23) *n* (%)	**No treatment (*N* = 4) *n* (%)**	**Total (*N* = 27) *n* (%)**
Age (years)			
Median	58.3	69.5	59.4
Range	35.9–76.4	55.9–77.5	35.9–77.5
Sex			
Male	16 (69.6)	1 (25.0)	17 (63.0)
Female	7 (30.4)	3 (75.0)	10 (37.0)
Tumor location			
Oral cavity	19 (82.6)	4 (100.0)	23 (85.2)
Oropharynx	4 (17.4)	0 (0.0)	4 (14.8)
cT			
T1	1 (4.3)	0 (0.0)	1 (3.7)
T2	13 (56.5)	2 (50.0)	15 (55.6)
T3	2 (8.7)	0 (0.0)	2 (7.4)
T4	7 (30.4)	2 (50.0)	9 (33.3)
cN			
N0	8 (34.8)	0 (0.0)	8 (29.6)
N1	5 (21.7)	1 (25.0)	6 (22.2)
N2	10 (43.5)	3 (75.0)	13 (48.1)
cM			
M0	23 (100.0)	4 (100.0)	27 (100.0)
Stage			
II	4 (17.4)	0 (0.0)	4 (14.8)
III	4 (17.4)	0 (0.0)	4 (14.8)
IV	15 (65.2)	4 (100.0)	19 (70.4)
ECOG performance status			
0	15 (65.2)	1 (25.0)	16 (59.3)
1	8 (34.8)	3 (75.0)	11 (40.7)
p16 status			
Negative	21 (91.3)	4 (100.0)	25 (92.6)
Positive	2 (8.7)	0 (0.0)	2 (7.4)

Pretreatment predictive biomarkers

PTEN-high was found in 40% (12/30), HER3-low in 24% (7/29), *EGFR*-amplified in 14% (4/29) and p16 was expressed in 7% (2/30). None of these biomarkers were significantly predictive of response by FDG-PET response or RECISTv1.1 (supplementary Tables S3 and S4, available at *Annals of Oncology* online). In the afatinib arm, PR was observed in 3 patients out of 6 (50%) and in 2 out of 14 (14%) in the PTEN high group and PTEN low group, respectively (raw and adjusted *P*-value = 0.131/0.656).

Of the 27 samples evaluable for *TP53* status, 74% were wild type and 26% showed a nonfunctional mutation. Among the 24 afatinib-treated patients, PMRs were more frequent in wild type tumors in comparison with mutated ones: 15/18 (83%) and 2/6 (33%), respectively (raw and adjusted *P*-value = 0.038 and 0.381). Response rates as per RECISTv1.1 were similar in wild type (27%) and mutated tumors (25%) (supplementary Tables S5 and S6, available at *Annals of Oncology* online).

Of the 23 eligible patients from the afatinib arm, 19 had sufficient material of adequate quality for gene-expression analysis. A supervised analysis according the FDG-PET response (PMR versus SMD) enabled to separate the samples in two classes having high and low Cluster3-hypoxia values, respectively ($P = 0.002$) (Figure 3). The performance of the Cluster 3-hypoxia expression in predicting metabolic response to afatinib, tested in terms of sensitivity and specificity by ROC analysis, reached a area under the curve of 0.843. When the supervised analysis was applied to response assessed by RECISTv1.1, no clear separation was recorded ($P = 0.171$).

Discussion

We investigated afatinib in the preoperative window period in treatment-naïve SCCHN patients selected for primary curative surgery. Our study met its primary end point as 70% of the patients achieved a partial metabolic FDG-PET response.

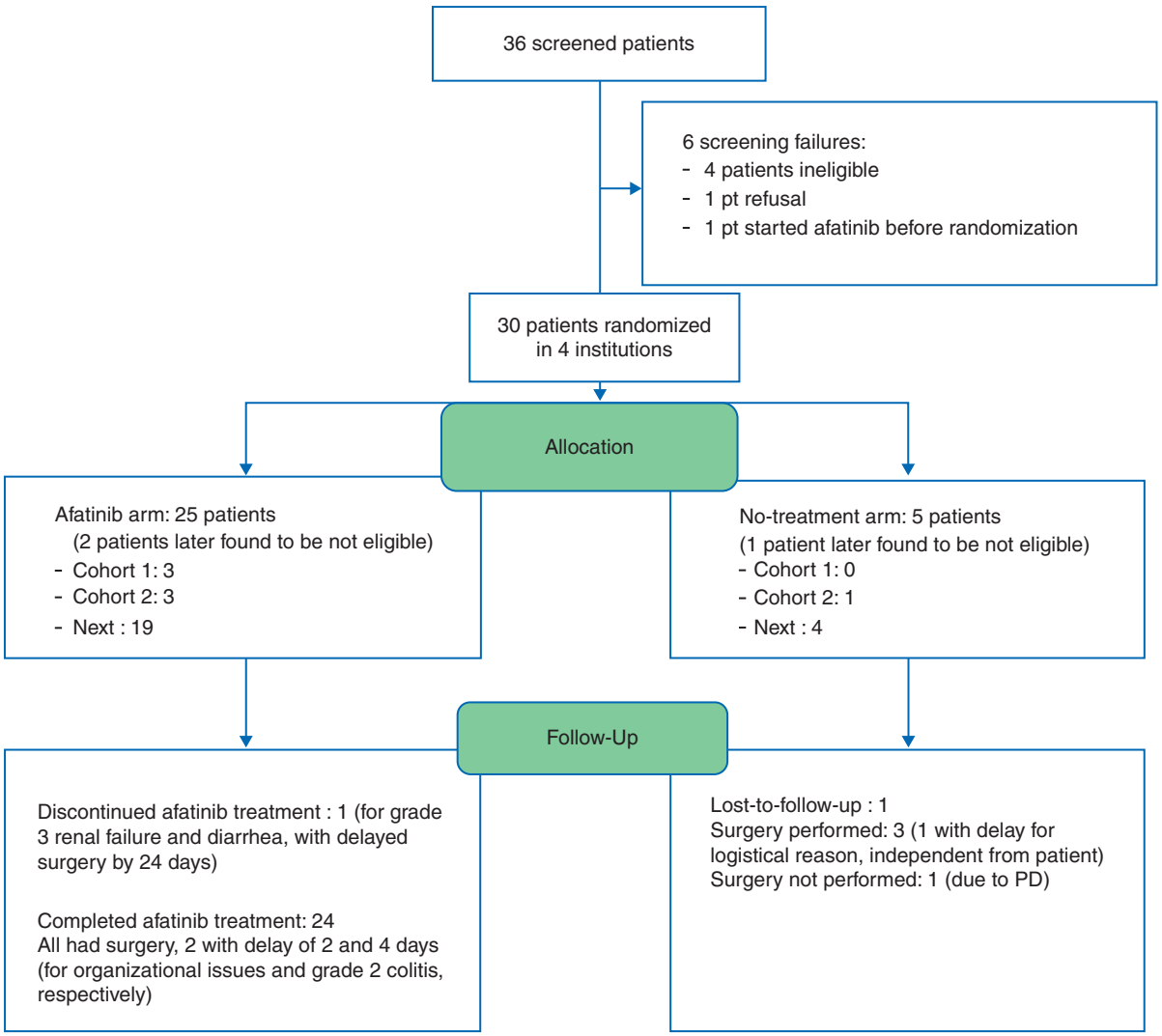

Figure 2. Consort diagram.

Twenty-two percent of the patients had also a PR according to RECISTv1.1 after only 2 weeks of treatment. Our efficacy data are similar to other trials that investigated tyrosine kinase inhibitors or anti-EGFR mAbs in the preoperative treatment of SCCHN [10–13]. A window study that investigated afatinib in the same setting reported 48% PMR and 7.3% response according to RECIST [11]. Erlotinib given for a median treatment time of 23 days gave a tumor shrinkage greater than 25% in 29% of the patients and lapatinib an ORR of 17% when administered for ≥4 weeks [12, 13]. The ORR reported in window studies is generally higher than the one observed in the recurrent setting where afatinib gave an ORR of 10%, probably because these patients are bearing untreated tumors that have not yet developed treatment resistance mechanisms.

High expression of PTEN, low expression of HER3 or p16 and EGFR amplification have been shown to be associated with increased benefit from afatinib in patient with recurrent disease [8]. We did not confirm the predictive value of these biomarkers. Several reasons could be incriminated such as the low number of patients resulting in low statistical power and the different clinical situations (curative versus palliative). *TP53* wild type and functional genomic data (Cluster3-hypoxia profile) were associated with afatinib FDG-PET response. Noteworthy, the loss of p53 has been reported to be associated with resistance to EGFR inhibitors [14] and cluster 3 expression correlated with long-PFS after cetuximab treatment in recurrent/metastatic SCCHN [4]. We acknowledge some limitations of our analyses. *TP53* status revealed a slightly higher rate of wild type tumors (75%) than what reported in literature; however, more than half of the patients had a T1–T2 stage, which are associated with a lower frequency of *TP53* mutations [15]. Moreover, we missed 17% of genomic analysis, and gene expression and PET-FDG were studied as continuous versus dichotomic variables, respectively.

Safety was as expected regarding afatinib and surgical comorbidities. Importantly, one patient had significant delay of surgery due to afatinib toxicity and another patient could not be operated. In a recent literature review, it has been shown that 7% of the patients included in window trials could not undergo surgery as per protocol

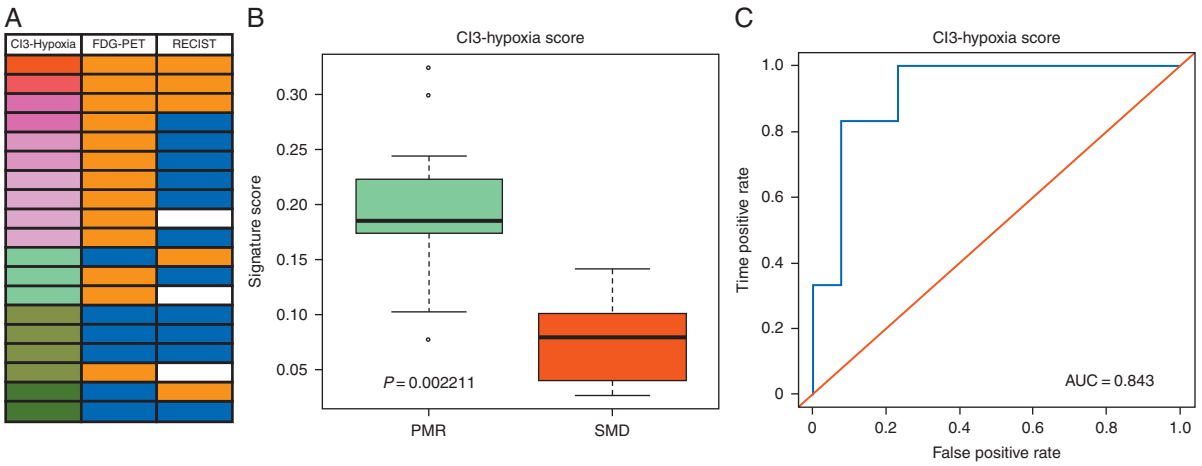

Figure 3. Supervised analysis of Cluster3-hypoxia score expression according to response to afatinib treatment. (A) Colour scattergram connecting Cluster3-hypoxia score and FDG-PET or RECIST 1.1 response. Cluster3-hypoxia score in colour scale ranging from red (high) to green (low); partial responding patients (yellow, $n = 13$ or $n = 5$, according to FDG-PET or RECIST 1.1, respectively); no responding patients (blue, $n = 6$ or $n = 12$, according to FDG-PET or RECIST 1.1, respectively). (B) Metabolic response according to FDG-PET; the box and whisker plots depict the median Cluster3 score in the indicated classes, interquantile (IQR) (boxes) and 1.5xIQR (wiskers) values. *P* value by two-tailed *t* test. (C) Performance of the Cluster3 expression in predicting FDG-PET response in terms of sensitivity and specificity by ROC analysis (area under the curve = 0.843).

[16]. In addition, time to treatment initiation increases the risk of death, particularly if this time is higher than 46–52 days [17]. This outlines the fact that this approach is not without any risk and should be conducted carefully. Importantly, the overall survival and PFS probabilities are within the expected ranges.

We demonstrated the feasibility of challenging window of opportunity studies in a multicentric and international setting. However, the accrual period was longer than planned and expected (33 months). The design of 56 preoperative biomarkers trials was reviewed and the median duration of accrual was 28 months (range: 9–98) [16]. The length of accrual may reflect the willingness of the patients to participate in a trial where the treatment benefit is questionable, and also the difficulties to organize such trials and harmonize procedures. Our study included strict rules regarding treatment duration and administration, timing of biopsies, CT-scan/MRI and surgery. We had also stringent QCs of FDG-PET and MRI.

FDG-PET was chosen as primary end point. However, despite a high percentage of patients with PMR (70%), it is unlikely that all these patients will derive a long-term benefit from afatinib. Therefore, the specificity of FDG-PET to predict anti-EGFR therapy activity could be too low and requires further investigation.

Despite these difficulties, window of opportunity studies are worthy to study the biological activity of new compounds and to investigate predictive biomarkers. We may also envisage that a window of opportunity study could be used to select the patients who respond to a particular treatment with the intent of continuing the investigated drug in the adjuvant setting. By doing so, the impact of window studies would be clinically more relevant.

Conclusion

In conclusion, afatinib given for 2 weeks to newly diagnosed SCCHN patients induces a high rate of metabolic responses. Although exploratory, the Cluster3-hypoxia gene signature and *TP53* status deserve further investigations as predictive biomarkers of ErbB family blockers.

Acknowledgements

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Disclosure

J-PM reports acting in an advisory role for Boerhingher-Ingelheim, Debio, Nanobiotix, Astra-Zeneca, Merck Sharp and Dohme. PB reports acting in advisory board for Astra-Zeneca, Merck-Serono, Tesaro, Kyowa-Kyrin and Roche. LFL reports acting in advisory board for EISAI, BMS, MSD, Merck–Serono, Debio, SOBI and Astrazeneca. All remaining authors have declared no conflicts of interest.

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