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A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck[†]

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Background: Afatinib is an oral, irreversible ErbB family blocker that has shown activity in epidermal growth factor receptor (EGFR)-mutated lung cancer. We hypothesized that the agent would have greater antitumor activity compared with cetuximab in recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) patients, whose disease has progressed after platinum-containing therapy.

Patients and methods: An open-label, randomized, phase II trial was conducted in 43 centers; 124 patients were randomized (1 : 1) to either afatinib (50 mg/day) or cetuximab (250 mg/m²/week) until disease progression or intolerable adverse events (AEs) (stage I), with optional crossover (stage II). The primary end point was tumor shrinkage before crossover assessed by investigator (IR) and independent central review (ICR).

Results: A total of 121 patients were treated (61 afatinib, 60 cetuximab) and 68 crossed over to stage II (32 and 36 respectively). In stage I, mean tumor shrinkage by IR/ICR was 10.4%/16.6% with afatinib and 5.4%/10.1% with cetuximab (P = 0.46/0.30). Objective response rate was 16.1%/8.1% with afatinib and 6.5%/9.7% with cetuximab (IR/ICR). Comparable disease control rates were observed with afatinib (50%) and cetuximab (56.5%) by IR; similar results were seen by ICR. Most common grade \geq 3 drug-related AEs (DRAEs) were rash/acne (18% versus 8.3%), diarrhea (14.8% versus 0%), and stomatitis/mucositis (11.5% versus 0%) with afatinib and cetuximab, respectively. Patients with DRAEs leading to treatment discontinuation were 23% with afatinib and 5% with cetuximab. In stage II, disease control rate (IR/ICR) was 38.9%/33.3% with afatinib and 18.8%/18.8% with cetuximab.

Conclusion: Afatinib showed antitumor activity comparable to cetuximab in R/M HNSCC in this exploratory phase II trial, although more patients on afatinib discontinued treatment due to AEs. Sequential EGFR/ErbB treatment with afatinib and cetuximab provided sustained clinical benefit in patients after crossover, suggesting a lack of cross-resistance. **Key words:** afatinib, cetuximab, recurrent HNSCC, metastatic HNSCC, EGFR inhibitor therapy

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¹List of where and when the study has been presented in part elsewhere: Previously presented at the 46th Annual Meeting of American Society of Clinical Oncology, 4–8 June 2010, Chicago, IL, USA; the 3rd Trends in Head & Neck Oncology (THNO), 3–5 November 2011, Rome, Italy; the Multidisciplinary Head and Neck Cancer Symposium, 26–28 January 2012, Phoenix, Arizona, USA; the European Conference on Head and Neck Oncology (EHNS), 18–21 April 2012, Poznan, Poland; the 10th Annual Meeting of the Japanese Society of Medical Oncology, 26–28 July 2012, Osaka, Japan and the 49th American Society of Clinical Oncology, May 31–June 4 2013, Chicago, IL, USA.

introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide [1]. Patients diagnosed with recurrent or metastatic (R/M) disease have a poor prognosis [2]. The majority of HNSCC tumors overexpress the epidermal growth factor receptor (EGFR/ErbB1), which correlates with poor clinical outcomes [3]; human epidermal growth factor receptor 2 (HER2/ErbB2) amplification also occurs [4].

Cetuximab (EGFR monoclonal antibody) is indicated for locoregionally advanced and R/M HNSCC patients [5–7]. However, the objective response (OR) to cetuximab monotherapy is

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modest (~13%) [5], and predictive biomarkers of efficacy are lacking. Somatic EGFR mutations in HNSCC are rare [4], and while earlier reports documented EGFR deletion mutation (EGFRvIII) in ~40% of HNSCC tumors [8], more recently, EGFRvIII mutations were only identified in <0.5% of 279 HNSCC samples from the Cancer Genome Atlas (TCGA) project [4].

Afatinib, an oral, irreversible ErbB family blocker [9, 10] has potent preclinical activity against wild-type and mutant EGFR (including EGFRvIII) and HER2, and is used in the treatment of patients with EGFR mutation-positive non-small-cell lung cancer [9, 11, 12]. In HNSCC, EGFR tyrosine kinase inhibitor therapy has been associated with low response rates [13–16] and has not been directly compared with cetuximab. We hypothesized that irreversible ErbB family blockade with afatinib would have greater antitumor activity compared with cetuximab, and that cross-resistance between them would not be universal, with some patients potentially benefitting from sequential treatment.

patients and methods

study design and patients

The study was conducted in 43 centers in Belgium, France, Spain and the United States. Eligible patients (aged \geq 18 years) had pathologically confirmed R/M HNSCC, progression following any line of prior platinumbased therapy, measurable disease [Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0], an Eastern Cooperative Oncology Group performance status (ECOG PS) of \leq 1, adequate end-organ function, and provided written informed consent. Key exclusion criteria included: receiving more than two chemotherapeutic regimens for R/M disease and progressive disease (PD) within 3 months of completion of intended curative treatment of localized/locoregional advanced disease.

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines, and approved by relevant regulatory and independent ethics committees.

randomization and masking

Patients were randomized in a 1 : 1 ratio to afatinib or cetuximab in stage I, stratified by number of prior chemotherapies for R/M HNSCC (0 versus \geq 1). In stage I, patients received afatinib (50 mg once daily) or cetuximab (loading dose of 400 mg/m² followed by weekly doses of 250 mg/m²) treatment until progression or intolerable adverse events (AEs). In stage II, patients who failed or experienced intolerable AEs on afatinib or cetuximab were able to cross over to the opposite treatment, cetuximab or afatinib (supplementary Figure S1, available at *Annals of Oncology* online).

procedures

Patients experiencing grade ≥ 3 drug-related AEs (DRAEs) according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) version 3.0 or grade ≥ 2 diarrhea, nausea, or vomiting for ≥ 7 consecutive days despite optimal supportive care, paused treatment (maximum 14 days). Following this and recovery to a grade ≤ 1 AE, afatinib was restarted with the dose reduced by 10 mg; this reduction could be repeated twice. Afatinib was discontinued after a third occurrence of AEs as specified above. Patients who did not recover within 14 days could cross over to afatinib or cetuximab in stage I, or be discontinued, if in stage II. Safety was assessed every 2 weeks during the first cycle and then every 4 weeks.

end points and assessments

Primary end point was tumor shrinkage (mm) before crossover, defined as the change from baseline in the smallest postrandomization sum of the longest diameters (SLDs) of the target lesions. Secondary end points included the best RECIST assessment, duration of OR, progression-free survival (PFS), overall survival (OS), safety, pharmacokinetic assessments (PK) and patient-reported outcomes (PRO).

Computed tomography (CT) scans or magnetic resonance imaging (MRI) were carried out at baseline and thereafter at 8-week intervals (stage I). The last image before crossover was taken as baseline for stage II and tumor assessments were carried out at weeks 4 and 8, and every 8 weeks following stage II treatment start. Tumor evaluation was conducted at investigational sites [investigator review (IR)] and by an independent central review (ICR).

Blood samples for PK analyses were collected from all patients who received afatinib in stage I and patients who crossed over from cetuximab to afatinib treatment in stage II. Plasma concentrations of afatinib were analyzed by a validated high-performance liquid chromatography tandem mass spectrometry method using $[D_6]$ afatinib as an internal standard.

PRO were assessed using the self-administered European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC QLQ)-C30 and its head and neck-specific module (QLQ-HN35) [17, 18]. Prespecified assessments included time to deterioration in global health status as well as head and neck-specific symptoms of pain and swallowing.

Immunohistochemistry (IHC) established p16 expression and EGFRvIII mutation status; the latter was also determined using quantitative reverse transcription polymerase chain reaction as previously described [19].

statistical analysis

Tumor shrinkage based on the continuous variable, SLD of target lesions, was chosen because it was expected to be more sensitive in detecting differences between treatment groups, compared with a binary variable, such as response rate [20]. In determining sample size, 40 patients per treatment group with at least one postrandomization tumor assessment were expected to provide ~80% power to detect a difference of 0.38 standard deviation in the true mean tumor shrinkage between groups, using a one-sided α level of 0.20. This could provide ~80% power to detect a difference of 18% in the objective response rate (ORR).

Comparisons between afatinib and cetuximab were made via analysis of covariance for tumor shrinkage, Cochran's statistics for best RECIST assessment, log-rank test and Cox proportional hazards regression for PFS and OS. PRO analysis focused on time to deterioration (defined as a 10-point change towards worsening from baseline score on a 0–100 point scale) for: global health status (Q29 and Q30 in C30), pain (Q9 and Q19 in C30) and swallowing (Q35 to Q38 in H&N35). Safety end points were analyzed descriptively.

For stage I, efficacy analyses included all randomized patients, and safety analyses comprised the treated population. Efficacy and safety analyses in stage II included all treated patients.

results

patient population

Between October 2007 and June 2011, 124 patients were randomized to receive afatinib (62 patients) or cetuximab (62 patients) during stage I (Figure 1). Baseline characteristics were balanced (Table 1); although, there were more patients with ECOG PS 0 in the afatinib group [23 (37.1%)] versus cetuximab [11 (17.7%)].



Figure 1. Participant flow diagram. AE, adverse event.

tumor shrinkage

stage I. Comparable tumor reduction was observed in both afatinib and cetuximab groups (P = 0.57 per ICR and 0.76 per IR, Figure 2A and B). Per ICR, 16 of 47 (34%) afatinib-treated patients experienced tumor size reduction of >30% versus 9 of 48 (18.7%) on cetuximab (Figure 3).

stage II. Overall, 12/30 (40%) of afatinib- and 8/26 (30.8%) of cetuximab-treated assessable patients had a reduction in SLD by ICR (Figure 3). Waterfall plots show that one patient in each group experienced tumor size reduction of >30%.

RECIST-defined response. During stage I, confirmed ORR was 16.1% with afatinib and 6.5% with cetuximab (P = 0.09) by IR and 8.1% with afatinib and 9.7% with cetuximab (P = 0.78) by ICR (supplementary Table S1, available at *Annals of Oncology* online). There was disparity in agreement between IR and ICR, and in particular between reviewers within the ICR, where 49 of 106 cases (46%) required third-reader arbitration due to discrepancies between the first two readers. Disease control was achieved in 31 (50%) afatinib- and 35 (56.5%) cetuximab-treated patients by IR (P = 0.48) with similar findings using ICR in stage I (supplementary Table S1, available at *Annals of*

Oncology online). ORRs in both groups were similar per ICR, regardless of prior chemotherapy in the R/M setting; per IR, afatinib showed higher ORR in patients with prior chemotherapy in the R/M setting (supplementary Table S2, available at *Annals of Oncology* online).

During stage II, the disease control rate (IR/ICR) for patients who switched from cetuximab to afatinib was 38.9%/33.3% compared with 18.8%/18.8% for those switched from afatinib to cetuximab (supplementary Table S1, available at *Annals of Oncology* online). Interestingly, several patients on both treatments appeared to maintain disease control after crossover (Figure 4).

PFS and OS. In stage I, median PFS by ICR for afatinib- and cetuximab-treated patients was similar; 13.0 versus 15.0 weeks [hazard ratio (HR) 0.93, 95% confidence interval (CI) 0.62–1.38, P = 0.71, supplementary Figure S2A, available at *Annals of Oncology* online]. For stage II, median PFS for patients who crossed over to afatinib was 9.3 and 5.7 weeks for those crossing to cetuximab (HR 0.64, 95% CI 0.38–1.05, P = 0.08, supplementary Figure S2B, available at *Annals of Oncology* online).

Median OS was 35.9 weeks for afatinib- and 47.1 weeks for cetuximab-treated patients during stage I and II (HR 1.06, 95%

Table 1. Demographics, baseline disease characteristics and treatment history for randomized patients

	Afatinib	Cetuvimah		
	(N = 62)	(N=62)		
	((
Gender, n (%)	= (11.2)	10 (1 (1)		
Female	7 (11.3)	10 (16.1)		
Male	55 (88.7)	52 (83.9)		
Race, n (%)	1 (1 ()			
Black	1 (1.6)	4 (6.5)		
white	45 (72.6)	41 (66.1)		
American Indian/Alaska Natives	1 (1.6)	0		
Missing	15 (24.2)	17 (27.4)		
Age (years)				
Median (range)	58.0 (23-78)	58.0 (29-83)		
Weight (kg)				
Median (range)	70.0 (43–114)	61.3 (37–109)		
ECOG performance status				
0	23 (37.1)	11 (17.7)		
1	38 (61.3)	48 (77.4)		
2 ^a	0	1 (1.6)		
Missing	1 (2.6)	2 (3.2)		
Primary tumor site, n (%)				
Oral cavity	13 (21.0)	16 (25.8)		
Oropharynx	22 (35.5)	16 (25.8)		
Hypopharynx	10 (16.1)	9 (14.5)		
Larynx	8 (12.9)	12 (19.4)		
Nasopharynx	1 (1.6)	0		
Pharynx	1 (1.6)	1 (1.6)		
Sinus	3 (4.8)	2 (3.2)		
Unknown primary	3 (4.8)	6 (9.7)		
Missing	1 (1.6)	0		
Clinical stage at diagnosis, <i>n</i>	(%)			
I	3 (4.8)	4 (6.5)		
II 	3 (4.8)	6 (9.7)		
III	9 (14.5)	15 (24.2)		
IVa	28 (45.2)	23 (37.1)		
IVb	10 (16.1)	12 (19.4)		
IVc	8 (12.9)	2 (3.2)		
Missing	1 (1.6)	0		
Metastasis and recurrence				
Local only	17 (27.4)	19 (30.6)		
Distant only	19 (30.6)	18 (29.0)		
Both	24 (38.7)	24 (38.7)		
Missing	2 (3.2)	1 (1.6)		
Number of prior chemothera	n (%)	22 (52 2)		
1	28 (45.2)	33 (53.2)		
2	29 (46.8)	22 (35.5)		
3	3 (4.8)	5 (8.1)		
4	1 (1.6)	2 (3.2)		
Missing	1 (1.6)	0		
Prior chemotherapy for R/M	disease, $n(\%)$			
Yes	42 (67.7)	41 (66.1)		
No	20 (32.3)	21 (33.9)		
Other prior anticancer thera	pies, n (%)			
Surgery	48 (77.4)	45 (72.6)		
Kadiotherapy	56 (90.3)	60 (96.8)		
Missing	1 (1.6)	0		

Continued

Table 1. Continued

	Afatinib	Cetuximab					
	(N = 62)	(N = 62)					
EGFRvIII mutation status, <i>n</i> (%)							
Positive	0	0					
Negative	25 (40.3)	28 (45.2)					
Unknown	37 (59.7)	34 (54.8)					
p16 status, n (%)							
Positive	9 (14.5)	8 (12.9)					
Negative	25 (40.3)	23 (37.1)					
Unknown	28 (45.2)	31 (50.0)					

^aPatient with ECOG performance status 2 was recorded as a protocol violation.

^bAny chemotherapy received since diagnosis. Note: Percentage calculated from the total population; some factors total <100% due to missing data.

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

CI 0.70–1.62, P = 0.78, supplementary Figure S3, available at *Annals of Oncology* online).

patient-reported outcomes. During both stages, PRO outcomes were comparable in both treatment groups for global health status, pain and swallowing (supplementary Figure S4, available at *Annals of Oncology* online).

PK assessments. Afatinib plasma levels reached steady state by day 15 and trough plasma concentrations were generally stable over the observation period (56 days), with no apparent differences between stages I and II (supplementary Figure S5A, available at *Annals of Oncology* online). Afatinib plasma concentrations were similar across different administration routes (oral tablet, gastric feeding tube and dispersion) (supplementary Figure S5B, available at *Annals of Oncology* online).

EGFRvIII and p16 analysis. None of the 53 patients (25 afatinib, 28 cetuximab) with tumor samples for EGFRvIII mutation analysis harbored the EGFRvIII mutation. Of 65 patients (34 afatinib, 31 cetuximab) with samples for p16 analysis, 48 (74%) tested negative for p16 (25 afatinib, 23 cetuximab). Two responses were observed in p16-positive patients by ICR, one in each treatment group (supplementary Table S2, available at *Annals of Oncology* online).

AEs, dose reductions and treatment discontinuation. During stage I, 59/61 afatinib- and 51/60 cetuximab-treated patients had a DRAE, of which rash/acne and diarrhea were most common (Table 2). DRAEs led to dose reduction in 18 [29.5%; 9 (14.8%) rash/acne, 5 (8.2%) diarrhea, 3 (4.9%) mucosal inflammation and 1 (1.6%) fatigue] afatinib- and two (3.3%; one rash and one rash/skin fissures) cetuximab-treated patients. Discontinuation due to DRAEs occurred in 14 (23%) and 3 (5%) afatinib- and cetuximab-treated patients. Serious AEs that



Figure 2. (A) Primary end point: mean tumor shrinkage^a after treatment (stage I); (B) mean percentage change^b in tumor shrinkage (stage I). ^aTumor shrinkage was defined as the change from baseline in the smallest postrandomization sum of the longest diameters of the target lesions; adjusted mean change. Only patients with baseline and at least one postrandomization measurement are included in these analyses. Independent central review, n = 48 for afatinib and n = 48 for cetuximab; investigator review, n = 50 for afatinib and n = 55 for cetuximab. ^bAdjusted mean change. Only patients with baseline and at least one postrandomization measurement central review, n = 47 for afatinib and n = 48 for cetuximab; investigator review, n = 50 for afatinib and n = 55 for cetuximab.

were possibly treatment-related occurred in 19 (31.1%) and 2 (3.3%) of afatinib- and cetuximab-treated patients, of which one was fatal (grade 5 pyrexia in the afatinib group). Similar AEs were reported during stages I and II; grade \geq 3 rash/acne, diarrhea and dry skin occurred most often in stage II (Table 2).

discussion

This is the only reported randomized trial to compare an irreversible, small molecule ErbB family blocker with cetuximab in patients with R/M HNSCC who progressed after platinum-based chemotherapy and investigate dual sequential treatment with these ErbB family-targeting agents. Afatinib showed comparable activity to cetuximab and the sequential treatment appeared to sustain clinical benefit, demonstrating a lack of cross-resistance between the two agents. In addition, afatinib levels were similar across different administration routes, suggesting that optimal doses of afatinib can be achieved in tube-feeding patients.

The primary outcome measure of tumor shrinkage as a continuous variable (assessed using RECIST) was chosen as it provides distinct power advantages compared with otherwise identical trial designs that use categorical outcomes [21]. Continuous outcome measures can enable smaller, more efficient randomized trials and randomized trials are generally more informative than single-arm studies with historical controls. Here, tumor shrinkage and response rate results were exactly concordant and demonstrate that the study design using the continuous outcome variable did not influence findings.

Evidence of disease control was visible in both crossover treatment arms with sequential EGFR/ErbB-targeting therapy using cetuximab followed by afatinib or vice versa. This finding may be clinically meaningful, especially as few approved therapies and no targeted agents are available in this treatment setting and non-cross-resistance with any other commonly used agents is likely (e.g. cytotoxic chemotherapy). This is the first report in HNSCC where PD under treatment with an EGFR-targeting monoclonal antibody does not necessarily induce resistance to a subsequent small molecule ErbB-targeted agent. However, it is unclear what precise mechanism of action of afatinib this relates to and further mechanistic insights and biomarker discovery are required to decipher this. It is interesting to note that HER2 is altered in 3%–5% of HNSCC tumors as recently reported by TCGA and this could be a potential mechanism by which afatinib acts after failure [4].

We were unable to identify EGFRvIII mutations in 53 samples tested, and taken together with a report of head and neck cancer exome sequencing that also could not identify EGFRvIII mutations at the DNA level in 74 samples [22], there is no clear evidence that EGFRvIII is present at a meaningful frequency in HNSCC populations [4]. While preclinical data showed that afatinib potently inhibits EGFRvIII(+) cells, this is unlikely to be the underlying mechanism of action in HNSCC or differential activity compared with cetuximab.

Frequency of grade \geq 3 DRAEs was greater with afatinib than cetuximab, with grade \geq 3 diarrhea and rash accounting for more dose reductions and discontinuations in the afatinib group, although this did not translate into efficacy differences. Despite the greater proportion of DRAEs observed with afatinib, significant deterioration in PRO end points was not noted compared with cetuximab. Proactive management of AEs associated

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removal of ineligible patients from the study.

with EGFR-targeted therapies is essential and frequently successful in allowing patients to continue treatment [23, 24]. Of note, more recent studies with afatinib, including phase III trials in HNSCC, recommend a starting dose of 40 mg (instead

of 50 mg) based on safety evaluations (e.g. NCT01345682, NCT01345669 and NCT01856478).

Our data suggest that afatinib has comparable activity to cetuximab in R/M HNSCC. Evidence of a lack of cross-resistance

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Figure 3. Waterfall plot of maximum percentage tumor shrinkage in stage I and stage II according to independent central review. Patients were required to have a baseline and postbaseline measurement for inclusion in the assessment of the tumor shrinkage (and Response Evaluation Criteria In Solid Tumors assessment). Factors contributing to missing data points included adverse events (AEs) leading to withdrawal, death before the first scan assessment at 8 weeks, patient withdrawal from the study, patient crossover to stage II due to an AE without a follow-up assessment being carried out in stage I and the

original articles



Figure 4. Treatment duration and disease control in stages I and II. Each line denotes one patient and the blue portion is the treatment duration with afatinib and yellow corresponds to cetuximab. The solid dot associated with each line indicates the patient achieved disease control (DC) when treated with afatinib or cetuximab (again, differentiated by color) according to investigator review.

CTCAE grades	Stage I			Stage II				
	Afatinib ($N = 61$)		Cetuximab ($N = 60$)		Cetuximab \rightarrow afatinib (N = 36)		Afatinib \rightarrow cetuximab (N = 32)	
	Total, <i>n</i> (%)	59 (96.7)	32 (52.5)	51 (85.0)	11 (18.4)	31 (86.1)	17 (47.2)	22 (68.8)
Rash/acne ^a	48 (78.7)	11 (18.0)	46 (76.7)	5 (8.3)	20 (55.6)	9 (25.0)	14 (43.8)	4 (12.5)
Diarrhea	48 (78.7)	9 (14.8)	12 (20.0)	0	19 (52.8)	4 (11.1)	1 (3.1)	0
Stomatitis ^{a,b}	21 (34.4)	7 (11.5)	14 (23.3)	0	8 (22.2)	1 (2.8)	2 (6.3)	0
Fatigue ^a	20 (32.8)	3 (4.9)	13 (21.7)	1 (1.7)	4 (11.1)	1 (2.8)	2 (6.3)	0
Nausea	17 (27.9)	1 (1.6)	12 (20.0)	1 (1.7)	5 (13.9)	0	1 (3.1)	0
Vomiting	10 (16.4)	1 (1.6)	8 (13.3)	0	3 (8.3)	0	1 (3.1)	0
Dry skin	9 (14.8)	0	15 (25.0)	0	4 (11.1)	2 (5.6)	3 (9.4)	1 (3.1)
Dehydration	8 (13.1)	5 (8.2)	1 (1.7)	0	0	0	0	0
Decreased appetite	5 (8.2)	3 (4.9)	8 (13.3)	0	6 (16.7)	1 (2.8)	2 (6.3)	0
Nail effects ^{a,c}	4 (6.6)	0	6 (10.0)	1 (1.7)	2 (5.6)	0	3 (9.4)	0
Ocular effects ^{a,d}	4 (6.6)	0	6 (10.0)	1 (1.7)	5 (13.9)	1 (2.8)	0	0
Constipation	2 (3.3)	0	7 (11.7)	0	0	0	1 (3.1)	0

^aGrouped terms of closely related AEs. Table sorted by afatinib 'all grades' in stage I.

^bDuring stage I, the most frequently reported treatment-related AE within the grouped term 'stomatitis' was mucosal inflammation (afatinib 21.3% and cetuximab 13.3%).

^cDuring stage I, the most frequently reported AE within the grouped term 'nail effects' was paronychia (afatinib 4.9% and cetuximab 6.7%).

^dDuring stage I, the most frequently reported AEs within the grouped term 'ocular effects' were conjunctivitis (afatinib 3.3% and cetuximab 8.3%) and periorbital edema (afatinib 3.3% and cetuximab 0%).

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events.

between these agents demonstrated by sustained clinical benefit of sequential EGFR/ErbB family therapy in a subgroup of patients is novel and potentially clinically meaningful, especially if biomarkers could be used to select patients.

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disclosure

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appendix

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