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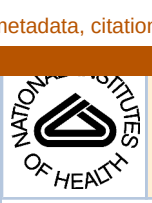

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A Multi-institutional Phase II study of the efficacy and tolerability of Lapatinib in patients with advanced hepatocellular carcinomas

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Abstract

Background—Hepatocellular carcinoma (HCC) is on the rise worldwide. HCC responds poorly to chemotherapy. Lapatinib is an inhibitor of EGFR and HER2/NEU both implicated in hepatocarcinogenesis. This trial was designed to determine the safety and efficacy of lapatinib in HCC.

Methods—A Fleming phase II design with a single stage of 25 patients with a 90% power to exclude a true response rate of < 10% and detect a true response rate of ≥30% was utilized. The dose of lapatinib was 1,500 mg/d administered orally in 28-day cycles. Tumor and blood specimens were analyzed for expression of *HER2/NEU/CEP17* and status of downstream signal pathway proteins.

Results—Twenty-six patients with HCC enrolled on this study. 19% had one prior therapy. Most common toxicities were diarrhea (73%), nausea (54%) and rash (42%). No objective responses were observed. Ten (40%) patients had stable disease (SD) as their best response including 6 (23%) with SD lasting > 120 days. Median progression-free-survival was 1.9 months and median overall survival 12.6 months. Patients who developed a rash had a borderline statistically significant longer survival. Tissue and blood specimens were available on >90% of patients. No somatic mutations in *EGFR* (exons 18–21) were found. In contrast to our previous findings, we did not find evidence of *HER2/NEU* somatic mutations. PTEN, P-AKT and P70S6K expression did not correlate with survival.

Conclusions—Lapatinib is well-tolerated but appears to benefit only a subgroup of patients for whom predictive molecular or clinical characteristics are not yet fully defined.

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Introduction

The annual mortality rate of hepatocellular carcinoma (HCC) is similar to its annual incidence, indicating a poor prognosis[1]. The rising incidence in the U.S. can be largely attributed to the increase in hepatitis C (HCV)[1]. Most patients with HCC have advanced disease at the time of diagnosis with no satisfactory treatment available[2–10]. The current standard of care in advanced HCC is sorafenib, an agent recently approved by the Food and Drug Administration based on a survival advantage versus placebo[11].

Potential targets for anticancer therapy in HCC include the epidermal growth factor receptor (EGFR) and HER2/NEU (EGFR2 or ERBB2), both over-expressed in HCC and directly implicated in hepatocarcinogenesis. Previous investigations indicate that EGFR is actively expressed in human HCC cells (in up to 85%), and EGF is required for the growth of those cells[12]. A recent study showed that the EGFR inhibitor gefitinib inhibits the growth of orthotopically implanted HCC tumor in the liver of mice[13]. In human studies, EGFR inhibition was found to increase survival in a number of malignancies, although levels of EGFR expression did not correlate with outcome[14–16] The literature contains conflicting data regarding *HER2/NEU* expression and its significance in HCC. Several studies have shown that *HER2/NEU* is rarely over-expressed in HCC and may not play a role in this disease[17–21]. Other studies have demonstrated that *HER2/NEU* is expressed in a significant number of HCCs, and may be an independent prognostic factor[22,23]. We recently reported a novel mutation (H878Y) in the activating tyrosine kinase domain of *HER2/NEU* in HCC, and similar to another Asian study found no *EGFR* mutations in exons 18–21[24,25]. Moreover, the EGFR inhibitor erlotinib demonstrated objective response rates of 0–10% with some patients having prolonged stable disease[26,27].

Lapatinib is a dual inhibitor of EGFR and HER-2/NEU by docking into the ATP binding site of the 2 receptors[28]. This results in inhibition of autophosphorylation and downstream signaling with consequent down-regulation of mitogen-activated protein kinase (MAPK), AKT, and p70S6 kinase (p70S6K) thereby inhibiting tumor growth[29]. In early clinical studies, lapatinib was well tolerated with preliminary evidence of anti-tumor activity in heavily pre-treated patients with various solid tumors. The most common adverse events included rash (25%) and diarrhea (27%)[28,30]. Lapatinib was recently approved by the FDA for use in metastatic breast cancer[31].

Considering all these previous findings, we hypothesized that an inhibitor of both EGFR and HER2/NEU would have activity in HCC. We conducted and report here a phase II study of single agent lapatinib in HCC to evaluate its efficacy and tolerability at a dose of 1500 mg given orally on a daily basis.

Patients and Methods

Eligible patients were required to have histologically confirmed unresectable advanced HCC and measurable disease per RECIST (Response Evaluation Criteria in Solid Tumors)[32], ≤ 1 prior systemic anticancer therapy; patients with prior cryotherapy, radiofrequency ablation, ethanol injection, transarterial chemoembolization or photodynamic therapy were allowed provided that greater than six weeks since that therapy and indicator lesion(s) were outside the area of prior treatment; if the only indicator lesion was inside the prior treatment area, a clear evidence of disease progression should be demonstrated. Additional criteria included life expectancy ≥ 12 weeks, ECOG performance status < 2, Child-Pugh score (CP) of ≤ 7 and the ability to take and absorb oral medications. Patients must have had normal organ function. Exclusion criteria included patients with prior treatment with EGFR inhibitors, > 450 mg/m^2 doxorubicin (given the potential with lapatinib for additional cardiotoxicity, a class effect

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toxicity seen with HER2/NEU inhibitors), major surgery occurring within three weeks prior to the planned start date, brain metastases, history of malignancy other than HCC within the previous 3 years except for adequately treated basal cell carcinoma, squamous cell cancer, or carcinoma of the cervix., uncontrolled intercurrent illness, pregnancy, HIV infection, and concomitant requirement for medication classified as CYP3A4 inducer or inhibitor.

Study Design

This was a National Cancer Institute (NCI) sponsored phase II, open label, multicenter trial led by The Ohio State University with the participation of University of Michigan, Virginia Commonwealth University, H. Lee Moffitt Cancer Center, and University of North Carolina. Lapatinib was provided by NCI/Cancer Therapy Evaluation Program. The primary objective of this study was to evaluate the objective response rate (ORR) as defined by RECIST criteria. Tissue and blood samples were required for all patients. Secondary objectives included evaluation of toxicity, overall survival, assessment of mutations of EGFR and HER2/neu genes and measurement of expression of proteins in signaling pathways relevant to lapatinib including HER2/neu, PTEN, P-Akt, and P70S6K.

Lapatinib administration and dose modifications

The starting dose and schedule of lapatinib was 1,500 mg/d orally without interruption in 28 days cycles. There were 3 levels of dose reductions planned (1250, 1000 and 750 mg/d) with patients taken off study if they needed additional dose reductions.

Assessment of response and toxicity

Radiological assessment was done by CT or MRI (as long as the same consistent measure was used serially) every 8 weeks and responses were measured according to the RECIST criteria. Toxicities were defined by the NCI-CTCAE version 3.0.

Correlative studies

Tissue and Blood acquisition

Either fresh tissue or paraffin embedded tissue from tumor blocks and adjacent normal tissue were required from patients before enrolling on this study. One blood sample (ACD 10 ml tube used for DNA analysis from peripheral blood mononuclear cells) was obtained before patients enrolled on study with a goal to examine germline mutations.

Immunohistochemistry analysis of PTEN, P-AKT and p70S6K

3–5-micron sections of tumor tissue were immunostained with monoclonal antibody 6H2.1 specific for the terminal 100 amino acids of human PTEN (Cascade Bioscience), polyclonal antibody against P-AKT and total AKT (Upstate Biotechnology), or monoclonal antibody against P70S6K and P70S6K (Mab 1A5, Cell Signaling) utilizing a modified avidin-biotin complex technique with antibody dilutions of 1:50– 1:250[33,34]. For p70S6K and pAKT IHC, the MDA-MB-468 cells were used in a cytoblock as a positive control. The cells were fixed and processed in the same fashion as a tissue biopsy (30 min in 10% NBF, standard tissue processing per our histology core). For PTEN, we optimized the protocol for renal tissue, and a positive case was selected and run with each batch. For each batch of IHC run, the appropriate control was run with the same conditions and concentrations, and a negative control was done by following the conditions but substituting the antibody incubation with a “null” PBS incubation. The sections were independently scored by NJ and CE after which a “consensus” scoring session was performed (no discrepancies noted). Most sections had internal controls (normal tissue). A consistent positive control for PTEN are endothelial cells and so when the tumor expressed to similar intensity as endothelial cells in the same specimen, it was scored

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as 2+, as is routine[34]. Decreased expression was scored 1+ and no expression 0. Phosphoprotein expression was compared to total protein expression for each of AKT and P70S6K between HCC and non-neoplastic cells, and scored as no expression, slightly increased (1+) and increased (2+) expression. Furthermore, expression of PTEN, AKT and P-AKT was noted to be nuclear or cytoplasmic in the carcinoma cells.

Assessment of HER2/NEU and enumeration of chromosome 17 (CEP17) by Fluorescence in situ hybridization (FISH)

FISH was done on formalin-fixed paraffin embedded tissue sections (FFPET). 4–6 um sections were placed on positively charged slides, dried and baked overnight at 56° C. The sections were deparaffinized in Hemo-De, dehydrated and air-dried. Subsequently the sections were treated with Pretreatment and Protease Solutions (Abbott Molecular, Downers Grove, IL) according to the manufacturer's protocol. LSI *HER2/NEU* and CEP17 probe mixture (Abbott Molecular, Downers Grove, IL) was applied to the tissue and co-denaturation and hybridization took place using HyBrite (Abbott Molecular, Downers Grove, IL). The following day, slides were washed, dried and counterstained with DAPI. Specimens were analyzed using Zeiss Axioscope-40 equipped with appropriate filters. Fifty cells per sample were scored. A ratio of > 2 of *HER2/NEU* to CEP17 probe signals was considered amplified. Control samples were run concurrently with the patients' samples.

EGFR and HER2/NEU mutation screening

Genomic DNA extracted from FFPET or frozen HCC were treated with sodium dodecyl sulfate and digested with proteinase K, followed by sodium chloride precipitation of protein[35]. The DNA in the supernatant was further purified and recovered by ethanol precipitation. Exons 18 to 21 (including exon-intron junctions and flanking intronic regions) of *EGFR* and exons 19 to 24 of *HER2/NEU* were amplified by PCR[24]. After PCR amplification, primers and free nucleotides were removed by digestion with Exonuclease I and Bacterial Antarctic Alkaline Phosphatase (New England Biolabs, Beverly, MA). PCR products were cycle sequenced at the Ohio State University Plant-Microbe Genomics Facility, using Applied Biosystems reagents on an ABI 3730. The resulting DNA sequences were compared using the online multiple sequence alignment program ClustalW2 (https://www.ebi.ac.uk/Tools/clustalw2/index.html). Sequence differences were independently verified by PCR amplification and cycle sequencing in the opposite direction.

Statistical Methods

The primary endpoint of this trial was the proportion of patients demonstrating objective response [ORR] as defined by RECIST. Based on results from studies of erlotinib in HCC which reported response rates of up to 9%, the trial was designed to detect objective response rates of $\leq 10\%$ versus $\geq 30\%$. Sample size was based on a single stage Fleming phase II design[36,37] with a 90% power and a 10% type I error. Lapatinib would be considered uninteresting if the true response probability was less than 10% and that the regimen was worthy of further study if the true response probability was $\geq 30\%$. With this design, an observed response rate of 20% or greater would be considered interesting. Target accrual was 25 patients. The secondary endpoints included median progression free survival (mPFS) and overall survival (mOS). OS was determined from the date of the start of Lapatinib therapy to death from any cause or the date of last observation. PFS was calculated from the date of start of Lapatinib therapy to disease progression or death, whichever occurred first. Actuarial survival curves were estimated using the method of Kaplan-Meier and 95% CIs for the medians were provided. Log-rank test examined the relationship between the survival and the presence of rash, or with HCV, or the expression level of different proteins.

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Results

Patient Characteristics (Table 1)

Twenty-six patients were enrolled between the dates of March 3, 2006 and May 14, 2007. Patient characteristics are included in Table 1. Of the 26 patients enrolled, 25 were evaluable for response (one patient passed away prior to restaging). All 26 patients were evaluable for toxicity and survival analysis.

Treatment Toxicity (Table2)

Only 12% of patients required dose reductions. The most common toxicities included diarrhea (73%), nausea (54%) and rash (42%). Grade 3 toxicities were noted in only 3 patients and included diarrhea (2), rash (1) and acute renal failure (1). All toxicities were reversible.

Treatment Efficacy (Table 3, Figure1 and Figure2)

A median of 2 cycles were administered (range 1–14). No patients had an objective response. 10 (40%) patients had stable disease (SD) including 6 (23%) with SD ≥ 120 days and 2 (8%) with SD > 1 year. Those 2 patients with the longest prolongation of disease stabilization were noted to both have a rash and be non-AFP secretors.. mPFS was 1.9 months (95% CI; 1.8–3.6) and mOS was 12.6 months (95% CI; 7.8–22.4 months) (Figure 1).

Patients who developed a rash had a mPFS (2.4 months ; 95% CI; 1.8–4.7 months) that is numerically superior to the mPFS of patients without a rash (1.8 months ;95% CI; 1.4–4.9 months), although the difference was not statistically significant (p= 0.25) (Figure 2a). mOS for patients with a rash was superior (16.2 months; 95% CI; 10.9-NA months) to patients who did not develop a rash (8.7 months; 95% CI; 1.8–16.0 months), and the difference was borderline statistically significant (p=0.07) (Figure 2b). Patients with HCV had a mOS of 11.8 months (95% CI; 2.3–22.4 months) and a mPFS of 3.6 months (95%CI; 1.8–5.2 months). When comparing these results to those of the general study population, mPFS trended to be better with HCV but the differences in PFS and OS curves were not statistically significant (p=0.73 for PFS and p=0.83 for OS).

Biological Markers

Tissue and blood specimens were available for 24 out of 26 (92%) patients

EGFR/ HER2/NEU mutations and protein expression

No somatic mutations in *EGFR* (exons 18–21) were found. We did not find evidence of *HER2/NEU* somatic mutations. In addition, *HER2/NEU* copy number was not elevated in our analysis using FISH. IHC also did not reveal increased *HER2/NEU* protein expression.

Immunohistochemistry analysis of PTEN, P-AKT and p70S6K (Table 4)

IHC staining was used to analyze expression and subcellular (nuclear or cytoplasmic) localization of PTEN, P-AKT and P70S6K. Univariate Cox regression models were fitted for different proteins (PTEN (nuclear component), PTEN (cytoplasmic component), P-AKT (nuclear component), P-AKT (cytoplasmic component), P70S6K (nuclear component), and P70S6K (cytoplasmic component) with no statistical evidence of correlation with OS (p-values are 0.49, 0.97, 0.66, 0.30, 0.95 and 0.65 respectively) or PFS (p-values are 0.18, 0.69, 0.88, 0.17, 0.61 and 0.61 respectively). Using Fisher exact test we found no correlation (for each of the above mentioned proteins) between the lack of expression (score 0 vs. scores 1 and 2), or expression level (score 0 vs. 1 vs. 2) and prolonged stable disease (defined as either ≥ 3 or ≥4 months). In addition, we were unable to show a correlation between expression level of protein

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and PFS or OS. Individual results for immunohistochemistry analysis results and individual results for PFS and OS are presented in Table 4.

Discussion

HCC represents one of the most challenging cancers. The rationale for this study was based on the demonstration of a role for EGFR and HER2/NEU signaling pathways in the carcinogenesis of HCC.

Results from this study revealed minimal activity of lapatinib as a single agent in treating patients with advanced HCC based on the lack of objective responses, the primary endpoint of the study. The choice of this primary endpoint may not have been optimal given the difficulty in assessing disease response by RECIST criteria[38]. However, the lack of activity of lapatinib is also supported by the short mPFS and relatively modest proportion of patients with stable disease. Sorafenib had a reported ORR of 2.3%[39]. However, the median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group. Other studies examining the role of EGFR inhibitors reported ORR ranges of 0–9% (Table 5[16,27], -[40–42]). In our study, we reported a mPFS of 1.9 months consistent with that reported from another study with lapatinib in HCC[41]. This uninteresting mPFS could be confounded by factors such as inclusion of patients with Child's Pugh score B (27%) and prior therapy in 19 % of patients. mOS with lapatinib was one of the highest reported in the literature. This may be partly explained by the use of sorafenib following progression in 40% of our patients, an agent with a known survival advantage in HCC[39]. Also noted, and similar to an effect which has been observed with EGFR inhibitors in a variety of other malignancies [15,43,44], was that survival was significantly improved in the subgroup of patients who developed a rash. This improvement in survival does not seem to be confounded by therapy beyond progression since 38% of patients who developed a rash received sorafenib vs. 54% in those who did not have a rash. This finding suggests a potential benefit from EGFR inhibition but development of rash may also be prognostic (i.e. patients able to develop rash may have a more favorable outcome regardless of the activity of the agent).

Another interesting observation from our study is that 3 out of the 4 patients with AFP lower than ULN (AFP-negative) had stable disease longer than 4 months including the only 2 patients with disease control longer than 12 months. Improved survival has been previously reported in patients with HCC whose AFP was normal when compared to those with elevated serum marker levels [45,46]. This prognostic finding may be related to the background liver disease for most patients with HCC and the prevalence of Child's Pugh score A seems to be higher in AFP-negative tumors[45]. Indeed, our AFP-negative patients were all found to have more favorable Child's Pugh scores (All 4 had a CP score of 5). It is unclear whether there is any added benefit in those patients from EGFR inhibition, and this question should be addressed in future randomized studies.

Interestingly, mPFS trended to be higher in patients with HCV although the differences in PFS and OS curves were not statistically significant with lapatinib when compared to the general population unlike what was noted in patients receiving sorafenib[37,47].

The drug was overall well tolerated with only 12% of patients requiring a dose reduction. The toxicity to lapatinib was predominantly gastrointestinal followed by cutaneous similar to other drugs that target EGFR/HER1. Of note, patients with Child's Pugh B (7) did not have any worse toxicity than those with Child's Pugh A (5 and 6).

We also performed a set of accompanying correlative studies of relevance to the targeted pathways. A strength of our study is the acquisition of tissue in > 90% of all patients enrolled. Similar to our previous findings[24], we found no activating *EGFR* mutations on this study.

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However, unlike our previous published findings[24], we found no activating somatic mutations in *HER2/NEU*. In addition, *HER2/NEU* copy number was not found to be elevated in our analysis using FISH (nor protein expression by IHC staining). Based on these observations, therefore, dual-specificity EGFR-TKIs may in fact be predicted to not be more efficacious than EGFR-TKI. We chose to examine PTEN and the AKT signaling pathway as there has been ample evidence in other solid tumors that loss of normal PTEN function or activation of the AKT pathway would predict for resistance to EGFR-TKIs even in the context of *EGRF* activation[48]. However, levels of PTEN, P-AKT and P70S6K, did not correlate with progression free survival or overall survival in the current study. As part of prioritizing the correlative studies we performed, we decided not to include EGFR expression levels or to look for *KRAS* mutations. EGFR expression has been documented in multiple studies to occur at high levels in HCC and did not seem to correlate with response[14–16]. Somatic mutations in the genes encoding the molecules in the KRAS pathway are rarely seen in HCC[47] and do not seem to have a predictive role for EGFR inhibition in this disease[49].

In conclusion, dual EGFR inhibition with lapatinib has minimal activity in HCC, although certain subgroups of patients (such as those who developed a rash, an effect attributable to EGFR/HER1 inhibition) had a more favorable outcome when compared to the overall study population. As such, results from this trial and others (table 4) encourage the continued development of a strategy to target EGFR-TK blockade as a single modality or preferably in combination (with VEGF or mTOR inhibitors) for treating HCC. Although our attempt to identify molecular or genetic predictors of a more favorable outcome was unsuccessful, enrichment strategies must continue to be investigated to achieve similar results to those in lung and colon cancer. Two possible mechanisms for EGFR inhibitor-related skin toxicity have been previously postulated. The first (likely) is more straightforward and relates to direct inhibition of cutaneous EGFR. The other (unlikely) relates the development of a rash as a manifestation to a systemic immunologic reaction[50]. Since HCC is a heterogeneous disease with multiple redundant signaling pathways and etiologies, the role of certain pathways may be different in various subgroups (HCV, for example). Future studies should consider a randomized approach with appropriate stratifications (by Child's Pugh score, AFP levels, presumed etiology of HCC etc…).

Statement of Translational Relevance

The rationale for this study was based on the demonstration of a role for EGFR and HER2/NEU signaling pathways in the carcinogenesis of HCC. Lapatinib appears to benefit only a subgroup of patients for whom predictive molecular or clinical characteristics are not yet fully characterized. For example, we found that although dual EGFR inhibition has minimal activity in HCC, certain subgroups of patients such as those who developed a rash, an effect attributable to EGFR/HER1 inhibition, had a significantly more favorable outcome when compared to the overall study population. This finding suggests a potential benefit from EGFR inhibition.. Other considerations from our results include findings that suggest that future studies should consider a randomized approach with appropriate stratifications (AFP levels, etiology etc…). Final results of accompanying correlative studies are also presented.

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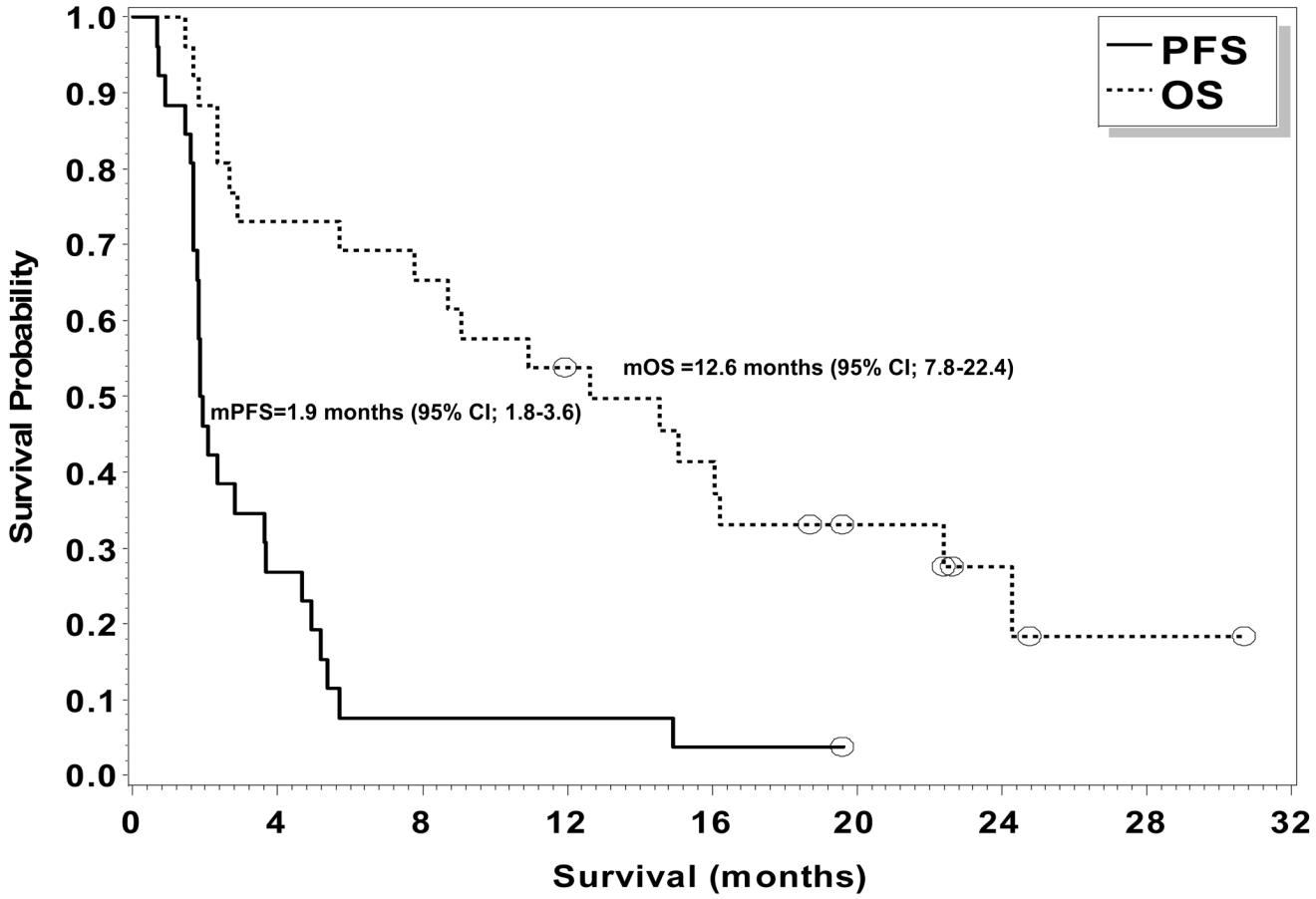

Figure 1.
Progression Free Survival (PFS) and Overall Survival OS Curves

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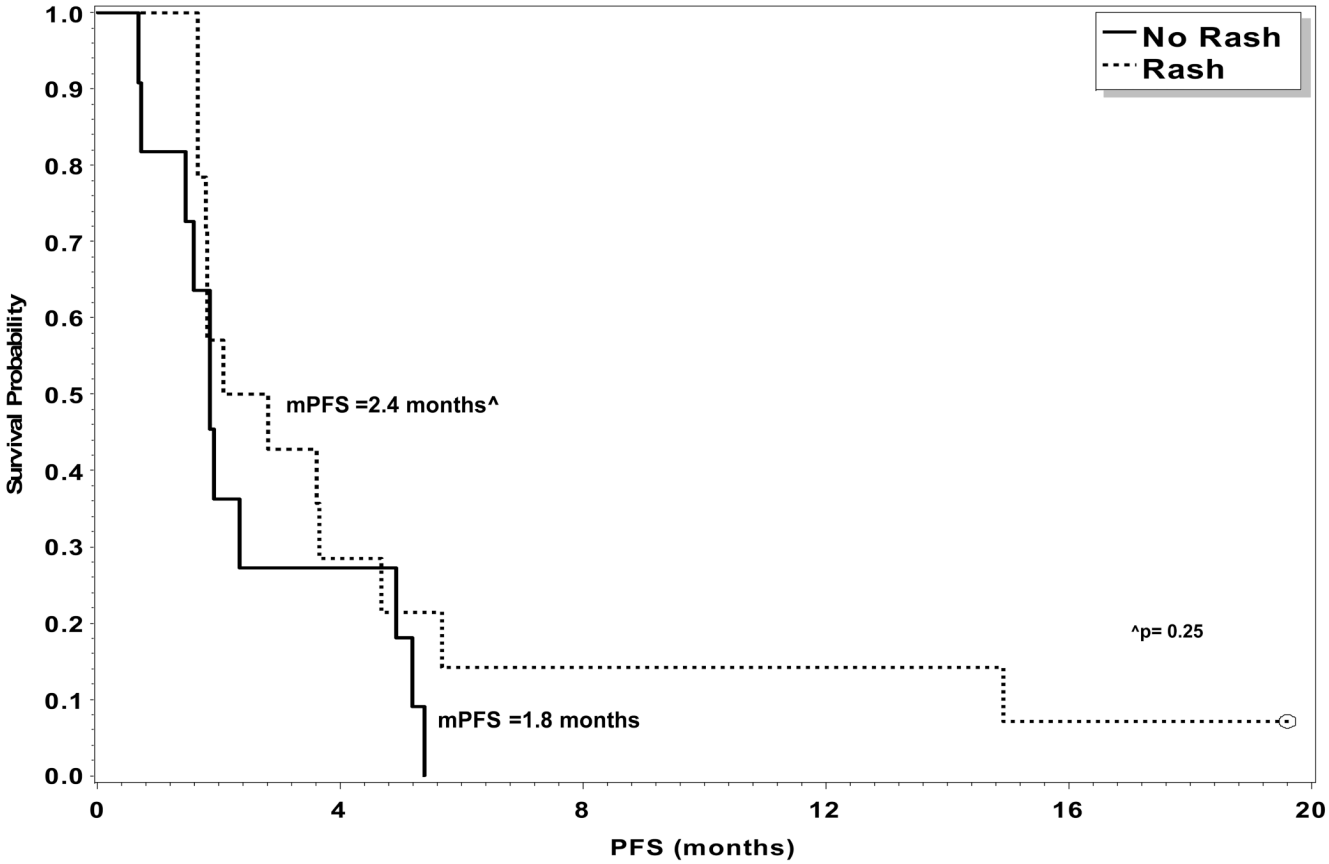

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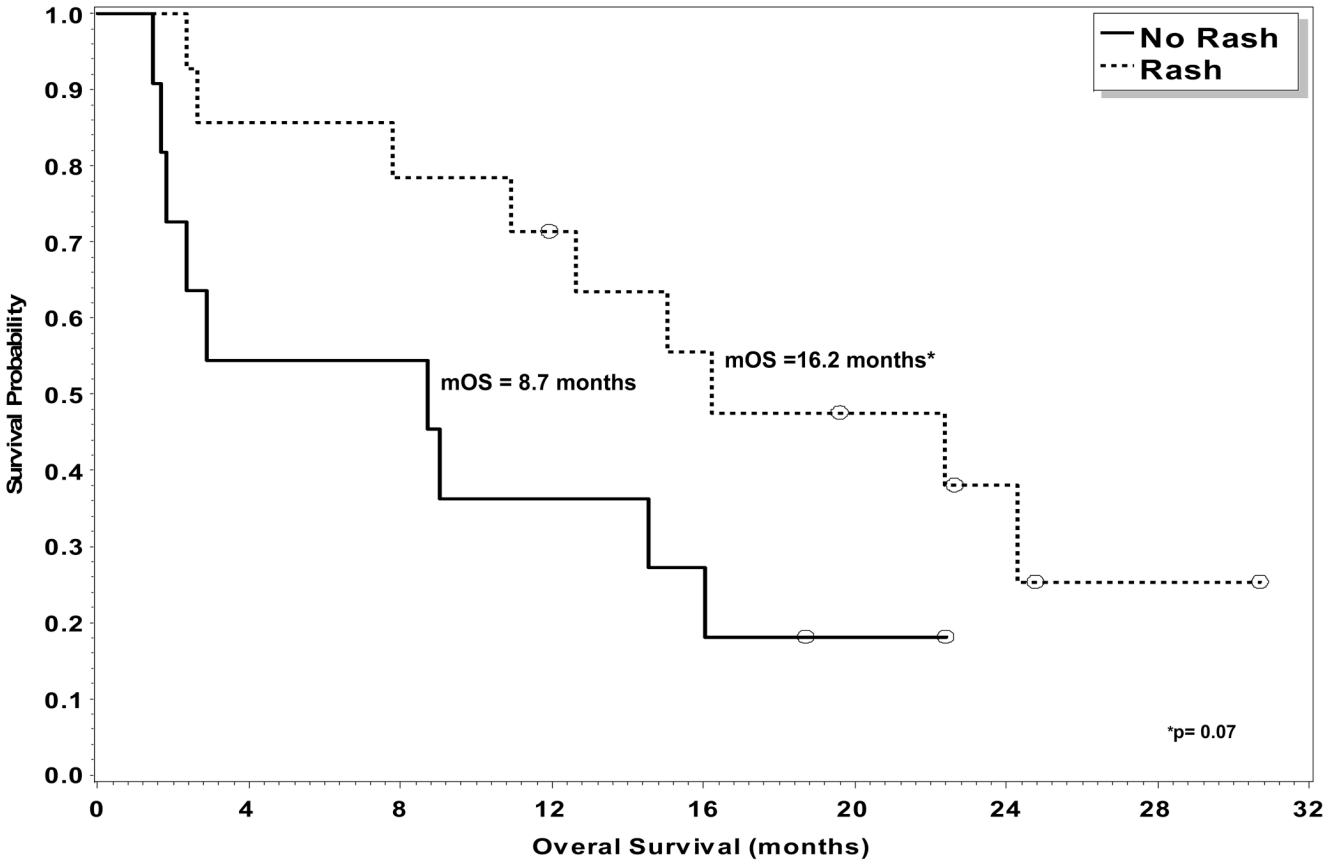

Figure 2.
Figure 2a: Progression Free Survival (PFS) According to Rash
Figure 2b: Overall Survival (OS) According to Rash

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Table 1

Patient Demographics and Characteristics

N	26
Male	18
Female	8
Age (years)	
Median	58
Range	29–81
Race/Ethnicity	
White	20
African American	4
Asian	1
Other	1
ECOG	
0	12
1	14
Prior Treatments	
X-Ray Treatment	3
Chemo-embolization	2
Surgery	16
Chemotherapy	3
Sites of Metastasis	
Lymph Nodes	8
Lungs	8
Spine	1
Bone	1
Adrenal Gland	1
Peritoneal Mets	1
Hepatic Mets	1
Chest Wall	1
Etiology	
Hepatitis B	3
Hepatitis C	8
Alcohol	4
Idiopathic	13
Child Pugh	
5	13
6	6
7	7
AFP	
> ULN	21
≤ULN	4

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Table 2

Toxicities (N=26)*

Toxicity	All Toxicities	Grade 1	Grade 2	Grade 3
Diarrhea	19	14	3	2
Nausea	14	10	4	0
Rash	13	10	2	1
Fatigue	11	8	3	0
Vomitting	7	5	2	0
Alkaline Phosphatase	5	4	1	0
ALT	5	3	2	0
AST	4	1	3	0
Hemoglobin	4	4	0	0
Hypoalbunemia	3	3	0	0
Leukpenia	2	2	0	0
Anorexia	3	2	1	0
Platelets	2	2	0	0
Creatinine	2	2	0	0
Hypocalcemia	2	2	0	0
Itching	2	2	0	0
Reflux	2	2	0	0

* There were no grade 4 toxicities

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Table 3

Efficacy Results[^]

Response	N %)	
Overall Response Rate	0 (0)	
Stable Disease	10 (40)	
Stable Disease > 120 days	6 (23)	
Poregressive Disease	16 (64)	
Non-evaluable	1(4)	
Median Progression Free Surival	1.9 mos	(95% CI; 1.8–3.6)
− Rash	1.8 mos	
+ Rash	2.4 mos[*]	
Median Overall Survival	12.6 mos	(95% CI; 7.8–22.4)
−Rash	8.7 mos	
+ Rash	16.2 mos[^]	

[^] Only 25 patients were evaluable for response; 26 for Progression Free Survival and Overall Survival.

[*] p= 0.25;

[*] p= 0.07

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Table 4

Individual results for Immunohistochemical stains, progression free survival (PFS) and overall survival (OS):

Patient	PTEN (N)	PTEN (C)	PAKT (N)	PAKT (C)	P70S6K (N)	P70S6K (C)	PFS (days)	OS(days)
1	0	0	0	1	1	1	43	43
2	0	1	0	1	0	1	21	54
3	0	1	0	1	0	1	147	436
4	0	1	1	1	1	2	49	451
5	ns	ns	ns	ns	ns	ns	170	>921
6	2	1	0	1	0	1	49	486
7	0	1	0	0	0	1	47	481
8	0	1	0	1	0	1	55	261
9	0	0	1	2	1	1	108	671
10	ns	ns	ns	ns	ns	ns	62	233
11	0	0	1	0	0	0	54	79
12	0	0	1	2	0	1	447	>743
13	0	0	1	2	0	1	57	86
14	0	1	1	2	0	1	70	70
15	0	1	0	1	2	1	53	70
16	0	1	1	2	2	2	109	679
17	0	1	ns	ns	0	1	55	672
18	0	1	0	0	0	1	155	271
19	0	1	0	1	0	1	26	170
20	1	1	0	0	0	0	49	378
21	ns	ns	1	2	2	1	20	50
22	1	2	0	0	1	1	161	561
23	0	1	0	1	0	1	140	358
24	1	1	0	0	0	0	>588	>588

ns= not scorable ; C=Cytoplasmic;N=Nuclear;
Please refer to text for scoring system (0–2)

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Table 5

Phase II Trials of EGFR Targeted Agents in HCC

	N	% Preatreated*	Response Rate (%)	Median PFS (months)	Median OS (months)
Erlotinib[26]	38	47	9	3.2	13
Erlotinib[27]	40	0	0	3.1	6.3
Gefitinib[38]	31	0	3	2.8	6.5
Lapatinib[39]	40	43	5	2.3	6.2
Cetuximab[40]	30	33	0	1.4	9.6

*Refers to patients who had exposure to prior therapy before enrolling on the study.