Trial Using Gilotrif for Advanced Penile Squamous Cell Carcinoma

Study Protocol, Statistical Analysis Plan & Informed Consent Form

NCT02541903

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Clinical Study Protocol

~~**EudraCT No.:**~~ **Protocol No.:** **BI Investigational Product:**	Gilotrif
Title:	A phase 2 trial using Gilotrif for Advanced Penile Squamous Cell Carcinoma following systemic therapy.
Clinical Phase:	2
Principal Investigator:	Lisle M. Nabell, MD

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Protocol version and date: 07/25/2017 version 4

INVESTIGATOR SIGNATURE PAGE

Study Title: A PHASE 2 TRIAL USING GILOTRIF FOR ADVANCED PENILE SQUAMOUS CELL CARCINOMA FOLLOWING SYSTEMIC THERAPY.

Protocol No.:

I herewith certify that I agree to adhere to the study protocol and to all documents referenced in the study protocol.

_____

Date

SPONSOR SIGNATURE PAGE

Study Title: PHASE 2 TRIAL USING GILOTRIF FOR ADVANCED PENILE SQUAMOUS CELL CARCINOMA FOLLOWING SYSTEMIC THERAPY.

Protocol Number:

I herewith certify that I agree to adhere to the study protocol and to all documents referenced in the study protocol.

_____

Date

CLINICAL STUDY PROTOCOL SYNOPSIS

Protocol date: 1/29/2015	**Protocol number:** 1200.x
Title of study:	A phase 2 trial using Gilotrif for Advanced Penile Squamous Cell Carcinoma following systemic therapy
Principal Investigator:	Lisle Nabell, MD
Study site(s) :	University of Alabama at Birmingham University of Southern California
Sponsor	University of Alabama at Birmingham(UAB)
Clinical phase:	2
Objective(s):	Primary: Clinical Progression Free Survival (PFS) at 6 months of patients with Penile Squamous Cell Carcinoma (PSCC) receiving Gilotrif following ≥ 1 prior systemic therapy regimen. Secondary: • Response Rate (RR) • Overall Survival (OS) • Toxicities Exploratory: • Tumor tissue molecular studies: HPV status (PCR), gene expression (nanostring) and IHC (EGFR, Her2, Her3, Her4) • Central pathology review and histologic subtype

Protocol date:	Protocol number:		
1/29/2015	1200.x		
Methodology:	This is a non-randomized 2-center phase II trial (N=29) to evaluate Gilotrif 40 mg po qd for patients with metastatic progressive PSCC following prior chemotherapy. Those progressing within 6 months of prior therapy will be enrolled with the goal of detecting PFS at 6 months after starting Gilotrif in ≥20% of patients, while PFS6 in <5% will be considered to be of poor interest. Selecting patients within 6 months of prior therapy will enrich for patients unlikely to attain PFS6 without active therapy. Patients will undergo clinical examination every 4 weeks and radiographic work-up at baseline and then every 8 weeks. Patients will continue therapy until progression or intolerable toxicities. Patients removed from therapy for reasons other than progression will be followed to identify progression or until initiation of other therapy. Twenty archival formalin-fixed paraffin embedded (FFPE) tissue slides per patient will be acquired for potential future analyses including histologic sub-type, HPV status, gene expression (nanostring) and IHC for EGFR, Her2, Her3, Her4. The eligible population of patients includes men with pathologically proven locally advanced or metastatic (lymph node or distant metastatsis i.e. N+ or M1) PSCC which has received ≥1 systemic chemotherapy regimens within the last 6 months with ECOG PS 0-2 & optimal organ function (Hb>8.5, ANC>1500/mm3, Platelet count>100K, Total bilirubin <1.5 of ULN, creatinine clearance >45 ml/minute, ALT and AST<2.5X ULN, for patients with liver involvement ALT and ALT<5X ULN). The disease should be measurable by RECIST 1.1 criteria. Gilotrif will be administered orally 40mg daily continuously. Continuous administration of 4 weeks is considered one cycle. Therapy will continue until progression (by RECIST 1.1) or severe toxicities. Patients removed from the trial for toxicities or other reasons will continue to be followed until progression or starting a new agent. Complete Blood Count (CBC) & Comprehensive metabolic panel (CMP) evaluations will be done performed on day 1 every 4 weeks. CT chest, abdomen and pelvis will be performed every 2 cycles (8 weeks). A bone scan will be performed only if bone pain or high alakaline phosphatase. Progression of disease will be defined clinically as the first occurrence of any of the following: 1) Progression as defined by RECIST 1.1 criteria 2) Death		
No. of patients:	29		

Protocol date: 1/29/2015	**Protocol number:** 1200.x		
Treatment:	Gilotrif 40 mg po once daily		
Indication :	Advanced Penile Squamous Cell Carcinoma having failed at least one prior chemotherapy		
Main criteria for inclusion:	Each patient will meet all of the following inclusion criteria to be enrolled in the study: • Patients will have pathologically proven PSCC • Progressive disease after ≥1 prior chemotherapy regimens • Prior regimen will be within 6 months • Measurable disease by RECIST 1.1 • ECOG performance status 0-2 (Appendix 10.3) • Patients with metastatic (lymph node or distant metastasis, i.e. N+ or M1) or locally advanced unresectable PSCC • Hemoglobin ≥ 8.5 g/dl • Absolute neutrophil count (ANC) > 1,500/mm3 • Platelet count > 100,000/mm3 • Total bilirubin < 1.5 x upper limit of normal (ULN) • Creatinine Clearance >=45ml/min, ALT and AST < 2.5 x the ULN. If the patient has liver involvement AST and ALT < 5 x the ULN will be accepted for inclusion • Resolution of all acute toxic effects of prior chemotherapy or surgical procedures to NCI CTCAE Version 4.03 Grade <1, in the opinion of the Treating Physician (Appendix 10.7) • Ability to understand and the willingness to sign a written informed consent document.		

Protocol date:	Protocol number:		
1/29/2015	1200.x		
Main criteria for exclusion:	Patients meeting any of the following exclusion criteria within 4 weeks (unless otherwise stated) of being enrolled are not to be enrolled in the study: • Patients will have recovered from toxicities from prior systemic anticancer treatment or local therapies. • Prior EGFR inhibitors • Patients who have undergone major surgery < 4 weeks or minor surgery < 2 weeks prior to registration. Wounds will be completely healed prior to study entry and patients recovered from all toxicities from surgery. Placement of a vascular access device is not considered major or minor surgery in this regard. • Prior radiation therapy is allowed as long as the irradiated area was not the sole source of measurable disease and radiotherapy was completed with recovery from toxicity, at least three weeks prior to enrollment. If the irradiated area is the only site of disease, there will be evidence of progressive disease. • Uncontrolled central nervous system (CNS) metastases (previously treated with radiation and off steroids is acceptable) • Patient with active or uncontrolled infection.		
Test product(s) :	Gilotrif		
dose:	40 mg per day		
mode of admin:	Oral		
Duration of treatment:	Therapy will continue until progression (as defined below) or severe toxicities. Progression of disease will be defined clinically as the first occurrence of any of the following. 1) Progression of disease by RECIST 1.1 2) Death Therapy is also discontinued for non-progression events: 1) Intercurrent illness that prevents treatment 2) Unacceptable adverse event(s) 3) Patient decides to withdraw from the study 4) General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.		

Protocol date: 1/29/2015	**Protocol number:** 1200.x		
Criteria for efficacy:	Primary: Progression-free survival at 6 months Secondary: Response, overall survival		
Criteria for safety:	Toxicities by CTCAE 4.03 criteria (Appendix 10.7)		
Statistical methods:	PFS6 is chosen as the primary end-point. Given the poor prognosis of this patient population and data from other studies of salvage therapy, a PFS6 of ≥20% is considered to be important for this regimen, while a PFS6 <5% will be considered to be of poor interest. A total of 27 evaluable subjects will be enrolled, 13 during stage 1 and 14 during stage 2 of a two-stage minimax design phase II study. The alpha level of the design is 0.05 and the power is 0.8. If no patients are free from progression at 6 months during the first stage then the trial ends with the conclusion that this drug is not worth further study. Otherwise it proceeds to the second stage. If less than 4 of the 27 patients are progression free at 6 months, it will be concluded that the drug is not worth further study. Given that 5-10% of enrolled patients are inevaluable, up to 29 patients may be enrolled.		
Study duration	This study will be conducted over 12-18 months. Accrual period will be 6-12 months.		

FLOW CHART

	-30 days	-14 days	Day 1 of every cycle (28 days)	Every 2 cycles	28 (± 3 days) post last treatment
REQUIRED ASSESSMENTS					
History	X		X		X
Height	X				
Physical examination		X	X		X
BP, weight		X	X		X
Smoking history	X				
ECOG performance status		X	X		X
CBC with differential		X	X		X
Chemistries (CMP)		X	X		X
Hepatitis panel (B, C)	X				
Adverse event and concomitant medication assessment	X		X		X
DISEASE ASSESSMENT					
CT chest , abdomen, pelvis	X			X	X
Bone Scan (if bone pain or high alkaline phosphatase)	X			X	
TREATMENT					
Gilotrif PO QD			X (1-28 days)		

CORRELATIVE STUDIES	
Collect 20 FFPE slides (15 sections of 10uM thickness, 5 sections of 5uM thickness) from archival biopsy for correlative studies (central pathology review, IHC, nanostring gene expression, HPV DNA)	X
FOLLOW-UP	
Disease progression and survival	X

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ABBREVIATIONS

eCRF	electronic Case Report Form
SAE	Severe Adverse Events
ADL	Activity of Daily Living
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ANOVA	Analysis of Variance
aPTT	activated Plasma Thromboplastin Time
AST	Aspartate Transaminase
AUC	Area Under Curve
BCL	B-Cell Lymphoma
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CCC	Comprehensive Cancer Center
CD	Cluster of Differentiation
CMP	Complete Metabolic Panel
CNA	Copy Number Alterations
COX	Cyclo-oxygenase
CRA	Clinical Research Associate
CSP	Clinical Study Protocol
CTCAE	Common Terminology Criteria for Adverse Events
CTMC	Clinical Trials Monitoring Committee
CTNMO	Clinical Trials Network Monitoring Office
DNA	Deoxyribose Nuclei Acid
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Co-operative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EOT	End Of Treatment
ERCC	Excisional Repair Cross Complementing
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
GGT	Gamma Glutamyl Transferase
Hep	Hepatitis
HER	Human EGF (Epidermal Growth Factor) Receptor
HPV	Human Papilloma Virus
HRAS	Human Rat Sarcoma
IHC	ImmunoHistochemistry
ILD	Inflammatory Lung Disease
INR	International Normalized Ratio
KRAS	Kirsten Rat Sarcoma

LN	Lymph Node
LOH	Loss Of Heterozygosity
mg	Milligram
MTD	Maximal Tolerated Dose
NCI	National Cancer Institute
NYHA	New York Heart Association
OS	Overall Survival
PC	Penile Carcinoma
PCR	Polymerase Chain Reaction
PFS	Progression Free Survival
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha
PK	Pharmacokinetics
PO	Per oral
PS	Performance Status
PSCC	Penile Squamous Cell Carcinoma
PTEN	Phosphatase and Tensin homologue
QAC	Quality Assurance Committee
QC	Quality Control
QD	Every Day
RAS	Rat Sarcoma
RB	RetinoBlastoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribosomal Nucleic Acid
SCC	Squamous Cell Carcinoma
SUSAR	Suspected Unexpected Severe Adverse Reactions
TKI	Tyrosine Kinase Inhibitor
TNM	Tumor Node Metastasis
TS	Thymidylate Synthetase
TSP	Thrombospondin
TTP	Time To Progression
UAB	University of Alabama at Birmingham
USC	University of Southern California
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

1.1.1 Introduction

In developed countries, penile squamous cell carcinoma (PSCC) is relatively rare and is considered an orphan disease, but less developed countries exhibit higher incidences. In 2014, 1640 new cases and 320 deaths from penile cancers were predicted to occur in the U.S.(1). The median age of diagnosis is ~62 years and the majority of patients are diagnosed at a localized stage, which is managed by surgery or radiation therapy. However, PSCC is a highly aggressive malignancy characterized by early locoregional spread with subsequent potential for distant dissemination.

1.1.2 Pathology, molecular biology and prognosis

Pathology

The vast majority of malignancies of the penis are squamous cell cancers (SCC), but other histologic types are observed in ~5% of cases, such as melanomas, basal cell carcinomas and sarcomas (2). The World Health Organization (WHO) classifies penile SCC, or PC, as usual, basaloid, verrucous, warty (condylomatous), papillary, sarcomatoid, adenosquamous and mixed (3). In a surgical series of 333 patients receiving homogeneous surgery, basaloid, sarcomatoid and adenosquamous carcinomas displayed the highest histological grade and deep tissue infiltration, while verrucous, papillary and condylomatous (warty) carcinomas were associated with low grade and superficial invasion. This relationship translated into distinct clinical behavior, with a higher 10-year survival rate for verrucous, adenosquamous, mixed, papillary and warty carcinoma (100%, 100%, 97%, 92% and 90%, respectively), while patients with the usual and basaloid types had 78% and 76% 10-year survival, respectively. Of note, 75% of patients with sarcomatoid carcinoma died, usually within a year of diagnosis (4). Interestingly, verrucous carcinomas appear to exhibit low p16 and HPV expression (5). Grading has an established prognostic role for PC with crucial clinical implications (6, 7). Higher grade and basaloid and warty tumors are more consistently associated with HPV, suggesting that distinct pathogenic pathways may drive tumors (8-10).

Molecular biology

Epidermal growth factor receptor (EGFR) over-expression appears to be almost universal and correlated with grade but not stage (11-13). In an American series, KRAS mutations and ERCC1 amplification appeared rare or absent, which may portend responsiveness to EGFR inhibitors and platinum chemotherapy. EGFR had the highest relative expression followed by thymidylate synthetase (TS). However, in a Spanish series (n=28), 22% of evaluable tumors had missense mutations in KRAS , suggesting there may be regional differences in biology (14). In another study, somatic missense mutations in PIK3CA, HRAS and KRAS were found in11 of 28 PC samples (39%) (15). PIK3CA mutations were found in all grades and stages, whereas HRAS and KRAS mutations were found in more advanced tumors. The mutations were mutually exclusive, suggesting that dysregulation of either pathway is sufficient for tumor growth. A preliminary examination of the COSMIC dataset (n=28) revealed p53 or PIK3CA mutations in 8 of 28 (29%) tumors (http://www.sanger.ac.uk/cosmic, accessed June 18, 2012) (16). EGFR, HER3 and HER4 protein overexpression was found in one study of 148 cases, although no *EGFR* gene amplification was detected (17). In this study, HPV-negative tumors expressed significantly more phosphorylated EGFR than HPV-positive cancers, which correlated with phosphorylation and activation of Akt signaling. Conversely,

HER3 expression was significantly more common in HPV-positive cases, which correlated with cytoplasmic localization of Akt1. PTEN protein expression was reduced in 62% of tumors but PTEN gene loss occurred only in 4%.

The epigenetic inactivation of thrombospondin (TSP)-1 and RAS association domain family (RASSF)-1A genes by hypermethylation seemed to confer prognostic significance in one study (n=24) (18). LN metastasis was significantly associated with negative p16 and combined LOH and promoter hypermethylation, but not with p53 alterations (19). Similarly, another study of 148 PCs demonstrated that HPV infection may engender p16 and p21 expression and RB suppression, but no association with p53 expression was detected (20). Nevertheless, p53 protein expression has been related to LN metastasis and poor survival in other studies (21-23). Moreover, studies indicate the potential importance of cell-cycle regulators and pro-survival proteins, e.g. p16, p21, telomerase and the Bcl-2 family (13, 24-26).

Another study of 26 cases reported DNA sequence copy number alterations (CNAs) similar to oral and esophageal SCCs (27). The most frequent copy number gains occurred in 8q24, 16p11-12, 20q11-13, 22q, 19q13, and 5p15, while the most common deletions occurred in 13q21-22, 4q21-32 and the X chromosome. The number of CNAs exhibited a possible correlation with clinical outcome, but the biological mechanisms remain undefined. Increased cyclo-oxygenase (COX)-2 and microsomal prostaglandin E synthase-1 were detected in penile intraepithelial neoplasia and carcinoma in one study, suggesting a pathogenic role for inflammation and a therapeutic role for COX-2 inhibitors (28). The potential role of angiogenesis was suggested by a case series reporting the activity of sorafenib and sunitinib (29).

Prognostic factors

PSCC is classified as usual, basaloid, verrucous, warty , papillary, sarcomatoid, adenosquamous and mixed (3). Better survival was observed for verrucous, adenosquamous, mixed, papillary and warty carcinomas, while patients with the usual and basaloid types had lower survival.

Pathologic TNM staging provides prognostic stratification after surgery (31). Furthermore, extranodal extension in inguinal LNs and pelvic LN involvement appear to be independently associated with decreased 5-year cancer specific survival (42% and 22%, respectively) (32). Nomograms have been reported for patients following penectomy to better predict cancer-specific survival and LN metastasis (33-35). These nomograms incorporate multiple variables in addition to stage to enhance prognostication including grade, venous or lymphatic embolization and type of surgery. Other studies have reported lymph node density, lack of koilocytosis and clear cell subtype to be prognostic (32, 35-49). In patients with locally advanced and advanced disease undergoing systemic fist-line chemotherapy, a recent analysis identified performance status and visceral metastasis as major prognostic factors (50). In this retrospective analysis of 140 men receiving first-line chemotherapy, the multivariate model of poor prognostic factors included visceral metastases ($p<0.001$) and ECOG-PS ≥ 1 ($p<0.001$) for both PFS and OS. A risk model showed that those with 0, 1 and both poor prognostic factors which was internally validated and demonstrated moderate discriminatory ability (c-statistic of 0.657 and 0.677 for OS and PFS). The median OS for the entire population was 9 months. Median OS was not reached, 8 and 7 months respectively for those with 0, 1 and both risk factors. Cisplatin-based regimens were associated with better OS ($p=0.017$), but not PFS ($p=0.37$), compared to non-cisplatin based regimens after adjusting for the 2 prognostic factors.

Additionally, molecular prognostic markers are suggested by some studies, e.g. p53, ki-67, E-cadherin, MMP-9, Annexins I and IV and decreased KAI1/CD82, a metastasis suppressor gene (21, 23, 51-54). Although HPV has been associated with high-grade tumors, the impact on outcomes is unclear with one study even demonstrating a favorable impact of HPV and another study showing a positive association with survival of p16, which is related to HPV (10, 55-57).

1.1.3 Current systemic chemotherapy for advanced PSCC

High level evidence for the value of systemic therapy does not exist in this orphan disease. The efficacy of adjuvant therapy is unproven. In patients with bulky primary disease or fixed or bulky inguinal or pelvic lymph nodes (LNs), multimodality therapy including neoadjuvant chemotherapy followed by surgery and node resection is offered (58-61). Generally, cisplatin-based combinations employed in the pre-and post-taxane era have demonstrated similar response-rates (25-50%) and survival. Hence, a single optimal neoadjuvant systemic regimen has not been established and the value of surgery following chemotherapy for those with LN involvement remains unproven.

Systemic chemotherapy alone is offered for men with distant metastases and clinical trials are strongly encouraged given the poor efficacy of currently available regimens. A variety of first-line cisplatin-based, systemic therapy regimens have been reported in mostly small single institution retrospective and phase II studies, as the rarity of this disease prohibits the conduct of large randomized trials (58, 59, 62-74). Older trials employed bleomycin and methotrexate as partners, while newer studies have investigated taxanes, 5-fluorouracil and gemcitabine combinations with median survivals ranging from 6 to 11 months. Historical data with combination BMP demonstrated a median survival of only 28 weeks (68, 75, 76). In the largest prospective study of this regimen, there were 5 complete and 8 partial responses in 40 evaluable patients for a 32.5% response rate (76). Unfortunately, in this study, 5 treatment related deaths occurred and 6 other patients had 1 or more life threatening toxic episodes. Hence, the toxicities of bleomycin-containing regimens have been recognized and considered to be prohibitive. However, outcomes with non-cisplatin based regimens are unclear. A recent study by our group evaluated prognostic factors in 140 patients receiving first-line chemotherapy and identified performance status and metastatic sites as major prognostic factors (77).

Second-line therapy is also not established, and taxanes have been used with marginal activity (78). In a prospective, multicenter phase II trial, 25 patients were enrolled and treated with paclitaxel 175 mg/m2 every 3 weeks. Partial responses were observed in 20%. The median PFS was only 11 weeks, and the median OS was 23 weeks.

Table 1. Reported studies of ≥ 10 patients receiving chemotherapy for advanced penile cancer

Author	Line of therapy	Regimen	Design	N	Clinical Response N (%)	Median PFS	Median OS
Gagliano(74)	First	Cisplatin	Phase II trial	26	4 (15.4)	NR	4.7 mo
Haas(76)	First	BMP	Phase II trial	40	13 (32.5)	NR	28 wk
Dexeus(68)	First	BMP	Retrospective†	14	10 (72)	NR	NR

Corral(75)	First	BMP	Phase II trial*	30	16 (55)	NR	11.5 mo
Di Lorenzo(79)	First	CF	Retrospective	25	8 (32)	20 wk	8 mo
Theodore(61)	First	CI	Phase II trial	28	8 (30.8)	NR	NR
Di Lorenzo(78)	Second	Paclitaxel$^{\pi}$	Phase II trial	25	5 (20)	11 wk	23 wk

BMP: Bleomycin-Methotrexate-Cisplatin; CF: Cisplatin-5FU; CI: Cisplatin-irinotecan; †12 of the 14 patients had penile primary site; *trial enrolled patients with squamous cell carcinoma of the penis, scrotum, bladder, renal pelvis, ureter or urethra; NR: not reported; $^{\pi}$Paclitaxel every 3 weeks

1.1.4 EGFR as a therapeutic target in PSCC, and its association with HPV status

Epidermal growth factor receptor (EGFR) overexpression appears to be almost universal and correlated with the grade, but not the stage (11, 12, 24). In an American series, KRAS (Kirsten rat sarcoma) mutations and ERCC1 (excision repair cross-complementing group 1) amplification appeared rare or absent, which may portend responsiveness to EGFR inhibitors and platinum chemotherapy. EGFR had the highest relative expression followed by thymidylate synthetase. EGFR, HER3 and HER4 protein overexpression was found in one study of 148 cases, although no EGFR gene amplification was detected (17). In this study, HPV-negative tumors expressed significantly more phosphorylated EGFR than HPV-positive cancers, which correlated with the phosphorylation and activation of Akt signaling. Conversely, HER3 expression was significantly more common in HPV-positive cases, which correlated with cytoplasmic localization of Akt1. HPV, especially HPV-16 and 18, has been associated with elevation of risk of developing PSCC.(80, 81) Higher grade and basaloid and warty tumors appear to be more consistently associated with HPV, suggesting that distinct pathogenic pathways may drive PSCC.

1.1.5 Nanostring platform for gene expression analysis of formalin-fixed paraffin embedded tumor

Gene expressing profiling performed by the nanostring technology, which utilizes formalin-fixed paraffin embedded (FFPE) tissue using the nCounter® appears highly promising (82). This technology provides robust data from FFPE tissue using the nCounter® GX Kit and offers high levels of precision and sensitivity (>1 copy per cell) without the need for amplification of ≥100 ng of RNA. Nanostring is a multiplexed (up to 800 genes per reaction) platform, which utilizes digital counting and excellent quantitative reproducibility by employing two ~50 base probes per mRNA that hybridize in solution. Multiple successful applications utilizing the nCounter System to subtype tumors, formulate tumor prognostic signatures, or discover novel targets for therapy have been reported in other malignancies (83-86). Notably, the 50-gene PAM50 signature (Prosigna^{TM}) derived from nanostring was approved by the US FDA in 2013 to assess the risk of distant recurrence at 10 years in postmenopausal women with hormone receptor-positive breast cancer. Indeed, the PAM50 gene score, which is enriched for proliferation-associated genes appeared more robust than the Oncotype DX® recurrence score in predicting recurrence (85).

1.1.6 Activity of EGFR inhibitors in PSCC

A potential role may exist for EGFR inhibitors in PSCC as shown in small retrospective studies of EGFR targeting monoclonal antibodies (87-89). In one retrospective study, all 13

patients with advanced PC expressed EGFR with 77% exhibiting 3+ levels of expression and received EGFR-targeted therapies, including erlotinib (n = 1), cetuximab (n = 3) or cetuximab, combined with platinum-based regimens (n = 9). The patients showed a median TTP of 3.2 months and a median OS of 9.8 months. Four (31%) patients survived between 13 and 48+ months, comparing favourably with historical survival when utilizing conventional chemotherapy. Anecdotal responses have been reported with panitumumab or combination docetaxel–cetuximab after cisplatin-based chemotherapy. Hence, a rationale exists to investigate the activity of EGFR inhibitors in general, and Gilotrif in particular, which is a pan-HER family inhibiting TKI.

1.2 DRUG PROFILE OF GILOTRIF

Gilotrif (BIBW2992) is a small molecule, selective and irreversible erbB family blocker. In preclinical models it effectively inhibits EGFR, HER2 and HER4 phosphorylation resulting in tumour growth inhibition and regression of established subcutaneous tumours derived from four human cell-lines known to co-express ErbB receptors.

For the latest information on the drug profile of Gilotrif, please refer to the current Investigator's Brochure (IB) (U03-3218). All references in this protocol concerning Gilotrif refer to the free base compound Gilotrif BI which is used as the oral formulation.

Gilotrif is moderately fast absorbed after oral administration. Maximum plasma concentrations of Gilotrif were achieved mainly at 2 to 5 hours after oral drug administration. Gilotrif maximum plasma concentrations and area under the curve increased slightly over-proportional with increasing doses in the therapeutic range of 20-50mg. Moderate to high inter- and intra-individual differences in plasma concentration were seen. Gilotrif is highly distributed out of the blood and has a moderate to high clearance. The overall gMean terminal half-life at steady state was 37.2 hours in cancer patients. Steady state was reached no later than 8 days after the first administration. The major route of elimination of Gilotrif was via faeces. After food intake, a decreased systemic exposure was observed compared to administration under fasted conditions. Therefore, Gilotrif should be taken without food (i.e. 1 hour before or 2 hours after food). The PK characteristics in Caucasian cancer patients were comparable to those observed in Japanese cancer patients.

Gilotrif is bound covalently to proteins to a variable extent and covalent protein adducts were the major circulating metabolites in the plasma. Gilotrif did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions based on this mechanism will occur.

Gilotrif is a substrate of the P-gp transporter. Concomitant administration of the potent P-gp inhibitor ritonavir did not relevantly change the exposure to 40 mg Gilotrif when taken simultaneously with or 6 h after Gilotrif but increased the bioavailability of Gilotrif (single dose of 20 mg) by 48% and 39% for AUC0-∞ and Cmax when given 1 h before Gilotrif, respectively. Pretreatment with the potent P-gp inducer rifampicin decreased the plasma exposure of 40 mg Gilotrif by 34 % Gilotrif (AUC0-∞) and 22 % (Cmax), respectively. Caution should be exercised when combining Gilotrif with potent P-gp modulators.
In pre-clinical studies Gilotrif is not irritant to intact skin but an ocular irritant. Gilotrif is mutagenic in a single bacteria strain, but did not show genotoxic potential in vivo when tested up to overt toxic/lethal doses. Studies on embryo-foetal development in rats and rabbits up to life-threatening doses have revealed no indication of teratogenicity.

Two phase I open label dose-escalation studies determined the MTD with continuous dosing of Gilotrif in patients with advanced solid tumours at 40mg and 50mg daily, respectively (90, 91). Adverse events (AE) observed with Gilotrif are consistent with those reported for other EGFR and dual EGFR/HER2 inhibitors. The most frequent investigator defined drug-related AEs were associated with gastrointestinal disorders (including diarrhoea, and stomatitis), skin and subcutaneous tissue disorders (rash, dry skin, pruritus, acneiform rash, acne), nail effects, epistaxis, fatigue and decreased appetite. Early and proactive management of diarrhoea, mucositis/stomatitis and skin rash together with treatment interruptions and dose reductions is recommended in line with recent guidelines in the management of common toxicities of EGFR and EGFR/HER2 TKIs and monoclonal antibodies (92-96).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 Rationale for performing the trial evaluating Gilotrif as salvage therapy for advanced PSCC

Gilotrif is a highly promising irreversible pan-EGFR inhibitor, which was recently approved for non-small cell lung cancer with EGFR mutations (97). Median PFS was 11.1 months for Gilotrif and 6.9 months for chemotherapy with cisplatin plus pemetrexed in a phase III trial (hazard ratio [HR], 0.58; 95% CI, 0.43 to 0.78; P = .001). Median PFS among those with exon 19 deletions and L858R EGFR mutations (n = 308) was 13.6 months for Gilotrif and 6.9 months for chemotherapy (HR, 0.47; 95% CI, 0.34 to 0.65; P = .001). The most common treatment-related adverse events were diarrhea, rash/acne, and stomatitis for Gilotrif and nausea, fatigue, and decreased appetite for chemotherapy. Given the tumor tissue studies providing robust supportive evidence for the expression of the EGFR family of proteins, a strong rationale may be made for investigating the role of Gilotrif as salvage therapy for advanced PSCC. Indeed, another phase II trial is evaluating dacomotinib, another pan-Her inhibitor as salvage therapy for PSCC (NCT01728233). Moreover, PSCC is an orphan malignancy and a strong rationale can be made for the approval of agents by regulatory agencies based on robust activity in phase II trials.

2.2 Study objectives

2.2.1 Primary objective

Progression-free survival (PFS) at 6 months of patients with advanced PSCC receiving Gilotrif following ≥1 prior systemic therapy regimen

2.2.2 Secondary objectives

- Response Rate (RECIST 1.1)
- Overall Survival
- Toxicities

2.2.3 Exploratory objectives

- Tumor tissue molecular studies: HPV status (PCR), gene expression (nanostring) and IHC (EGFR, Her2, Her3, Her4)
- Central pathology review and histologic subtype

2.3 Benefit-Risk Assessment

Gilotrif offers the prospect of prolonged PFS in a proportion of patients with progressive disease following systemic therapy for PSCC. Potentially some patients will exhibit a response accompanied by improvement in symptoms and quality of life. The major adverse

events are expected to be diarrhoea, rash/acne, and stomatitis, which are manageable and not life threatening. Given that patients with progressive PSCC following prior systemic therapy have no curative options and dismal outcomes with currently employed agents, the potential benefits with Gilotrif clearly outweigh the risks. Moreover, there are no agents approved by regulatory agencies for this disease.

3. DESCRIPTION OF DESIGN AND STUDY POPULATION

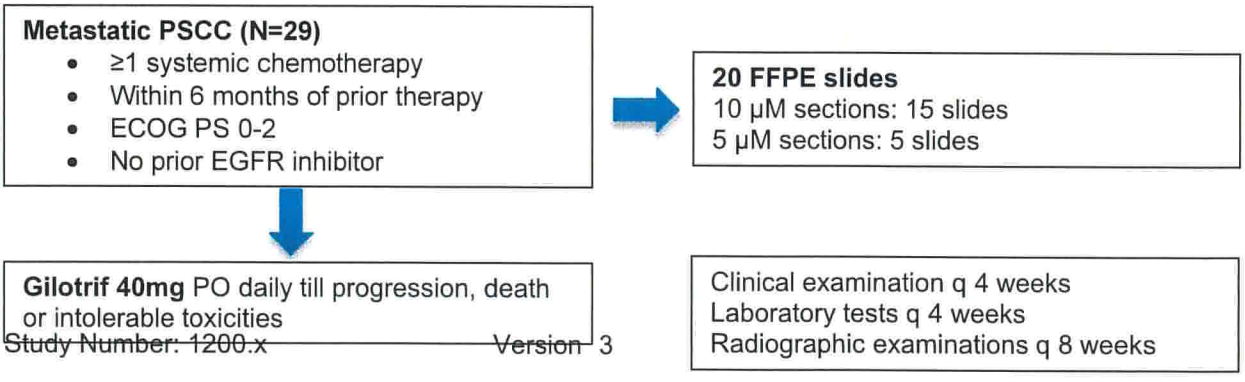
3.1 Overall study design and plan

This is a non-randomized 2-center phase II trial (overall N=29, evaluable N= 27) to evaluate Gilotrif 40 mg po qd for patients with locally advanced unresectable or metastatic progressive PSCC following prior chemotherapy. UAB is the coordinating institution and the other participating institution is the University of Southern California (USC). Patients will undergo clinical examination every 4 weeks and radiographic work-up at baseline and then every 8 weeks. Patients will continue therapy until progression or intolerable toxicities. Patients removed from therapy for reasons other than progression will be followed to identify progression or until initiation of other therapy. Twenty archival formalin-fixed paraffin embedded (FFPE) tissue slides per patient will be acquired for future analyses including histologic sub-type, IHC for EGFR, Her2, Her3, Her4, gene expression by nanostring for a panel of kinase and cancer associated genes and Human Papilloma Virus status by PCR (polymerase chain reaction) for HPV-DNA.

The eligible population of patients includes men with pathologically proven locally advanced or metastatic (lymph node or distant metastasis i.e. N+ or M1) PSCC which has received >=1 systemic chemotherapy regimens within last 6 months with ECOG PS 0-2 & optimal organ function (Hb>8.5, ANC>1500/mm3, Platelet count>100K, Total bilirubin <1.5 of ULN, creatinine clearance >45ml/min, ALT and AST<2.5X ULN, for patients with liver involvement ALT and ALT<5X ULN). The disease should be measurable by RECIST 1.1 criteria. Gilotrif will be administered orally 40mg daily continuously. Continuous administration of 4 weeks is considered one cycle. Therapy will continue until progression (by RECIST 1.1) or severe toxicities. Patients removed from the trial for toxicities or other reasons will continue to be followed until progression or starting a new agent. Complete Blood Count (CBC) & Comprehensive metabolic panel (CMP) evaluations will be done performed on day 1 every 4 weeks. CT chest, abdomen and pelvis will be performed every 2 cycles (8 weeks). A bone scan will be performed only if bone pain or high alkaline phosphatase are observed. An evaluable patient is defined as any patient who qualifies for the trial and receives at least one dose of study drug.
Progression of disease will be defined clinically as the first occurrence of any of the following:

1) Progression in measurable disease as defined by RECIST criteria
2) Death

Trial schema



3.2 Discussion of study design

Given that there are no approved agents and PSCC is an orphan disease, demonstration of activity and benefit of a salvage systemic agent in a nonrandomized phase II trial is reasonable. Currently used agents, e.g. taxanes, yield marginal activity and exhibit median PFS and OS of only ~3 months and ~6 months, respectively (Table 1). Given the lack of validated predictive biomarkers for efficacy and the universal presence of EGFR in PSCC, all patients will be enrolled without biomarkers to select a subgroup. Those progressing within 6 months of prior therapy will be enrolled with the goal of detecting PFS at 6 months (PFS6) in ≥20% of patients, while PFS6 in <5% will be considered to be of poor interest. The attainment of PFS at 6 months by ≥20% of patients is considered of significant interest, since this was not achieved in the second-line trial that evaluated paclitaxel (78). Selecting patients within 6 months of prior therapy will enrich for patients unlikely to attain PFS6 without active therapy.

Trial schedule

	-30 days	-14 days	Day 1 of every cycle (28 days)	Every 2 cycles	28 (± 3 days) post last treatment
REQUIRED ASSESSMENTS					
History	X		X		X
Height	X				
Physical examination		X	X		X
BP, weight		X	X		X
Smoking history	X				
ECOG performance status		X	X		X
CBC with differential		X	X		X
Chemistries (CMP)		X	X		X
Hepatitis panel (B, C)	X				
Adverse event and concomitant medication assessment	X		X		X
DISEASE ASSESSMENT					
CT chest , abdomen, pelvis	X			X	X
Bone Scan (if bone pain or high alkaline phosphatase)	X			X	
TREATMENT					
Gilotrif PO QD			X (1–28 days)		
CORRELATIVE STUDIES					
Collect 20 FFPE slides (15 sections of 10uM thickness, 5 sections of 5uM thickness) from archival biopsy for correlative studies (central pathology review, IHC, nanostring gene expression, HPV DNA)	X				
FOLLOW-UP					
Disease progression and survival					X

3.3 Selection of study population

General Guidelines

Eligible patients will be entered on study centrally at the Kirklin Clinic, UAB Hospitals, and USC (research nurse to be designated by Elizabeth Busby Director of Oncology Clinical Trials, CSU, UAB). All sites should call the Study Monitor at UAB to verify agent availability. Following registration, patients should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be cancelled. The Study Monitor should be notified of cancellations as soon as possible.

Registration Process

The Clinical Trials Network Monitoring Office (CTNMO) of the UAB Comprehensive Cancer Center (CCC) coordinates investigator-initiated clinical trials under Good Clinical Practice conditions at participating sites to achieve timely study subject enrolment. Once a study subject has been screened and deemed eligible for study entry by the participating site, a study-specific study subject eligibility checklist, a copy of the dated and signed consent form, and corresponding source documentation are faxed to the participating site study coordinator for eligibility verification. Subsequently, a study-specific number is assigned to the study subject and sent to the participating site. Finally, a Patient Registration Form is completed and faxed by the CTNMO site to the participating study coordinator. Queries regarding data accuracy are forwarded from the CTNMO to the participating site coordinator for clarification or correction. Once the participating site addresses queries, any corrected data forms or copies of corrected source documentation are faxed to the CTNMO.

3.3.1 Main diagnosis for study entry

Patients who have been detected with histology confirmed Penile Squamous Cell Carcinoma (PSCC) and who have documented failure after at least one prior chemotherapy

3.3.2 Inclusion criteria

1. Each patient will meet all of the following criteria to be enrolled in the study: Histologically or cytologically confirmed PSCC.
2. Patients with metastatic (lymph node or distant metastasis, i.e. N+ or M1) or locally advanced unresectable PSCC.
3. Progressive disease after ≥ 1 prior chemotherapy regimens.
4. Measurable disease by RECIST 1.1 criteria.
5. Prior regimen within 6 months
6. ECOG performance status *0-2 (Appendix 10.3).*
7. Adequate organ function, defined as all of the following:
   - Absolute neutrophil count (ANC) > 1500 / mm^3. Platelet count >100,000 / mm^3.
   - Estimated creatinine clearance ≥ 45ml / min. Refer to A*ppendix* 10.2.
   - Total Bilirubin < 1.5 times upper limit of institutonal normal; Aspartate amino transferase (AST) or alanine amino transferase (ALT) < 2.5 times the upper limit of institutional normal (ULN).
   - Hemoglobin ≥ 8.5 g/dl.
8. Resolution of all acute toxic effects of prior chemotherapy or surgical procedures to NCI CTCAE version 4.03 grade < 1, in the opinion of the Treating Physician (Appendix 10.7).
9. Ability to understand and willingness to sign a written informed consent that is consistent with ICH-GCP guidelines. Age ≥18 years or age of majority at the participating site, whichever is greater.

10. Availability of 20 archival formalin-fixed paraffin embedded (FFPE) tumor tissue slides (15 of 10 µM thick sections, and 5 of 5 µM thick sections)

3.3.3 Exclusion criteria

Patients meeting any of the following exclusion criteria within 4 weeks (unless otherwise stated) of being enrolled are not to be enrolled in the study.

1. Patients will have recovered from toxicities from prior systemic anticancer treatment or local therapies.
2. Prior EGFR inhibitors.
3. Major surgery within 4 weeks or minor surgery within 2 weeks before registration or scheduled for surgery during the projected course of the study. Wounds will be completely healed prior to study entry and patients recovered from all toxicities from surgery. Placement of vascular access device is not considered major or minor surgery in this regard.
4. Prior radiation therapy is allowed as long as the irradiated area was not the sole source of measurable disease and radiotherapy was completed with recovery from toxicity, at least 3 weeks prior to enrollment. If the irradiated area is the only site of disease, there will be progressive disease.
5. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3 (Refer to Appendix 10.6), unstable angina or poorly controlled arrhythmia as determined by the investigator. Myocardial infarction within 6 months prior to registration.
6. Any history of or concomitant condition that, in the opinion of the Investigator, would compromise the patient's ability to comply with the study or interfere with the evaluation of the efficacy and safety of the test drug
7. Previous or concomitant malignancies at other sites, except effectively treated non-melanoma skin cancers, ductal carcinoma in situ or effectively treated malignancy that has been in remission for more than 3 years and is considered to be cured.
8. Requiring treatment with any of the prohibited concomitant medications listed in Section 4.2.3 that cannot be stopped for the duration of trial participation
9. Known pre-existing interstitial lung disease
10. Any history or presence of poorly controlled gastrointestinal disorders that could affect the absorption of the study drug (e.g. Crohn's disease, ulcerative colitis, chronic diarrhea, malabsorption)
11. Active hepatitis B infection (defined as presence of Hep BsAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) and/or known HIV carrier.
12. Meningeal carcinomatosis
13. Patients with active brain or subdural metastases are not eligible, unless they have completed local (radiation) therapy and have discontinued the use of corticosteroids or have been on stable dose of corticosteroids for at least 4 weeks before starting study treatment. Any symptoms attributed to brain metastases will be stable for at least 4 weeks before starting study treatment.
14. Any active or uncontrolled infection.

3.3.4 Removal of patients from therapy or assessments

Patients will be removed from study when any of the criteria listed below applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

1. Progression of disease as defined by measurable disease using RECIST 1.1
2. Death
3. Intercurrent illness that prevents further administration of treatment
4. Unacceptable adverse event(s)
5. Patient decides to withdraw from the study
6. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

3.3.5 Premature discontinuation of the study as a whole

The study will be discontinued in event of

1. Deviation in conduct of protocol
2. No accrual in first year
3. >1 death attributable to toxicity from study drug
4. If no patient, out of 13 accrued patients achieves PFS6 at the end of stage 1, this study will be stopped.

3.4 Exploratory tumor tissue studies and central pathology review

Archival formalin-fixed paraffin-embedded (FFPE) tumor slides will be obtained for central pathology review and molecular studies. Fifteen slides of 10 μM thickness sections each and 5 slides of 5 μM thickness sections each will be obtained. Following central pathology review for determining histologic subtype, tumor will be demarcated from adjacent normal tissue on the H+E slide to guide procurement of tumor-enriched samples. The 10 μM sections will be used for RNA isolation toward gene expression profiling for ~800 cancer-promoting, kinase, DNA-damage repair, bladder cancer-specific and stem cell panel genes by the nanostring platform performed centrally at UAB Cancer Center. A total surface area of tumor 100 mm^2 is adequate to harvest the necessary amount of RNA (100 ng) using the RNAeasy Mini Kit (Qiagen), and the quality of the RNA will be assessed via the 260/280 ratio using nanodrop. Dr Eddy S. Yang at UAB Radiation Oncology Dept. will perform the nanostring studies as described in previous publications utilizing the nCounter by inputting RNA directly into a hybridization reaction containing color-coded molecular barcodes representing the genes of interest [56].

A minimum of 100 ng of genomic double-stranded DNA (dsDNA) will be isolated from tumor alone for restoration and downstream applications. Genomic DNA will then be isolated using the QIAamp DNA FFPE Tissue Kit on the QIAcube robotic platform (QIAgen, Germantown, MD). dsDNA is quantified using the QuantIT Pico Green dsDNA kit (Invitrogen, Carlsbad, CA) and quality control (QC) is performed by the Illumina FFPE QC kit and real time PCR. If the DNA passes the required QC threshold (5 CT within the QC positive control), the restoration will be performed by using the Infinium HD FFPE Restore kit (Illumina, San Diego, CA). Real time PCR probes for the HPV16 and HPV18 E6 region will be designed using the GeneAssist Copy Number Assay design tool (Invitrogen). Real time PCR quantification of viral load will then be performed using 100 pg of genomic DNA, the HPV16 and HPV18 primer/probe sets and eukaryotic 18S primer/probe set as normalizer in separate reactions. HPV viral load is then calculated as HPV16E6/18S and HPV18E6/18S.

Immunohistochemistry (IHC) will be performed on the 5µM section slides for EGFR, Her2, Her3 and Her4 by previously described methods using appropriate controls.

4. TREATMENTS

4.1 Treatment(s) to be administered

4.1.1 Identity of investigational product

Substance (INN) (Brand name):	**Gilotrif**
Pharmaceutical form:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	20, 30 and 40 mg film-coated tablets (the dose of Gilotrif in the film-coated tablets is related to the free base equivalent to Gilotrif)
Route of administration:	Oral
Posology	Once daily
Timings	Gilotrif should be taken at least 1 hour before or 2 hours after meal. A missed dose should not be taken within 12 hours of next dose.

4.1.2 Method of assigning patients to treatment groups

This is one arm non-randomized study and all enrolled patients will receive Gilotrif.

4.1.3 Selection of dose(s) in the study

All patients will receive 40 mg of Gilotrif PO qd.

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 Gilotrif

Patients will take a single oral dose of Gilotrif each day starting at a dose of 40 mg, continuously, until the development of progressive disease or unacceptable adverse events. Dose escalation and reductions of Gilotrif can occur.

The medication should be taken at the same time each day (± 2 hours) without food (at least one hour before or at least two hours after a meal).

Missed doses of Gilotrif can be made up during the same day. Otherwise, the dose will be skipped and patients should take the next scheduled dose at the usual time. Patients with emesis will not take a replacement dose.

If dosing of whole tablets is not possible, Gilotrif tablets can also be dispersed in approximately 100 ml of non-carbonated drinking water. No other liquids should be used.

The tablet should be dropped in the water, without crushing it, and occasionally stirred for up to 15 min until the tablet is broken up into very small particles. The dispersion should be drunk immediately. The glass should be rinsed with approximately 100 ml of water which should also be drunk. The dispersion can also be administered through a naso-gastric tube. Medication will be dispensed in bottles containing 30 tablets at the beginning of each treatment course. For administrative purposes, a treatment course is defined as 28 days. Treatment will start when patient is eligible and enrolled and stop when the patient is diagnosed with disease progression or for any reason detailed in section 3.3.4. Study drug will be prescribed by the investigator and may be dispensed either by the investigator, study coordinator or affiliated pharmacy.

General Properties of Gilotrif

Following oral administration of Gilotrif tablets, the peak Gilotrif plasma concentration occurs in 2-5 hours. Covalent adducts to protein are major circulating metabolites of Gilotrif and enzymatic metabolism of Gilotrif is minimal. In humans, primary excretion is via the faeces (85%). The elimination half-life of Gilotrif is 37 hours. Steady concentration is achieved after 8 days of repeat dosing.

4.1.4.2 Dose reduction for Gilotrif

Treatment related toxicities will be managed by treatment interruptions and subsequent dose reductions of Gilotrif according to the schedule described in Table 4.1.4.1: 1. Dose reductions will apply to individual patients only. Once the dose has been reduced, it cannot be increased later.

To prevent the development of more severe adverse events, treatment related diarrhoea, nausea and vomiting or rash should be managed early and proactive as described in Section 4.2.

Table 4.1.4.1: 1 Dose reduction scheme for Gilotrif

AE type and CTCAE Grade	Action	Dose reduction scheme
Events <u>related to study drug:</u>		
• Diarrhoea Grade 2 persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration	Pause treatment until patient has recovered to Grade ≤1 or baseline[1].	If patient was receiving 40 mg, resume treatment at a dose of 30 mg.
• Reduced renal function to ≥ Grade 2 as measured by serum creatinine, proteinuria or decrease in glomerular filtration rate of more than 50% from baseline	Resume treatment at reduced dose according to schedule opposite.	If patient was receiving 30 mg, resume treatment at a dose of 20 mg. If patient was receiving 20 mg, discontinue Gilotrif.
• Any drug related AE Grade ≥3	If patient has not recovered to Grade ≤1 or baseline[1] within 21 days	

	study treatment will be permanently discontinued[2].	
Acute onset and/or unexplained worsening of pulmonary systems (dyspnoea, cough, fever)	Pause Gilotrif while clinical assessment to exclude ILD is completed.	If ILD is ruled out as a cause of symptoms, grade symptoms and relatedness and report as AEs. If AEs are not related, resume Gilotrif at current dose. If AEs are drug related, follow directions in row above. If ILD is confirmed, discontinue Gilotrif

1 Baseline is defined as the CTCAE Grade at the start of treatment
2 In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with Gilotrif will be decided in agreement between the sponsor and the investigator.

In the event of any unrelated adverse events, the investigator may choose to interrupt the medication for up to 14 days, but no dose reduction should occur. If the medication is interrupted for more than 14 days, the decision to continue with Gilotrif will be made by the sponsor in agreement with the investigator.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is a non-randomized one arm study and will not employ any blinding of patients to treatment regimen.

4.1.5.2 Procedures for emergency unblinding

Not applicable

4.1.6 Packaging, labelling, and storage

Medication numbers will be unique to each bottle and will be used for tracking purposes only.

4.1.6.1 Gilotrif

Gilotrif will be supplied as film-coated tablets. Available dosage strengths will be 20, 30 or 40 mg. Tablets will be supplied in HDPE, child-resistant, tamper-evident bottles. .

Bottles/boxes will be labelled according to local regulations and will include the following as a minimum;

- Study number (1200.x)
- Product name (Gilotrif)

- Contents of the bottle (30 tablets)
- Tablet strength (mg)
- Batch number
- Medication number
- Use-by date
- Storage information
- Instructions for use

Sponsor name and address: Guru Sonpavde, MD
Bladder Cancer Director
Dana Farber Cancer Institute
450 Brookline Avenue, D1230F
Boston, MA 02215

- A statement that the medication is for clinical study use only
- A caution statement

A new bottle of medication will be dispensed on day 1 of each course, regardless of the number of tablets remaining in the bottle from the previous course. The patient will initially receive one bottle of 40 mg tablets and in the event that dose reduction is necessary the patient will return to the clinic and new medication will be dispensed.

4.1.7 Storage conditions

Gilotrif will be stored in the original package in order to protect from light. Film-coated tablets are humidity-sensitive; therefore, bottles will be kept tightly closed to protect from moisture. Tablets will be stored according to label instructions.

4.1.8 Drug accountability

Drug supplies, which will be provided by Boehringer Ingelheim, will be kept in a secure, limited access storage area under the storage conditions. A temperature log will be maintained to make certain that the drug supplies are stored at the correct temperature.

A designated person will maintain records of the product's delivery to the study site, the inventory at the site, the use by each patient, and destruction of the unused study drug.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and study patients. The responsible person will maintain records that document adequately that the patients were provided the doses specified by the CSP and reconcile all investigational product(s) received from Boehringer Ingelheim. The responsible person will verify that all unused or partially used drug supplies have been returned by the clinical study patient.

4.2 Management of adverse events, concomitant therapy, restrictions and rescue treatment

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

4.2.1.1 Rescue medication

Rescue medications to reverse the actions of Gilotrif are not available. There is no specific antidote for overdosage with Gilotrif. Potential adverse events should be treated symptomatically. Common adverse events of treatment with Gilotrif with specified management recommendations and/or requirements include diarrhoea, and rash/acne. To improve tolerability and the probability of clinical benefit, patients should receive prompt and appropriate supportive care at the first signs of symptoms. Suggested treatments for AEs are described below.

4.2.1.2 Concomitant treatment(s)

Concomitant medications or therapy to provide adequate supportive care may be given as clinically necessary.

After study enrollment, palliative radiotherapy may be given for bone pain or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range according to institutional standards. The irradiated area cannot be used for tumor response assessment. During palliative radiotherapy, study treatment should be delayed and may be resumed once the patient has recovered from any radiation associated toxicity. If medication is interrupted for more than 14 days, the decision to continue will be made by the sponsor in agreement with the investigator. Continuous interruption of >28 days due to palliative radiotherapy will not be allowed.

All concomitant therapy, including anaesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, will be recorded in the (e)CRF during the screening and treatment period, starting from the date of signature of informed consent, and ending at the EOT visit. After the EOT visit, only concomitant therapy indicated for treatment of an AE has to be reported.

In case of major surgery (as judged by the investigator), it is recommended to stop treatment with Gilotrif around one week prior to the surgery, and to restart treatment after complete wound healing. If Gilotrif is interrupted for more than 14 days, the decision to continue will be made by the sponsor in agreement with the investigator.

4.2.1.3 Emergency procedures

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude interstitial lung disease (ILD). Study drugs should be interrupted pending investigation of these symptoms. If interstitial lung disease is diagnosed, study drug will be permanently discontinued and appropriate treatment instituted as necessary.

Patients who present with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with Gilotrif should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment with Gilotrif should be carefully considered. Gilotrif should be used with caution in patients with a history of keratitis,

ulcerative keratitis or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration.

4.2.2 Management of expected adverse events

Dermatologic adverse events and diarrhoea are the most common side-effects associated with treatment with Gilotrif. Treatment of these side-effects should be proactive and should be started as early as possible after onset of symptoms.

4.2.2.1 Management of diarrhoea and hydration status following treatment with Gilotrif

Diarrhoea occurs at a high frequency and generally begins within 2 weeks of exposure to Gilotrif. Although usually mild to moderate, diarrhoea may lead to dehydration and compel treatment modification or discontinuation, so early management is essential (Table 4.2.2.1: 1). At the time of initiation of treatment with Gilotrif patients should be given a supply of loperamide to keep with them at all times or access to Gilotrif should be confirmed; and patients should be counselled on the appropriate use.

Patients will be advised to drink an adequate amount of fluids to make up for the fluid lost through diarrhoea. (94)

Table 4.2.2.1: 1 Grade specific treatment recommendations for Gilotrif related diarrhoea

Severity (CTCAE Grading)	**Description**	**Intervention concerning Gilotrif treatment**	**Specific intervention**
Mild (Grade 1)	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	Continue same dose	Stop laxatives and advise patient to drink at least 8-10 glasses of water of clear fluids per day; 4 mg (2 tablets) of loperamide to be taken immediately, followed by 2 mg (1 tablet) after each loose stool until bowel movements cease for 12 hours
Moderate (Grade 2)	Increase of 4-6 stools per day over baseline; i.v. fluids indicated < 24 hours; moderate increase in ostomy output compared with baseline; not interfering with ADL	Continue same dose unless Grade 2 diarrhoea continues for ≥ 2 days (48 hours) in which case treatment will be interrupted until recovered to ≤ Grade 1 followed by dose reduction	Continue loperamide; assess for dehydration and electrolyte imbalance; consider IV fluids and electrolyte replacement
Severe (Grade	Increase of ≥ 7 stools per day over	Dose interruption until recovered to	See Grade 2; plus: an infectious process

3)	baseline; incontinence; IV fluids > 24 hours; hospitalization; severe increase in ostomy output compared with baseline; interfering with ADL	≤Grade 1 followed by dose reduction*	should be ruled out with stool cultures; aggressive iv fluid replacement ≥ 24 hours; hospitalization to monitor progress; consider prophylactic antibiotics if patient is also neutropenic;
Life threatening (Grade 4)	Life-threatening consequences (e.g. haemodynamic collapse)	Dose interruption until recovered to ≤Grade 1 followed by dose reduction*	See Grade 3

* If despite optimal supportive care and a treatment interruption, diarrhoea does not resolve to CTC AE Grade ≤ 1 within 14 days, treatment with Gilotrif will be permanently discontinued. In the event that the patient is deriving obvious clinical benefit according to the investigator's judgement, further treatment with Gilotrif will be decided in agreement between the sponsor and the investigator.

4.2.2.2 Management recommendations for dermatological AEs following treatment with Gilotrif

Dermatologic AEs of Gilotrif include rash, acne, dermatitis acneiform, and dry skin. General recommendations for prophylaxis are summarized in Table 4.2.2.2: 1 and grade-specific treatment recommendations are summarized in Table 4.2.2.2: 2. For dose adjustment of Gilotrif refer to Table 4.1.4.1.2.

Specific interventions should be reassessed at least after 2 weeks or at any worsening of symptoms, in which case the specific intervention should be adjusted and, depending on own clinical experience, early involvement of a dermatologist should be considered. (93).

Table 4.2.2.2: 1 General recommendations for prophylaxis while receiving Gilotrif

Personal hygiene	Use of gentle soaps and shampoos for the body, e.g. pH5 neutral bath and shower formulations and tepid water. Use of very mild shampoos for hair wash. Only clean and smooth towels are recommended because of potential risk of infection. The skin should be patted dry after a shower, whereas rubbing the skin dry should be avoided. Fine cotton clothes should be worn instead of synthetic material. Shaving has to be done very carefully. Manicure, i.e. cutting of nails, should be done straight across until the nails no longer extend over the fingers or toes. Cuticles are not allowed to be trimmed because this procedure increases the risk of nail bed infections
Sun protection	Sunscreen should be applied daily to exposed skin areas regardless of season. Hypoallergenic sunscreen with a high SPF (at least SPF30, PAPA free, UVA/UVB protection), preferably broad spectrum containing zinc oxide or titanium dioxide are recommended Patients should be encouraged to consequently stay out of the

	sun. Protective clothing for sun protection and wearing a hat should be recommended.
Moisturizer treatment	It is important to moisturize the skin as soon as anti-EGFR therapy is started. Hypoallergenic moisturizing creams, ointments and emollients should be used once daily to smooth the skin and to prevent and alleviate skin dryness. Note: avoid greasy creams (e.g. petrolatum, soft paraffin, mineral oil based) and topical acne medications
Prevention of paronychia	Patients should keep their hands dry and out of water if ever possible. They should avoid friction and pressure on the nail fold as well as picking or manipulating the nail. Topical application of petrolatum is recommended around the nails due to its lubricant and smoothing effect on the skin.

Table 4.2.2.2: 2 Grade specific treatment recommendations of skin reactions to Gilotrif

Severity (CTCAE Grading)	**Description**	**Specific intervention**
ACNEIFORM RASH		
Mild (Grade 1)	Macular or papular eruptions or erythema without associated symptoms	Consider topical antibiotics, e.g. clindamycin 2% or topical erythromycin 1% cream of metronidazole 0.75% or topical nadifloxacin 1%; Isolated scattered lesion: cream preferred Multiple scattered areas: lotion preferred
Moderate (Grade 2)	Macular or papular eruptions with pruritus or other associated symptoms; localized desquamation or other lesions covering <50% of BSA	Topical treatment as for Grade 1 plus short term topical steroids, e.g. prednicarbate cream 0.02% plus an oral antibiotic (for at least 2 weeks) e.g. Doxycycline 100mg b.i.d. or Minocycline hydrochloride 100mg b.i.d
Severe (Grade 3)	Severe, generalized erythroderma or macular, popular or vesicular eruption; desquamation covering ≥ 50% of BSA; associated with pain, disfigurement, ulceration or desquamation	Topical and systemic treatment as for Grade 2. Consider referral to dermatologist Consider systemic steroids
Life threatening	Generalized exfoliative,	See Grade 3

(Grade 4)	ulcerative, or bullous dermatitis	Systemic steroids are recommended
EARLY AND LATE XEROTIC SKIN REACTIONS - PRURITUS		
Mild (Grade 1)	Mild or localized	Topical polidocanol cream. Consider oral antihistamines, e.g. diphenhydramine, dimethindene, cetirizine, levocetirizine, desloratidine, fexofenadine or clemastine)
Moderate (Grade 2)	Intense or widespread	See Grade 1 plus oral antihistamines; Consider topical steroids, e.g. topical hydrocortisone
Severe (Grade 3)	Intense or widespread and interfering with activities of daily living (ADL)	See Grade 2.
XEROSIS (DRY SKIN)		
Mild (Grade 1)	Asymptomatic	Soap-free shower gel and/or bath oil. Avoid alcoholic solutions and soaps. Urea- or glycerin-based moisturizer. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Moderate (Grade 2)	Symptomatic, not interfering with ADL	See Grade 1. In inflammatory lesions consider topical steroids (e.g. hydrocortisone cream)
Severe (Grade 3)	Symptomatic, interfering with ADL	See Grade 2. Topical steroids of higher potency (e.g. prednicarbate, mometasone furoate) Consider oral antibiotics
FISSURES		
Mild (Grade 1)	Asymptomatic	Petroleum jelly, Vaseline® or Aquaphor for 30 minutes under plastic occlusion every night, followed by application of hydrocolloid dressing; antiseptic baths (e.g. potassium permanganate therapeutic baths, final concentration of 1:10,000, or povidone-iodine baths) Topical application of aqueous silver nitrate solutions to fissures
Moderate (Grade	Symptomatic, not interfering with ADL	See Grade 1. Consider oral antibiotics.

2)		
Severe (Grade 3)	Symptomatic, Interfering with ADL	See Grade 2.
1 If Grade 2 rash persists for ≥7 days despite treatment and is poorly tolerated by the patient, the investigator may choose to pause treatment up to 14 days followed by a reduction in the dose of Gilotrif according to the dose reduction scheme in Table 4.1.4.2: 1		

4.2.2.3 Management of mucositis/stomatitis

General and grade specific recommendations are described in Table 4.2.3.3:1. For dose adjustment refer to Section 4.1.4 and for restrictions on concomitant therapies refer to Sections 4.2.3 and 10.1.

Treatment is supportive and aimed at symptom control. These may include atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in one quart of water every four hours); avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide; dietary manoeuvres such as promotion of soft, non-irritating foods like ice-creams, mashed/cooked vegetables, potatoes and avoidance of spicy, acidic or irritating foods such as peppers, curries, chillies, nuts and alcohol. If the patient is unable to swallow foods or liquids, parenteral fluid and/or nutritional support may be needed. Examples of some of the agents suggested in Table 4.2.3.3:1 include: topical analgesics –viscous lidocaine 2%; mucosal coating agents - topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals – nystatin suspension. (adapted from (98)).

Table 4.2.3.3: 1 Grade specific treatment recommendations of study-drug related mucositis/stomatitis

Severity (CTCAE grading)	Description	Treatment recommendations	Intervention concerning Gilotrif treatment/ dose modification
Mild (Grade 1)	Minimal symptoms; normal diet	Oral rinses with agents such as non-alcoholic mouth wash, normal saline, diluted salt and baking soda solution .	No change .
Moderate (Grade 2)	Symptomatic, but can eat and swallow modified diet	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.	Maintain dose if tolerable; Hold dose if intolerable until recovery to grade ≤1, then restart at the same dose.
Severe (Grade 3)	Symptomatic and unable to adequately aliment or hydrate orally	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated .	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4.

Life threatening (Grade 4)	Symptoms associated with life-threatening consequences	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated	Hold dose until recovery to grade ≤1 or baseline, then restart at the reduced dose according to Section 4.1.4

4.2.3 Restrictions

4.2.3.1 Restrictions regarding concomitant treatment

Concomitant medications, or therapy to provide adequate supportive care, may be given as clinically necessary.

Palliative radiotherapy may be given as described in Section 4.2.1.2.

Additional experimental anti-cancer treatment and/or standard chemo-, immunotherapy, hormone treatment, or radiotherapy (other than palliative radiotherapy for symptom control) is not allowed concomitantly with the administration of study treatment.

Gilotrif is a substrate of the P-gp transporter. Caution should be exercised when combining Gilotrif with P-gp modulators. For a list of potent P-gp inhibitors and inducers see Appendix 10.1.

4.2.3.2 Restrictions on diet and life style

Patients should be advised to avoid any foods known to aggravate diarrhoea.

To prevent skin related adverse events it is recommended to avoid intense irradiation with UV light and harsh detergents, see also Section 4.2.2.2.

4.3 Treatment compliance

The study medication will be given in accordance with the protocol and the instructions of a site investigator.

The appropriate number of Gilotrif tablets for 4 weeks of treatment will be provided to patients to be self-administered at home. Patients will be asked to bring the remaining trial medication at the end of each *4 weeks* to the investigator site for a compliance check. The remaining film-coated tablets will be counted by the investigator/site staff and recorded at the investigator site. Discrepancies between the number of tablets remaining and the calculated number of tablets the patients should have taken will be documented and explained. At the end of each *4 weeks*, any remaining medication will be collected. If the patient is eligible for further treatment, a new bottle of study medication will be dispensed.

The investigator and/or the sponsor can withdraw a patient from the study in the event of serious and persistent non-compliance which jeopardizes the patient's safety or render study results for this patient unacceptable. Patients who do not attend a minimum of *75%* of scheduled study visits, unless due to exceptional circumstances, should be discussed with the sponsor and be evaluated for compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 Efficacy

5.1.1 End point(s) of efficacy

5.1.1.1 Primary endpoint

Progression-free survival (PFS) at 6 months (PFS6)

5.1.1.2 Secondary endpoints

1. Measurable disease response rate (RECIST)
2. Survival
3. Toxicities

5.1.1.3 Exploratory endpoints

- Tumor tissue studies: IHC for EGFR, Her2, Her3, Her4, gene expression by nanostring for a panel of kinase and cancer associated genes and Human Papilloma Virus status by PCR (polymerase chain reaction) for HPV-DNA
- Central pathology review

5.1.2 Assessment of efficacy

5.2 Safety

5.2.1 Grading of adverse events

Adverse events graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (99).

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

5.2.2.1.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

5.2.2.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

The following hospitalizations are not considered to be serious adverse events (SAEs) because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol

- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug

5.2.2.1.3 Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 in the (e)CRF.

5.2.2.1.4 Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

5.2.2.1.5 Worsening of the underlying disease or other pre-existing conditions

Occurrence of death due to underlying cancer should not be reported as an adverse event or serious adverse event. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event. However, if there is any uncertainty about a finding being due solely to progression of cancer, the finding should be reported as an adverse event or serious adverse event as appropriate.

5.2.2.1.6 Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF, if they are judged clinically relevant by the investigator.

5.2.2.1.7 Significant adverse events

If the investigator determines any protocol-specific significant event is related to study drug, the administration of the study drug will be managed according to section 4.1.4 of the protocol.

5.2.2.1.8 Protocol-specifies significant events

Pregnancy

If a spouse or partner of a subject becomes pregnant while enrolled in this clinical trial or up to three months following administration of Gilotrif, they will be followed through the outcome of the pregnancy by the Investigator. If the outcome of the pregnancy meets a criterion for immediate classification as an SAE—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the Investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

5.2.2.1.9 Expected adverse events

For expected (listed) AEs of Gilotrif, see the current version of the Investigator's Brochure (IB).

5.2.2.2 Adverse event and serious adverse event reporting

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Serious Adverse Events (SAEs) are reported by the participating site Lead Investigator within 24 hours to the Clinical Trial Network Monitoring Office (CTNMO) Manager (Pam Dixon) by email (pamdixon@uab.edu) or by fax (205) 975-9875. The 24 hour paging number for the CTNMO Manager is (205) 934-3411, beeper #5904. The CTNMO Manager is then responsible for reporting SAEs to the UAB IRB and protocol P.I. in accordance with study-specific requirements. SAEs occurring at CTNMO sites are reported to the UAB IRB as "non-UAB" events.

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

An AE will be considered an SAE when the nature or severity of the event is not consistent with the current Investigator's Brochure. It is also the responsibility of the participating site Lead Investigator to report SAEs to the local site IRB and to submit copies of that report to the CTNMO Manager. It is the CTNMO Manager's responsibility to report the SAE to the Clinical Trials Monitoring Committee (CTMC), UAB IRB, sponsor/Principal Investigator (Lisle Nabell, MD from UAB) and industry funder. This submission of IND Safety Reports will be cross referenced according to local regulations to Boehringer-Ingelheim Investigation New Drug (IND) at the time of submission.

Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. AEs reported must also be reported in routine study data submissions. Safety will be monitored throughout the study by physical examinations, review of adverse events (AEs), and laboratory studies. The frequency of safety monitoring procedures is outlined in Section 5.2.3, 5.2.4 and 5.2.5. Criteria that will be used throughout the study for dose interruption, reduction, and discontinuation of chemotherapeutic agents are specified in Section 4.1.4.2.

Data and Safety Monitoring Plan

The UAB Comprehensive Cancer Center Data and Safety Monitoring Plan (DSMP) instituted by the CTNMO will monitor subjects treated at UAB and the other 2 institutions participating in the trial. The Clinical Trials Monitoring Committee (CTMC) on a weekly basis will closely monitor adverse reactions observed during treatment. The CTMC is responsible for data and safety monitoring of the trial and adherence to the DSMP. The office of CTNMO will also report any SAE at participating sites outside UAB to the CTMC. The independent Quality Assurance Committee (QAC) is responsible for oversight of the operation of CTMC, including adherence to the DSMP. Reports from the CTMC are reviewed monthly by the QAC.

Protocol Management and Oversight of Participating Site

Dr. Lisle Nabell functions as the sponsor of the trial at UAB and at the participating sites. The participating sites will utilize their respective IRB of record. The Lead Investigator at participating site(s) will be responsible for ensuring that all the required data will be collected and entered onto the Case Report Forms. A teleconference between UAB CTNMO and participating sites every 3 months will ensure discussion of AEs seen across all sites. UAB PI, CTNMO manager and participating site Lead Investigators will discuss management of AEs, and impact of AEs on trial conduct. The CTNMO office will report the outcome of these discussions at CTMC meeting every month. Periodically, monitoring visits will be conducted by CTNMO manager and the participating site Lead Investigator will provide access to his/her original records to permit verification of proper data entry. At the completion of the study, all case report forms will be reviewed by the CTNMO manager and will require his/her final signature to verify the accuracy of the data.

Table 5.2.2.2:1 AE/SAE reporting requirements

Time period	**Reporting requirements**
From signing of informed consent to ≤28 days after last trial drug administration	Report all AEs and SAEs regardless of relatedness or whether the trial drug was administered. This includes all deaths.
Post-treatment (>28 days after last trial drug administration)	Report only SAEs which are considered related to trial treatment or trial design. Death should be reported as an SAE only when considered related to trial treatment or trial design (because death is an endpoint and will be followed-up separately).

All adverse events, serious and non-serious, will be collected, documented and reported to the sponsor by the Lead site investigator on the appropriate CRFs / SAE reporting forms (BI SAE report forms).

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For each adverse event, the investigator will provide the onset date, end date, CTCAE grade, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

Adverse events with onset within first administration of Gilotrif therapy and 28 days after last administration of Gilotrif will be considered as on treatment. All AEs, including those persisting after end of study treatment will be followed up until they have resolved or have been sufficiently characterised or the principal investigator decides to not further pursue them.

Serious and non-serious adverse events occurring later than 28 days after last administration of trial drugs will only be reported in case they are considered drug-related or trial (procedure) related.

Adverse Event Characteristics

- CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03.
- "Expectedness": AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are bold and italicized in the CAEPR.
- Attribution of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

Expedited Adverse Event Reporting

Expedited AE reporting for this study must use the reporting procedures briefly outlined in the table below.

Expedited Reporting Guidelines – Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last dose of the Investigational Agent on Phase 2 and 3 Trials

	Grade 1	**Grade 2**	**Grade 2**	**Grade 3**		**Grade 3**		**Grades 4 & 5[2]**	**Grades 4 & 5[2]**
	Un-expected and Expected	**Unexpected**	**Expected**	**Unexpected with Hospitalization**	**Unexpected without Hospitalization**	**Expected with Hospitalization**	**Expected without Hospitali-zation**	**Unexpected**	**Expected**
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment require reporting as follows:

24-hour notification followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although a 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE within 24 hours of learning of the event followed by a complete report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported.
- Use the protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

5.2.2.3 Responsibilities for SAE reporting

Upon inclusion into a trial, the patient's condition is assessed (e.g. documentation of history / concomitant diagnoses and diseases), and relevant changes from baseline are noted subsequently.

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through through 28 days following cessation of treatment) will be collected, documented by the investigator.

The investigator shall report all SAEs and non-serious AEs which are relevant to a reported SAE by fax using BI IIS SAE form to BI Unique Entry Point as detailed below in accordance with the following timelines:

• within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;

• within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

900 Ridgebury Road

Ridgefield, CT 06877

Fax: 1-203-837-4329

E-mail: PVglobalcasemanagement@BoehringerIngelheim.com

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship and expectedness with the investigational drug to all AEs as defined in the listed adverse event section of Boehringer Ingelheim's (BI's) Investigator Brochure for the Product.

The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period), it should be reported to BI if investigator considers it as relevant to the BI study drug.

5.2.3 Assessment of safety laboratory parameters

Safety laboratory samples will be analyzed *at the individual participating site laboratory.* Safety laboratory examinations will include hematology, biochemistry and urine examinations. Table 5.2.3: 1 presents the laboratory tests to be performed.

Table 5.2.3:1 Clinical Laboratory Tests

Category	Parameters
Hematology	haemoglobin, haematocrit, platelet count, blood cell count (WBC)
Chemistry	
Electrolytes	sodium, potassium, calcium, magnesium,
Liver function tests	alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyltransferase (GGT), total bilirubin
Renal function parameters	Blood urea/blood urea nitrogen (BUN), creatinine; Creatinine clearance (see Section 10.2).
Other	glucose, albumin.

The investigator should complete additional evaluations of laboratory tests as clinically indicated. Any abnormal findings from these investigations need to be reported as an Adverse Event.

5.2.4 Assessment of other safety parameters

5.2.4.1 Physical examination, vital signs, height and weight

A full physical exam will include cardiopulmonary examination, examination of the regional lymph nodes, and examination of the abdomen and an assessment of the mental and neurological status. Additional symptoms which have not been reported during a previous examination will be clarified. Wherever possible the same investigator should perform this examination.

A complete physical examination will be done at Screening, Day 1 of every treatment cycle, and at the End-of-Treatment visit. A symptom-directed examination is to be performed on all other visits.

5.2.4.2 Vital signs

Blood pressure [systolic and diastolic], pulse rate, temperature, height (cm) and body weight (kg) and ECOG performance status (see section 10.3) will be assessed at the times specified in the flow chart.

5.3 Other

5.3.1 Demographics and history

Demographics (sex, birth date), information on smoking and alcohol history, and baseline conditions will be collected during the screening visit.

The date of first histological diagnosis (month and year may be sufficient), type of tumour histology, biomarker-status (if appropriate), and initial levels of tumour marker (if appropriate) will be reported in the (e)CRF. The number and locations of metastatic sites (if appropriate) as well as the stage according to the tumour, (lymph) node, metastasis (TNM) classification will be provided as obtained at diagnosis and at the inclusion into the trial. Previous surgery and radiotherapy will be reported.

Previously administered chemo- or radiotherapy will be reported including start and end dates (month and year may be sufficient), the therapy protocol with the number of courses (chemotherapy), total radiation dose and radiation field (radiotherapy) and the best response obtained (complete response, partial response, stable disease, progressive disease, unknown).

5.4 Appropriateness of measurements

The RECIST criteria 1.1 (section 10.4) (100) to be used for evaluation of tumour response are well established and scientifically accepted. The US NCI CTCAE criteria Version 3.0 (or 4.0) are used in the assessment of adverse events in cancer patients.

6. INVESTIGATIONAL PLAN

6.1 Visit schedule

6.1.1 Treatment period

In case a patient misses the scheduled study visit but reports to the investigative site before the next scheduled study visit, the missed visit will be performed. The current date and reason for the delayed visit will be noted in the source documentation. All subsequent study

visits should take place at the start of the next treatment cycle per the flow chart. In the event of any study drug interruption or delay of treatment, the tumour assessment scheduled will not be changed.

6.1.2 End-of-Treatment and Follow-up period.

In the case study medication is permanently discontinued due to reasons other than disease progression, withdrawal of consent, or ability to access Gilotrif outside of the protocol, patients will be followed up for tumour response until disease progression. Follow up will be every *1 month* to document the date of disease progression. Tumor assessment data collection will be discontinued upon progression of the tumour and/or the patient commences other anti-cancer treatment. The investigator will maintain contact every *3 months*, whether by telephone or out-patient attendance, with the patient or the patient's family.

6.1.3 Observational Period

Vital status contacts will occur every 4 weeks, as specified in the flow chart.

Endpoint Sweep

Before each pre-specified data analysis, the site will contact patients and/or their health care providers to collect patients' vital status to ensure that the most up-to-date vital status information is presented in the analysis. Death information from public sources, e.g. death registry, obituary listing, etc. can also be used when it available and verifiable. This approach is referred to as an endpoint sweep in the literature.

6.2 Details of study procedures at selected visits

6.2.1 Screening period

Patients, who have confirmed diagnosis of PSCC and availability of archived biopsy specimen, will undergo screening in 2 visits. First visit will be 30 days before day 1 of cycle 1 and second visit will be 14 days prior to day 1 of cycle 1.

On first visit, the patients will be seen in outpatient clinic and a detailed history will be taken about details pertaining to their course of disease which will include smoking history, demographic information like age, and ethnicity as well as assessment of concomitant medication and adverse events seen in the past if any. Their heights will be recorded and the patients will then undergo CT scan of chest, abdomen and pelvis and details about lesions and spread of cancer will be noted. If the patient has complaints of bone pain in the past, they will also undergo an additional bone scan to determine spread of disease to the bone. All the imaging details will be recorded as baseline records which will be compared to determine disease progression in follow up scans.

At the second visit for screening in outpatient clinic, the patients will have their blood pressure and weight recorded. They will then undergo detailed physical examination by the study doctor. About 10 ml of blood will be withdrawn in laboratory for routine complete blood count with differential count along with complete metabolic panel.

The study doctor will calculate ECOG performance status from the information collected at screening visit.

All details collected in the 2 visits will be first recorded in patient case files and then transferred to CRF provided by the sponsor.

For those patients who will be determined eligible for the study, archived tumor biopsy specimen will be obtained and reviewed by central laboratory. This specimen will be used to prepare 20 Formalin Fixed Paraffin Embedded slides. Of these, 15 slides will have sections of 10 µM thickness while 5 slides will have sections of 5 µM thickness. The slides with 10 µM thickness will be sent to Dr. Eddy Yang's laboratory situated in UAB Department of Radiation Oncology for gene expression studies using nanostring technology. Immunohistochemistry studies and HPV DNA analysis will be conducted on 5 µM thick sections.

6.2.2 Treatment period(s)

Patients who are eligible for the study, will then start treatment cycles with Gilotrif 40 mg per day dosage. Patient taking oral Gilotrif tablets every day for 28 days will have completed one cycle. On day 1 of each cycle patient will visit clinic.
History will be taken on course of disease since screening and during the cycle of treatment along with adverse events assessment during treatment cycle; weight and blood pressure will be recorded; detailed physical examination will be conducted; blood will be withdrawn for routine complete and differential blood count as well as complete metabolic profile.
Patients will receive bottle of Gilotrif tablets for entire cycle and instructions will be given about intake of medication and other precautions as mentioned in section 4.1.4.1.
On day 1 of 2^{nd} cycle and on follow-up visits every 8 weeks thereof, patients will undergo CT scan of chest, abdomen and pelvis to document response of disease to the medication. If the patient had undergone baseline Bone scan at screening visit, a repeat bone scan will be conducted along with CT scan.
ECOG performance status will be calculated at each visit to determine if patient is tolerating the treatment well.
Details of assessments done for safety considerations of patients on treatment have been discussed in detail in sections 5.2.3, 5.2.4 and 5.3.

6.2.3 End of study treatment and follow-up period

Once the patient stops taking treatment for any reason (disease progression, adverse events or withdrawal of consent), a repeat CT scan of chest, abdomen and pelvis will be conducted 28 ± 3 days after the last dose of Gilotrif.
All other assessments will be repeated at this follow-up visit that were conducted on day 1 of each cycle. ECOG performance status will be calculated and recorded.

6.2.4 Observational Period

During the Observation Period, collection of the following information may be completed during a clinic visit, telephone contact, or search of a public access source (for date of death):

- Vital status
- Study medication related AEs, see section 5.2.2.2
- Anti-cancer therapy, including radiotherapy <<*disease specific details*>>

The method of contact and the date of contact will be recorded in the (e)CRF.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 Statistical design-model

Given the poor prognosis of this patient population and data from other studies of salvage therapy, a PFS6 of ≥20% is considered to be important for this regimen, while a PFS6 <5% will be considered to be of poor interest. A two-stage minimax design will be used which will enroll a maximum of 27 subjects: 13 during stage 1 and 14 during stage 2. If no patients are free from progression at 6 months among 13 patients during the first stage, then the trial ends with the conclusion that this drug is not worth further study. Otherwise the trial proceeds to the second stage. Since some (5-10%) accrued patients may not be evaluable, up to 29 patients will be enrolled.

7.2 Null and alternative hypotheses

The null hypothesis for this study is that PFS at 6 months will occur in less than 5% after treating with Gilotrif whereas the study alternative hypothesis is that PFS at 6 months will be observed in 20% or more of all patients, which will signify important activity of Gilotrif in this patient population.

7.3 Planned analyses

This trial will be conducted with Intention-To-Treat and all patients for whom PFS6 is evaluable and can be calculated will be included in the final analysis for estimating progression free survival. Statistical significance will be defined as a p-value < 0.05.

7.3.1 Primary analyses

The primary endpoint of this study is the rate of progression free survival (PFS) at 6 months with a window of plus or minus two weeks to give leeway for CT scans to be performed (PFS6). If four or more of the total 27 patients remain progression free at 6 months, this drug will be considered to be of significant interest.

7.3.2 Secondary analyses

The secondary endpoints are not formally powered for, but will be examined in the evaluable population. RECIST responses, regression and toxicities will be analyzed as secondary endpoints. Descriptive statistics including frequencies and proportions will be calculated to summarize safety and toxicity outcomes. Specifically, the number of adverse events (AE) and serious adverse events (SAE) will be tabulated and summarized. Point estimates and two-sided, exact binomial (Clopper-Pearson) 95% confidence intervals (CI) will be calculated to estimate the incidence of AEs and SAEs. The precision of these estimates, i.e., width of the confidence interval, will depend on the estimated incidence of each outcome. The table below gives the exact 95% confidence intervals for a range of incidences, assuming 27 evaluable subjects.

Number of subjects experi cing event	Estimated Incidence	95% Exact CI for Incidence		Width of CI
		Lower Limit	Upper Limit	
1	0.037	0.001	0.190	0.189
2	0.074	0.009	0.243	0.234
4	0.148	0.042	0.337	0.295
7	0.259	0.111	0.463	0.352

14	0.519	0.319	0.713	0.394

The Kaplan-Meier method will be used to estimate OS rates over time with standard errors estimated using Greenwood's formula. Chi-square or Fisher's exact test will be employed to determine bivariate association of biomarker status with PFS6 and objective response.

NanoString technology will be applied to measure the expression of candidate cancer and kinase genes that may predict outcomes and benefit from Gilotrif, and six internal reference genes (101). The nSolver text files (.csv) and NanoString .rcc files will be imported into Partek Genomic Suite 6.6 (PGS, Saint Louis, MO) for statistics and bioinformatics analysis. The differential expressions are determined by ANOVA. A gene list is then created after false discovery rate (FDR) p value correction by Benjamini and Hochberg method (102). Further functional analysis including gene-gene interactions and signaling pathways will be conducted by using Ingenuity Pathway Analysis (IPA, Redwood City, CA). Due to small study numbers, exact logistic regression models will be used to explore whether tumor biomarker (EGFR, Her2, Her3, Her4, nanostring gene expression) expression predicts for response and freedom from progression. Prognostic impact of gene expression, HPV status and IHC studies will be performed using Cox proportional hazards regression. Variables of interest will be evaluated after adjusting for performance status and presence of visceral metastases. Impact of statistically significant variables will be described using hazard ratios, 95% confidence intervals, and concordance statistics. These results are hypothesis-generating and will require external validation.

7.3.3 Interim analyses

At the end of Stage 1, when 13 patients have been recruited and PFS6 has been calculated for these subjects, an interim analysis will be conducted to determine futility of the study. If none of these subjects are progression free at 6 months, the study will be stopped early due to futility and we will conclude the drug is of poor interest. If one or more subjects are progression free, we will proceed to Stage 2.

7.4 Handling of missing data

All efforts and precautions will be undertaken to maintain integrity of data.

7.5 Determination of sample size

SAS version 9.3 was used to calculate power and determine sample size. The justification for the proposed sample size is based on applying an exact test for a binomial proportion to Simon's two-stage minimax design(103). A one-sided significance level of 5% was used. Under this design, we will have approximately 80% power (80.1%) to reject the null hypothesis that PFS < 5% in favour of PFS6 ≥ 20%.

A total of up to 29 patients will be enrolled including 27 evaluable patients for this trial. Accrual period will be ~12 months. Follow-up will be at least 6 months after the last patient starts therapy. Thus, the overall duration of the trial is expected to be ~18 months.

8. INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

This study will be initiated only after all required legal documentation has been reviewed and approved by the University of Alabama at Birmingham Comprehensive Cancer Center's (UAB CCC) Clinical Trials Review Committee (CTRC), Institutional Review Board (IRB) and Office of Sponsored Programs (OSP) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

8.1 Study approval, patient information, and informed consent

Prior to patient participation in the study, written informed consent will be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature will be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information will be given to each patient or the patient's legally accepted representative.

The patient will be informed that his/her personal study-related data will be used by the Principal Investigator in accordance with the local data protection law. The level of disclosure will also be explained to the patient.

The patient will be informed that his / her medical records may be examined by authorised monitors (CRA) or Clinical Quality Assurance auditors appointed by the Principal Investigator, by appropriate EC members, and by inspectors from regulatory authorities.

8.2 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by ECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this clinical study.

8.3 Records

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the (e)CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The investigator may need to request previous medical records or transfer records, specific to this study; also current medical records will be available.

For (e)CRFs all data will be derived from source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, EC review and regulatory inspection, providing direct access to all related source data / documents. (e)CRFs and all source documents, including progress notes and copies of laboratory and medical test results will be available at all times for review by the on-site monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Trials Network Monitoring Office (CTNMO) and auditor will review all (e)CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 Listedness and expedited reporting of Adverse Events

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. For Gilotrif, this is the current version of the Investigator's Brochure.

8.4.2 Expedited reporting to health authorities and EC

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs), to health authorities, UAB CCC Clinical Trials Monitoring Committee (CTMC), and IRB will be done as per UAB CCC Data Safety Monitoring plan.

8.5 Statement of confidentiality

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using unique alpha-numeric identifier composed of first two letters of Institution's acronym name and 3 digit serial number starting from 001 (e.g. – first patient from UAB will be assigned UA001 and so forth).

Treatment data can be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the EC and the regulatory authorities.

8.6 Completion of study

The IRB will be notified about the end of the trial (last patient/patient out, unless specified differently in Section 6.2.3 of the protocol) or early termination of the trial.

8.7 Protocol violations

In event of protocol violations, the UABCCC CTMC or IRB will have authority to recommend closure of the study. The sponsors will be notified accordingly.

8.8 Compensation available to the patient in the event of trial related injury

UAB does not pay the patients for any events related to the trial. However such patients will be offered appropriate care and this will be billed to their insurance.

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10. APPENDICES

10.1 Appendix 1: List of potent inhibitors and inducers of P-glycoprotein (MDR1)

Inhibitors	Inducers
Amiodarone	Carbamazepine
Azithromycin	Phenytoin
Captopril	Rifampicin
Carvedilol	St John's Wort
Clarithromycin	Phenobarbital Salt
Conivaptan	Tipranavir
Cyclosporine	Ritonavir
Diltiazem	
Dronedarone	
Erythromycin	
Felodipine	
Itraconazole	
Ketoconazole	
Lopinavir	
Nelfinavir	
Ritonavir	
Quinidine	
Ranolazine	
Saquinavir	
Tacrolimus	
Ticagrelor	
Verapamil	

The information on potent inhibitors and inducers of P-glycoprotein may evolve, it is important for the investigator to assess such status on concomitant.

10.2 Appendix 2: Cockcroft-gault formula

The following formula may be used for estimated creatinine clearance rate (eC_{CR}) using Cockcroft-Gault formula. The use of on-line calculators or formulas which are institution standards for eC_{CR} and differ slightly may also be used. The calculations and results will be filed in the patient's chart.

When serum creatinine is measured in mg/dL;

$$eC_{CR} = \frac{(140 - \text{Age}) \cdot \text{Mass}(\text{in kilograms}) \cdot [0.85 \, if \, Female]}{72 \cdot \text{Serum Creatinine}(\text{in mg/dL})}$$

10.3 Appendix 3: ECOG performance status scale

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead.

10.4 Appendix 4: Tumour response assessment according to RECIST 1.1

Response criteria for target lesions

1. Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) will have a reduction in short axis to < 10mm)
2. Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters
3. Progression (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum will also demonstrate an absolute increase of a least 5 mm (note: the appearance of one or more new lesions is also considered progression).
4. Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest sum diameters while on study

Response criteria for non-target lesions

1. Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes will be non-pathological in size (< 10mm short axis)
2. Non-CR/ Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits.
3. Progression (PD):	Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression)

Overall response

Target lesions	Non-Target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10.5 Appendix 6: NYHA Classification for heart failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

10.6 Appendix 7: NCI-CTCAE Version 4.03

Common Terminology Criteria for Adverse Events (CTCAE) of the
National Cancer Institute (NCI) v4.03

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http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf