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A phase I study afatinib/carboplatin/paclitaxel induction chemotherapy followed by standard chemoradiation in HPV-negative or high-risk HPV-positive locally advanced stage III/IVa/IVb head and neck squamous cell carcinoma

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Abstract

Introduction—Afatinib is an ErbB family receptor inhibitor with efficacy in head and neck squamous cell carcinoma (HNSCC). A phase I trial was conducted to determine the maximally tolerated dose (MTD) of afatinib in combination with carboplatin and paclitaxel as induction chemotherapy (IC).

Material and Methods—Patients with newly diagnosed, locally advanced HPV-negative or HPV-positive HNSCC with a significant smoking history were enrolled. Afatinib alone was given daily for two weeks as lead-in and subsequently given with carboplatin AUC 6 mg/ml*min and paclitaxel 175 mg/m^2 every 21 days as IC. Afatinib was started at a dose of 20 mg daily and dose escalated using a modified Fibonacci design. After completion of IC, afatinib was discontinued and patients received concurrent cisplatin 40 mg/m^2 weekly and standard radiation. Toxicity was assessed using CTCAE version 4.0.

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Conflict of interest

All other authors have no conflict of interest.

Results—Seven of nine patients completed afatinib lead-in and IC. Five patients had partial response and two patients had stable disease after IC. Dose level 1 (afatinib 20 mg) was well tolerated with one grade 3 (ALT elevation) and one grade 4 (neutropenia) toxicities. However, dose level 2 (afatinib 30 mg) was not well tolerated with nine grade 3 (pneumonia, abdominal pain, diarrhea, pancytopenia, and UTI), two grade 4 (sepsis) and one grade 5 (death) toxicities.

Conclusions—The MTD of afatinib given with carboplatin AUC 6 mg/ml*min and paclitaxel 175 mg/m^2 is 20 mg daily. Combination of afatinib at doses higher than 20 mg with carboplatin and paclitaxel should be administered with caution due to the toxicities.

Keywords

afatinib; carboplatin; paclitaxel; head and neck squamous cell carcinoma; efficacy; toxicity; ABCB1; phase I trial

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) causes a significant morbidity worldwide with the incidence of approximately 550,000 cases per year [1]. The most common risk factors are tobacco use and human papillomavirus (HPV) infection [2,3]. At diagnosis, a majority of patients present with locally advanced disease, but patients with HPV-positive HNSCC have a more favorable survival compared to patients with HPV-negative HNSCC [4–6]. However, there is a clear interaction between tobacco use and HPV-related carcinogenesis reflected by the worse survival of patients with HPV-positive HNSCC and smoking history compared to non-smokers [6,7]. While overall survival (OS) is 80–90% for HPV-positive non-smokers given concurrent chemoradiation (CRT), HPV-negative or HPV-positive smokers have a significantly lower OS ranging from 40–70% [6,8,9]. For these patients, various strategies have been explored to improve the survival such as induction chemotherapy (IC) followed by CRT [10–12]. However, these IC regimens have proven to be relatively toxic, and there is a clear need for an effective regimen that is less toxic with the potential for improved efficacy in an intermediate to high risk population.

Epidermal growth factor receptor (EGFR) has been well established as a biomarker of poor prognosis and a therapeutic target [13–16]. The most studied EGFR inhibitor in HNSCC is cetuximab which is a monoclonal antibody against EGFR and approved by Food and Drug Administration for use as a monotherapy or a combination with radiation or chemotherapy in HNSCC [17]. When cetuximab was combined with chemotherapy as a part of IC regimens, the efficacy and safety were favorable with a high response rate [18,19]. However, cetuximab may induce infusion reaction, and its weekly and intravenous administration is inconvenient for some patients [20]. Afatinib is an irreversible inhibitor of the ErbB-family tyrosine kinase receptors, EGFR (erbB1/HER1), HER2 (erbB2), and HER4 (erbB4) and administered orally with daily dosing [21,22]. In a randomized phase II trial of cetuximab or afatinib in 124 patients with recurrent and/or metastatic HNSCC, the disease control rate of afatinib was comparable to cetuximab (afatinib 50% and cetuximab 56.5%) [21]. In a randomized phase III trial, afatinib demonstrated a statistically significant improvement in progression-free survival (PFS) over methotrexate monotherapy in 483

patients with recurrent and/or metastatic HNSCC (median 2.6 months versus 1.7 months, respectively; p=0.030) [23]. In addition, current data suggest that afatinib may be more effective than methotrexate in patients with recurrent and/or metastatic p16-negative compared to p16-positive HNSCC (Median PFS p16-negative: afatinib 2.7 months vs. methotrexate 1.6 months; p16-positive: afatinib 2.0 months vs. methotrexate 2.3 months) [24].

However, the objective response rate of afatinib as a monotherapy is modest at 10% in patients with recurrent and/or metastatic HNSCC [23]. Therefore, afatinib has been evaluated in combinations with commonly used chemotherapeutic agents including platinums, 5-FU, and taxanes [25]. In the phase Ib study, a treatment-related grade 5 toxicity was observed in the afatinib, cisplatin, and paclitaxel arm, but none in the afatinib, cisplatin, and 5-FU arm, suggesting the severe toxicity may be related to paclitaxel. Afatinib is known to modulate ABC transporters, ABCB1 (a.k.a. Pglycoprotein) and ABCG2 (a.k.a. BCRP), in several cancer cell lines by competitively blocking substrate transport and downregulating mRNA and protein expression of the transporters [26,27]. Paclitaxel is an ABCB1 and ABCG2 substrate, and platinum is an ABCG2 substrate [28–30]. Because our hypothesis is that patients with the *ABCB1* variants who are already at risk of increased chance of paclitaxel-related toxicities may have had an even greater risk of toxicities given the combination of afatinib and paclitaxel, we evaluated the *ABCB1* rs1045642 (C3435T) and rs2032582 (G2677T) and not *ABCG2* variants for their association with paclitaxel-related toxicities as the literature supports this association [30].

The current study was to select newly diagnosed, locally advanced HNSCC patients with poor prognosis according to HPV status and smoking habits, in whom the need for additional therapeutic options is pressing, and demonstrate the safety of adding afatinib to the established IC regimen of carboplatin and paclitaxel.

MATERIAL AND METHODS

Patient Selection

Eligible patients had histologically confirmed diagnosis of squamous cell carcinoma, operable or inoperable tumors, stage III (T3N0-1) and IVA-B (T1-4 N2-3M0 or T4N0-1M0) of oral cavity, oropharynx, hypopharynx and larynx. For patients with oropharynx primary, either HPV negative or HPV positive with a > 10 pack year tobacco history or current smokers were eligible. HPV status was determined before the enrollment in only non-smokers with oropharynx primary by HPV *in-situ* hybridization and/or p16 immunostaining. Patients had measurable disease of primary, nodes or both by clinical and radiographic methods per RECIST v1.1. Patients had no prior therapy, including surgery with curative intent, chemotherapy, radiation therapy, immunotherapy, EGFR targeted therapies, or any other investigational agents. Only ECOG performance status of 0 or 1 was allowed. Patients had normal hepatic, renal and bone marrow function. Patients with a history of allergic reactions attributed to compounds of similar chemical or biological composition to afatinib, or other agents used in study were excluded (clinicaltrials.gov registration number: NCT01732640).

Study Design

Initially this study was designed as a phase I/II trial with a planned enrollment of 6–18 patients in the phase I portion and 53 patients in the phase II portion. However, the phase II portion of the study was aborted due to the unexpected grade 4 and 5 toxicities and poor accrual. We report the phase I portion of the study alone. Eligible patients were treated with a 14-day lead-in with afatinib alone and subsequently treated with 2 cycles of IC with carboplatin AUC 6 mg/ml*min IV Day 1, paclitaxel 175 mg/m^2 IV Day 1, and oral afatinib as a continuous daily dosing. Each cycle was repeated every 21 days (Figure 1). Three dose levels of afatinib were planned: 20, 30, and 40 mg. The dose escalation of the phase I portion commenced in a standard 3+3 Fibonacci design.

Dose limiting toxicity (DLT) was defined as grade 3 or 4 neutropenia (i.e., absolute neutrophil count < 1000 cells/mm^3) that was associated with a fever > 38.5°C or lasting longer than 5 days; grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia; and any grade 3 or 4 non-hematologic toxicity per CTCAE criteria which were probably or definitely related to study therapy. During the CRT, stomatitis, pharyngitis, mucositis, or dermatitis were not considered to be a dose limiting toxicity unless it was grade 4 that did resolve to < grade 2 with a radiation treatment break (not to exceed 10 days) or with withholding chemotherapy (not to exceed 2 weekly doses). The maximally tolerated dose (MTD) was defined as the dose of afatinib in which < 2 of 6 patients experience a DLT with the next higher dose having at least 2 of up to 6 patients experiencing a DLT. No dose escalations or de-escalations are permitted within each subject's treatment.

After completion of 2 cycles of IC, patients were assessed for response by CT/MRI and clinical exam. After the IC, all patients received CRT with weekly cisplatin 40 mg/m^2 IV. The sequential CRT began 2–3 weeks after the completion of the second cycle of IC. The patients were evaluated with a MRI or CT, and FDG PET approximately 12 weeks after completion of CRT.

Statistics

The primary objective of this phase I trial was to determine the MTD or recommended phase II dose of afatinib in a combination with fixed doses of carboplatin and paclitaxel as an IC regimen. The dose escalation of the phase I commenced in a standard 3+3 design. Subjects were assigned to a dose level in the order of study entry.

ABCB1 single nucleotide polymorphism (SNP) genotyping

Genomic DNA was extracted from whole blood using standard methods. Samples were genotyped for *ABCB1* rs1045642 (C3435T) and rs2032582 (G2677T) via Sanger sequencing using two different amplification reactions. A 251-base pair target region was amplified using 100 μM input forward (5'-TAG CAA ACT TTG GGA CAG GAA TAA T-3') and reverse (5'-AGT AAG CAG TAG GGA GTA ACA AAA TAA CAC-3') primers to determine the *ABCB1* rs2032582 (G2677T) SNP allele. A 415-base pair target region was amplified using 100 μM input forward (5'-CAC AAG GAG GGT CAG GTG AT-3') and reverse (5'-TGT TTT CAG CTG CTT GAT GG-3') primers for the *ABCB1* rs1045642 (C3435T) SNP allele. The reactions were amplified using 100 ng of genomic DNA for the

ABCB1 rs2032582 (G2677T) amplicon and 50 ng of genomic DNA for the *ABCB1* rs1045642 (C3435T) amplicon at a volume of 50 μL using 2X PCR Master Mix (Promega Corporation, Madison, WI) and water. The amplifications occurred under the following PCR cycling conditions: Initial denaturation, 94°C for 2 minutes; 35 cycles of 1 minute of cyclic denaturation at 94°C, 30 seconds of cyclic annealing at 60°C, 1 minute of cyclic extension at 72°C; final extension for 10 minutes at 72°C. The product amplicons were purified using the QuickStep™2 PCR Purification Plate and 10 μL QuickStep™2 SOPE Resin (Edge BioSystems, Gaithersburg, MD). Samples were sequenced with 3–5 μL of purified amplicon and 2 μM input of each respective forward primer using the BigDye® terminator v1.1 Cycle Sequencing Kit (Applied Biosystems, Austin, TX) under the following thermocycler conditions: Initial denaturation, 96°C for 1 minute; 25 cycles of 10 seconds of cyclic denaturation at 96°C, 5 seconds of cyclic annealing at 50°C, 4 minutes of cyclic extension at 60°C. The amplified product was purified using a QuickStep™2 PCR Purification Plate and analyzed on the Applied Biosystems 3730xl DNA Analyzer.

Determination of the HPV tumor status by immunohistochemistry (IHC) and/or in situ hybridization (ISH) for tumors from primary oropharynx site

Immunohistochemistry was performed to determine p16 expression using a p16 mouse monoclonal antibody (predilute, mtm-CINtech, E6H4) and high-risk HPV status was determined by ISH using a cocktail probe (GenPoint HPV Probe Cocktail, Dako) as previously described [6]. The p16 IHC positivity was defined as strong diffuse staining in greater than 70% of the tumor cells.

RESULTS

Patient Characteristics

From April, 2013 to July, 2014, ten patients were consented, and nine patients were enrolled on the trial from two participating institutions, Johns Hopkins University and Vanderbilt University. One patient failed the screening. Characteristics of the patients are listed in Table 1. Of nine enrolled patients, eight were male, and one was female. Median age was 58. ECOG performance status was 0 for six patients and 1 for three patients. Primary sites were one oral cavity, six oropharynx and two larynx. Within the six oropharyngeal tumors, the high-risk HPV and/or strong p16-staining status were positive in three, negative in two, and unknown in one.

Efficacy

Five patients had partial response and two patients had stable disease after the completion of the IC regimen (Figure 2). One patient with the most tumor shrinkage (81.5%) received afatinib 30mg daily in the dose level 2 and had HPV-positive disease. Two other patients in the dose level 2 withdrew prior to the first planned response assessment due to toxicities and death.

Toxicity Assessment

Toxicity was considered evaluable if a patient received any therapy on the study. Six patients in the dose level 1 with afatinib 20 mg tolerated the IC regimen well with one grade

3 (ALT elevation) and one grade 4 (neutropenia) toxicities (Table 2). However, dose level 2 with afatinib 30 mg was not well tolerated in 3 patients with nine grade 3 (pneumonia, abdominal pain, diarrhea, pancytopenia, and UTI), two grade 4 (sepsis) and one grade 5 (death) toxicities. Only one of the three completed the IC regimen. The severity of profound and early onset pancytopenia seen in these two patients was unusual, particularly in newly diagnosed patients with ECOG 0 or 1 who have never been treated with chemotherapy, and these toxicities were attributed to be study drug related in combination with every 21 day carboplatin and paclitaxel.

ABCB1 Genotyping Results

DNA samples were available from nine of nine enrolled patients. One of the nine patient did not consent for research use of the collected biospecimen; therefore, eight DNA samples were tested for SNP in *ABCB1* rs1045642 (C3435T) and rs2032582 (G2677T; Table 3). While the patient with grade 4 sepsis had *ABCB1* rs1045642 C/C and rs2032582 G/G genotypes, the patient with grade 5 toxicity had *ABCB1* rs1045642 T/T and rs2032582 T/T genotypes which have been associated with increased propensity to develop myelosuppression given paclitaxel [31].

DISCUSSION

The combination of afatinib with carboplatin and paclitaxel as an IC regimen was well tolerated at the dose level of 1 (20 mg) in patients with newly diagnosed, locally advanced HNSCC. The 20 mg daily dosing is consistent with the phase II dosing determined by a phase Ib trial of afatinib in a combination with cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil (5-FU) in patients with advanced solid tumors which included patients with unresectable and/or metastatic cancers in gastrointestinal, head and neck, gynecologic, skin, lung, and other disease sites [25]. During the dose escalation of the arm with afatinib, cisplatin, and paclitaxel, two of the five patients experienced DLT at the 30mg dose, and the phase II dose of afatinib 20 mg with cisplatin 75 mg/m^2 and paclitaxel 175 mg/m^2 was determined. During the dose escalation of the arm with afatinib, cisplatin and 5-FU, two of the three patients experienced DLT in the afatinib 30 mg, cisplatin 100 mg/m^2, and 5-FU 1000 mg/m^2 group and the afatinib 40 mg, cisplatin 75 mg/m^2, and 5-FU 750 mg/m^2 group resulting the phase II dose of afatinib to be 30 mg with cisplatin 75 mg/m^2 and 5-FU 750 mg/m^2. This prior study and our data suggest that the combination of afatinib with a paclitaxel-containing regimen may be more toxic.

In close assessment of our patients who experienced DLTs, both patients experienced profound early onset pancytopenia during the first cycle considering they had been chemotherapy naive. The first patient with the DLT was a 48-year old woman with T4N0M0 laryngeal primary disease. She tolerated two weeks of afatinib lead-in treatment well at a dose of 30 mg. After the first cycle of the IC regimen, she was admitted to the hospital for severe abdominal pain and diarrhea on Day 4 and discharged with oral antibiotics on Day 6. She was hospitalized again on Day 8 with intractable abdominal pain, diarrhea, weakness, hypotension and tachycardia. She was admitted to medical intensive care unit for bilateral

pneumonia, sepsis and pancytopenia (white blood cell count of 0.2 K/cu mm, hemoglobin 7.5 g/dL and platelet count 17 K/cu mm). She was discharged from the hospital on Day 18.

The second patient with the DLT was a 58-year old man with history of hypertension, heavy smoking, heavy drinking, and HPV-negative T4bN2cM0 base of tongue primary disease. He tolerated two weeks of afatinib lead-in treatment at a dose of 30 mg. After the first cycle of the IC, he developed shortness of breath with cough, fatigue, low grade fever and abdominal pain with diarrhea on Day 3 evening. He developed excruciating pain, diarrhea and shortness of breath on Day 4 morning. He was instructed to go to the Emergency Department (ED). While he was walking down stairs to go to ED, he collapsed and lost consciousness. When the emergency response service arrived, he was pulseless. His cardiac rhythm showed v-fibrillation which turned into pulseless electrical activity after a shock. Paramedics successfully resuscitated him to normal sinus rhythm. He was brought into ED and placed on a mechanical ventilator. At this point, white blood cell count was 0.25 K/cu mm, hemoglobin was 11 g/dL, and platelet count was 69 K/cu mm. His chest X-ray showed diffuse consolidation throughout the right lung. The patient's family discussed prognosis with an ED physician and decided to withdraw care. The patient expired.

Our experience raises a concern for a drug interaction among afatinib, carboplatin and paclitaxel although there was no systemic alteration of paclitaxel pharmacokinetics noted on a small number of patients in the phase Ib trial of afatinib, cisplatin, and paclitaxel [25]. Because of the small sample size in the previous study and difference in the study design (our study had 2 weeks of lead-in period with afatinib alone), an interaction cannot be ruled out. While no plasma or intratumoral pharmacokinetics or pharmacodynamics were performed to evaluate direct modulation of ABCB1 and ABCG2 by afatinib in our trial, an interaction at the drug transporter level is a plausible explanation for the increased toxicity observed at 30 mg of afatinib. Paclitaxel is a substrate of both transporters with an association between *ABCB1* 3435C>T and *ABCB1* 2677G>T genotypes and neutropenia [29,31,32]. Of note, ABCB1 is very important in myeloid stem cells [33]. Thus, afatinib may be inhibiting the myeloid stem cell's ability to efflux paclitaxel resulting in a high intracellular paclitaxel concentration and subsequently causing the early onset and profound pancytopenia as we have observed. We speculate whether the lead-in with afatinib had saturated the ABCB1 transporter when paclitaxel was infused worsening the toxicity. Indeed, the patient with grade 5 toxicity had the variant *ABCB1* genotypes which may have predisposed to more profound pancytopenia. Carboplatin and cisplatin are not substrates of ABCB1 but are of ABCG2 [28]. While association between the *ABCG2* variant (rs2231142, C421A) and improved median PFS in ovarian cancer patients treated with platinum and taxanebased chemotherapy has been reported, data are not available assessing increased toxicities [34].

Furthermore, our study opens a question whether addition of afatinib 20 mg daily which is only 50% of the recommended monotherapy dose to chemotherapy would be sufficient to exert anti-tumor activity or render synergistic activity compared to delivering chemotherapy alone. Even though afatinb 40 mg daily is the recommended dose, the majority of patients require dose reductions to 30 mg (>50%) or 20 mg (17%) due to long-term tolerability issues [35]. In a recent study, the dose reductions did not appear to compromise clinical

activity in EGFR mutant-positive non-small cell lung cancer patients suggesting that it may be acceptable to indivudalize therapy based on tolerability [36]. Therefore, evaluation of afatinib 20 mg daily in combination with chemotherapy may warrant further evaluation for efficacy beyond the toxicity evaluation in newly diagnosed patients and in a combination with established treatments in HNSCC such as chemotherapy and radiation therapy. In addition, future development should consider the HPV/p16 status in the clinical trial design considering less clinical efficacy was observed in patients with recurrent and/or metastatic p16-positive compared to p16-negative HNSCC given afatinib monotherapy [24]. Further development of afatinib in combination regimens will require additional studies to identify the appropriate dose and dosing schedule.

While our data are limited, it sufficiently supports that the MTD of afatinib given with carboplatin AUC 6 mg/ml*min and paclitaxel 175mg/m2 every 21 day is 20 mg daily, and the combination of afatinib with paclitaxel-containing chemotherapy regimens should be administered with caution due to the toxicities potentially related to paclitaxel clearance. An alternative would be to consider evaluating daily afatinib with weekly doses of carboplatin and paclitaxel instead of every 21 day doses. Further studies are required to delineate the role of afatinib in management of newly diagnosed HNSCC.

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Highlights

1. Maximum tolerated dose of afatinib with carboplatin/paclitaxel is 20 mg daily.
2. Afatinib at doses >20 mg with carboplatin/paclitaxel should be used with caution.
3. Afatinib needs further evaluation in management of newly diagnosed HNSCC.

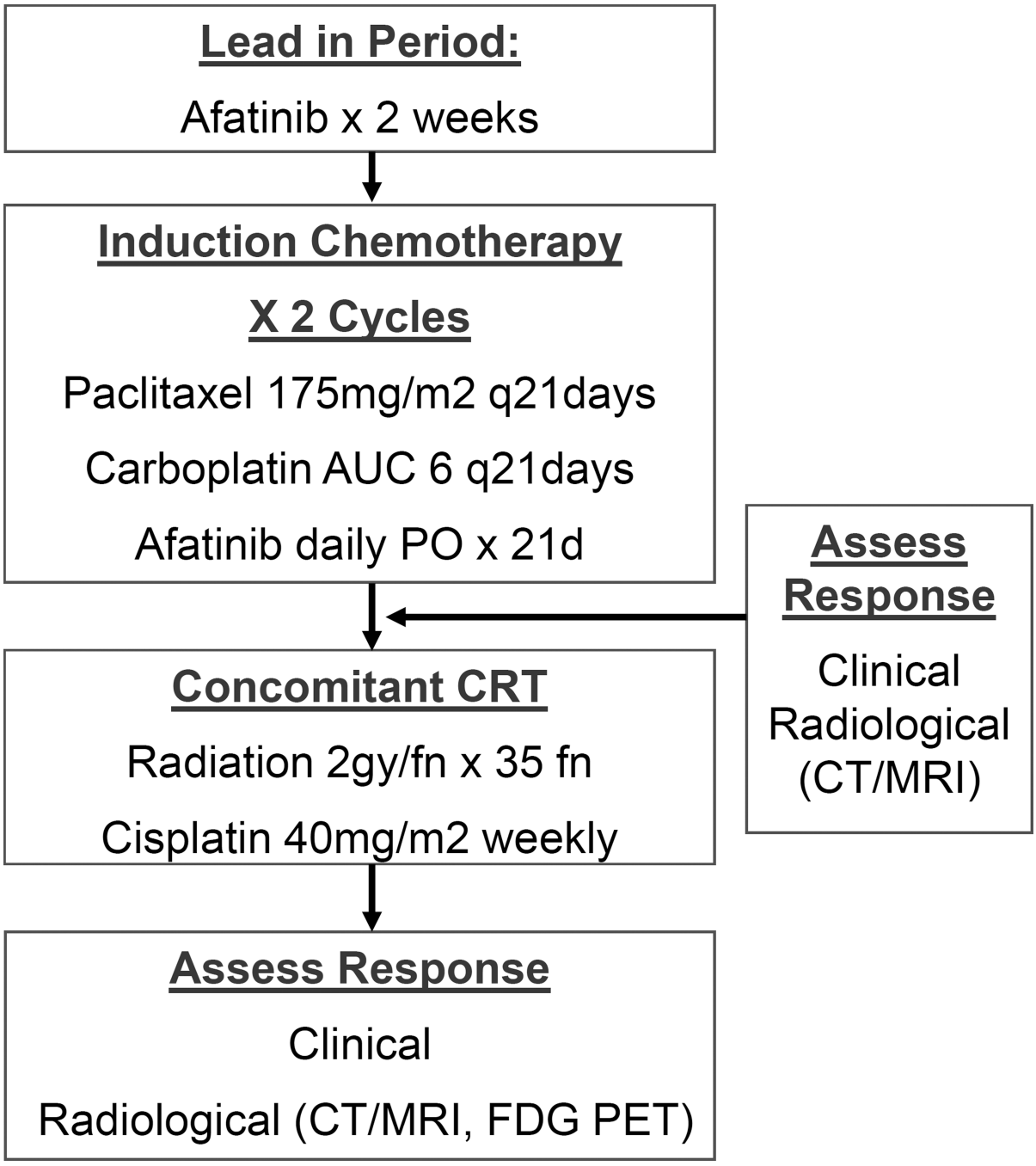

Figure 1.
Study Schema

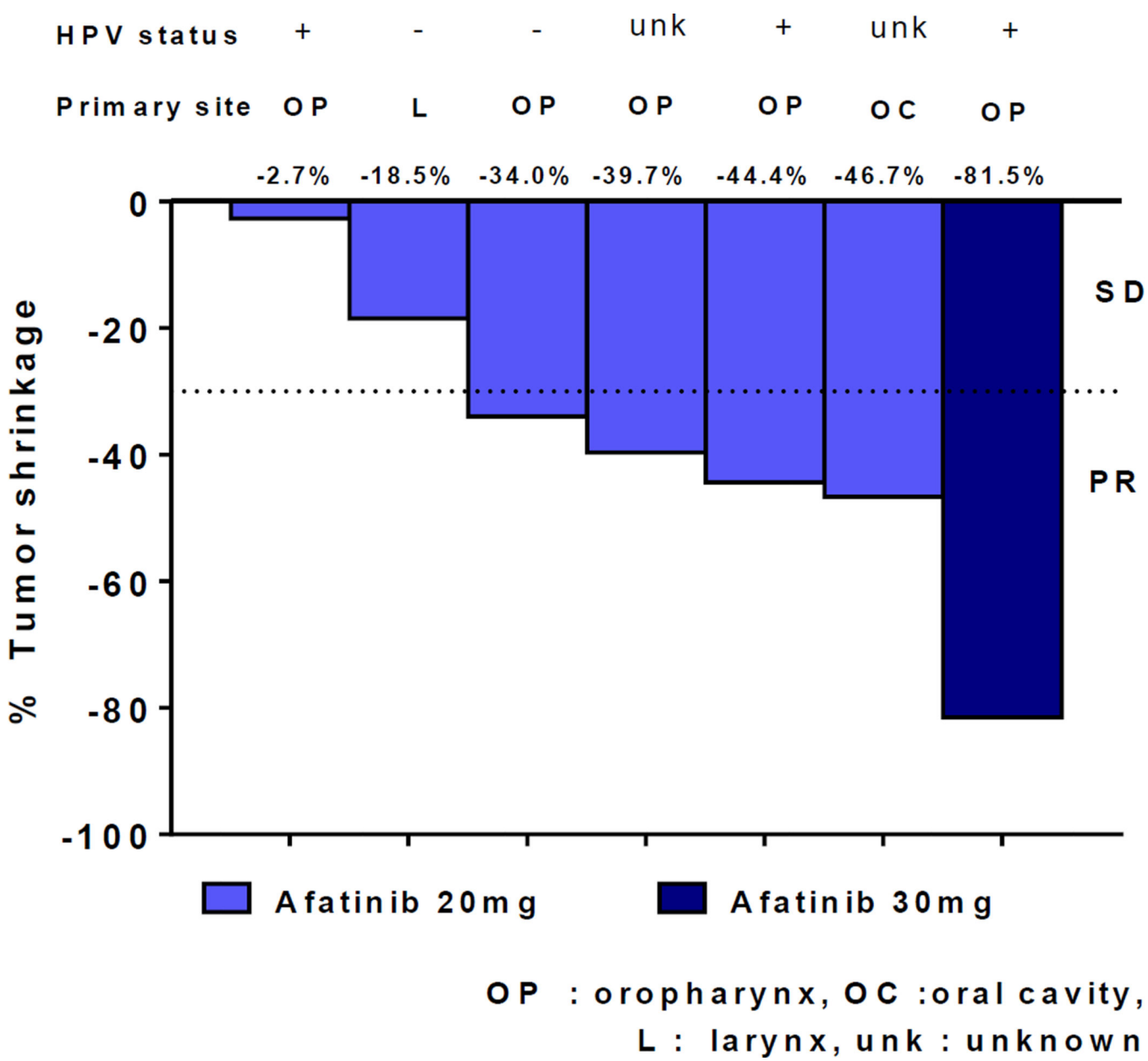

Figure 2.
Waterfall plots of response rates after the induction chemotherapy; afatinib, carboplatin and paclitaxel.

Table 1

Patient Demographic and Clinical Characteristics

Gender		N (%)
	Male	8 (88.9)
	Female	1 (11.1)
Age [years]		
	Median	58 (48 – 68)
	< 60 [N (%)]	5 (55.6)
	≥ 60 [N (%)]	4 (44.4)
Race		N (%)
	White/Caucasian	6 (66.7)
	Black/African American	3 (33.3)
ECOG Status at Baseline		N (%)
	0	6 (66.7)
	1	3 (33.3)
Disease Site		N (%)
	Larynx	2 (22.2)
	Oropharynx	6 (66.7)
	Oral Cavity	1 (11.1)

Table 2

Number of patients with grade 3–5 toxicity possibly, probably, or definitely attributing to afatinib by CTCAE version 4.0

Dose Level	Adverse Event	Grade 3	Grade 4	Grade 5
Dose Level 1				
	Neutropenia		1	
	Elevated ALT	1		
Dose Level 2				
	Pneumonia	2		
	Abdominal Pain	2		
	Diarrhea	1		
	Pancytopenia	2		
	UTI	2		
	Death			1
	Sepsis		2	
Total		10	3	1

TABLE 3

ABCB1 single nucleotide polymorphism (SNP) genotyping

Sample ID	HPV Status	ABCB1 RS1045642 (3435C>T)	ABCB1 RS2032582 (2677GT>A)
01001	negative	C/T	G/T
01002	positive	C/T	Inconclusive
01004*	N/A	T/T	T/T
02001	N/A	C/T	Inconclusive
02002#	N/A	C/C	G/G
02003	positive	C/C	G/T
02004	positive	T/T	G/T
02005	positive	T/T	G/T

* Grade 5 toxicity

Grade 4 toxicity