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PROTOCOL

TITLE:	A Phase 1b/2 Study of Ibrutinib Combination Therapy in Selected Advanced Gastrointestinal And Genitourinary Tumors
PROTOCOL NUMBER:	**PCYC-1128-CA**
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	124674
EudraCT NUMBER:	2015-003656-40
SPONSOR MEDICAL MONITOR:	[redacted]
SPONSOR:	Pharmacyclics LLC 995 East Arques Avenue Sunnyvale, CA 94085-4521 United States of America
DATE FINAL:	7 August 2015
Amendment 1:	16 February 2016
Amendment 2.0:	25 January 2019

PROTOCOL APPROVAL PAGE

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I have carefully read Protocol PCYC-1128-CA entitled "A Phase 1b/2 Study of Ibrutinib Combination Therapy in Selected Advanced Gastrointestinal And Genitourinary Tumors". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics, and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics. All data pertaining to this study will be provided to Pharmacyclics. The policy of Pharmacyclics LLC requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Pharmacyclics LLC representative is authorized to sign the protocol and any

[redacted]

Jan-25-2019

Date

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SYNOPSIS

Study Title:	A Phase 1b/2 Study of Ibrutinib Combination Therapy in Selected Advanced Gastrointestinal and Genitourinary Tumors
Protocol Number:	PCYC-1128-CA
Study Phase:	1b/2
Indication:	Previously-treated metastatic renal cell carcinoma (RCC), advanced urothelial carcinoma, advanced gastric (including gastro-esophageal [GEJ]) adenocarcinoma, and metastatic colorectal adenocarcinoma (CRC)
Study Duration:	Estimated to be 72 months
Number of Subjects:	Total = up to 308 • Metastatic renal cell carcinoma (RCC): n = up to 73 • Advanced (locally recurrent and/or metastatic) urothelial carcinoma (UC): n = up to 120 • Advanced (locally recurrent and/or metastatic) gastric adenocarcinoma (GC): n = up to 57 • Metastatic colorectal adenocarcinoma (CRC): n = up to 58
Investigational Product and Reference Therapy:	Ibrutinib (IMBRUVICA) will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Everolimus is available for oral (PO) administration. Paclitaxel is available for intravenous (IV) administration. Docetaxel is available for intravenous (IV) administration. Cetuximab is available for intravenous (IV) administration.
Objectives:	**Phase 1b:** **Primary Objective:** • To determine the recommended Phase 2 dose (RP2D) of ibrutinib in combination with everolimus in RCC, paclitaxel in UC, docetaxel in GC, and cetuximab in CRC • To confirm the RP2D of single-agent ibrutinib in UC cohort 5 **Secondary objectives:** • To assess the overall response rate (ORR) in each cohort • To assess the safety and tolerability of ibrutinib combination or single-agent therapy in each cohort • To assess the disease control rate (DCR) in each cohort • To evaluate the pharmacokinetics (PK) of ibrutinib combination therapy in cohorts 1-4 **Phase 2:** **Primary Objectives:** • To assess progression-free survival (PFS) of ibrutinib combination therapy in RCC and UC cohort 2

	• To assess the ORR of ibrutinib combination therapy in GC and CRC, and ibrutinib as a single agent in UC cohort 5 **Secondary Objectives:** • To assess the PFS of ibrutinib combination therapy in GC and CRC, and ibrutinib as a single agent in UC cohort 5 • To assess the ORR of ibrutinib combination therapy in RCC and UC cohort 2 • To assess the duration of response (DOR) in each cohort • To assess the disease control rate (DCR) in each cohort • To assess the median overall survival (OS) of ibrutinib combination or single-agent therapy in each cohort • To assess the safety and tolerability of ibrutinib combination or single-agent therapy in each cohort **Exploratory Objectives:** • [redacted]
Study Design:	This is an open-label, Phase 1b/2 multi-center study to assess the safety and efficacy of ibrutinib combination or single-agent therapy in subjects with previously treated RCC, UC, GC, and CRC. Each cohort in this study will assess a different malignancy and/or anticancer agent (in combination, or as single-agent ibrutinib), and follow an independent and parallel design. The study will consist of an initial Phase 1b portion primarily to assess the safety of ibrutinib, in combination with each anticancer agent, or as a single agent, in order to determine the RP2D for each cohort. A subsequent Phase 2 portion will assess the primary endpoints of PFS (with an incorporated interim analysis) for the genitourinary (GU) malignancies (RCC and UC cohort 2) and ORR using a Simon's minimax 2-stage design for the gastrointestinal (GI) malignancies (GC and CRC), and UC cohort 5. **Phase 1b** Safety and dose-limiting toxicity (DLT) assessment will be evaluated in 3-9 subjects at each dose level of ibrutinib in a 3+3+3 design in cohorts 1-4. A starting dose of ibrutinib of 560 mg daily will be combined with the specified anticancer agent in the following tumor types, in 5 separate and parallel cohorts: • RCC cohort 1: ibrutinib + everolimus • UC cohort 2: ibrutinib + paclitaxel • GC cohort 3: ibrutinib + docetaxel • CRC cohort 4: ibrutinib + cetuximab For single-agent ibrutinib the dose will be 840 mg. • UC cohort 5: single-agent ibrutinib 840 mg A dose level review committee (DLRC) will evaluate the safety data at the completion of the initial Phase 1b portion in each cohort to determine the

	RP2D, prior to continuing with enrollment into the Phase 2 portion, with the exception of cohort 5, single-agent ibrutinib. The DLT observation period will encompass 21 days after the initiation of combination therapy. Phase 1b of the study (cohorts 1-4) will follow a 3+3 +3 design with 3-9 subjects at each dose level. At each dose level, DLT assessment will be performed in the first 3 subjects. If 1 of 3 subjects experience a DLT during the first treatment cycle, the same dose level will be expanded to 6 subjects, and if 2 of the 6 experience a DLT, the same dose level will be expanded to 9 subjects. At the 560 mg/day dose level (DL 1), if 0 out of 3, 1 out of 6 or 2 out of 9 subjects (≤22%) experience a DLT during the first treatment cycle, dose escalation to 840 mg/day will occur. At DL 1, (560 mg/day), if ≥33% of subjects experience a DLT (eg, >2 out of 6 or >2 out of 9 subjects), the dose will be de-escalated to 420 mg/day (dose level minus 1; DL -1). At the dose level 2 (DL 2; 840 mg/day) cohort, subjects will be enrolled in a similar fashion. For UC cohort 5, the single-agent dose of 840 mg will be confirmed and documented in the first 6 patients; safety data will be described. For the Phase 1b portion of cohort 5, if 2 subjects within the initial cohort of 6 subjects experience a DLT, an additional 3 subjects will be enrolled at the same dose level. If 3 or more of 6 subjects experience a DLT, dose de-escalation will occur. If subject incidence of DLTs during the DLT observation period is <33.3% (ie, ≤1 of 6 or ≤2 of 9), this dose level will be considered safe to proceed to Phase 2, and will be defined as the RP2D. The RP2D will be determined when 6-9 subjects at the dose level complete the DLT observation period based on the totality of the data including dose reductions (of both ibrutinib and the combination therapy), treatment-limiting toxicities (outside of DLTs), the available pharmacokinetic data and the toxicity profile obtained during Phase 1b. In order to determine the RP2D dose level, a minimum of 6 DLT-evaluable subjects will be required at the RP2D dose level who are defined to have completed at least 21 days of treatment with ibrutinib in combination with the relevant anticancer agent, after the initiation of therapy at the start of Cycle 1. For UC cohort 5, a DLT-evaluable subject will have ≥ 90% compliance with ibrutinib during Cycle 1 (the first 21 days). At each dose level, the decision of de-escalation will be made for at least 6 DLT-evaluable subjects. However, if at any time in a given dose level, 3 subjects experience a DLT, additional enrollment within the dose level will be stopped. A DLT is defined as any Grade 3 or higher non-hematologic or Grade 4 hematologic adverse event (AE) occurring during the DLT observation period (ie, 21 days after the initiation of combination therapy at the start of Cycle 1) and considered to be at least possibly related to the study treatment (ibrutinib or combination) with the following clarifications: • Grade 4 diarrhea and vomiting • Grade 3 nausea, diarrhea or vomiting despite maximum medical supportive care and persisting >3 days • Grade 3 fatigue persisting >7 days

	• Grade 3 infusion reaction that does NOT resolve with appropriate clinical management • Grade 3 rash lasting >7 days that does NOT resolve with appropriate clinical management • Grade 4 neutropenia or leukopenia for >7 days duration (irrespective of adequate growth factor support) • Grade 3 thrombocytopenia with clinically significant bleeding • Grade 4 thrombocytopenia If a subject experiences a DLT during the DLT observation period, the subject will discontinue treatment. Dose reductions will not be permitted during the DLT observation period. However, any other subject(s) tolerating the dose level through the DLT observation period will continue to receive the same dose of study drugs even if a dose escalation or de-escalation occurs for subsequent study subjects. Any Phase 1b subjects who discontinue one or more study drugs or require a dose reduction within 21 days after initiation of therapy at the start of Cycle 1 will be replaced, unless the discontinuation is in association with a DLT. Subjects (cohorts 1-4) who miss one or more scheduled doses of either study drug within 21 days after initiation of therapy at the start of Cycle 1 will continue (more than 2 doses of ibrutinib for cohort 5). However, such a subject will not be evaluable for DLT assessment, and will be replaced for DLT assessment purposes. After Cycle 1, all subjects will be treated until unacceptable toxicity or disease progression, whichever occurs first. Tumor assessment by CT/MRI will occur every 6 weeks (2 cycles) and will be evaluated according to RECIST 1.1 guidelines. After the RP2D has been defined for a cohort, enrollment in Phase 2 will commence in that cohort. **Phase 2** For each cohort in the study a separate analysis will be performed to evaluate the response and safety profile. Tumor assessment by CT/MRI will occur every 6 weeks and will be evaluated according to RECIST 1.1 guidelines. Subjects will be treated until unacceptable toxicity or disease progression. **RCC** Cohort 1, subjects will receive ibrutinib administered PO at the RP2D in combination with everolimus (6 hours after ibrutinib) at a dose of 10 mg PO daily in 21-day cycles until unacceptable toxicity or disease progression occurs. Subjects will be enrolled until a total of 55 subjects have been treated, including any subjects from Phase 1b who were treated at the RP2D level. **Urothelial carcinoma** Cohort 2, subjects will receive ibrutinib administered PO at the RP2D in combination with paclitaxel at a dose of 80 mg/m^2 administered as a 60-minute IV infusion weekly in 21-day cycles until unacceptable toxicity or disease progression occurs. Subjects will be enrolled until a total of 55 subjects have been treated,

	including any subjects from Phase 1b who were treated at the RP2D level and satisfy the inclusion criteria for the Phase 2 portion. Cohort 5, subjects will receive ibrutinib administered PO at 840 mg in 21-day cycles until unacceptable toxicity or disease progression occurs. Thirteen subjects will be enrolled into stage-1of the Simon's 2-stage design, including any subjects from Phase 1b who were treated at the confirmed Phase 2 dose level and satisfy the inclusion criteria of the Phase 2 portion. If at least 1 subject has a tumor response (PR or CR) by RECIST 1.1 criteria, this cohort will proceed to the stage-2 portion and enroll an additional 14 subjects. **Gastric adenocarcinoma** Cohort 3, subjects will receive ibrutinib administered PO at the RP2D in combination with docetaxel at a dose of 60-75 mg/m^2 administered as a 60-minute IV infusion every 3 weeks in 21-day cycles until unacceptable toxicity or disease progression occurs. Twenty-one subjects will be enrolled into stage-1of the Simon's 2-stage design, including any subjects from Phase 1b who were treated at the RP2D level and satisfy the inclusion criteria of the Phase 2 portion. If at least 2 subjects have a tumor response (PR or CR) by RECIST 1.1 criteria, this cohort will proceed to the stage-2 portion and enroll an additional 18 subjects. **CRC** Cohort 4, subjects will receive ibrutinib administered PO at the RP2D in combination with cetuximab at a dose of 400 mg/m^2 administered initially as a 120-minute IV infusion then weekly 250 mg/m^2 IV over 60 minutes in 21-day cycles until unacceptable toxicity or disease progression occurs. Twenty-two subjects will be enrolled into stage-1 of the Simon's 2-stage design, including any subjects from Phase 1b who were treated at the RP2D level and satisfy the inclusion criteria of the Phase 2 portion. If at least 3 subjects have a tumor response (PR or CR) by RECIST 1.1 criteria this cohort will proceed to stage-2 portion and enroll an additional 18 subjects. In all cohorts, subjects who are dosed at the RP2D level and withdraw prior to the completion of at least 2 cycles of combination therapy, for reasons other than unacceptable toxicity or disease progression, may be replaced after consultation with the Sponsor. For the GC, CRC, and UC cohort 5, if a subject in stage-1 discontinues prior to the first tumor response assessment for reasons other than disease progression, the subject may be replaced. Enrollment may continue into stage-2, while waiting for the response evaluation and analysis from the stage-1 portion to be completed. If the number of responders observed among the evaluable subjects in stage-1 is less than the number of responders required to proceed per the Simon's 2-stage design, the relevant cohort may be terminated for futility.
Population:	Subjects with: • **RCC:** Minimum of 1 and maximum of 4 prior regimens, one of which must have included a VEGF-TKI. • Urothelial carcinoma:

	– **Cohort 2:** Minimum of 1 and maximum of 2 prior regimens, one of which must have included a platinum-based regimen. – **Cohort 5:** Minimum of 1 and maximum of 2 prior regimens, one of which must have included a checkpoint inhibitor. • **GC:** Minimum of 1 and maximum of 3 prior regimens, one of which must have included a fluoropyrimidine based regimen. • **CRC:** Minimum of 2 and maximum of 4 prior regimens. Prior regimens must have included both an irinotecan and an oxaliplatin-based regimen unless the subject is considered intolerant to irinotecan.
Centers:	Multicenter
Inclusion Criteria:	*Disease Related* 1. Histologically confirmed: • RCC (clear cell) • Urothelial carcinoma (transitional cell) • Gastric or GEJ adenocarcinoma • K-RAS or N-RAS wild-type EGFR expressing CRC 2. One or more measurable lesions per RECIST 1.1 criteria. 3. The following prior criteria should be followed: • Metastatic RCC: minimum of 1 and maximum of 4 prior regimens, one or more of which must have included a VEGF-TKI • Advanced (locally recurrent and/or metastatic) UC: – UC cohort 2: minimum of 1 and maximum of 2 prior regimens, one of which must be a platinum-based regimen – UC cohort 5: Single-agent ibrutinib: minimum of 1 and maximum of 2 prior regimens, one of which must have included a checkpoint inhibitor. • Advanced (locally recurrent and or metastatic) gastric or GEJ adenocarcinoma: minimum of 1 and maximum of 3 prior regimens one of which must be a fluoropyrimidine based regimen • Metastatic CRC: minimum of 2 and maximum of 4 prior regimens, which must have included both an irinotecan- and an oxaliplatin-based regimen or unable to tolerate irinotecan chemotherapy 4. Each subject must be assessed by the investigator to be a suitable candidate for treatment with everolimus, docetaxel, paclitaxel cetuximab, or ibrutinib monotherapy as appropriate according to their type of cancer. 5. Female subjects of childbearing potential must have a negative serum or urine pregnancy test within 3 days of the first dose of study drug. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy) are exempt from this criterion. 6. Male and female subjects of reproductive potential must agree to

	perform complete abstinence[1] or to use both, a highly effective method of birth control (implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], or sterilized partner) and a barrier method (eg, condoms, cervical rings, cervical condoms, sponge) during the period of therapy and for 90 days after the last dose of ibrutinib, everolimus, docetaxel, and paclitaxel; 6 months after the last dose of cetuximab (6 months for all study drugs in UK only). *Laboratory* 7. Adequate hematologic function independent of platelet transfusion and growth factor support for at least 7 days prior to enrollment, with the exception of pegylated G-CSF (granulocyte-colony stimulating factor pegfilgrastim) and darbopoeitin which requires at least 14 days, defined as: • Absolute neutrophil count >1500 cells/mm^3 (1.5 x 10^9/L) • Platelet count >80,000 cells/mm^3 (80 x 10^9/L) for cohort 1 (RCC) • Platelet counts >100,000 cells/mm^3 (100 x 10^9/L) for cohorts 2, 5 (UC), 3 (GC) and 4 (CRC) • Hemoglobin ≥8.0 g/dL for cohorts 1 (RCC), 2, 5 (UC), and 3 (GC) • Hemoglobin ≥9.0 g/dL for cohort 4 (CRC) 8. Adequate hepatic and renal function defined as: • Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) ≤5.0 x upper limit of normal (ULN) if liver metastases, or ≤3 x ULN without liver metastases • Alkaline phosphatase <3.0 x ULN or ≤5.0 x ULN if liver or bone metastases present • Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin, such as hemolysis) with the exception of subjects in the GC cohort where docetaxel is administered, these subjects must have bilirubin within normal limits (WNL) • Estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault) *Demographic* 9. Men and women ≥18 years of age . 10. Eastern Cooperative Oncology Group (ECOG) performance status 0-1. For subjects with RCC or CRC, an ECOG score of 2 may be acceptable if approved by the medical monitor.
Exclusion Criteria:	*Disease-Related* 1. Anticancer therapy (chemotherapy, antibody therapy, molecular targeted therapy, or investigational agent) within 28 days of the first dose of

[1] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

	study drug (4 weeks for nitrosureas, mitomycin C, or antibody based therapies). 2. Prior treatment with: • Everolimus or temsirolimus (RCC cohort) • Any taxane (UC cohort 2) • Any taxane (GC cohort) • Cetuximab or panitumumab (CRC cohort) 3. Prior radiotherapy to measurable lesion, unless documented progression has occurred post-irradiation. 4. Lack of recovery from previous therapeutic radiation (persistence of Grade ≥2 radiation-related toxicity) or planned radiation therapy during the study period. *Concurrent Conditions* 5. Any uncontrolled active systemic infection including any infection requiring systemic IV treatment which was completed ≤7 days before Cycle 1 Day 1. 6. History of other malignancies, except: • Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and felt to be at low risk for recurrence by investigator • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease • Adequately treated carcinoma in situ without current evidence of disease 7. Prior treatment with ibrutinib or other BTK inhibitor. 8. ALT and/or AST >1.5 x ULN and alkaline phosphatase >2.5 x ULN (GC cohort only). 9. Known allergy or hypersensitivity to ibrutinib or any other component of combination therapy, including polysorbate 80 or Cremophor® EL (polyoxyethylated castor oil). 10. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE) version 4.03, Grade 0 or 1. 11. Known bleeding disorders (eg, von Willebrand's disease) or hemophilia. 12. Grade ≥3 sensory peripheral neuropathy. 13. History of stroke or intracranial hemorrhage within 6 months prior to enrollment. 14. Known brain or leptomeningeal disease (CT or MRI scan of the brain required only in case of clinical suspicion of central nervous system involvement). 15. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV): *Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen or hepatitis C antibody must have a negative polymerase*

<table>
<tr><td></td><td>
chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
16. Major surgery within 4 weeks of first dose of study drug.
17. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
18. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure, as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment.
19. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
20. Unable to swallow capsules and/or tablets.
21. Concomitant use of warfarin or other Vitamin K antagonists.
22. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix 12).
23. Lactating or pregnant.
24. Unwilling or unable to participate in all required study evaluations and procedures.
25. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
</td></tr>
<tr><td>Study Treatment:</td><td>
One cycle of treatment is 21 days in length and consists of daily administration of ibrutinib as monotherapy or in combination with the relevant anticancer agent. Treatment will continue as long as the subject is without (RESIST 1.1) disease progression and not experiencing unacceptable toxicity. If one component of a combination regimen is discontinued prior to RECIST 1.1 determined disease progression, the other component may be continued until disease progression or unacceptable toxicity.
Phase 1b:
Dosing Regimen in Cohorts 1-5
<table>
<tr><th>Cohort</th><th>DL-1</th><th>DL 1</th><th>DL 2</th></tr>
<tr><td>Cohort 1
RCC</td><td>ibrutinib:
420 mg PO qd
everolimus[1]</td><td>ibrutinib:
560 mg PO qd
everolimus[1]</td><td>ibrutinib:
840 mg PO qd
everolimus[1]</td></tr>
<tr><td>Cohort 2
UC</td><td>ibrutinib:
420 mg PO qd
paclitaxel[2]</td><td>ibrutinib:
560 mg PO qd
paclitaxel[2]</td><td>ibrutinib:
840 mg PO qd
paclitaxel[2]</td></tr>
<tr><td>Cohort 3
GC</td><td>ibrutinib:
420 mg PO qd
docetaxel[3]</td><td>ibrutinib:
560 mg PO qd
docetaxel[3]</td><td>ibrutinib:
840 mg PO qd
docetaxel[3]</td></tr>
<tr><td>Cohort 4
CRC</td><td>ibrutinib:
420 mg PO qd
cetuximab[4]</td><td>ibrutinib:
560 mg PO qd
cetuximab[4]</td><td>ibrutinib:
840 mg PO qd
cetuximab[4]</td></tr>
</table>
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	Cohort 5 UC SA Ibrutinib | ibrutinib 560 mg PO qd | ibrutinib: 840 mg PO qd | NA PO = orally, qd = daily, qweek = weekly, q3weeks = every 3 weeks [1] everolimus: 10 mg PO qd [2] paclitaxel: 80 mg/m^2 IV qweek [3] docetaxel: 60 mg/m^2 - 75 mg/m^2 IV q3weeks [4] cetuximab: 400 mg/m^2 IV, then 250 mg/m^2 qweek **Phase 2:** The RP2D established in Phase 1b for ibrutinib (840 mg, 560 mg, 420 mg) PO daily, as monotherapy or in combination with specified anticancer agent, will be given in 21-day cycles. **Dose Modifications** Dose modifications for toxicity (with the exception of Cycle 1 of Phase 1b, when no dose modifications are permitted) will be made separately for each agent in accordance with the algorithms contained within the IMBRUVICA,everolimus, paclitaxel, docetaxel, and cetuximab prescribing information, as appropriate.
Concomitant Therapy:	Antiemetics are permitted in all cohorts if clinically indicated. Standard supportive care medications are permitted, including growth factor support. In addition, for paclitaxel, docetaxel, and cetuximab premedication prior to administration is recommended in order to prevent severe hypersensitivity reactions or rashes. **Prohibited Concomitant Therapy** Strong CYP3A inhibitors should be avoided. Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Ibrutinib should be used with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising and ibrutinib should be withheld in the event of any bleeding events. Supplements such as fish oil and vitamin E preparations should be avoided.
Safety Plan:	This study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. Adverse events (AEs) and serious adverse events (SAEs) will be reviewed by the Sponsor on an ongoing basis to identify safety concerns. A DLRC will evaluate the safety data at the completion of the initial Phase 1b portion in each cohort, prior to continuing with enrollment into the Phase 2 portion.
Statistical Methods and Data Analysis:	The DLT Evaluable Population consists of subjects from Phase 1b who complete at least 21 days of treatment with ibrutinib in combination with the relevant anticancer agent or single-agent ibrutinib after the initiation of therapy at the start of Cycle 1, and those who did not complete the DLT observation period due to a DLT event. The DLT Evaluable Population will be used for DLT assessments. The Safety Population consists of all subjects who receive at least one dose of any study drug. The Safety Population for ibrutinib, consisting of all

	subjects treated with at least one dose of ibrutinib at any dose level, will be used for the analysis of the safety data. The Efficacy Evaluable Population, consisting of eligible subjects who receive at least one dose of ibrutinib at the RP2D level as either a single agent or in combination with the relevant anticancer agent, will be used for the primary analysis of efficacy data. **Primary Efficacy Analysis** The primary efficacy endpoints of Phase 2 are: **Progression-free survival (PFS)** in accordance with RECIST 1.1 criteria, in the RCC and UC cohort 2. Distribution of PFS will be summarized for each cohort using the Kaplan-Meier estimate. The median time of PFS will be estimated and the corresponding 2-sided 90% Brookmeyer-Crowley confidence interval (CI) with the log-log-transformed Greenwood variance estimate will be calculated to test the hypotheses. **Overall response rate (ORR)** in the GC,CRC, and UC cohort 5. The proportion of subjects who achieve a complete response (CR) or partial response (PR) according to RECIST 1.1 criteria will be determined and corresponding 2-sided 90% exact binomial CI will be calculated. **Secondary Efficacy Analysis** • DCR will be determined in each cohort and corresponding 2-sided 90% CIs will be generated. DCR is defined as the proportion of subjects who achieve a best response of CR, PR or SD ≥6 weeks in accordance with RECIST 1.1 criteria. • DOR will be calculated for responsders in each cohort. • PFS in the GC, CRC, and UC cohort 5 will be summarized for each cohort using the Kaplan-Meier estimate of the median and corresponding 2-sided 90% CIs. • ORR in the RCC and UC cohort 2 will be determined for each cohort and corresponding 2-sided 90% CIs will be generated. • Overall survival (OS) will be summarized for each cohort using the Kaplan-Meier estimate of the median and corresponding 2-sided 90% CIs. **Exploratory Analysis:** • [redacted] **Safety Analysis** Detailed tabulations of safety data (AEs, clinical laboratory tests and other safety endpoints) will be summarized by treatment cohort.
Interim Analysis:	**RCC** A single interim analysis for futility will take place when the 25th subject

	dosed at the RP2D level has completed 6 months of follow-up. The proportion of subjects that are PFS event-free at 6 months will be assessed along with other safety and efficacy data in making the determination if the study should continue. **UC cohort 2** A single interim analysis for futility will take place when the 25th subject dosed at the RP2D level has completed 4 months of follow-up. The proportion of subjects PFS event-free at 4 months will be assessed along with other safety and efficacy data in making the determination if the study should continue. **GC, CRC, and UC cohort 5** These cohorts employ a Simon's 2-stage minimax design involving the ORR endpoint. Thus the data supporting proceeding to the second stage will be the best response rate of CR or PR in combination with other safety and efficacy data.
Sample Size Determination:	The number of subjects required to be treated with ibrutinib at the RP2D level for the efficacy evaluation is determined for each disease cohort using the following methods. **RCC** The primary endpoint is the median PFS. A sample size of approximately 55 efficacy-evaluable subjects will provide 80% power at a 1-sided 0.05 significance level when testing the null hypothesis median PFS $\leq$4.9 months versus the alternative hypothesis median PFS $\geq$8.6 months. The median PFS for everolimus is assumed to be 4.9 months under the null hypothesis. The study is designed to detect a 75% increase in median PFS to 8.6 months for ibrutinib in combination with everolimus. With the assumption of an exponential distribution for PFS, the sample size n = 55 to achieve a minimum of 80% power is determined by a simulation method with the data cut time for analysis to be at 6 months following the last subject enrollment. **UC cohort 2** The primary endpoint is the median PFS. A sample size of approximately 55 efficacy-evaluable subjects will provide 80% power at a 1-sided 0.05 significance level when testing the null hypothesis median PFS $\leq$2.3 months versus the alternative hypothesis median PFS $\geq$4.1 months. The median PFS for paclitaxel is assumed to be 2.3 months under the null hypothesis. The study is designed to detect a 78% increase in median PFS to 4.1 months for ibrutinib in combination with paclitaxel. With the assumption of an exponential distribution for PFS, the sample size n = 55 to achieve a minimum of 80% power is determined by a simulation method with the data cut time for analysis to be at 6 months following the last subject enrollment. **UC cohort 5** A total of up to 27 subjects are to be enrolled based on Simon's 2-stage design. In stage-1, 13 subjects will be enrolled and if at least one responder is observed, an additional 14 subjects will be enrolled in stage-2. At the end of the study, if there are 4 or more responders, the null hypothesis will be rejected and the study treatment would be considered acceptable for further clinical development. This Simon's 2-stage design would provide 80% power to test the historical

	response rate of 5% (null hypothesis) against the target response rate of 20% (alternative hypothesis) at a 1-sided significance level of 0.05. At the interim analysis, for the stage-1 data, the proportion of responding subjects will be assessed along with other safety and efficacy data in making the determination if the study should continue. **Gastric adenocarcinoma** A Simon's 2-stage minimax design is selected based on the proportion of subjects having an overall response to study treatment of CR or PR. In this Simon's 2-stage design, a total of 39 subjects are to be enrolled in two stages. In stage-1, 21 subjects will be enrolled, and if at least 2 subjects are responders, an additional 18 subjects will be enrolled in stage-2. At the end of the study, if there are 6 or more responders, then the null hypothesis is rejected and the study treatment would be acceptable for further clinical development. This Simon's 2-stage design provides at least 80% power to test the historical ORR rate of 7% (null hypothesis) against the target ORR of 20% (alternative hypothesis) at a 1-sided significance level of 0.05. At the interim analysis, for the stage-1 data, the proportion of responding subjects will be assessed along with other safety and efficacy data in making the determination if the study should continue. **CRC** A Simon's 2-stage minimax design is selected based on the proportion of subjects having an overall response to study treatment of CR or PR. In this Simon's 2-stage design a total of 40 subjects are to be enrolled in two stages. In stage-1, 22 subjects will be enrolled and if at least 3 subjects are responders, an additional 18 subjects will be enrolled in stage-2. At the end of the study if there are 8 or more responders, then the null hypothesis is rejected and the study treatment would be acceptable for further clinical development. This Simon's 2-stage design provides at least 80% power to test the historical ORR rate of 10% (null hypothesis) against the target ORR of 25% (alternative hypothesis) at a 1-sided significance level of 0.05. At the interim analysis, for the stage-1 data, the proportion of responding subjects will be assessed along with other safety and efficacy data in making the determination if the study should continue.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BMX	Bone Marrow Tyrosine Kinase Gene in Chromosome X kinase
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CR	complete response
CRC	colorectal adenocarcinoma
CRF	case report form (paper or electronic as appropriate for this study)
CRR	clinical response rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P
DCR	disease control rate
DL	dose level
DLRC	dose level review committee
DLT	dose limiting toxicity
DOR	duration of response
EDC	electronic data capture
eCRF	electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ETK	Epithelial and Endothelial Tyrosine Kinase

FCR	Fludarabine, cyclophosphamide, and rituximab
FP	Fluoropyrimidine
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
GC	Gastric adenocarcinoma
GCP	Good Clinical Practice
GEJ	gastro-esophageal junctional
GEP	Gene Expressing Profile
GI	Gastroinstestinal
GU	Genitourinary
HER2	human epidermal growth factor receptor 2
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	independent review committee
ITK	interleukin-2-inducible T-cell kinase
IV	Intravenous
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MRU	medical resource utilization
NSCLC	non-small-cell lung cancer
ORR	Overall Response Rate
OS	Overall survival
PD	Progressive disease
PDn	Pharmacodynamics

PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetic
PO	oral
PR	Partial response
PRF	Patient Registration Form
PRO	patient reported outcomes
RP2D	Recommended Phase 2 Dose
REAL	Revised European American Lymphoma
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RCC	renal cell carcinoma
R-CHOP	rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone
QLQ-C30	EORTC core quality of life questionnaire
QTc	QT interval corrected for heart rate
SA	single agent
SAE	serious adverse event
SD	Stable Disease
TEAEs	treatment-emergent adverse events
TEC	Tyrosine Kinase Expressed in Hepatocellular Carcinoma
Tmax	time to maximum plasma concentration
TTP	Time to tumor progression
ULN	Upper limit of normal
UC	urothelial carcinoma
US	United States
VEGF	vascular endothelial growth factor
WNL	within normal limits
WHO	World Health Organization

1. BACKGROUND

1.1. Disease Background

1.1.1. Metastatic Renal Cell Carcinoma (RCC)

Renal cell carcinoma (RCC) accounts for 2% to 3% of all adult malignancies, 5% of epithelial tumors overall, constitutes the seventh most common cancer in men and the ninth most frequent in women (Rini 2009, Costa 2007). Worldwide, there are approximately 209,000 new cases and 102,000 deaths per year. In the US, about 64 000 new cases are diagnosed annually, with 14,000 deaths due to RCC (Siegel 2014b).

Life expectancy in RCC has been progressively increasing over the last two decades, with improvements for localized disease from a 5 year survival of 88.4% in 1992-1995 to 91.8% in 2004-2010. For advanced disease, 5 year survival over the same two periods has improved from 7% to 12% (SEER 2015 [Kidney and Renal Pelvis Cancer]) but obviously still remains dismal, emphasizing the fact that advanced RCC is an essentially incurable condition, despite significant and intensive recent progress in the management of the disease.

Although survival is influenced by a number of factors, including i) tumor stage, ii) tumor grade, iii) extent of local spread, iv) regional lymph node involvement and v) metastatic spread at initial presentation (Lam 2007, Dall'Oglio 2007, Zisman 2001, Eggener 2006) prognosis is primarily dependent on disease stage. About 75% of renal carcinomas are diagnosed whilst still non-metastatic (Altekruse 2010, Maclennan 2012) whilst approximately 25% of cases have metastatic disease at presentation (Janzen 2003).

Survival correlates closely with disease stage at diagnosis. Organ-confined disease (pathologic Stage I or II) confers the best prognosis, with 5-year cancer specific survival rates after nephrectomy ranging from 71% to 97% (Frank 2005), which effectively equates to a cure in most cases. For patients with locally advanced tumors (Stage III), 5-year cancer-specific survival rates after nephrectomy decrease to about 20% to 53% and once RCC has metastasized, the 5-year survival rate is less than 10% (Mekhail 2005, Motzer 1999).

Renal carcinoma is histologically diverse, with clear-cell disease as the most frequent sub-type in adults, representing 70% to 85% of cases (Algaba 2011). The majority of the remainder are accounted for by papillary (types I and II), chromophobe and collecting duct carcinomas.

1.1.1.1. Management of Metastatic Renal Cell Carcinoma (RCC)

Management of RCC: Advanced Disease

For patients with either metastatic or locally recurrent disease, systemic therapy is the main approach employed. There remains however a potential role for local interventions, such as nephrectomy and/or metastectomy, in a limited number of cases (Flanigan 2004, Karam 2011). In particular, cytoreductive nephrectomy may be of value in selected patients, if not already performed previously (Marcus 1993, Rini 2007), as there is a theoretical argument this might attenuate primary tumor mediated down-regulation of the micro-environmental immune system

and hence enhance anti-tumor cytotoxic lymphocyte activity, thus augmenting the efficacy of subsequent systemic therapy (Rosenberg 1998, Flanigan 2006).

Systemic therapy of advanced disease has undergone dramatic change over the past decade. Prior to the advent of targeted agents clinical efficacy with available therapies was extremely limited, as RCC is inherently resistant to cytotoxic therapy, radiation, or hormone therapy, with only cytokine based immunotherapy having shown clinically useful activity (Nelson 2007, Coppin 2008).

Currently, five agents (sunitinib, pazopanib, bevacizumab plus interferon, temsirolimus) are widely used in first-line therapy with three others employed for second-, or subsequent lines of treatment (everolimus, axitinib, sorafenib). However, despite the recent emergence of a number of mechanistically novel agents, which can extend median survival by more than two years in the advanced setting, none are curative, with a five year survival rate for metastatic disease of only about 10%, even with the most modern of single or combination treatment strategies (Hudes 2011, Tamaskar 2009, Czarnecka 2015, Xu 2015, Zhi 2014). Hence, there is an ongoing need for new combination approaches to further improve longer term outcomes.

1.1.1.2. First-line Therapy

Treatment strategies are closely related to and determined by a patient's individual risk categorization.

Recent results with currently available therapies in the first-, second- and third-line setting are summarized below in Table 1.

Table 1. Results from First-, Second-, and Third-line Therapies for Metastatic RCC

Line of Therapy	Eligibility	Std Cohort	Exp Cohort	RR		Median PFS			Median OS		
				S	E	S	E	p	S	E	P
First-Line	Therapy-naive	IFN	Sunitinib (Motzer 2009)	6	31	5.0	11.0	<0.001	21.8	26.4	0.05
	Therapy-naive	Sunitinib	Pazopanib (Motzer 2013b)	24	31	9.5	8.4	NS	NR	NR	
	Therapy-naive	IFN	Bev-IFN (Rini 2008)	13	26	5.2	8.5	<0.0001	NR	NR	
	Therapy-naive	Placebo-IFN	Bev-IFN (Escudier 2010)	NR	NR	5.4	10.2	<0.0001	NR	NR	
	Therapy-naïve or post-cytokine	Placebo	Pazopanib (Sternberg 2010)	3	32	4.2	9.2	<0.001	20.5	22.9	0.02
	Therapy-naïve or post-cytokine	Sorafenib	Tivozanib (Motzer 2013c)	23	33	9.1	11.9	0.042	28.8	29.3	0.10
	Therapy-naive	Sorafenib	Axitinib (Hutson 2013b)	15	32	10.1	6.5	NS	NR	NR	
	Therapy-naïve	IFN	Temsirolimus (Hudes 2007)	5	9	1.9	3.8	<0.001	7.3	10.9	0.01
Second-Line	Post-cytokine	Placebo	Sorafenib (Escudier 2007, Escudier 2009a)	0	2	2.8	5.5	0.01	15.2	17.8	0.15
	Post-cytokine	Placebo	Pazopanib (Sternberg 2010)	3	29	4.2	7.4	<0.001	NR	NR	

	1 prior therapy (cytokine, TKI, mTOR)	Sorafenib	Axitinib (Rini 2011, Motzer 2013a)	9	19	4.7	6.7	<0.0001	20.1	19.2	0.37
	Post-TKI	Placebo	Everolimus (Motzer 2008, Motzer 2010)	0	1	1.9	4.9	<0.001	13.0	13.5	0.23
	Post-TKI	Sorafenib	Temsirolimus (Hutson 2013a)	8	8	3.9	4.3	0.19	16.6	12.2	0.01
Third-Line	Post-TKI + Post-mTOR	Dovitinib	Sorafenib (Motzer 2014)	6	4	3.6	3.7	0.063	11.0	11.1	0.35

For good and intermediate risk disease, broadly anti-angiogenic approaches such as pazopanib, sunitinib or the combination of bevacizumab plus IFN would all be first-line treatments of choice, resulting in median progression-free survival (PFS) to 8-11 months. Sorafenib is not however a preferred first-line option, following a failure to demonstrate improved outcome when compared to interferon-α (Escudier 2010, Escudier 2009b). Axitinib is not recommended as a first-line therapy due to the lack of superiority when compared to pazopanib. Tivozanib recently failed to receive FDA approval due to inconsistent PFS and OS results (Aveo Inc Press Release 2013).

Although complete remissions can occur in a small fraction of patients with TKIs, discontinuation of therapy usually leads to relapse and so it is unclear how much these treatment approaches are altering the fundamental underlying biology of the disease (Albiges 2012, Johannsen 2009).

The mTOR inhibitor temsirolimus is widely used for first-line management of poor risk disease, due to encouraging data generated from a Phase 3 trial in this specific patient population, in which temsirolimus prolonged median overall survival (10.9 versus 7.3 months, $p = 0.008$) compared to IFN-α in patients exhibiting ≥3 poor risk factors (Hudes 2007).

Phase 3 trials evaluating pazopanib, sunitinib and bevacizumab-IFN have enrolled only a small proportion of patients (5% to 10 %) with poor risk disease. In the case of sunitinib however, subgroup analysis of the pivotal Phase 3 trial, as well as an expanded access program in a broader population of patients with metastatic RCC, demonstrated efficacy and feasibility in those with poor risk disease, suggesting that TKIs, notably sunitinib, may be an alternative therapeutic option to mTOR inhibitors for this group of patients (Gore 2009, Motzer 2009).

In general, available first-line agents can prolong PFS although temsirolimus is the only therapy to have shown a survival advantage, possibly due to methodological complexities of cross over from control cohorts upon disease progression in many of the clinical trials of TKIs.

1.1.1.3. Second-line Therapy

Second-line Therapy: Post First-line Cytokines

Outcomes with second-line therapy are to an extent determined by the nature of the regimen used in the first-line setting. For patients treated with first-line cytokine therapy, the use of the anti-angiogenic agents sorafenib, pazopanib and axitinib have shown promising and broadly comparable outcomes in Phase 3 trials, although pazopanib appears to be associated with the longest PFS (7.4 months). In studies involving a direct placebo comparison, pazopanib did not show a clear survival advantage whilst sorafenib was superior to placebo only when adjusted for

patients crossing over from placebo to active treatment (final median OS sorafenib versus placebo 17.8 versus 15.2 months respectively, HR 0.88; p = 0.146; when post–cross-over placebo adjusted, median OS 17.8 versus 14.3 months, respectively; HR 0.78; p = 0.029).

Second-line Therapy: Post First-line TKIs

Following first-line VEGF inhibitors, second-line therapy with everolimus, temsirolimus, sorafenib and axitinib have demonstrated benefits in PFS, with values of 4–5 months having been recorded.

The pattern of second-line response may be influenced by the preceding first-line therapy. In a direct comparison of axitinib and sorafenib, median progression-free survival was 12.1 months for axitinib and 6.5 months for sorafenib (HR 0.46 p <0.0001) in patients who had previously received cytokines. In patients previously treated with sunitinib, median PFS was 4.8 months for axitinib and 3.4 months for sorafenib (HR 0.741 p = 0.0107).

When the mTOR inhibitor everolimus was compared with placebo, following first-line TKI therapy, median OS was comparable (14.8 months [everolimus] versus 14.4 months [placebo] HR, 0.87; p = 0.162), with 80% of patients in the placebo cohort crossing over to everolimus. When corrected for crossover however, survival was 1.9-fold longer (95% confidence interval [CI], 0.5-8.5) with everolimus compared to placebo.

When the mTOR inhibitor temsirolimus was compared with sorafenib, following first-line TKI therapy, although median PFS values were comparable (3.9 versus 4.3 months for sorafenib versus temsirolimus respectively, p =0.19) there was a significant survival advantage in favor of sorafenib (median OS 16.6 versus 12.3 months respectively, HR, 1.31 p = 0.01). The median OS of 16.6 months reported for sorafenib after TKI first-line therapy was similar to the median OS of 17.8 months reported after cytokine first-line therapy.

These findings, suggesting that second-line TKI therapy may be superior to mTOR inhibitors, following first-line TKIs are supported to an extent by recent retrospective analyses comparing second-line VEGF and mTOR inhibitors in the post-TKI setting. Anti-VEGF agents appear as effective as those with alternate mechanisms of action, even in patients who are primarily refractory to anti-angiogenic approaches (Vickers 2010, Heng 2011), suggesting that anti-VEGF agents are as effective as those with alternate mechanisms of action, even in patients who are primarily refractory to anti-angiogenic approaches.

Thus, second-line VEGF inhibitors have been reported to be more effective than mTOR inhibitors, even in patients highly resistant to VEGF TKIs, suggesting that all of the VEGF TKIs have a modest degree of non-cross resistance, possibly explained by different molecular targets or differential affinity for target interaction (González Larriba 2012, Sun 2013). This feature may explain the finding that for patients who have progressed on either sunitinib or sorafenib, switching to the alternate TKI can result in meaningful clinical efficacy in the second-line setting (Zama 2010, Dudek 2009, Eichelberg 2008, Sablin 2009).

Second-line Therapy: Post First-line mTOR Inhibitors

In contrast to post first-line cytokine or TKI therapy, there is little evidence available to guide therapy following failure of mTOR inhibitors. For example, the AXIS trial of axitinib compared to sorafenib included only 3% of patients who received second-line therapy following temsirolimus (Rini 2011). Probably the strongest evidence comes from a retrospective database study in which third-line sorafenib appeared active and feasible after first-line sunitinib and second-line everolimus or temsirolimus in terms of the toxicity profile and median PFS (median PFS 4 months, median OS 7 months since sorafenib treatment) (Di Lorenzo 2010).

1.1.1.4. Third-line Therapy

Following failure of both a TKI and an mTOR inhibitor as first and second-line therapies, third-line salvage therapy is limited, less established and more experimental. Approaches essentially consist of various permutations of available targeted therapies to select a third-line agent which has not already been used in earlier stages of treatment. Sorafenib has been most extensively examined in this advanced setting with a Phase 3 trial finding a median PFS of about 3.5 months and an OS of 11.1 months (Motzer 2014). Similarly, a recent retrospective study of third-line sorafenib following prior TKI and mTOR inhibitor therapy reported a median PFS of 4 months and a median OS of 7 months, with a 23.5% response rate to sorafenib (Di Lorenzo 2010).

The value of third-line therapy is supported by a recent retrospective analysis showing that survival increases commensurately with the number of successive lines of therapy employed. The median OS in patients who received only one targeted therapy was 14.9 months from the time of first-line therapy initiation, with a PFS of 6.7 months. In contrast, the median OS in patients who received two lines of therapy was 21.0 months, measured from the time of first-line therapy initiation (95% CI 19.1–23.5 months), with a PFS of 3.4 months, measured from the time of second-line therapy initiation (95% CI 3.0–3.9 months). Patients who received three or more lines of therapy had an OS of 39.2 months, measured from the time of first-line initiation (95% CI 36.3–41.9 months), with PFS of 4 months, measured from the time of third-line therapy initiation (95% CI 3.4–4.5 months) (Ko 2014).

Conclusion

Patients with advanced RCC are incurable and have an OS of less than two years. Once first-line therapy has failed, second-line or beyond treatment strategies achieve PFS of less than five months on average. In particular, mTOR inhibitor monotherapy with either temsirolimus or everolimus in patients who failed prior TKI therapy results in response rates of less than 10% and short PFS times of less than five months.

Strategies to improve on these results have to date been limited by largely preclusive toxicity and/or limited additional efficacy arising from attempts to combine targeted agents together, including previous combinations of TKIs with everolimus (Harzstark 2011, Molin 2012, Escudier 2010) or temsirolimus (Patel 2009, Patnaik 2007). For clear cell RCC therefore, combinations of TKIs and mTOR inhibitors appear to be either impracticable or feasible only at attenuated doses, resulting in diminishing efficacy and added toxicity. The proposed combination

of everolimus and ibrutinib thus represents a novel and potentially beneficial approach which may improve the currently extremely limited outcomes which can currently be achieved with existing treatment choices.

1.1.2. Urothelial Carcinoma

Cancer of the bladder is the 4th most common cancer in American men and the 9th most common in women (Siegel 2015). More than 70,000 new cases are diagnosed each year in the United States (US), accounting for approximately 16,000 deaths annually. In recent decades the overall incidence of bladder cancer appears to have been rising, probably due to the latent effects of tobacco abuse and industrial carcinogens, as well as the overall aging of the population (Ries 2003).

Ninety percent of bladder cancers are transitional cell carcinomas (Eble 2004). Other types are relatively uncommon, including lymphoepithelioma-like or sarcomatoid carcinomas, micropapillary or nested variants and primary squamous cell carcinomas and adenocarcinomas (Amin 2013).

There 3 three basic patterns of disease, depending on the degree of invasiveness at presentation, with distinct and separate natural histories and management strategies. Although most newly diagnosed tumors (75%) are still superficial and non-invasive, up to 25% will initially present with detrusor muscle invasion, half of which will involve metastatic disease (Yafi 2011b). Furthermore, of tumors that are superficial to begin with, 20% will progress, despite intra-vesical chemo- and immunotherapy, to eventually become muscle-invasive (Cookson 1997, Yafi 2011a). Muscle invasiveness in turn is associated with a significant (50%) incidence of local relapse and/or metastatic spread.

There are therefore a significant proportion of patients with bladder cancer who will eventually develop advanced disease. In the advanced disease setting, almost 90% of patients eventually die of cancer related complications, with a median survival of just 3-6 months, due to the relative ineffectiveness of existing chemotherapeutic options. There is therefore a significant unmet need for new treatment strategies for this intractable patient population.

1.1.2.1. Muscle Invasive Tumors

Radical cystectomy with extended lymphadenectomy is usually considered to be the standard treatment of MIBC (Gakis 2013, Stimson 2010). However, even after successful surgery for locally advanced disease, there is a significant rate of recurrence (up to 56 % among patients with pathological stage T3 invasion of perivesical tissue), most commonly manifesting as distant metastases, presumably implying the presence of occult micrometastases at the time of surgery (Skinner 1984, Bassi 1999).

In view of the limited ability of surgery alone to effect long term disease control, extensive attempts have been made to optimize the use of neo-adjuvant or adjuvant chemotherapy. The neo-adjuvant use of a combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) has shown a reduced rate of residual disease post-surgery of 15% versus 38% for surgery alone

(p<0.01), associated with a consequent improvement in median survival of 77 versus 46 months (although this just failed to reach statistical significance, p = 0.06) (Grossman 2003).

Additional support for the role of neoadjuvant cisplatin-based combination chemotherapy comes from a large, randomized, Phase 3 MRC/EORTC trial showing superior survival for those who received neoadjuvant chemotherapy compared to cystectomy or radiation therapy alone, with a statistically significant increase in 10-year survival from 30% to 36% (International Collaboration of Trialists 1999, Griffiths 2011). The median survival for the chemotherapy group was 44 months and for the no-chemotherapy group was 37.5 months, a difference of 6.5 months.

A subsequent meta-analysis of controlled trials testing neoadjuvant cisplatin-based chemotherapy reported a 14% decrease in the relative risk of death, and a 5% absolute improvement in OS (p = 0.003) (ABC Meta-analysis Collaboration 2005).

Therefore, it appears that the use of neo-adjuvant therapy can result in significant pathological downgrading of tumors and that this translates into a reduced liability for metastatic spread and an improvement in OS. In contrast, the role and relevance of adjuvant therapy in the post-surgical management of invasive bladder cancer remains unclarified.

Individual studies have shown a survival advantage comparing surgery alone to the use of cisplatin based adjuvant regimens (3 year PFS of 40% versus 70%, 10 year PFS of 13% versus 43%, median OS of 2.4 versus 4.3 years, 10 year OS of 17% versus 27% respectively) (Lehmann 2006, Stöckle 1996, Skinner 1991). Two recent meta-analyses have also suggested a 25% relative reduction in the risk of death for adjuvant chemotherapy compared to control but both noted significant methodological limitations to interpreting these findings (ABC Meta-analysis Collaboration 2005, Ruggeri 2006). Similarly, there has to date been no confirmation of the value of adjuvant therapy from a sufficiently large randomized prospective trial (Hussain 2009), with additional evidence suggesting comparable results (of 50% 5-year survival) for either adjuvant chemotherapy, or chemotherapy delayed until disease relapse (Cognetti 2012).

Furthermore, compared to neoadjuvant therapy, there are frequently substantial limitations to the delivery of effective chemotherapy in the postoperative setting, as a result of declines in patient performance status or serious postoperative complications (Donat 2008). The precise role of adjuvant therapy in the management of invasive disease therefore remains unclear but current data on balance suggest its use may be associated with a delay to recurrence and hence be justified in those at high risk of relapse (Millikan 2001). Similarly, the role of adjuvant radiotherapy or chemoradiotherapy in invasive disease is unclear. However, as local recurrence rates can be as high as 70% in patients with positive surgical margins (Herr 2004), the empirical use of radiotherapy (with or without cisplatin) is used on a patient by patient basis (Zaghloul 1992, Cozzarini 1999).

Overall, management of invasive bladder disease with surgery and neo-adjuvant chemotherapy can result in over 50% of patients surviving 3 years and remaining free of metastatic spread for that period of time. It does however mean that about half of all patients will eventually develop locally

recurrent or metastatic disease, thus delivering them to the patient pool population requiring therapy for advanced disease.

1.1.2.2. Recurrent Local or Metastatic Advanced Disease

Local recurrence develops in about 20% of patients who have undergone radical cystectomy, with a median time to recurrence of approximately 9 months. About 70% will also have concurrent distant metastases. Conversely, distant metastasis without local recurrence occurs in another 20% of cases, with a median time to recurrence of about 20 months (Honma 2004, Fukuta 2009, Mitra 2012, Stein 2006).

Management of advanced disease is essentially systemic chemotherapy or more recently immunotherapy, with little or no additive benefit derived from chemoradiotherapy and no established role for surgery, except that surgical consolidation after a major and durable response to systemic chemotherapy may be beneficial in very carefully selected patients (Yafi 2009).

Overall, despite its prominence in the management of advanced bladder cancer, chemotherapy has achieved little progress over the last few decades with cisplatin, which was first noted to have activity in bladder cancer back in 1976, still remaining the cornerstone of systemic strategies (Yagoda 1976).

Whilst conventional chemotherapy in the neoadjuvant (Grossman 2003, Griffiths 2011) and (potentially) adjuvant setting (ABC Meta-analysis Collaboration 2005, Svatek 2010), particularly with platinum-based regimens, has shown promising results in the management of locally muscle invasive tumors, little improvement has been achieved in the outcomes of patients with recurrent or metastatic disease (Pal 2013). Almost 90% of those patients eventually die of cancer related complications, with a median survival of 3-6 months, which is not significantly longer than survival in the absence of treatment, where 5 year survival is 0-18% (Babaian 1980, Yagoda 1985, Hoffman 2008). In general, longer term survival with combination chemotherapy has only been demonstrated in the best risk patients (ie, good performance status, no visceral or bone disease and normal alkaline phosphatase and lactate dehydrogenase levels). By contrast, poorer risk groups have very limited tolerability for combination chemotherapy and consequently have extremely low complete remission rates (Yafi 2011b, Bajorin 1999).

The 3 most active drugs in advanced disease are cisplatin, taxanes and gemcitabine and the first-line management of metastatic disease largely involves combination regimens of either methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or gemcitabine and cisplatin (GC). Either regimen results in response rates of 45%, a time to progressive disease (PD) of about 7.5 months and a median OS of 14-15 months. Longer term follow-up also suggests that MVAC and GC are essentially comparable, with 5 year PFS of 11.3 versus 9.8% and 5 year OS of 15.3 versus 13% respectively (von der Maase 2000, von der Maase 2005). Less toxic deaths have however been recorded with GC compared to MVAC (1 versus 3% respectively).

In an attempt to improve on outcomes, a 2 weekly dose dense regimen of MVAC chemotherapy plus granulocyte colony stimulating factor was compared with classic MVAC, with superior results reported for the more intensive regimen which resulted in overall response rates (ORR) of

64% versus 50%, median PFS of 9.5 versus 8.1 months, median survival of 15.1 versus 14.9 months and a two year OS of 36.7% versus 26.2 %, respectively (Sternberg 2001b, Sternberg 2006). Five year survival rates were 21.8% versus 13.5%. There was one death from toxicity in each cohort, whilst more patients died due to malignant disease in the MVAC cohort (76%) than in the dose dense MVAC cohort (64.9%). Overall however, dose dense MVAC was less toxic than standard MVAC.

Highly aggressive therapy with dose dense MVAC therefore produces only marginal improvements in relative reduction of the risk of progression and death compared to standard MVAC combination therapy, with the vast majority of patients still dying from PD. In the absence of better alternatives, it has however become an established regimen in place of standard MVAC as an alternative to GC therapy.

More recently, data has emerged supporting the utility of taxane based regimens in the first-line setting. Alternative regimens include cisplatin + paclitaxel (Burch 2000), gemcitabine + paclitaxel (Meluch 2001), carboplatin + gemcitabine + paclitaxel (Bellmunt 2000, Hainsworth 2005) and cisplatin + gemcitabine + docetaxel (Hussain 2001). These combinations have shown modest activity in early stage trials, with CR rates of 7-32% and median OS times of 11-24 months.

Overall therefore, taxane alternatives to the established regimens of MVAC and GC do not appear to offer anything better in terms of enhanced efficacy or attenuated toxicity, emphasizing the chemotherapeutic nihilism characterizing the advanced stages of this particular disease.

Studies involving single agent taxanes have been small in size (ranging from 14-45 patients) and have shown limited outcomes. Three studies involving paclitaxel reported partial response (PR) rates of 5-10% and PFS of 2.2 to 7 months. Although only one study involved docetaxel, outcomes appeared to be marginally better than for paclitaxel, with a PR rate of 13%, a duration of response of 3.8 months and a median OS of 9 months. However, 60% of the patients developed myelosuppression, and dose reduction was required. The exceptionally small patient numbers in all of these trials renders the results little more than anecdotal and so it is not possible to make meaningful comparisons across these studies, except to conclude that the overall activity of taxanes as second-line single agents is very limited.

Results for second-line taxane combinations are summarized below in Table 2.

Table 2. Results from Second-line Taxane Combination for Urothelial Carcinoma

Regimen	Reference	N	CR (%)	PR (%)	ORR (%)	PFS (months)	OS (months)
Docetaxel + Ifosfamide	Krege 2001	22	20		25		
Docetaxel + Gemcitabine +	Bamias 2004	9	30	22			

Regimen	Reference	N	CR (%)	PR (%)	ORR (%)	PFS (months)	OS (months)
Carboplatin							
Paclitaxel + MTX + Cisplatin	Bellmunt 2002	25	0	40			
Paclitaxel + MTX	Chen 2004	20			31		5.0
Paclitaxel + Ifosfamide	Vaishampayan 2005	13	15				
Paclitaxel + Carboplatin	Tu 1995	44	2	5	16	4	6
Paclitaxel + Gemcitabine	Kaufman 2004	6	16	16			
Paclitaxel + Gemcitabine	Fechner 2006	11	26	13	44		
Paclitaxel + Gemcitabine	Meluch 2001	15			47		
Paclitaxel + Gemcitabine	Albers 2008	50	12.5	26		2.7	7.8
Paclitaxel + Gemcitabine	Sternberg 2001a	15			27		8.0
Paclitaxel + Gemcitabine	Kanai 2008	20	5	25		4.5	11.5
Paclitaxel + Gemcitabine	Suyama 2009	30	3	30		5.5	11.3

Interpretation of these trials is limited by the small numbers involved and the fact that some included patients who have failed previous neo-adjuvant/adjuvant therapy in addition to those who have received prior first-line metastatic treatment. The most widely studied regimen is paclitaxel combined with gemcitabine and the variability of the results seen (CR rates ranging from 3 to 26% and OS from 5 to 11.5 months) exemplifies the complexities of assessing clinical outcomes from very limited numbers of patients in this clinically and biologically diverse end stage population. At best it could be concluded, on a balance of probabilities, that the addition of alternative

chemotherapy agents to docetaxel or paclitaxel results in modest improvements in disease control compared to either agent alone.

To date, novel targeted approaches have also unfortunately shown limited promise in the advanced setting as single agents, with low response rates generally of less than 10% and PFS values of only a few months. Attempts to combine them with conventional chemotherapy have been limited by the emergence of significant toxicity, particularly for the anti-angiogenic agents bevacizumab and sunitinib where virtually no patients were able to tolerate full doses of concomitantly administered (GC) chemotherapy. Agents examined include trastuzumab (in combination with paclitaxel, gemcitabine and carboplatin) (Hussain 2007), gefitinib (Petrylak 2010), lapatinib (Wülfing 2009), erlotinib (Pruthi 2010), cetuximab (in combination with gemcitabine and cisplatin [Grivas 2012] and in combination with paclitaxel [Wong 2012]), sunitinib (in combination with gemcitabine and cisplatin [Galsky 2013]), sorafenib (Dreicer 2008), pazopanib (Necchi 2012, Pili 2011), bevacizumab (in combination with gemcitabine and paclitaxel [Hahn 2011]), temsirolimus (Gerullis 2012), bortezomib (Rosenberg 2008) and vorinostat (Cheung 2008).

It is too early to determine the role, if any, of various permutations of these agents in the management of advanced disease. The only targeted agent which has to date reported results, when combined with a taxane, is the cetuximab and paclitaxel regimen, which demonstrated a 25% response rate (CR rate 10%) and median PFS and OS of 16 and 42 weeks, respectively. However, this study involved only 28 patients, many of whom had been treated with prior neoadjuvant or adjuvant chemotherapy rather than receiving first-line metastatic treatment only and mixed histologies were also permitted. At first sight, these outcomes do not appear to be significantly better than those achievable when paclitaxel is combined with gemcitabine, although further experience with this regimen is required to assess the potential utility of combining targeted agents and taxanes.

More recently, immunotherapeutic approaches with checkpoint inhibitor (CPI) therapy have demonstrated significant clinical activity in the second-line setting of patients who have progressed on front-line platinum based chemotherapy, and for the first-line treatment of patients for whom platinum based chemotherapy is not indicated.

Within the last two years, the **second-line** management of UC malignancy has been transformed by the arrival of 5 new checkpoint inhibitors approved by the FDA for patients with locally advanced or metastatic UC whose disease has progressed during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy.

These include:

Drug Name	Date of FDA Approval
Atezolizumab	May 2016
Nivolumab	February 2017
Pembrolizumab	May 2017
Avelumab	May 2017
Durvalumab	May 2017

Additionally, two agents are approved for potential use in the **first-line** setting:
Pembrolizumab: approved (May 2017) for patients with locally advanced or metastatic UC who are not eligible for platinum-containing chemotherapy:

- **Atezolizumab**: approved (April 2017) for patients with locally advanced or metastatic UC who are not eligible for platinum-containing chemotherapy
- Approvals with nivolumab, pembrolizumab, durvalumab, atezolizumab and avelumab in the **second-line setting** were based on overall response rates of 15-20% (compared to historical or contemporaneous control rates of ~10%)[2,3,4,5,6] although in some cases these were greater for patients with higher levels of tumor PD-1 or PD-L1 expression.[7]

Furthermore, there was no significant between-group difference in the duration of PFS in the total population (HR for death or disease progression, 0.98; 95% CI 0.81 to 1.19; *p*= 0.42) or among patients who had a tumor PD-L1 combined positive score of ≥10% (HR 0.89; 95% CI 0.61-1.28; p = 0.24]. In the total population, ORR was significantly higher in the pembrolizumab group (21.1%; 95% CI 16.4-26.5) *versus* chemotherapy (11.4%; 95% CI 7.9-15.8) (p = 0.001).

A recent update of longer-term follow-up from the KEYNOTE-045 study reported that the OS benefit with pembro v chemo was seen in all PD-L1 expression subgroups,and was maintained regardless of age, ECOG PS, prior therapy, liver metastases, baseline hemoglobin, time from last chemo, histology, risk factor group, and choice of chemo.[8]

Of note, it was recently reported that atezolizumab *failed* to show a survival advantage in a second-line study designed similar to that of pembrolizumab[9]

From the currently available **second-line** results with checkpoint inhibitors in advanced UC (when used as an alternative to chemotherapy), it is clear that whilst they can provide superior efficacy outcomes in terms of overall response, their effects on prolonging survival are modest (and as yet limited to pembrolizumab) with no convincing evidence that checkpoint inhibitors improve progression free survival, when compared to generally used chemotherapy agents.

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[2] Rosenberg J. *et al*. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016; 387: 1909–1920.
[3] Bellmunt J. *et al*. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376:1015-1026.
[4] Massard C. *et al.* Safety and Efficacy of Durvalumab (MEDI4736), an Anti–Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer. J Clin Oncol 2016; 34:3119-3125.
[5] Patel M. *et al*. Avelumab in patients with metastatic urothelial carcinoma: Pooled results from two cohorts of the phase 1b JAVELIN Solid Tumor trial. J Clin Oncol 2017;35:330-330.
[6] Sharma P. *et al*. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017;18(3):312-322.
[7] ORR of approximately 25% for patients with higher levels of PD-L1 treated with durvalumab, nivolumab, atezolizumab.
[8] Bellmunt J. *et al.* Two-year follow-up from the phase 3 KEYNOTE-045 trial of pembrolizumab (pembro) vs investigator's choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer (UC). J Clin Oncol, no. 6_suppl(February 20 2018) 410-410.
[9] Roche Press Release: Roche provides update on phase III study of TECENTRIQ® (atezolizumab) in people with previously treated advanced bladder cancer.10MAY2017.[10] Vaughn D. *et al.* Health-Related Quality-of-Life Analysis From KEYNOTE-045: A Phase III Study of Pembrolizumab Versus Chemotherapy for Previously Treated Advanced Urothelial Cancer. J Clin Oncol 2018;36(16):1579-1587.

They appear however to be less toxic than chemotherapy, which is a significant potential advantage in a patient population generally characterized as biologically frail and intolerant of toxicity. Additionally, a recently reported health related quality of life (HRQoL) analysis from the prmbrolizumab KEYNOTE-045 trial conluded that **i**) pembrolizumab prolonged the time to deterioration in HRQoL assessments compared with chemotherapy, **ii**) that patients treated with pembrolizumab had stable or improved global health status/quality of life (whereas those who were treated with investigator's choice of chemotherapy experienced declines in global health status/quality of life) and that **iii**) combined with efficacy and safety outcomes, data support pembrolizumab as standard of care for patients with platinum-refractory advanced urothelial cancer.[10]

In the **first-line setting**, preliminary results from the ongoing KEYNOTE-052 study of pembrolizumab suggested a slightly lower overall response rate (29%) than achievable with cisplatin regimens, although the duration of response appeared to exceed that of chemotherapy in historical control data.[11] A similar overall response rate (23.5%) was seen with first-line atezolizumab in the same cisplatin ineligible setting[12]

A recent update of the pembrolizumab KEYNOTE-052 study,[13] with more mature follow-up, reported the following findings:

Confirmed ORR was 28.9% (95% CI 24.3-33.8); [CR: 8.1% and PR: 20.8%].

- Median duration of response was not reached (NR) (95% CI, 21.4 mo to NR);
- Median OS was 11.5 (95% CI 10.0-13.3); [6-and 12-mo OS rates: 67.2% and 47.5%, respectively
- In patients with a PD-L1 expression ≥10% ORR was 47.3% (95% CI, 37.7-57.0) and median OS was 18.5 mo (95% CI 12.2 mo to NR).
- Checkpoint inhibitors therefore clearly display activity in both the first- and second-line setting. Although their overall efficacy would appear to be modest, they nonetheless represent a significant therapeutic advance in a disease where chemotherapy generally results in even more limited outcomes, often at the cost of preclusive toxicity.

The role of PD-L1 expression as a predictor of activity with checkpoint inhibition is however slightly divergent, depending upon disease setting, In the second-line context, it is apparemt that pembrolizumab activity is evident at all PD-L1 levels, although any survival benefit appears to be

[10] Vaughn D. *et al.* Health-Related Quality-of-Life Analysis From KEYNOTE-045: A Phase III Study of Pembrolizumab Versus Chemotherapy for Previously Treated Advanced Urothelial Cancer. J Clin Oncol 2018;36(16):1579-1587.
[11] Balar A. *et al.* Pembrolizumab (pembro) as first-line therapy for advanced/unresectable or metastatic urothelial cancer: Preliminary results from the phase 2 KEYNOTE-052 study. Annals Oncol 2016;27, Issue suppl_6: LBA32_PR.
[12] Balar A. *et al.* Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389:67-76.
[13] Vucky J. *et al.* Updated efficacy and safety of KEYNOTE-052: A single-arm phase 2 study investigating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). J Clin Oncol , no. 15_suppl(May 20 2018) 4524-4524.

incrementally related to successively higher levels of PD-L1 expression, with the greatest effect obtained with PD-L1 levels ≥10%.

In the first-line setting, evidence is increasingly suggesting that higher PD-L1 levels may be an essential pre-requisite for checkpoint inhibitor monotherapy and it is of note that in the US and Europe, regulators have recently issued a safety warning against the use of front-line single-agent immune checkpoint inhibition for patients with **PD-L1–low expressing** cisplatinum-ineligible UC.[14] This, followed findings of lower overall survival in the pembrolizumab and atezolizumab monotherapy arms for patients with low levels of PD-L1 espression [PD-L1 CPS expression of <10% and PD-L1 IC of <5% respectively) compared with platinum-based chemotherapy, in two ongoing Phase III studies (KEYNOTE-361 and IMvigor130, which are evaluating pembrolizumab and atezolizumab, respectively, with or without chemotherapy compared with chemotherapy or immunotherapy alone).

However, the dynamic complexity between PD-L1 expression and disease setting is emphasized by the fact that patients who are ineligible for *any* platinum based regimen can still receive treatment with either pembrolizumab or atezolizumab, *irrespective* of PD-L1 status.

In the current study, the treatment arm of ibrutinib plus pembrolizumab is therefore intended to improve further on the efficacy achievable with pembrolizumab monotherapy in currently approved indications for urothelial malignancy.

The inclusion of an ibrutinib single-agent arm is intended to facilitate interpretation of findings with both the existing ibrutinib + paclitaxel combination. Additonally, the assessment of the potential efficacy of single-agent ibrutinib in this area of high unmet medical need to follow up on an initial evaluation of data from the ongoing ibrutinib + paclitaxel UC cohort 2. UC cohort 2 data are strongly suggestive of superior activity when compared to historic data for single-agent taxane therapy in comparable clinical settings of advanced urothelial malignancy.

Conclusion

In view of the exceptionally limited outcomes available with single and combination agents, including taxanes, in the post first-line setting, the proposed combination of ibrutinib and paclitaxel offers promise as a novel regimen that may improve outcomes beyond those currently available with existing therapeutic strategies.

Additionally, the cohort evaluating single-agent ibrutinib is being added to evaluate the proof of activity of ibrutinib in an unmet medical need setting,

[14] FDA limits the use of Tecentriq and Keytruda for some urothelial cancer patients. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm612484.htm[15] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

1.1.3. Advanced Gastric or Gastro-esophageal Junctional (GEJ) Adenocarcinoma

Esophago-gastric cancer is the ninth most common cancer and second highest cause of cancer-related mortality worldwide, resulting in more deaths than breast and colon cancer combined (Jemal 2010). Histologically, the disease is divided into squamous cell carcinoma (SCC) and adenocarcinoma (Siegel 2015). SCC is the most common variant in eastern Europe and Asia, whilst adenocarcinoma is predominant in North America and western Europe, accounting for 70% of diagnoses in these two regions. Although adenocarcinoma currently occurs mainly in white males, the incidence of this histological subtype is progressively increasing in men of all ethnic backgrounds, as well as in women (Bertuccio 2009).

Esophago-gastric carcinoma is predominantly a male disease of mid to late adulthood but there are very marked variations in incidence, more so than for any other solid tumor, according to sex, geographical area, racial and economic background. The annual age adjusted incidence amongst males varies from less than 5 cases per 100,000 amongst whites in the US (Siegel 2013) to up to 12.5 per 100,000 in some regions of France and even more than 100 cases per 100,000 in parts of China. In most countries, the disease is two to four times more frequent in men as compared to women (Crew 2004, Buas 2013).

While the incidence of (distal) gastric cancer in the west is falling markedly, the incidence of esophageal adenocarcinoma in men has risen 65% in the last 35 years. Cancers involving the proximal stomach and esophago-gastric junction (GEJ) are increasing at a rate exceeding that of any other malignancy except melanoma and lung cancer. In western countries, the most common site of upper gastrointestinal disease is now the lower third of the esophagus (Trivers 2008, Blot 1991). The reason for this increase in esophageal malignancy is unclear but neoplastic progression is strongly associated with a rising incidence of the pre-malignant metaplastic condition, Barrett's esophagus (Enzinger 2003, Jin 2009, Shaheen 2002). This in turn is caused by gastro-esophageal reflux disease and, along with obesity, smoking and alcohol intake, is one of the strongest risk factors for malignant transformation. Distal gastric cancers are therefore probably becoming rarer due to a declining incidence of helicobacter pylori infection (Eslick 1999), whilst the incidence of adenocarcinomas of the proximal stomach and distal esophagus is growing due to increasing rates of obesity and gastro-esophageal reflux disease (Pera 1993, Blot 1991). These findings might partly explain the persistingly poor prognosis of the disease, as proximal lesions are biologically more aggressive and have a worse prognosis, stage for stage, than do distal gastric cancers (Wanebo 1993).

In general, esophago-gastric cancer is a desperate disease as it tends to present at a late advanced stage (Lerut 2004), and most patients (80–90%) in high-income non-Asian countries (such as the US) are either diagnosed with advanced disease or develop a recurrence within 5 years of undergoing surgical resection (Price 2012). Consequently, mortality is high, with only 8% of patients surviving more than five years, resulting in a median survival of just 9 months.

Treatment approaches to esophago-gastric cancer at diagnosis are based upon tumor stage and location, histological type and a patient's general medical condition. Independent prognostic factors for long-term survival include tumor and nodal (N/T) category and grading for

adenocarcinoma, as well as N/T category and localization for squamous cell carcinoma (Rice 2010, Chau 2004, Abdalla 2004).

For advanced disease, there are no significant overall differences in survival outcomes according to sex, racial background, histological type or tumor location (esophageal, esophago-gastric junctional or gastric) (Fareed 2009, Roy 2013, Wagner 2010, Stahl 2013, Waddell 2013, NCCN v3 2015[Esophageal and Esophagogastric Junction Cancers], NCCN v3 2015[Gastric Cancer]).

For patients with metastatic or locally advanced disease, multivariate analysis has identified 4 prognostic factors following fluoropyrimidine (FP)-based therapy: i) performance status, ii) presence of liver metastases, iii) presence of peritoneal metastases, iv) elevated alkaline phosphatase levels. These 4 factors in turn define three risk groups (good, moderate and poor risk). Compared with the good risk group, the moderate group has a nearly two-fold increase in the risk of death, whereas those patients with a poor risk have a 3.5-fold increase in the odds of death. This results in a corresponding difference of 7.7 months in median survival and 37.5% in 1-year survival between the good and the bad risk groups (Chau 2004).

1.1.3.1. Non-metastatic Disease

Surgery is the only potentially curative strategy for patients with esophago-gastric cancer. Potentially curative surgery by itself (RO – complete resection) without supportive pre- or post-operative systemic therapy is regarded as standard treatment only in carefully selected medically fit patients with localized squamous cell histology (Omloo 2007, Hulscher 2002).

For all other patients with locally confined or loco-regionally resectable disease (anything ≥stage 1B) combined modality approaches are standard, as up to 80% of patients undergoing resection with curative intent will eventually develop locoregional recurrence (Gunderson 2002), explaining why 5-year survival rates after surgery alone are only 34% to 70% for patients with Stage I and II disease and 7% to 20% for Stage III and IV disease (Hundahl 2000).

1.1.3.2. Advanced Disease: First-line Management

The vast majority (90%) of patients will either present with, or relapse into, advanced (metastatic or loco-regionally recurrent) disease. There is currently no universally accepted first-line standard of care chemotherapy regimen for these patients, which results in substantial regional variations in practice. Whichever treatment is chosen however, outcomes are generally poor, with a median OS of only 8–12 months after first-line chemotherapy, although this is an improvement over life expectancy with best supportive care alone (Wagner 2006).

In North America, first-line cisplatin–fluorouracil or irinotecan- fluorouracil regimens are the most commonly used and are essentially equivalent, resulting in a one year survival rate of only 30%, a median survival of 8-10 months and response rates of just 20 to 30% (Dank 2005, Van Cutsem 2006). Irinotecan-based regimens may however be a better option for patients for whom cisplatin is contra-indicated for whatever reason.

More recent data suggest that capecitabine based doublet regimens may provide equivalent, if not marginally better, efficacy to fluorouracil ones (Kang 2009b, Okines 2009, Moehler 2010).

Triplet chemotherapy consisting of ECF (epirubicin, cisplatin, fluorouracil), ECX (epirubicin, cisplatin, capecitabine), EOF (epirubicin, oxaliplatin, fluorouracil), or EOX (epirubicin, oxaliplatin, capecitabine) is also used, depending on a patient's performance status and other disease characteristics. In a direct comparative trial, median survival times for ECF, ECX, EOF and EOX were 9.9 months, 9.9 months, 9.3 months, and 11.2 months, respectively. Survival rates at 1 year were 37.7%, 40.8%, 40.4%, and 46.8%, respectively. Median PFS times were 6.2 months, 6.7 months, 6.5 months and 7.0 months respectively, whilst overall response rates were 40.7%, 46.4%, 42.4% and 47.9% respectively (Cunningham 2008). Whilst survival appeared to be slightly longer with the EOX regimen (but with a higher incidence of Grade 3 or 4 diarrhea or neuropathy), there was little to choose between the four triplet combinations, with each providing marginal improvements over doublet therapy efficacy and only a modest prolongation of survival relative to best supportive care.

The alternative non-anthracycline based triplet regimen of fluorouracil, leucovorin, and irinotecan (FOLFIRI) has recently been compared to ECX and resulted in a significantly longer time to treatment failure (TTF) (5.1 versus 4.2 months; $p = 0.008$), although there was no significant difference between the two groups in median PFS (5.3 versus 5.8 months; $p = 0.96$), median OS (9.5 versus 9.7 months; $p = 0.95$), or response rate (39.2% versus 37.8%) (Guimbaud 2014).

In Europe, the taxane based triplet combination of docetaxel, cisplatin and fluorouracil (DCF) is widely used and is also approved by FDA in the US. When compared to cisplatin and fluorouracil alone, small improvements were seen in ORR (37% versus 25%), TTP (5.6 months versus 3.7 months) and OS (9.2 versus 8.6 months) respectively, although at the cost of notably increased toxicity (Van Cutsem 2006). A subsequent trial showed a trend towards a greater ORR with DCF compared to ECF or cisplatin and docetaxel (DC) alone but again the cost of significant myelosuppression and infective complications. The ORR was 25.0% for ECF, 18.5% for DC, and 36.6% for DCF. Median OS times were 8.3, 11.0, and 10.4 months for ECF, DC, and DCF, respectively (Roth 2007).

The usage of triplet over doublet combinations, whichever individual drugs are involved, is therefore frequently a judgment of limited additional efficacy at the cost of significantly greater toxicity, which becomes a difficult balancing act when optimizing individual patient treatment strategies.

Despite the varied doublet and triplet combinations employed, response rates and survival remain equally low, with a significant burden of toxicity and considerable patient inconvenience due to the demanding nature of the regimens (Power 2010, Shah 2010). There is therefore a real need for additional combination strategies and the exploitation of novel therapeutic targets, particularly as to date, the use of non-chemotherapy additions to conventional chemotherapy approaches has produced mixed results.

In contrast to colorectal disease, the results of studies with anti-angiogenic agents in advanced gastric cancer, as a potential first-line treatment, have so far been disappointing (Tanigawa 1997, Bang 2011, Kang 2012b), despite strong evidence that VEGF expression increases with advancing stage and tumor burden (Eroglu 1999, Karayiannakis 2002), is linked to tumor aggressiveness

(Kim 2009) and conveys a poor prognosis in advanced esophago-gastric cancer (Maeda 1996, Song 2002). Bevacizumab has been evaluated in combination with cisplatin and capecitabine chemotherapy for the first-line treatment of locally advanced or metastatic disease in a large randomized Phase 3 trial. Although bevacizumab was associated with a significantly longer PFS versus placebo (median, 6.7 versus 5.3 months; hazard ratio [HR], 0.80; p = 0.0037) and higher ORR (46.0% versus 37.4%; p = 0.0315), the difference in overall survival (OS) did not reach statistical significance (12.1 versus 10.1 months; HR, 0.87; p = 0.1002) (Ohtsu 2011).

However despite the overall negative results, a subgroup analysis subsequently suggested that bevacizumab tended to improve OS in non-Asian patients with high versus low levels of plasma VEGF-A (Van Cutsem 2012), indicating that there may be some benefit for suitably selected patient sub-groups. Similarly, a Phase 2 study examined bevacizumab combined with irinotecan and cisplatin in US patients with metastatic or unresectable gastric or esophago-gastric junctional adenocarcinoma, most of whom had received no prior chemotherapy. The addition of bevacizumab resulted in a 65% ORR, a time to progression of 8.3 months and a median OS of 12.3 months, which compared favorably with historical data for irinotecan and cisplatin alone at the participating centers, again suggesting that bevacizumab may to a certain extent be clinically active in this advanced disease setting (Shah 2006).

HER-2 amplification/overexpression has been associated predominantly with esophago-gastric junctional and gastric tumors. HER-2 amplification and HER-2 overexpression in gastric cancer range from 12-27% and 9-23% respectively (Tanner 2005, Yan 2010, Chua 2012). In the US, the proportion of HER-2 positive gastric disease appears to be about 12% and is three times more common in intestinal than diffuse sub-types (19% versus 6%) (Kunz 2012), a similar finding to that seen in western populations in general (Janjigian 2012, Bang 2009). For esophago-gastric junctional tumors, HER-2 over expression is much more variable (2-45%) (Moelens 2011), with both expression and amplification being twice as common in adenocarcinoma compared to squamous histologies (Dreilich 2006, Schoppmann 2010).

The prognostic significance of HER2 overexpression or amplification in advanced gastric and esophago-gastric cancer has historically been controversial. Although HER-2 positivity is associated with a poor prognosis in metastatic breast cancer (Kaptain 2001) studies on the prognostic value of HER-2 status in esophago-gastric cancer have been contradictory (Park 2006, Begnami 2011, Sasano 1993). However, the recent weight of evidence from the largest prospective study to date on the prognostic value of HER-2 over-expression or amplification suggests that HER-2 status has little relevance (Van Cutsem 2012), a proposition supported by a recent international collaborative analysis of the issue (Shah 2011).

Despite uncertainty around the exact pathogenetic and prognostic role of HER-2, the use of the anti-HER-2 antibody trastuzumab, in combination with chemotherapy (capecitabine plus cisplatin or fluorouracil plus cisplatin), can clearly improve outcomes in first-line therapy for gastric and esophago-gastric cancer (Bang 2010). The Phase 3 TOGA trial demonstrated an improvement in median OS from 11.1 months with chemotherapy alone to 13.8 months (p = 0.0046) with the addition of trastuzumab. Secondary endpoints of PFS (6.7 versus 5.5 months, p = 0.0002) and response rate (47.3% versus 34.5%, p = 0.0017) were also improved. The regimen did not

significantly increase toxicity, resulting in it being approved as the first molecularly targeted agent for gastric and esophago-gastric junction adenocarcinoma in the US and Europe.

However, benefit was only seen in patients with tumor scores of ICH 3^+ or ICH 2^+ and FISH positive (OS 16 versus 11.8 months) compared to those with scores of ICH 0 or ICH 1^+ and FISH positive (OS 10 versus 8.7 months). Furthermore, longer term follow up has shown that the hazard ratio for OS decreased from 0.74 to 0.80, with a corresponding reduction in median OS from 2.7 months to just 1.4 months, representing an approximate 50% decrease in the effect of trastuzumab over time (Trastuzumab 2010).

Despite encouraging outcomes with trastuzumab, results with lapatinib (a small molecule inhibitor of HER-2 and epidermal growth factor receptor (EGFR) tyrosine kinases) have been more equivocal, with for example one recent randomized Phase 3 trial (of patients with IHC2^+ and FISH amplified, or IHC 3^+, or FISH, CISH, or SISH amplified disease) recording a significant benefit in ORR (27% versus 9%; $p < 0.001$) but no significant improvement in PFS or OS (median 12.2 versus 10.5 months) with the addition of lapatinib to capecitabine plus oxaliplatin as first-line treatment of advanced HER-2-positive disease (Hecht 2013a).

Overall therefore, the first-line management of advanced esophago-gastric cancer remains anchored around conventional chemotherapy regimens which result in a median survival of less than a year, with a marginal eight week or so improvement in OS for the 10-20% of patients who are candidates for the addition of anti-HER-2 (trastuzumab) targeted therapy. Alternate targeted agent combinations have been disappointingly ineffective in terms of conferring any additional benefit beyond that already achievable with conventional chemotherapy.

1.1.3.3. Advanced Disease: Post First-line Management

The second-line management of patients with recurrent or refractory disease remains suboptimal, as evidenced by the extremely unfavorable prognosis of this group of patients, who have an OS of only 3-4 months (Hartgrink 2009, Wilson 2005, Park 2011). In the third-line setting, treatment outcomes are worse still, with response rates of less than 5% and an OS of about eight weeks on average (Nishimura 2014, Cho 2013, Lee 2013).

Post first-line treatment predominantly consists of single agent chemotherapy employed on an empirical basis according to individual physician and institutional policies. However, in contrast to the limited role of more targeted agents in the first-line setting, there appears to be a greater potential utility for more selective approaches in the second-line and beyond.

Table 3 summarizes some of the more commonly used single agent approaches in the post first-line setting, where randomized comparative data are available.

Table 3. Single Agent Approaches in the Post First-line Setting for Advanced Gastric or GEJ Adenocarcinoma

Drug	Trial	n	OS (months) Rx Cohort Placebo	Line
Docetaxel	COUGAR-02 (Ford 2014)	168	5.2 3.6 HR 0.67 (0.49-0.92) p = 0.01	2nd
Irinotecan	Thuss-Patience et al (Thuss-Patience 2011)	40	4.0 2.4 HR 0.48 (0.25-0.92) p = 0.48	2nd
Docetaxel or Irinotecan	Kang et al (Kang 2012a)	133	5.3 3.8 HR 0.657 (0.485-0.891) p = 0.007	2nd+
Ramucirumab	REGARD (Fuchs 2014, Wilke 2014)	355	5.2 3.8 HR 0.776 (0.603-0.998) p = 0.047	2nd
Apatinib	Li J et al (Li J 2013)	144	4.8 2.5 HR 0.37 (0.22-0.62) p <0.001	3rd+

Single agent chemotherapy treatment, predominantly with docetaxel or irinotecan, results in overall response rates of less than 10% but can improve OS by about 6-8 weeks when compared to

best supportive care. The limited efficacy available with such conventional approaches has inevitably prompted extensive examination of more targeted strategies in this patient population.

Recent evidence from a Phase 2 study of trastuzumab and paclitaxel in Asian patients suggests that trastuzumab may retain activity in the second-line setting, The study primary endpoint, of ORR, was 37% (95% CI 23%-52%), with one patient (2.2%) having a complete response (CR). Median PFS was 5.09 months (95% CI 3.79-6.49 months); time to treatment failure, 5.09 months (95% CI 3.72-6.49 months); and OS, 16.81 months (95% CI: 13.54-18.65 months) (Iwasa 2013). Similarly, another recent Asian study reported encouraging outcomes from trastuzumab combined with a range of chemotherapy agents in the second-line or beyond setting, with findings of a disease control rate of 65.0%, a median PFS was 6.1 months (95% CI 3.0-9.2) and a median OS was 11.1 months (95% CI 8.4-13.7) (Zhandg 2014).

These studies conducted in Asian populations are suggestive of encouraging survival rates, which need to be examined further in controlled trials in differing geographical territories, but clearly raise the possibility that trastuzumab has a potential role in the management of very advanced disease settings (Won 2014, Ku 2015).

As far as anti-angiogenic approaches to advanced esophago-gastric disease are concerned, relatively optimistic results were recently reported from a randomized, placebo-controlled Phase 3 study in predominantly North America and European territories with ramucirumab (a monoclonal antibody specifically binding to vascular endothelial growth factor receptor 2) (Spratlin 2011) which showed a significantly longer PFS (2.1 versus 1.3 months, $p < 0.001$) and OS (5.2 versus 3.8 months, $p = 0.047$) than patients given placebo (Fuchs 2014). A second trial comparing ramucirumab combined with paclitaxel to paclitaxel alone also confirmed the superiority of ramucirumab for ORR (28% versus 16%, $p < 0.001$), PFS (4.4 versus 2.9 months, $p < 0.001$) and OS (9.6 versus 7.4 months, $p = 0.017$) (Wilke 2014).

These studies therefore suggest that ramucirumab, either as a single agent, or in combination, may have utility in prolonging survival by about 6-8 weeks.

More recently still, apatinib (a small-molecule VEGFR tyrosine kinase inhibitor) (Tian 2011) has shown activity in the third-line setting compared to placebo. Statistically significant improvements in favor of apatinib were documented for median PFS (3.67 versus 1.40 months, $p = 0.0017$) and median OS (4.83 versus 2.50 months, $p < 0.001$), respectively. The overall response rates were however very low (9%, and 0% respectively) (Li 2013).

Conclusion

Overall, although response rates with salvage therapy are low (typically less than 10%), it is clear that second-line therapy can achieve a significant survival improvement when compared to best supportive care alone (Kim 2013, Elimova 2014), although any advantage seen is normally only a matter of weeks rather than months. Whilst there are significant regional variations reported for outcomes with targeted therapies, it would appear that anti-HER-2 and anti-angiogenic strategies may confer some limited additional utility beyond that achievable with chemotherapy but any incremental improvements are marginal at best. There is therefore a significant need for new

therapeutic combination options for the treatment of gastric and esophago-gastric cancer in the post-first-line setting.

Combinations of targeted agents (trastuzumab and ramucirumab) with taxanes (paclitaxel) have shown that increased activity can be achieve over single agent taxane therapy and so there is a high probability that combining the target agent ibrutinib with the taxane docetaxel may result in usefully additive activity.

1.1.4. Metastatic Colorectal Adenocarcinoma (CRC)

Colorectal cancer (CRC) has a worldwide annual incidence of 917,000, is the second leading cause of cancer-related death in Western nations (Mathers 2006, Ferlay 2013) and the third highest contributor to cancer mortality in the US (Siegel 2014a). In 2013, there were almost 97,000 new cases of colon cancer and 40,000 cases of rectal cancer in the US, with approximately 50,000 combined deaths due to the two malignancies.

While the age of onset varies, CRC is predominantly diagnosed in older patients. The median age is 71 years and 65% of patients will be ≥65 years at diagnosis. The median age at death is 75 years, with 75% of these occurring in patients 65 years or older (SEER 2015 [epidemiology and end results]). More than 90% of colorectal carcinomas are adenocarcinomas originating from epithelial cells of the colorectal mucosa (Hamilton 2010). Other much rarer types include neuroendocrine, squamous cell, adenosquamous, spindle cell and undifferentiated carcinomas (Fleming 2012).

Three quarters of patients present with ≤ Stage III disease and are managed with surgery combined with adjuvant chemotherapy plus/minus biological agents, resulting in 5-year disease-free and OS rates of about 65% and 73%, respectively. For patients who are Stage I or II, a 5-year survival figure of 90% is now routine (Siegel 2015). However, distant metastases are present in 25% of patients at the time of diagnosis, and will develop in another 25% at some point in time, most frequently within 12 months of initial presentation. Once colorectal cancer reaches this advanced stage, it remains an incurable condition with a median survival of about two years. As recurrence rates following surgery are low (<10%) the preponderance of advanced disease is accounted for by metastatic malignancy (Ahmed 2014, Fakin 2015).

Therapeutic strategies for all stages of colorectal disease predominantly comprise cytotoxic fluoropyrimidine regimens, combined with irinotecan or oxaliplatin. Additionally, anti-angiogenic agents and/or anti-EGFR monoclonal antibodies are widely employed in the metastatic setting.

To date, immunotherapy (predominantly therapeutic vaccines or adoptive cellular therapies) for colorectal disease remains experimental, without an established role in current management strategies (Gallagher 2010, Restifo 2012, Xiang 2013, Boncheva 2013, Diaz 2015, Pernot 2014).

1.1.4.1. Non-Metastatic Disease

Surgery for colorectal cancer is determined by the stage of disease at diagnosis and ranges from simple endoscopic resection of malignant polys to wide resection for more advanced disease. Adjuvant therapy is generally recommended for all patients with Stage III colonic disease and for selected higher risk patients with earlier surgical staging (NCCN Guidelines v2 Colon

Cancer 2015, LaBianca 2013). The use of regimens consisting of oxaliplatin combined with 5-FU and leucovorin (FOLFOX) or capecitabine and oxaliplatin (Cape-OX) have shown 5-year disease-free and OS rates of approximately 65% and 73%, respectively (Andrè 2004, Andrè 2009, Kuebler 2007, Haller 2011).

The use of neo-adjuvant therapy in resectable non-metastatic colon cancer is much less established than adjuvant therapy and contrasts markedly with the management of rectal cancer, where neo-adjuvant strategies are predominant. In rectal disease, longer term outcomes following resection are heavily influenced by the use of pre-operative radiotherapy for early stage disease (Sebag-Montefiore 2009, van Gijn 2011) and neo-adjuvant FP chemoradiotherapy for more extensive late stage presentations (Braendengen 2008, Hofheinz 2012). The addition of other cytotoxics, such as oxaliplatin or irinotecan, to 5-FU or capecitabine does not appear to result in improved outcomes, with comparable results for either monotherapy or doublet combinations in terms of a 15% to 20% pathological complete response rate, 70% sphincter sparing surgery, 5% local recurrence rate, 70% 3-year disease-free survival, and 90% 3-year OS (Gérard 2012, O'Connell M 2014, Aschele 2011, Roh 2011).

1.1.4.2. Metastatic Disease

Whilst local recurrence rates are very low (approximately 5%) following resection of colonic and rectal primary tumors, distant metastases are present in 25% of patients at the time of diagnosis, and will develop in another 25% at some point in time, most frequently within 12 months of initial diagnosis (Chibaudel 2012, Siegel 2014b), except in a small minority of surgically resectable cases (Foster 1977), metastatic disease is essentially incurable, although median survival may now approach 30 months with optimal currently available therapy (Coinou 2014, Goldberg 2006, Goldberg 2007).

1.1.4.3. Resectable Metastatic Disease

Treatment strategies for metastatic disease are predicated on whether the tumor burden is potentially resectable or not. Approximately half of patients with CRC develop hepatic metastases during the course of their disease (Steele 1989) accounting for death in at least two thirds of those with colorectal malignancy.

Although the majority of patients have unresectable metastatic disease, upfront surgery is an option in about 20% of selected cases (Mella 1997, Park 2013) specifically when liver or pulmonary metastases are limited in number and size, although in most cases down staging with initial chemotherapy is attempted.

The finding that patients with initially unresectable liver metastases can become resectable after responding to chemotherapy and have a better long-term outcome than patients treated with chemotherapy alone (Morris 2010) has therefore led to the introduction of "conversion chemotherapy" into clinical practice. For such neoadjuvant down staging strategies, the addition of an EGFR targeted or anti-angiogenic agent to a cytotoxic doublet or triplet are probably the most effective combination regimens.

Five-year survival rates of 30% to 50% can be achieved through successful removal of up to three liver metastases (Adam 2001), with more recent studies showing that resection of an even greater volume of disease is possible, provided enough viable liver can be preserved to provide adequate liver function (Fong 1999, Kemeny 2013). Furthermore, 5-year survival rates achievable with surgery following neoadjuvant chemotherapy appear comparable to results in patients with immediately resectable disease not requiring initial chemotherapy (Adam 2004).

However, surgical resection of metastatic disease is rarely curative, with recurrence occurring in the majority of patients with hepatic lesions, usually within 6-12 months (Rees 2008, Spelt 2012), although even for patients surviving to 5 years disease-free, recurrences still occur in about 15% of cases (Viganò 2008).

Resection of technically suitable lung metastases can also achieve 25% to 35% 5-year survival rates in carefully selected patients (Schmoll 2012).

For patients with metastatic disease which carries a very low or zero probability of future resection, systemic therapy is employed with the aims of achieving shrinkage of symptomatic tumor deposits and/or delaying progression and prolonging survival (Van Cutsem 2014, NCCN v2 Guidelines Colon Cancer 2015, NCCN v2 Guidelines Rectal Cancer 2015). If left untreated, median survival in this patient population is about 6 months (Golan 2013, Ronnekleiv-Kelly 2011).

Systemic Therapy for Non-Resectable Metastatic Disease

The first-line management of CRC has been in a significant state of evolution for many years, with continual refinements of chemotherapy sequencing and the introduction of a range of anti-angiogenic and EGFR-targeted therapies. Survival outcomes with varying treatment approaches are summarized below (Costi 2014).

Table 4. Survival with Varying Treatment Approaches for Non-resectable Metastatic Disease

Treatment Approach	Survival Outcome
BSC	4-6 mo
5-FU/Leucovorin	12-14 mo
5-FU(bolus) or FOLFIRI	15-16 mo
FOLFOX or CAPEOX	19-20 mo
5-FU(bolus)+ Bevacizumab	20.3 mo
FOLFOX6	21.5 mo
FOLFIRI + Bevacizumab	24 mo
FOLFIRI + Cetuximab	28 mo

1.1.4.4. First-line Systemic Therapy

Chemotherapy

The backbone of first-line salvage chemotherapy generally consists of a FP, either intravenous (IV) 5-fluorouracil (5-FU) given with leucovorin (LV) or oral capecitabine, in various combinations and schedules (Douillard 2000, de Gramont 2000, Van Cutsem 2004). Whilst about 15% of patients are treated with an FP regimen alone, the vast majority receive combination therapy with either 5-FU/LV/oxaliplatin (FOLFOX) or 5-FU/LV/irinotecan (FOLFIRI).

Both regimens provide higher response rates, longer PFS and better OS than 5-FU/LV alone. FOLFI|RI and FOLFOX have similar activity in terms of response rate (54% and 56%) and PFS (8.4 and 8.0 months) (Tournigand 2004, Colucci 2005). Median survival of 14-15 months with FOLFIRI or FOLFOX alone compares favorably to median survival outcomes of about 10 months with 5-FU/LV regimens. Median survival of about 21 months is achievable if the two regimens are used sequentially (one being initiated second-line, once progression has been documented with the other when used first-line) (Tournigand 2004). Although both regimens have a similar pattern of efficacy, each has a differing toxicity profile, with irinotecan causing more alopecia and severe diarrhea, whilst oxaliplatin is associated with a higher incidence of polyneuropathy. They also have potentially different interactions with biological combination anticancer agents.

Chemotherapy + Anti-angiogenic Agents

The addition of bevacizumab to oxaliplatin- or irinotecan-based chemotherapy has demonstrated improved PFS (oxaliplatin: 9.4 versus 8.0 months for bevacizumab versus placebo and irinotecan: 10.6 versus 6.2 months for bevacizumab versus placebo) and prolonged survival (oxaliplatin: 21.3 versus 19.9 months for bevacizumab versus placebo and irinotecan: 20.3 versus 15.6 months for bevacizumab versus placebo) (Hurwitz 2004, Saltz 2008) with effects apparent in both wild-type and mutated KRAS disease (see below) (Rosen 2008). The magnitude of survival benefit appears however to be higher with irinotecan (HR 0.66, $p < 0.001$) than with oxaliplatin (HR 0.89, $p = 0.77$).

Recently, in an attempt to augment the activity of bevacizumab based regimens, the combination of oxaliplatin and irinotecan (FOLFOXIRI) plus bevacizumab was explored and found to produce one of the longest survivals reported to date (median: 29.8 versus 25.8 months), (Cremolini 2015, Nipp 2015). The greater toxicity of this triplet + anti-angiogenic combination has however limited its usefulness, leaving the positioning of this more aggressive approach in treatment strategies currently unclear. The findings from this study may indeed define a threshold beyond which cytotoxic based combination therapy cannot provide additional efficacy at an acceptable cost of toxicity.

Chemotherapy + Anti-EGFR Agents

An alternative first-line combination strategy to bevacizumab regimens is the addition of anti-EGFR agents. Expression or up-regulation of the EGFR gene occurs in 60 to 80 percent of CRC cases (Messa 1998, Porebska 2000) and gene expression is associated with poor survival (Mayer 1993, Klapper 2000). However, to date no clear association has been demonstrated

between EGFR expression and response to anti-EGFR therapy (Cunningham 2004, Ciardiello 2003).

The potential benefit of anti-EGFR antibodies in all treatment lines, either as a single agent or in combination with any chemotherapy regimen, is however limited to patients *without* KRAS mutated disease, as alterations in this downstream pathway confer significant resistance (Karapetis 2008, Amado 2008, EMA EU). In fact, treatment with anti-EGFR antibodies may even be harmful; to patients with RAS mutated status, especially when combined with oxaliplatin (Van Cutsem 2014).

Approximately half of patients are therefore excluded at the outset from anti-EGFR therapy by virtue of having a relevant mutation, with exon 2 KRAS mutations (mutations on codon 12 and 13 of exon 2) occurring in approximately 40% of CRC cases and other less frequent KRAS and NRAS mutations in an additional 10%–15% (Douillard 2013, Tejpar 2014).

Although the KRAS wild-type is predictive for response to anti-EGFR antibody therapies, most patients with KRAS codon 12 and 13 wild-type tumors still do not respond to anti-EGFR therapy (Allegra 2009, Karapetis 2008). Mutations in other downstream effectors of the EGFR signaling pathway, particularly BRAF, NRAS, PTEN and PI3 kinase, are therefore probably also exerting an additional negative effect on response (Di Nicolantonio 2008, Samuels 2005, Frattini 2007, Perrone 2009).

These findings have led to the recently evolved concept of quadruple negative (BRAF, KRAS, PTEN and PI3 kinase) disease as an optimal marker of responsiveness to anti-EGFR agents, with a probability of response of 50% in the absence of any alteration, 4% with 1 alteration and 0% with ≥2 alterations (Sartore-Bianchi 2009, Laurent-Puig 2009).

In patients with KRAS wild-type tumors, the addition of the anti-EGFR antibody cetuximab to either FOLFIRI or FOLFOX produces an improvement in median PFS (FOLFIRI: 9.9 versus 8.4 months for cetuximab versus, p=0.048 and FOLFOX: 7.7 versus 7.2 months for cetuximab versus placebo (p = 0.16) (Van Cutsem 2009, Bokemeyer 2009). Similarly, the addition of an alternate anti-EGFR antibody panitumumab to FOLFOX was significantly superior to FOLFOX alone in terms of PFS (9.6 versus 8.0 months for panitumumab versus placebo (p = 0.02) (Douillard 2010).

However, whilst a trend is seen for an improvement in OS in all cetuximab or panitumumab cohorts, only the combination of cetuximab and FOLFIRI has achieved statistical significance when compared to FOLFIRI alone (23.5 versus 20 months, respectively, p = 0.0093) (Van Cutsem 2011), although interpretation of these findings is complicated by methodological uncertainty over the number of patients crossing over from the control to the cetuximab cohort following initial disease progression (Grothey 2012).

Two additional first-line Phase 3 trials, in patients with KRAS wild-type disease, of oxaliplatin based chemotherapy, with or without the addition of cetuximab, failed to find an improvement in either PFS or OS following the addition of cetuximab (Maughan 2011, Tveit 2011), suggesting that any survival benefit for anti-EGFR based therapy in patients with wild-type disease may be

derived from combination with irinotecan-based regimens. This is a similar finding to the combination use of bevacizumab, where a significant increase in survival was only seen in the context of an irinotecan chemotherapeutic backbone.

The addition of both an anti-angiogenic agent and an anti-EGFR agent to chemotherapy (either irinotecan- or oxaliplatin-based) appears to have a negative impact on survival (Hecht 2008, Tol 2009), although the molecular basis for this negative interaction is unclear.

Interpreting outcomes, and in particular OS, with varying permutations of first-line regimens is complicated by the fact that three-quarters of patients receive second-line therapy, predominantly with the alternative chemotherapy regimen to the one they received in the first-line setting. As discussed below, therapy of advanced disease is dictated by a strategy that the greatest long term benefit is derived from utilizing the largest possible number of regimens and lines of therapy. Whilst therefore, the selection of an initial first-line regimen will be based on a variety of patient and physician-preference factors, including potential toxicities (eg, risk of perforation and arterial thromboembolic events for bevacizumab, infusion-related reactions and skin alterations for cetuximab, neuropathy for oxaliplatin and diarrhea for irinotecan) (Formica 2015) results have to be viewed in the context of subsequent second-line (and increasingly third-line and beyond) regimens the patient will receive, which tend to result in broadly comparable OS for most patients.

1.1.4.5. Second-line Systemic Therapy

Overall survival in colorectal cancer has been strongly correlated to the total number of active agents a patient receives over the history of their disease (Grothey 2004). This finding has evolved into the concept of a continuum of care, whereby patients should be treated with all available active agents in the second-, third-line and even beyond (Coinu 2014, Goldberg 2007).

Following progression on first-line therapy, approximately 70% of patients receive second-line treatment and in more than half of cases this is within 12 months of a first-line regimen (Scheithauer 1993, Hine 1984). Second-line treatment strategies are largely determined by the therapy that patient received previously whereby patients generally receive the alternate oxaliplatin- or irinotecan-based regimen from the one used in the first-line context (Chibaudel 2012). Thus irinotecan-based chemotherapy is the treatment of choice after oxaliplatin-based therapy failure and vice-versa.

Whilst single or sequential monotherapy strategies are available in selected cases of poorer performance patients (Koopman 2007, Seymour 2007), the vast majority of second-line patients are treated with combination chemotherapy and targeted agents from the outset.

Summary of Second-line Regimens

Numerous therapeutic options are available in the second-line setting, although there are a number of varying permutations of chemotherapy, anti-angiogenic and anti-EGFR agents, the utility of which depend upon the particular regimen used in the first-line context.

Median survival after initiation of second-line chemotherapy alone is approximately 10 months, although modest incremental improvements of about 8 weeks are possible with selected use of biological and/or targeted agents. The chemotherapy sequences of oxaliplatin-based first-line

regimens followed by irinotecan-based second-line treatment and the converse of irinotecan-based followed by oxaliplatin-based strategies result in broadly comparable OS (20.6 months and 21.5 months respectively) (Tournigand 2004).

Bevacizumab can significantly prolong survival when combined with FOLFOX and probably FOLFIRI too and is an option to consider in the second-line, even beyond the first progression following a previous bevacizumab-containing therapy. Additionally, aflibercept or ramucirumab are newer alternative anti-angiogenic options for use in combination with FOLFIRI. However, in either case, OS is only extended by about 6-8 weeks.

In KRAS wild-type patients, there appears to be no additional value, in terms of OS, from combining either cetuximab or panitumumab with irinotecan-based regimens in patients who have received first-line oxaliplatin therapy. However, in patients previously treated with first-line irinotecan, the combination of cetuximab and irinotecan may actually be superior to oxaliplatin based therapy, with a trend towards longer survival, although this has not yet been shown to be statistically significant.

There appears to be no apparent superiority between mechanistically differing targeted agents in the second-line setting, with no difference in PFS or OS seen in a recent randomized Phase 2 trial evaluating panitumumab + FOLFIRI versus bevacizumab + FOLFIRI in patients with wild-type KRAS disease previously treated with a bevacizumab + oxaliplatin-based regimen in the first-line (Hecht 2013b).

Overall therefore, a variety of agents can be used in varying permutations in the second-line setting, resulting in widely variable outcomes, although few have shown a significant increase in the median OS of about 12 months which can be achieved with second-line chemotherapy alone.

1.1.4.6. Third-line Systemic Therapy

After exposure to sequential oxaliplatin- and irinotecan-based treatment, about 20-40% of patients are still able and willing to receive third-line therapy (Bennouna 2013, Hong 2012), although many of the available treatment options will have been exhausted at earlier stages. The clinical value of post second-line therapy also remains to be firmly established, due to a dearth of randomized trials in this advanced setting. Whilst proceeding from first-line to second-line treatment with a chemotherapy regimen plus a biological agent prolongs survival, there is little robust evidence that treating beyond the second-line confers an advantage for an overall metastatic patient population. However, one recent retrospective analysis concluded that newly diagnosed patients had an untreated adjusted median survival time of 6.8 months but each line of chemotherapy/biologic led to longer survival: 11.9 months, 23.2 months, and 26.4 months for first-line treatment only, second-line treatment, and subsequent treatments, respectively with colon cancer–specific mortality hazard ratios of 0.637, 0.398 and 0.364 ($p < .001$) (Hanna 2014) Benefits of treatment therefore persist but are substantially reduced by the time the third-line setting is reached.

There are 4 broad strategies for third-line treatment which are currently supported by clinical trial data (Grothey 2006).

i) Cetuximab or Panitumumab Monotherapy

Studies suggest that cetuximab and panitumumab have activity as third-line monotherapy, when compared to best supportive care, with greatest efficacy in the wild-type KRAS population. In a study of patients with up to 5 lines of prior therapy, a median OS of 6.1 months was recorded with cetuximab, compared to 4.6 months for best supportive care ($p = 0.005$). The estimated proportions of patients who were alive without documented objective progression of disease at 3 and 6 months were 41% and 15%, respectively, in the cetuximab group and 24% and 3%, respectively, in the supportive-care group ($p < 0.001$). Partial responses occurred in 8.0% of patients in the cetuximab group compared to 0% with supportive care ($p < 0.001$) (Jonker 2007). Another study of cetuximab monotherapy in patients refractory to irinotecan, oxaliplatin, and a FP reported response rates of 12.4 %, a median PFS of 1.4 months and a median OS of 6.6 months (Lenz 2006).

Similar findings were seen in a study of panitumumab versus best supportive care in the third-line treatment of advanced disease. Panitumumab significantly prolonged median PFS (8 versus 7.3 weeks, HR, 0.54, $p < 0.0001$) and improved response rates (10% versus 0%, $p < 0.0001$). However, no difference was observed in OS (HR, 1.00), which may have been explained by a large proportion of patients in the BSC cohort crossing over upon progression (Van Cutsem 2007). A large randomized comparison of panitumumab versus cetuximab in third-line KRAS wild-type patients who had progressed after irinotecan- and oxaliplatin-based regimens found comparable results for ORR (22% versus 19%) median PFS (4.1 versus 4.4 months) and median OS (10.4 versus 10 months), respectively (Price 2014).

ii) Irinotecan-based Regimens

Third-line patients refractory to both irinotecan- and also oxaliplatin-based chemotherapy, showed a synergy when treated with the combination of irinotecan and cetuximab, with response rates of 23%, compared to 11% for cetuximab alone. Furthermore, the HR for disease progression in the combination therapy group compared with the monotherapy group was 0.54 (median PFS 4.1 versus 1.5 months, $p < 0.001$). Median OS was 8.6 months for the combination and 6.9 months for cetuximab monotherapy (HR 0.91, $p=0.48$) (Cunningham 2004). These findings were both consistent with similar earlier studies (Saltz 2001, Saltz 2004) and also confirmed in a subsequent much larger trial involving the addition of cetuximab to 4 different irinotecan regimens, which resulted in overall PFS rates of 61% at 12 weeks, and 34% at 24 weeks. Median OS was reported to be 9.2 months (Wilke 2006).

An additional Phase 2 study of irinotecan refractory patients who had received a median of three prior regimens (range 1-8) randomized treatment to a combination of cetuximab, bevacizumab and irinotecan (CBI), or cetuximab and bevacizumab alone (CB). For the CBI cohort, time to tumor progression (TTP) was 7.3 months and the response rate was 37%; for the CB cohort, TTP was 4.9 months and the response rate was 20%. The OS for the CBI cohort was 14.5 months and the OS for the CB-alone cohort was 11.4 months. The toxicity of the CBI regimen appeared manageable (Saltz 2007). Although this was a more heavily pretreated population than earlier studies of cetuximab and irinotecan, the pattern of efficacy was broadly comparable and suggested that greater efficacy could be obtained with a three drug regimen. However, due to poor study

recruitment, no formal statistical comparisons were performed between the two groups, thus reducing the strength of any conclusions which can be drawn.

iii) Regorafenib Monotherapy

Recently regorafenib (an oral multikinase inhibitor of a broad range of angiogenic, oncogenic, and stromal kinases) (Wilhelm 2011) has been approved for use in patients previously treated with FP-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy and, if KRAS wild-type, an anti-EGFR therapy. Whilst the ORR was very low (1.6% for regorafenib and 0.4% for placebo) statistically significant improvements were seen in median PFS (2.0 months versus 1.7 months, $p<0.0001$) and median OS (6.4 months versus 5.0 months, $p=0.005$) in favor of regorafenib (Grothey 2013). These findings suggest that the main effect of regorafenib on metastatic disease seems to be stabilization, rather than tumor shrinkage, supported by the fining that whilst few patients achieved an objective tumor response with regorafenib, 41% recorded stable disease (SD) as their best response (compared to 15% in the placebo group).

Although the recorded difference in median OS was modest at 1.4 months and the overall median OS of 6.4 months is at the lowest end of reported survival figures for this patient population, the HR of 0.77 translates into a 23% reduction in risk of death in this population of patients with very poor prognosis and a high unmet clinical need. Furthermore, the study represents the first randomized Phase 3 trial in which a small-molecule kinase inhibitor has shown significant OS benefit in patients with treatment refractory metastatic colorectal cancer.

iv) Bevacizumab Combination Therapy

In contrast to the first- and second-line settings, to date, bevacizumab combined with chemotherapy has shown limited activity in the third-line context, although reported outcomes are not dissimilar to those recorded for anti-EGFR agents. One study of bevacizumab combined with 5-FU/LV in patients who had progressed after both irinotecan-based and oxaliplatin-based chemotherapy regimens reported an ORR of 4% with a median PFS of 3.5 months and median OS of 9.0 months (Chen 2006). Another study evaluated bevacizumab plus FOLFIRI or FOLFOX in metastatic colorectal cancer cases after failure of both FOLFIRI and FOLFOX. Results were modest, with a reported ORR of 9.5%, median PFS of 5.3 months and median OS of just 9.5 months (Kang 2009a). Further studies of bevacizumab in the advanced chemoresistant setting have also reported a median OS in the range 9-13 months (Lievre 2009, Vincenzi 2009, Geva 2013).

Summary of Third-line Therapy

Whilst first- and second-line treatment strategies are relatively well defined, therapeutic choices in the third-line context are both more limited and significantly less effective. Randomized studies permitting assessment of differing treatment approaches are also much less common than in earlier disease stages. Response rates in this advanced population are universally low, (1.6% to 25%) with a limited PFS (1.4-5.3 months) and OS (6.6 to 13 months). Treatment choices consist primarily of targeted agent monotherapy. The combination of cetuximab with irinotecan chemotherapy appeared superior to irinotecan alone, although outcomes were variable and overlapped those recorded in other studies for cetuximab by itself. A triple agent approach of irinotecan, cetuximab

and bevacizumab has provided the longest OS seen in this advanced disease setting, suggesting that greater future efficacy may be obtained through more optimal and extensive combination strategies with chemotherapeutic and biological agents.

The relative lack of efficacy of bevacizumab means that the most active third-line therapies are based on anti-EGFR agents, which are only effective in wild-type KRAS tumors and even then in only a minority of case. Consequently, there is no standard third-line therapy for patients with mutated KRAS tumors and for patients with wild-type KRAS tumors who receive anti-EGFR treatment as first- or second-line therapy (Chibaudel 2012).

Overall therefore, there is significant room for additional novel therapeutic approaches to improve outcomes in the third-line and beyond setting.

1.2. Ibrutinib Overview

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) for the treatment of B-cell malignancies.

Ibrutinib has been approved in many regions, including the US and EU, for indications covering the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) who have received at least 1 prior therapy, first-line treatment of patients with CLL with a deletion of the short arm of chromosome 17 (del17p) or a *TP53* mutation, and patients with Waldenström's macroglobulinemia. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure (IB).

1.2.1. Summary of Nonclinical Data

Ibrutinib is a first-in-class, potent, orally administered covalent inhibitor of Bruton's tyrosine kinase (BTK) currently under investigation in various B-cell malignancies.

For the most comprehensive nonclinical and clinical information regarding ibrutinib, please refer to the current version of the IB.

1.2.1.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the Btk (Pan 2007). In vitro, ibrutinib is a potent inhibitor of Btk activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of Btk results in sustained inhibition of Btk catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added

directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current IB.

1.2.1.2. Safety Pharmacology and Toxicology

No treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs. Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and in the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog). In studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (area under the concentration-time curve [AUC]) in patients administered the dose of 560 mg daily, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals. Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

For the most comprehensive information regarding nonclinical safety pharmacology and toxicology, please refer to the current version of the IB.

1.2.2. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, please refer to the current version of the IB.

1.2.2.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-

fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

For the most comprehensive information regarding pharmacokinetics (PK) and product metabolism, please refer to the current version of the IB.

1.2.3. Summary of Clinical Safety

For the most comprehensive clinical information regarding ibrutinib, please refer to the current version of the IB.

1.2.3.1. Monotherapy Studies

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

1.2.3.2. Combination Therapy Studies

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in B-cell malignancies, which included 1 randomized-control study, are summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Hypertension	

1.2.4. Risks

1.2.4.1. Bleeding-related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 6.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures.

1.2.4.2. Cardiac Arrhythmias

Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia including some fatal events have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.2.4.3. Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

1.2.4.4. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other

infectious agents. Should symptoms be severe or prolonged, ibrutinib treatment should be modified as directed in the protocol dose modification guidelines.

1.2.4.5. Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Although causality has not been established, cases of progressive multifocal leukoencephalopathy and hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated.

1.2.4.6. Second Primary Malignancies

Second primary malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Second primary malignancies including non-skin carcinomas have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer.

1.2.4.7. Rash

Rash has been commonly reported in subjects treated with either single-agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.2.4.8. Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities.

1.2.4.9. Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines as needed (see Section 5.3.1.4).

1.2.4.10. Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.2.5. Summary of Clinical Data

A summary of safety and efficacy from the interim analysis for PCYC-1128-CA cohorts that had completed an interim or stage 1 analysis is presented below:

RCC

Amoung the 39 treated subjects in the ibrutinib 840 mg + everolimus cohort the most common adverse events, ie, those that occurred in ≥ 25% of subjects were diarrhea (56%), epistaxis (54%), anemia and mucosal inflammation (44%), nausea, fatigue, decreased appetite (41%), stomatitis (38%), and thrombocytopenia, asthenia and pyrexia (26%). Adverse events Grade ≥ 3 (in >5% of subjects) were anemia (26%), hyperglycemia (15%), diarrhea (13%), stomatitis (10%), hypertension and mucosal inflammation (8%), dyspnea, hypophosphataemia, nausea, pleural effusion, pneumonia, proteinuria and rash maculo-papular (5.1%). Median treatment duration in months was 2.8 and 2.8 for ibrutinib and everolimus, respectively. The proportion of subjects with an AE leading to discontinuation were as follows: both ibrutinib and everolimus (23%), ibrutinib only (8%), everolimus only (10%).

For the first 25 efficacy evaluable subjects, median time on study was 10.5 months. Median PFS was 5.55 months (90% confidence interval [CI] 2.96, 8.05). PFS rate at 4 months based on Kaplan-Meier point estimate was 58.1% (90% CI 39.9%, 72.6%). Median OS was NE (90% CI 11.99, NE). Overall response rate was 0% (0/25).

UC (Cohort 2)

Among the 44 treated subjects, the most common adverse events, ie, those that occurred in ≥ 25% of subjects were diarrhea (68%), asthenia (52%), decreased appetite (41%), alopecia (34%), anemia and fatigue (32%), vomiting (30%), constipation and pyrexia (27%), and nausea (25%). Adverse events Grade ≥ 3 (in >5% of subjects) were asthenia (18%), anemia (16%), peripheral sensory neuropathy (11%), urinary tract infection (9%) and diarroea (7%). Median treatment duration in months was 2.0 and 1.3 for ibrutinib and paclitaxel, respectively. The proportion of subjects with an AE leading to discontinuation of both ibrutinib and paclitaxel was 11.4%; ibrutinib only, 2%; and paclitaxel only, 20%.

For the first 29 efficacy evaluable subjects who were dosed at the RP2D level, median time on study was 7 months and follow up is ongoing. Median PFS was 3.6 months (90% CI 1.58,5.36). PFS rate at 4 months based on Kaplan-Meier point estimate was 50% (90% CI 33.8%, 64.2%). Median OS was 14.7 months (90% CI 7.69, 15.93). Overall response rate was 41% (12/29) with 90% CI 25.9%, 58.3%.

CRC

Among the 54 treated subjects the most common adverse events, ie, those that occurred in ≥ 25% of subjects were dermatitis acneiform (67%), fatigue (37%), stomatitis (35%), diarrhea (33%) paronychia and dry skin (26%). Adverse events Grade ≥ 3 (>5% of subjects) were dermatitis acneiform (17%), abdominal pain and stomatitis (6%). Median treatment duration in months was 2.1 for ibrutinib and cetuximab. The proportion of subjects with an AE leading to discontinuation of both ibrutinib and cetuximab was 11%; ibrutinib only, 0%; and cetuximab only. 0%.

For the first 22 efficacy evaluable subjects who were dosed at the RP2D level, median time on study was 3.3 months and follow up is ongoing. Median PFS was 4.67 months (90% CI3.48, 5.55). PFS rate at 3 months based on Kaplan-Meier point estimate was 76.0% (90% CI 52.8%, 88.9%). Median OS was 8.94 months (90% CI 4.67, NE). Overall response rate was 13.6% (3/22) with 90% CI 3.8%, 31.6%.

1.3. Study Rationale

1.3.1. Rationale in Specific Solid Tumors

Ibrutinib exerts multiple interactive mechanisms of action which individually and collectively suggest that it may have activity in solid tumors such as RCC, UC, GC and CRC.

There are 4 predominant mechanisms of action of ibrutinib that may be operative in these solid tumor types: i) changes in the tumor microenvironment, eg, inhibition of mast cell function, ii) changes in immune profiles, eg, alteration of Th1/Th2 polarity, iii) direct inhibition of EGFR kinase activity, and iv) inhibition of ETK.

Changes in the Tumor Microenvironment

Several emerging lines of evidence suggest that BTK inhibition in solid tumors may be relevant due to modulation of the tumor microenvironment. These mechanisms may be applicable for a wide range of solid tumor types. Ibrutinib has been shown to inhibit in vivo tumor growth in a *myc*-driven genetically engineered pancreatic islet cell carcinoma model, and more recently in a KRAS driven pancreatic ductal adenocarcinoma model. This was attributed in both models to inhibition of mast-cell degranulation with a resulting anti-angiogenic effect (Soucek 2011, Masso-Valles 2013). New data have just been published showing that treating *p53ER/ER;LSLKRasG12D;pdx1-Cre* mice with both ibrutinib and standard of care gemcitabine, ameliorated the toxicity and significantly extended survival when compared to gemcitabine alone. Additonally, in subcutaneous xenografts (PDX) of a patient derived tumor in the NOD/SCID mouse model a significant survival advantage was seen in single agent ibrutinib treated mice compared to control mice (Masso-Valles 2015).

Extensive correlative evidence points to a role of infiltrating mast cells in progression of numerous tumor types (Dalton 2012), as does direct functional evidence from genetically engineered models (Soucek 2007, Chang 2011, Ma 2013). BTK is known to be essential for IgE-stimulated basophile degranulation (Iwaki 2005), a function which has been shown to be inhibited by ibrutinib (MacGlashan 2011), and which was also inhibited in mast-cell models (Soucek 2011, Masso-

Valles 2013). Ibrutinib treatment in these reports was also associated with decreases of $Gr1^+$ infiltrating myelomonocytic cells which may contribute pro-angiogenic and pro-proliferative signaling. All described mechanisms may contribute to an anti-tumor effect.

Mast cells have previously been proposed as targets for cancer therapy (Soucek 2007). Soucek et al. have shown that the oncogene *myc* can instruct a complex inflammatory program involving recruitment of mast cells, which are necessary in the tumor microenvironment for the physical expansion and maintenance of tumors. In a mouse pancreatic ductal adenocarcinoma model comprised of transgenic animals with pancreas-specific expression of $KRAS^{G12D}$ (Hingorani 2003), which is one of the most common mutations in pancreatic cancer, it was shown that inflammatory cells including mast cells are present in the tumor microenvironment. Building on the work from Soucek and Hingorani, new data has been published showing that treating *p53ER/ER;LSLKRasG12D;pdx1-Cre* mice with both ibrutinib and standard of care gemcitabine, ameliorated the toxicity and significantly extended survival when compared to gemcitabine alone. Additonally, in subcutaneous xenografts (PDX) of a patient derived tumor in the NOD/SCID mouse model a significant survival advantage was seen in single agent ibrutinib treated mice compared to control mice (Masso-Valles 2015). BTK is required for mast cell degranulation and when given in approved doses, ibrutinib achieves nearly complete BTK occupancy for 24 hours. In the model, mast cells are still recruited to the tumor microenvironment, but are no longer degranulating (Soucek 2012). Further, ibrutinib was shown to reduce tumor proliferation and tumor vasculature (Soucek 2012). Ibrutinib also reduced inflammatory cell infiltration and reduced collagen deposition. Mice that were treated with ibrutinib had a survival benefit (Soucek 2012).

Changes in Immune Profiles – Alteration of Th1/Th2 Polarity

Ibrutinib is also an irreversible inhibitor of interleukin-2-inducible kinase (ITK) (Iwaki 2005, Dubovsky 2013). ITK is a member of the TEC family of kinases and retains close homology with the BTK active site including conservation of the cysteine residue which ibrutinib binds to covalently. Patients with CLL treated with ibrutinib have been shown to have shifts of T-helper (Th) polarization to a more favorable Th1 bias (Dubovsky 2013). In addition, studies of T-cell function in vitro and in murine neoplastic (CLL), parasitic infection (Leishmania major), and infectious disease (Listeria monocytogenes) models in vivo, analyses have confirmed ibrutinib as a clinically relevant and physiologically potent ITK inhibitor (Dubovsky 2013). ITK inhibition reduces Th2-dominant immune responses and potentiates Th1-based responses (Dubovsky 2013). This shift in the Th1/Th2 ratio may directly potentiate anti-tumor activity through an increased tumor influx of cytotoxic $CD8^+$ T cells, as well as augmenting the effects of concomitantly administered cytotoxic chemotherapy.

Recently, Levy et al studied ibrutinib in combination with an anti-PDL1 checkpoint inhibitor in CT26 colon cancer cells in a mouse model. (Sagiv-Barfi 2015) Compared to controls, tumor volume in mice treated with ibrutinib or the anti-PDL1 inhibitor demonstrated no inhibition to modest inhibition ($p=0.038$). However, in combination the tumor volume was markedly decreased ($p=0.002$) which also resulted in a cure to about 30% of the mice. The effects seen in these mice were T cell mediated and the mice that were cured developed long term memory as they rejected CT26 tumors upon rechallenge.

Animal models of lymphoma have demonstrated activity when BTK and PD-L1 inhibitors are combined. BALB/c mice implanted with the syngeneic A20 B-cell lymphoma have been widely used to study immunotherapy for DLBCL and FL (Donnou 2012). A20 cells express BTK but are insensitive to ibrutinib in vitro and in vivo. In this model, a PD-L1 blocking antibody had modest effect on tumor growth whereas the tumor cells remained insensitive to ibrutinib. On combining the two antagonists, however, a complete tumor regression in 50% of treated animals was observed. Mechanistic studies implicated T cells as responsible for the tumor eradication. Mice treated with the combination therapy, but not with either single agent, mounted a robust and tumor-specific T-cell response. The superior efficacy of the ibrutinib/anti-PD-L1 combination was reproduced in a second model using the J558 plasmacytoma cells, which are also insensitive to ibrutinib. The results strongly suggest that ibrutinib has an immune-modulating property that enhances the anti-tumor effect of PD-L1 blockade (manuscript submitted).

The effects of the combination of an anti–PD-L1 antibody and ibrutinib in suppressing tumor growth were additionally documented in mouse models of a variety of solid tumors, such as triple negative breast cancer. The enhanced therapeutic activity of PD-L1 blockade by ibrutinib was accompanied by enhanced antitumor T-cell immune responses. These preclinical results suggest that the combination of PD1/PD1-L blockade and ibrutinib should be tested in the clinic (Sagiv Barfi 2015).

Direct Inhibition of EGFR Kinase Activity

Ibrutinib has been shown to inhibit EGFR (Honigberg 2010) and to inhibit growth of non small cell lung cancer (NSCLC) cells carrying EGFR gene mutations both in vitro and in vivo (Gao 2014), suggesting ibrutinib can function as an EGFR inhibitor.

As discussed above, human EGFR is over-expressed in many tumors, in particular colorectal cancer. The combination of cetuximab and erlotinib has been examined in a Phase 2 study of EGFR-therapy naïve patients who had failed prior oxaliplatin and irinotecan regimens (Weikhardt 2012). The ORR was 31% (95% CI, 26% to 57%), with a median PFS of 4.6 months (95% CI, 2.8 to 5.6 months). Eleven out of a total of 50 patients were KRAS mutant and as expected no activity was seen in this group. When excluded from the analysis, the ORR was 41% (95% CI, 26% to 57%) with a median PFS of 5.6 months (95% CI, 2.9 to 5.6 months) in KRAS wild-type patients. Overall, 48% of patients experienced Grade 3 and 4 skin rashes. Although this was an uncontrolled trial, the findings are certainly suggestive of augmented clinical activity with the combination of the two agents possessing overlapping but complimentary targeting of the EGFR receptor (Laurent-Puig 2012). Although toxicity was significant, the combination appears to produce a manageable side effect profile, which is further supported by findings of acceptable toxicity from a Phase 1 study combining cetuximab, erlotinib and bevacizumab in patients with metastatic colorectal cancer (Falchook 2014). These findings of an apparent additive clinical effect from dual EGFR blockade through use of a monoclonal antibody and a kinase inhibitor combined suggest that the combination of cetuximab and ibrutinib may also possess clinically useful activity in this disease setting.

Given the multiple active pharmacological profile of ibrutinib, which includes EGFR inhibition as well as a number of other potential anti-tumor properties, there is a strong scientific rationale, supported by broad clinical precedent, for examining the mechanistically complimentary combination of ibrutinib and cetuximab in patients with metastatic colorectal carcinoma. The immunomodulatory and anti-tumor mast cell modulating effects of ibrutinib also suggest that it may have useful clinical activity when combined with everolimus, docetaxel and paclitaxel in RCC, bladder and esophago-gastric/gastric advanced disease settings.

Direct Inhibition of ETK

ETK (also termed BMX) is another member of the Tyrosine Kinase Expressed in Hepatocellular Carcinoma (TEC) family of nonreceptor tyrosine kinases (including ITK and BTK) where ibrutinib has activity. ETK is expressed on epithelial cells including renal and bladder epithelium.

RCC cells treated with everolimus alone potently inhibited p-S6, a downstream target of mTOR, and significantly inhibited proliferation. Everolimus induced up-regulation of pAkt and/or pErk, two key pro-survival molecules for various tumors. Such compensatory changes of signaling pathways have been suggested to attenuate anti-tumor actions of everolimus (Yang 2011, Holland 2012). The addition of ibrutinib counteracted the up-regulation of pAkt and pErk induced by everolimus and enhanced its anti-proliferative activities. In vivo, ibrutinib alone showed no or modest anti-tumor activity in syngeneic Renca tumor model or 786-0 xenografts; whereas when combined with mTOR inhibitor, such as everolimus, ibrutinib significantly enhanced activities of mTOR inhibitor (Data on file).

ETK expression in RCC cell lines was studied by Zhuang (Zhuang 2014). ETK was highly expressed in the RCC cell lines compared to normal renal tissue. To examine the function of ETK in the RCC cell lines, ETK was knocked down by transfecting 2 cell lines with ETK siRNA. This resulted in decreased proliferation, migration, and invasion. Additionally, flow cytometry demonstrated that ETK siRNA promoted apoptosis.

ETK was studied in bladder cancer cell lines by Guo et al. (Guo 2011). Higher levels of ETK expression were found in high grade or more invasive tumors. To evaluate the role of ETK in these cell lines knockdown ETK expression by shRNA was performed. This resulted in increased apoptosis, and inhibition of migration and invasion.

1.3.2. Dosing Rationale

560 mg Starting Dose

In contrast to studies of B-cell diseases, there are multiple possible enzymatic targets whose inhibition could contribute to efficacy in solid tumors.

The key target for mast cells and tumor infiltrating myelo-monocytic cells is BTK, whose inhibition can likely be achieved at well tolerated doses.

- ITK occupancy (up to 70%) has been achieved in studies of ibrutinib in patients with CLL and cGVHD using 420 mg ibrutinib daily. From this, it can be inferred that a somewhat

higher dose would be optimal for clinical indications where this target is mechanistically implicated.

- The IC_{50} values of ibrutinib for EGFR and HER2 are significantly higher than that for BTK in kinome assays, however the concentrations required for cellular enzymatic inhibition, and inhibition of growth of sensitive cell lines in vitro is similar to or only slightly higher than for BTK.
- Growth inhibition of a breast cancer xenograft in vivo has furthermore been noted with doses that are effective but not fully optimal for BTK occupancy or for in vivo inhibition of lymphoma xenografts. Therefore, doses within the range which have been studied for lymphoma (up to 12.5 mg/kg/day or 840 mg/day) and shown to have a safety profile similar to that of approved or "standard" doses (420 or 560 mg/day) may be effective in clinical treatment of sensitive tumors that are driven by ErbB family members.
- Additionally, three clinical studies, PCYC-1135-CA, PCYC-1136-CA, and LYM 1002, established 560 mg as the RP2D for ibrutinib in combination with PDL-1/PD1 checkpoint inhibitors in the setting of advanced B-cell malignancies and/or solid tumors. Given the experience of these trials and urothelial cohort 2, 560 mg of ibrutinib is considered an appropriate starting dose for the Phase 1b portion in UC when administered in combination with pembrolizumab with an allowance for a dose de-escaltion to 420 mg based on DLRC review.

Additionally, there was no MTD from the Phase 1 studies with ibrutinib. Due to the expected heterogeneity in the sensitivity profile of clinical cancers and patient pharmacokinetics, a starting dose of 560 mg/day has been selected for this study with allowance for either dose escalation or de-escalation design in Phase 1.

840 mg Starting Dose

The recommended Phase 2 dose (RP2D) of ibrutinib for UC cohort 2 was 840 mg in combination with paclitaxel at 80 mg/m^2 IV weekly. For UC cohort 5, single agent ibrutinib at 840 mg/day provides higher exposures that allows for the inhibition of of ITK and ETK (BMX). Thus 840 mg daily will be the dose to be confirmed in cohort 5.

2. STUDY OBJECTIVE

2.1. Primary Objectives

Phase 1b

- To determine the recommended Phase 2 dose (RP2D) of ibrutinib in combination with everolimus in RCC, paclitaxel in UC cohort 2, docetaxel in GC, and cetuximab in CRC
- To confirm the RP2D of single-agent ibrutinib in UC cohort 5

Phase 2

- To assess progression-free survival (PFS) of ibrutinib combination therapy in RCC and UC cohort 2
- To assess the ORR of ibrutinib combination therapy in GC and CRC, and ibrutinib as a single agent in UC cohort 5

2.2. Secondary Objectives

Phase 1b

- To assess the ORR of ibrutinib combination therapy in each cohort
- To assess the safety and tolerability of ibrutinib combination therapy in each cohort
- To assess the disease control rate (DCR) in each cohort
- To evaluate the pharmacokinetics (PK) of ibrutinib combination therapy in cohorts 1-4

Phase 2

- To assess the PFS of ibrutinib combination therapy in GC and CRC, and ibrutinib as a single agent in UC cohort 5
- To assess the ORR of ibrutinib combination therapy in RCC and UC cohort 2
- To assess the DOR in each cohort
- To assess the DCR in each cohort
- To assess the median OS of ibrutinib combination or single-agent therapy in each cohort
- To assess the safety and tolerability of ibrutinib combination or single-agent therapy in each cohort

2.3. Exploratory Objective(s)

- [redacted]

3. STUDY DESIGN

3.1. Overview of Study Design

This is an open-label, Phase 1b/2 multi-center study to assess the safety and efficacy of ibrutinib monotherapy in subjects with previously-treated UC and ibrutinib combination therapy in subjects with previously treated RCC, UC, GC, and CRC as listed below. Each cohort in this study will assess a different malignancy and anticancer agent in combination or ibrutinib as a single agent and follow an independent and parallel design:

- Metastatic RCC
- Advanced (locally recurrent and/or metastatic) urothelial transitional carcinoma.
- Advanced (locally recurrent and/or metastatic) gastric adenocarcinoma
- Metastatic CRC

This Phase 1b/2 study is divided into 2 parts. An initial Phase 1b portion will evaluate the safety and tolerability of single agent ibrutinib and ibrutinib in combination with each anticancer agent to assess any dose limiting toxicity in order to determine the RP2D for each cohort.

The Phase 2 portion will assess primary endpoints of PFS (with an incorporated interim analysis) for RCC and UC cohort 2 and ORR using a Simon's minimax 2-stage design for the gastrointestinal (GI) malignancies: GC, CRC, and UC cohort 5. Further details on statistical considerations for design and analysis will be described in the SAP.

Phase 1b

The Phase 1b portion of this study is performed independently in five separate cohorts defined by the clinical indication; RCC, UC, GC, and CRC. For cohorts 1-4 safety and dose limiting toxicity (DLT) assessment will be evaluated in 3-9 subjects at each dose level in a 3+3+3 design. At each dose level, DLT assessment will be performed in the first 3 subjects. If 1 of 3 subjects experience a DLT during the first treatment cycle, the same dose level will be expanded to 6 subjects, and if 2 of the 6 experience a DLT, the same dose level will be expanded to 9 subjects. At the 560 mg/day dose level (DL 1), if 0 out of 3, 1 out of 6 or 2 out of 9 subjects (≤22%) experience a DLT during the first treatment cycle, dose escalation to 840 mg/day will occur. At DL 1 (560 mg/day), if ≥33% of subjects experience a DLT (eg, >2 out of 6 or >2 out of 9 subjects), the dose will be de-escalated to 420 mg/day (dose level minus one; DL -1). At the 840 mg/day dose level (DL 2) cohort, subjects will be enrolled in a similar fashion.

For UC cohort 5, the single-agent dose of 840 mg will be confirmed and documented in the first 6 patients safety data will be described.

For cohorts 1-4 the RP2D will be determined when 6-9 subjects complete the DLT observation period based on the totality of the data including dose reductions (of both ibrutinib and the combination therapy), treatment-limiting toxicities (outside of DLTs), the available pharmacokinetic data and the toxicity profile obtained during Phase 1b. In order to determine the RP2D dose level, a minimum of 6 DLT-evaluable subjects will be required at the RP2D dose level who are defined to have completed at least 21 days of treatment with ibrutinib in combination with the relevant anticancer agent, after the initiation of therapy at the start of Cycle 1. At each dose level, the decision of de-escalation will be made for at least 6 DLT-evaluable subjects. However, if, at any time in a given dose level, 3 subjects experience a DLT, additional enrollment within the dose level will be stopped.

For UC cohort 5 a DLT-evaluable subject will require ≥ 90% compliance with ibrutinib during Cycle 1 (the first 21 days). Subjects who miss more than 2 scheduled doses of ibrutinib within 21 days after the initiation of therapy at the start of Cycle 1 will be replaced (DLT-evaluable subject) unless the missed dose was due to a DLT.

The cohorts will be:

- RCC: ibrutinib + everolimus (cohort 1)
- Urothelial carcinoma:
  - ibrutinib + paclitaxel (cohort 2)
  - ibrutinib single agent (cohort 5)
- GC: ibrutinib + docetaxel (cohort 3)
- CRC: ibrutinib + cetuximab (cohort 4)

A dose level review committee (DLRC) will evaluate the safety data at the completion of the initial Phase 1b portion in each cohort to determine the RP2D, prior to continuing with enrollment into the Phase 2 portion (enrollment may not be held for UC cohort 5 as safety data is available for more than 40 subjects for ibrutinib 840 mg in combination with paclitaxel data. The DLRC will review the safety data in the first 6 evaluable subjects enrolled in cohort 5 to confirm 840 as the

single-agent dose. Members of this committee will include the Medical Monitor or designee, a Drug Safety representative, a Biostatistician, and at least 2 participating investigators/designees.

The DLT observation period will encompass 21 days after the initiation of study treatment.

A DLT is defined as any Grade 3 or higher non-hematologic or Grade 4 hematologic AE occurring during the DLT observation period (ie, 21 days after the initiation of combination therapy at the start of Cycle 1) and considered to be at least possibly related to the study treatment (ibrutinib or combination) with the following clarifications:

- Grade 4 diarrhea and vomiting
- Grade 3 nausea, diarrhea or vomiting despite maximum medical supportive care and persisting >3 days
- Grade 3 fatigue persisting >7 days
- Grade 3 infusion reaction that does NOT resolve with appropriate clinical management
- Grade 3 rash lasting >7 days that does NOT resolve with appropriate clinical management
- Grade 4 neutropenia or leukopenia for >7 days duration (irrespective of adequate growth factor support)
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia

If a subject experiences a DLT during the DLT observation period, the subject will discontinue treatment. Dose reductions will not be permitted during the DLT observation period. However, any other subject(s) tolerating the dose level through the DLT observation period will continue to receive the same dose of study drugs even if a dose escalation or de-escalation occurs for subsequent study subjects.

Any Phase 1b subjects who discontinue one or more study drugs, or require dose reduction within 21 days after the initiation of therapy at the start of Cycle 1 will be replaced, unless the discontinuation is in association with a DLT. Subjects who miss one or more scheduled doses (more than 2 doses for UC cohort 5) of either study drug within 21 days after the initiation of therapy at the start of Cycle 1 will continue. However, such a subject will not be evaluable for DLT assessment, and will be replaced for DLT assessment purposes.

After Cycle 1, all subjects will be treated until unacceptable toxicity or disease progression, whichever occurs first. Tumor assessment by CT/MRI will occur every 6 weeks (2 cycles) and will be evaluated according to RECIST 1.1 guidelines. After the RP2D has been defined for each cohort, enrollment in Phase 2 will commence in that cohort.

Phase 2

For each cohort in the study a separate analysis will be performed to evaluate the efficacy and safety profile. Tumor assessment by CT/MRI will occur every 6 weeks and will be evaluated according to RECIST 1.1 guidelines. Subjects will be treated until unacceptable toxicity or disease progression.

Renal Cell Carcinoma (Cohort 1):

Subjects will receive ibrutinib administered PO at the RP2D (840 mg) in combination with everolimus (6 hours after ibrutinib) at a dose of 10 mg PO daily in 21-day cycles until unacceptable toxicity or disease progression occurs.

Subjects will be enrolled until a total of 55 subjects have been treated, including any subjects from Phase 1b who were treated at the RP2D level and satisfy the Phase 2 inclusion criteria.

Urothelial Carcinoma:

Cohort 2

Subjects will receive ibrutinib administered PO at the RP2D (840 mg) in combination with paclitaxel at a dose of 80 mg/m^2 administered as a 60-minute IV infusion weekly in 21-day cycles until unacceptable toxicity or disease progression occurs.

Subjects will be enrolled so that a total of 55 have been treated, including any subjects from Phase 1b who were treated at the RP2D level and satisfy the Phase 2 inclusion criteria.

Cohort 5

Cohort 5 will receive single-agent ibrutinib administered PO daily at RP2D in 21-day cycles until unacceptable toxicity or disease progression occurs. Thirteen subjects will be enrolled into stage-1of the Simon's 2-stage design, including any subjects from Phase 1b who were treated at the confirmed Phase 2 dose level and satisfy the inclusion criteria of the Phase 2 portion. If at least 1 subject has a tumor response (PR or CR) by RECIST 1.1 criteria, this cohort will proceed to the stage-2 portion and enroll an additional 14 subjects.

The DLRC will review data on the safety of ibrutinib after the first 6 evaluable subjects who have completed at least 21 days of follow-up after the initiation of therapy or discontinued study treatment due to DLT prior to Day 21. Enrollment may continue during DLRC review. The safety of single-agent ibrutinib for the first six patients will be fomally documented. Depending on the outcome of their review, the DLRC may:

a) Confirm the RP2D of 840 mg.

b) The dose level of ibrutinib should be reduced to 560 mg.

Additionally, in cohort 5 a paired biopsy sub-group (n = 5-10 with paired biopsy samples that are evaluable) will be enrolled from consenting subjects. Consent to pre- and on-treatment biopsies is required, if lesions are safe and accessible, according to investigator's assessment. Subjects without consent to biopsy can still be enrolled, after obtaining agreement with the medical monitor. The subjects in the sub-group will receive the same treatment of ibrutinib PO in 21-day cycles but will have a pre-treatment biopsy and an on treatment biopsy after the completion of Cycle 2 but ideally before the completion of Cycle 3. Ibrutinib should be held for 3 days after the pre-treatment biopsy. Study treatment is not required to be held for on-treatment biopsy via cystoscopy; however, on the day of the on-treatment biopsy the ibrutinib dose should be delayed until after the biopsy is performed and it is confirmed that there are no signs of clinical bleeding. Enrollment in this sub-group will be discontinued in the setting of low efficacy at the

determination of the Sponsor. An IRC may be implemented and scans may be collected from the sites to support this cohort if efficacy data require independent confirmation for health authorities.

In Summary:

Cohort 5 will enroll 13 subjects in Stage 1 and then 14 subjects in Stage 2 (depending on ≥1 CR/PR in Stage 1)

- Up to 10 of the total of 27 subjects will be enrolled in a sub-group that requires a paired biopsy
- Sub-group will be closed if Simon stage-1 success criteria is not met

Gastric Adenocarcinoma

Subjects will receive ibrutinib administered PO at the RP2D in combination with docetaxel at a dose of 60 mg/m^2 - 75 mg/m^2 administered as a 60-minute IV infusion every 3 weeks in 21-day cycles until unacceptable toxicity or disease progression occurs.

Twenty-one subjects will be enrolled into stage-1 of the Simon's 2-stage design, including any subjects from Phase 1b who were treated at the RP2D level and satisfy the Phase 2 inclusion criteria. If at least 2 subjects have a tumor response (PR or CR) by RECIST 1.1 criteria this cohort will proceed to stage-2 and enroll an additional 18 subjects.

Colorectal Adenocarcinoma

Subjects will receive ibrutinib administered PO at the RP2D in combination with cetuximab at a dose of 400 mg/m^2 administered initially as a 120-minute IV infusion then weekly 250 mg/m^2 IV over 60 minutes in 21-day cycles until unacceptable toxicity or disease progression occurs.

Twenty-two subjects will be enrolled into stage-1 of the Simon's 2-stage design, including any subjects from Phase 1b who were treated at the RP2D level and satisfy the Phase 2 inclusion criteria. If at least 3 subjects have a tumor response (PR or CR) by RECIST 1.1 criteria this cohort will proceed to stage-2 and enroll an additional 18 subjects.

For the GC and CRC cohorts, if a subject in stage-1 discontinues prior to the first tumor response assessment for reasons other than disease progression, the subject may be replaced.

Subjects who are dosed at the RP2D level and withdraw prior to the completion of at least 2 cycles of combination therapy, for reasons other than unacceptable toxicity or disease progression, may be replaced after consultation with the Sponsor.

Enrollment may continue into stage-2, while waiting for the response evaluation and analysis from the stage-1 to be completed. The number of responders observed among the stage-1 evaluable subjects will be used in combination with other safety and efficacy data when making the determination to proceed to stage-2.

3.2. Safety Plan

This study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. Adverse events and SAEs will be reviewed by the Sponsor on an ongoing basis to identify safety concerns.

A dose level review committee (DLRC) will evaluate the safety data at the completion of the initial Phase 1b portion in each cohort, prior to continuing with enrollment into the Phase 2 portion.

Members of this committee will include the Medical Monitor or designee, a Drug Safety representative, a biostatistician, and 2 participating investigators.

A summary of the early safety data observed in 3 cohorts is detailed in Section 1.2.5.

3.3. Study Population and Treatment

Subjects will have one of the following:

- **RCC:** Minimum of 1 and maximum of 4 prior regimens, one of which must include a VEGF-TKI
- **UC cohort 2:** Minimum of 1 and maximum of 2 prior regimens, one of which must have included a platinum based regimen
- **UC cohort 5:** Minimum of 1 and maximum of 2 prior regimens, one of which must have included a checkpoint inhibitor.
- **GC:** Minimum of 1 and maximum of 3 prior regimens, one of which must have included a fluoropyrimidine (5-FU) based regimen
- **CRC:** Minimum of 2 and maximum of 4 prior regimens for metastatic disease, which must have included both an irinotecan and an oxaliplatin based regimen unless subject is considered intolerant to irinotecan

Phase 1b

Dosing will be as follows in Table 5:

Table 5. Dosing Regimen in Cohorts 1-5

Cohort	DL-1	DL 1	DL 2
Cohort 1 RCC	ibrutinib: 420 mg PO qd everolimus[1]	ibrutinib: 560 mg PO qd everolimus[1]	ibrutinib: 840 mg PO qd everolimus[1]
Cohort 2 UC	ibrutinib: 420 mg PO qd paclitaxel[2]	ibrutinib: 560 mg PO qd paclitaxel[2]	ibrutinib: 840 mg PO qd paclitaxel[2]
Cohort 3 GC	ibrutinib: 420 mg PO qd docetaxel[3]	ibrutinib: 560 mg PO qd docetaxel[3]	ibrutinib: 840 mg PO qd docetaxel[3]
Cohort 4 CRC	ibrutinib: 420 mg PO qd cetuximab[4]	ibrutinib: 560 mg PO qd cetuximab[4]	ibrutinib: 840 mg PO qd cetuximab[4]
Cohort 5 UC	ibrutinib 560 mg PO qd	ibrutinib 840 mg PO qd	NA

PO = orally, qd = daily, qweek = weekly, q3weeks = every 3 weeks

[1] everolimus: 10 mg PO qd

[2] paclitaxel: 80 mg/m^2 IV qweek

[3] docetaxel: 60 - 75 mg/m^2 IV q3weeks

[4] cetuximab: 400 mg/m^2 IV, then 250 mg/m^2 qweek

One cycle of treatment is 21 days in length and consists of daily administration of ibrutinib in combination with the relevant anticancer agent or as a single agent. Treatment will continue as long as the subject is without disease progression and not experiencing unacceptable toxicity. After Cycle 1 (the DLT assessment period) if one component of a combination regimen is discontinued prior to RECIST 1.1 determined disease progression, the other component may be continued until disease progression or unacceptable toxicity.

Phase 2

The recommended Phase 2 Dose (RP2D) established in Phase 1b for ibrutinib (840 mg, 560 mg, or 420 mg) PO daily, or in combination with the relevant anticancer agent, will be given daily in 21-day cycles.

Treatment will continue daily as long as the subject is without disease progression and not experiencing unacceptable toxicity. If one component of a combination regimen is discontinued prior to RECIST 1.1 determined disease progression, the other component may be continued until disease progression or unacceptable toxicity.

3.4. Replacement of Subjects

In the Phase 1b portion of the study, subjects who discontinue one or more study drugs not due to a DLT, or require a dose reduction within 21 days after the initiation of therapy at the start of Cycle 1 will be replaced, unless the discontinuation is in association with a DLT. Subjects who miss one or more scheduled doses (more than 2 doses for cohort 5) of either study drug within 21 days after the initiation of therapy at the start of Cycle 1 will continue. However, such a subject will not be evaluable for DLT assessment, and will be replaced for DLT assessment purposes.

For the purpose of efficacy evaluation, subjects who are dosed at the RP2D level and withdraw prior to the completion of at least 2 cycles of combination therapy, for reasons other than unacceptable toxicity or disease progression, may be replaced after consultation with the Sponsor.

For the GC, CRC, and UC cohorts, if a subject in stage-1 of the Simon's 2-stage design discontinues prior to the first tumor response assessment for reasons other than disease progression, the subject may be replaced.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

To be enrolled in the study, each potential subject must satisfy all of the following inclusion criteria:

Disease Related

1. Histologically confirmed:
    - RCC (clear cell)

- UC (transitional cell)
- Gastric or GEJ adenocarcinoma
- K-Ras or N-Ras wild-type EGFR expressing CRC

2. One or more measurable lesions per RECIST 1.1 criteria
3. The following prior criteria should be followed:
   - Metastatic RCC: minimum of 1 and maximum of 4 prior regimens, one or more of which must have included a VEGF-TKI
   - Advanced (locally recurrant and or metastatic) UC:
   – UC cohort 2: minimum of 1 and maximum of 2 prior regimens, one of which must have included a platinum based regimen
   – UC cohort 5: Minimum of 1 and maximum of 2 prior regimens, one of which must have included a checkpoint inhibitor
   - Advanced (locally recurrent and or metastatic) gastric or GEJ adenocarcinoma: minimum of 1 and maximum of 3 prior regimens one of which must have included a fluoropyrimidine regimen
   - Metastatic CRC: minimum of 2 and maximum of 4 prior regimens, which must have included both an irinotecan and an oxaliplatin based regimen unless unable to tolerate irinotecan chemotherapy
4. Each subject must be accessed by the investigator to be a suitable candidate for treatment with everolimus, paclitaxel, docetaxel, cetuximab, or single-agent ibrutinib as appropriate according to their type of cancer
5. Female subjects of childbearing potential must have a negative serum or urine pregnancy test within 3 days of the first dose of study drug. Female subjects who are of non-reproductive potential (ie, post-menopausal by history- no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy) are exempt from this criterion
6. Male and female subjects of reproductive potential must agree to perform complete abstinence[15] or to use both, a highly effective method of birth control (implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], or sterilized partner) and a barrier method (eg, condoms, cervical rings, cervical condoms, sponge) during the period of therapy and for 90 days after the last dose of ibrutinib, everolimus, docetaxel, and paclitaxel; 6 months after the last dose of cetuximab.(6 months for all study drugs UK only)

Laboratory

7. Adequate hematologic function independent of platelet transfusion and growth factor support for at least 7 days prior to Screening and enrollment , with the exception of pegylated G-CSF

[15] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

(granulocyte-colony stimulating factor pegfilgrastim) and darbopoeitin which require at least 14 days , defined as:

- Absolute neutrophil count ≥1500 cells/mm^3 (1.5 x 10^9/L)
- Platelet count >80,000 cells/mm^3 (80 x 10^9/L) for cohort 1 (RCC)
- Platelet counts >100,000 cells/mm^3 (100 x 10^9/L) for all UC cohorts
- Hemoglobin ≥8.0 g/dL. for cohort 1 (RCC),all UC cohorts, and cohort 3 (GC)
- Hemoglobin ≥9.0 g/dL for cohort 4 (CRC)

8. Adequate hepatic and renal function defined as:
   - Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) ≤5.0 x upper limit of normal (ULN) if liver metastases, or ≤3 x ULN without liver metastases
   - Alkaline phosphatase <3.0 x ULN or ≤5.0 x ULN if liver or bone metastases present
   - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin, such as hemolysis) with the exception of subjects in the GC cohort where docetaxel is administered, these subjects must have bilirubin within normal limits (WNL)
   - Estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault)

Demographic

9. Men and women ≥18 years of age
10. Eastern Cooperative Oncology Group (ECOG) performance status 0-1. For subjects with RCC or CRC, an ECOG score of 2, may be acceptable after discussion with the medical monitor

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

Disease-Related

1. Anticancer therapy (chemotherapy, antibody therapy, molecular targeted therapy, or investigational agent) within 28 days of the first dose of study drug (4 weeks for nitrosureas, mitomycin C, or antibody based therapies).
2. Prior treatment with:
   - Everolimus or temsirolimus (RCC cohort 1)
   - Any taxane (UC cohort of ibrutinib + paclitaxel) (cohort 2)
   - Any taxane (GC cohort 3)
   - Cetuximab or panitumumab (CRC cohort 4)
3. Prior radiotherapy to measurable lesion, unless documented progression has occurred post-irradiation.
4. Lack of recovery from previous therapeutic radiation (persistence of Grade ≥2 radiation-related toxicity), or planned radiation therapy during the study period.

Concurrent Conditions

5. Any uncontrolled active systemic infection including any infection requiring systemic IV treatment which was completed ≤7 days before Cycle 1 Day 1.

6. History of other malignancies, except:
   - Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and considered to be at low risk for recurrence by investigator
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without current evidence of disease
7. Prior treatment with ibrutinib or other BTK inhibitor.
8. ALT and/or AST >1.5 x ULN and alkaline phosphatase >2.5 x ULN (GC cohort only).
9. Known allergy or hypersensitivity to ibrutinib or any other component of combination therapy, including polysorbate 80 or Cremophor® EL (polyoxyethylated castor oil).
10. Unresolved toxicities from prior anti-tumor therapy, defined as having not resolved to CTCAE, version 4.03, Grade 0 or 1.
11. Known bleeding disorders (eg, von Willebrand's disease or hemophilia).
12. Grade ≥3 sensory peripheral neurophathy.
13. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
14. Known brain or leptomeningeal disease (CT or MRI scan of the brain required only in case of clinical suspicion of central nervous system involvement).
15. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
16. Major surgery within 4 weeks of first dose of study drug.
17. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
18. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure, as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment.
19. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
20. Unable to swallow capsules and/or tablets.
21. Concomitant use of warfarin or other vitamin K antagonists.
22. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix 12).
23. Lactating or pregnant.
24. Unwilling or unable to participate in all required study evaluations and procedures.

25. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).

5. TREATMENT OF SUBJECTS

5.1. Enrollment

Subjects will be assigned to one of 5 study cohorts depending on their type of cancer. Enrolled subjects will receive open-label ibrutinib capsules in combination with the specified anticancer agent, or open-label ibrutinib alone (UC cohort 5).

5.2. Study Treatment

Phase 1b: Subjects will be enrolled in up to 3 dose cohorts (DL 1, DL 2, or DL-1)

Phase 2: Subjects will be treated at the RP2D as determined in Phase 1b.

Phase 1b Dosing and Stopping Rules

The Phase 1b portion of this study is performed independently in five separate cohorts defined by the clinical indication; RCC, UC, GC, and CRC. Phase 1b will follow a 3+3+3 design (cohorts 1-4) with 3-9 subjects at each dose level. At each dose level, DLT assessment will be performed in the first 3 subjects. If 1 of 3 subjects experience a DLT during the first treatment cycle, the same dose level will be expanded to 6 subjects, and if 2 of the 6 experience a DLT, the dose level will be expanded to 9 subjects. At the 560 mg/day dose level (DL 1), if 0 out of 3, 1 out of 6 or 2 out of 9 subjects (≤22%) experience a DLT during the first treatment cycle, dose escalation to 840 mg/day will occur. At DL 1 (560 mg/day), if ≥33% of subjects experience a DLT (eg, >2 out of 6 or >2 out of 9 subjects), the dose will be de-escalated to 420 mg/day (dose level minus one; DL-1). At the 840 mg/day dose level (DL 2), cohorts of subjects will be enrolled in a similar fashion.

The RP2D will be determined or confirmed when 6-9 subjects complete the DLT observation period based on the totality of the data including dose reductions, treatment-limiting toxicities (outside of DLTs), the available pharmacokinetic data and the toxicity profile obtained during Phase 1b. In order to determine the RP2D dose level, a minimum of 6 DLT evaluable subjects will be required at the RP2D dose level who are defined to have completed at least 21 days of treatment with ibrutinib in combination with the relevant anticancer agent, after the initiation of therapy at the start of Cycle 1. At each dose level, the decision of de-escalation will be made for at least 6 DLT-evaluable subjects. However, if, at any time in a given dose level, 3 subjects experience a DLT, additional enrollment within the dose level will be stopped

For UC cohort 5, the single-agent dose of 840 mg will be confirmed and documented in the first 6 patients; safety data will be described.

For UC cohort 5, a DLT-evaluable subject will have ≥ 90% compliance with ibrutinib during Cycle 1 (the first 21 days). Subjects who miss more than 2 scheduled doses of ibrutinib within 21 days after the initiation of therapy at the start of Cycle 1 will be replaced (DLT-evaluable subject) unless the missed dose was due to a DLT. At each dose level, the decision of de-escalation

will be made for at least 6 DLT-evaluable subjects. However, if at any time in a given dose level, 3 subjects experience a DLT, additional enrollment within the dose level will be stopped. If a subject experiences a DLT during the DLT observation period, the subject will discontinue treatment. Dose reductions will not be permitted during the DLT observation period. However, any other subject(s) tolerating the dose level through the DLT observation period will continue to receive the same dose of study drugs even if a dose de-escalation occurs for subsequent study subjects.

A DLT is defined as any Grade 3 or higher non-hematologic or Grade 4 hematologic AE occurring during the DLT observation period (ie, 21 days after the initiation of combination therapy at the start of Cycle 1) and considered to be at least possibly related to the study treatment (ibrutinib or combination) with the following clarifications:

- Grade 4 diarrhea and vomiting
- Grade 3 nausea nausea, diarrhea or vomiting despite maximum medical supportive care and persisting >3 days
- Grade 3 fatigue persisting >7 days
- Grade 3 infusion reaction that does NOT resolve with appropriate clinical management
- Grade 3 rash lasting >7 days that does NOT resolve with appropriate clinical management
- Grade 4 neutropenia or leukopenia for >7 days duration (irrespective of adequate growth factor support)
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia

A dose level review committee (DLRC) will evaluate the safety data at the completion of the initial Phase 1b in each cohort, prior to continuing with enrollment into the Phase 2 portion for that given cohort. Members of this committee will include the medical monitor or designee, a Drug Safety representative, a Biostatistician, and at least 2 participating investigators/designees.

Phase 1b

Dosing will be as follows in the Table below (Table 5 in Section 3.3), given in 21-day cycles:

Cohort	DL-1	DL 1	DL 2
Cohort 1 RCC	ibrutinib: 420 mg PO qd everolimus[1]	ibrutinib: 560 mg PO qd everolimus[1]	ibrutinib: 840 mg PO qd everolimus[1]
Cohort 2 UC	ibrutinib: 420 mg PO qd paclitaxel[2]	ibrutinib: 560 mg PO qd paclitaxel[2]	ibrutinib: 840 mg PO qd paclitaxel[2]
Cohort 3 GC	ibrutinib: 420 mg PO qd docetaxel[3]	ibrutinib: 560 mg PO qd docetaxel[3]	ibrutinib: 840 mg PO qd docetaxel[3]
Cohort 4 CRC	ibrutinib: 420 mg PO qd cetuximab[4]	ibrutinib: 560 mg PO qd cetuximab[4]	ibrutinib: 840 mg PO qd cetuximab[4]
Cohort 5 UC	ibrutinib 560 mg PO qd	ibrutinib 840 mg PO qd	NA

PO = orally, qd = daily, qweek = weekly, q3weeks = every 3 weeks

[1] everolimus: 10 mg PO qd

[2] paclitaxel: 80 mg/m^2 IV qweek

[3] docetaxel: 60 - 75 mg/m^2 IV q3weeks

[4] cetuximab: 400 mg/m^2 IV, then 250 mg/m^2 qweek

One cycle of treatment is 21 days in length and consists of daily administration of ibrutinib as a single agent or in combination with the relevant anticancer agent. Treatment will continue as long as the subject is without disease progression and not experiencing unacceptable toxicity. After Cycle 1 (the DLT assessment period) if one component of a combination regimen is discontinued prior to RECIST 1.1 determined disease progression, the other component may be continued until disease progression or unacceptable toxicity.

Phase 2

The recommended Phase 2 dose (RP2D) established in Phase 1b for ibrutinib (840 mg, 560 mg, or 420 mg) PO daily, or in combination with the specified anticancer agent, will be given in 21- day cycles.

Tumor assessment by CT/MRI will occur every 6 weeks and will be evaluated according to RECIST 1.1 guidelines. Subjects will be treated until unacceptable toxicity or disease progression.

UC cohort 5:

Single-agent ibrutinib will be given at the RP2D PO daily in 21-day cycles. Treatment will continue until unacceptable toxicity or disease progression. Tumor assessment by CT/MRI will occur every 6 weeks and evaluated according to RECIST 1.1 guidelines.

A biopsy sub-group (n =5-10 with paired biopsy samples that are evaluable) will be enrolled from consenting subjects. Consent to pre- and on-treatment biopsies is required, if lesions are safe and accessible, according to investigator's assessment. Subjects without consent to biopsy can still be enrolled, after obtaining agreement from the medical monitor. The subjects in the sub-group will receive the same treatment of ibrutinib PO in 21-day cycles but will have a pre-treatment biopsy and an on treatment biopsy after the completion of Cycle 2 and ideally before the completion of Cycle 3. Ibrutinib should be held for 3 days after the pre-treatment biopsy. Study treatment is not required to be held for on treatment biopsy via cystoscopy; however, on the day of the on-treatment biopsy the ibrutinib dose should be delayed until after the biopsy is performed and it is confirmed that there are no signs of clinical bleeding. Enrollment in this sub-group will be discontinued in the setting of low efficacy at the determination of the Sponsor. An IRC may be implemented and scans may be collected from the sites to support this cohort if efficacy data requires independent confirmation for health authorities.

5.3. Study Medication

5.3.1. Ibrutinib

5.3.1.1. Formulation/Packaging/Storage

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib IB for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.1.2. Dose and Administration

Ibrutinib 840 mg, 560 mg, or 420 mg (6x, 4x, or 3x 140 mg capsules respectively) will be administered orally once daily with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed together intact and subjects should not attempt to open capsules or dissolve them in water. Each dose of ibrutinib should be taken at approximately the same time each day. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix 14).

If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

The first dose will be given in the clinic on Day 1, after which subsequent dosing will normally be on an outpatient basis. Following the first dose only of ibrutinib combination therapy on Day 1, subjects will remain in the clinic for 2 hours after completion of administration of the last agent in the combination, in order to assess any acute toxicity.

For subjects receiving IV combination therapies (paclitaxel, docetaxel, and cetuximab) on days when ibrutinib is to be administered, ibrutinib will be taken in the clinic approximately 30 minutes prior to commencement of IV drug delivery.

For subjects receiving the oral combination agent (everolimus), ibrutinib will be taken approximately 6 hours prior to everolimus.

Ibrutinib will be dispensed to subjects in bottles on Day 1 of each cycle. Unused ibrutinib dispensed during previous cycles must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned capsules must not be redispensed.

5.3.1.3. Overdose

Any dose of study drug administered in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg in clinical trials. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 11.4 for further information regarding AE reporting.

5.3.1.4. Dose Modification for Adverse Reactions

With the exception of Cycle 1 of Phase 1b (when dose modifications are not permitted in the absence of a DLT), the dose of ibrutinib should be modified according to the dose modification guidelines in Table 6 if any of the following toxicities occur:

- Grade 4 neutropenia (ANC <500/μL) for more than 7 days. Refer to Section 6.1 for instruction regarding the use of growth factor support
- Grade 3 thrombocytopenia (platelets <50,000/μL) in the presence of clinically signaificant bleeding events
- Grade 4 thrombocytopenia (platelets <25,000/μL)
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy
- Any other Grade 4 or unmanageable Grade 3 toxicity

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.2.4).

In the event that the investigator feels deviation from the recommendations above is required, the medical monitor should be consulted for approval.

Table 6. Ibrutinib Dose Modifications

Hematologic Adverse Events	
Occurrence	**Action to be Taken**
First	Withhold ibrutinib until recovery to an ANC ≥750 or platelets >25,000 with no evidence of Grade ≥2 bleeding; may restart at previous dose level
Second	Withhold ibrutinib until recovery to an ANC ≥750 or platelets >25,000 with no evidence of Grade ≥2 bleeding; may restart at 1 dose level lower
Third	Withhold ibrutinib until recovery to an ANC ≥750 or platelets >25,000 with no evidence of Grade ≥2 bleeding; may restart at 1 dose level lower
Fourth	Discontinue ibrutinib
Non-Hematologic Adverse Events	
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at previous dose level
Second	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower
Fourth	Discontinue ibrutinib

Dose changes must be recorded in the Dose Administration eCRF. At the investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

5.3.2. Everolimus

5.3.2.1. Formulation/Packaging/Storage

A commercial preparation of everolimus will be used and should be stored and administered according to the manufacturer's instructions.

Refer to the pharmacy manual/site investigational product manual for guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.2.2. Dose and Administration

Everolimus 10 mg tablets should be taken orally once daily at the same time every day, either consistently with food or consistently without food. Four (4) x 2.5 mg tablets or two (2) x 5.0 mg tablets may be substituted if 10 mg tablet strength is not available. Tablets should be swallowed whole with a glass of water and should not be broken or crushed. Everolimus should be taken approximately 6 hours after ibrutinib capsules. The use of moderate or strong CYP3A inhibitors/inducers should be avoided as should use of grapefruit, Seville oranges and St John's Wort (Hypericum perforatum).

Everolimus will be administered in continual 21-day cycles. If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra tablets to make up the missed dose.

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing will normally be on an outpatient basis.

Everolimus will be dispensed to subjects on Day 1 of each cycle. Unused everolimus dispensed during previous cycles must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned tablets must not be redispensed.

5.3.2.3. Overdose

Any dose of everolimus administered in excess of that specified in this protocol is considered to be an overdose. Reported experience with everolimus overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose.

5.3.2.4. Dose Modification for Adverse Reactions

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of everolimus therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered. For further details of dosage reductions for everolimus related toxicity, reference should be made to the everolimus prescribing information.

5.3.3. Paclitaxel

5.3.3.1. Formulation/Packaging/Storage

A commercial preparation of paclitaxel should be stored and prepared according to manufacurer's instructions.

Refer to the pharmacy manual/site investigational product manual for guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.3.2. Dose and Administration

All subjects treated with paclitaxel should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H2 antagonists (such as cimetidine or ranitidine). A typical regimen would be dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel.

Paclitaxel should be administered as a 60-minute (±10 minutes) infusion through an in-line filter with a microporous membrane not greater than 0.22 microns. Paclitaxel should be given at a dose level of 80 mg/m^2, once weekly, in continual 3 weekly cycles.

Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Subjects who have developed severe hypersensitivity reactions should not be rechallenged with paclitaxel, which should be discontinued.

Hypotension, bradycardia, and hypertension have been observed during administration of paclitaxel, but generally do not require treatment. Occasionally paclitaxel infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of infusion, is recommended. Severe conduction abnormalities have been documented with paclitaxel treatment, in some cases requiring pacemaker placement. However, continuous cardiac monitoring is not required except for subjects with serious conduction abnormalities.

Paclitaxel has been associated with the ocular disorders of cystoid macular edema. As such, it is important to monitor eye symptoms while subjects are dosed on these drugs; also it is important to advise subjects of the risk associated with wearing contact lenses and developing keratitis while on study.

CBC should be reviewed prior to initiating each cycle of paclitaxel. Paclitaxel should not be administered to subjects with pre-treatment neutrophil counts of less than 1500 cells/mm^3.

Paclitaxel is a substrate of CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is administered with substrates, inhibitors or inducers of CYP2C8 or CYP3A4.

Following the first dose only of paclitaxel combination therapy (on Cycle 1 Day 1) subjects will remain in the clinic for 2 hours after completion of administration, in order to assess any acute toxicity.

5.3.3.3. Overdose

There is no known antidote for paclitaxel overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis.

Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose.

5.3.3.4. Dose Modification for Adverse Reactions

Subjects should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. In the case of severe neutropenia (<500 cells/mm^3 for 7 days or more) or severe neuropathy during a course of paclitaxel therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

Extreme caution should be exercised if giving paclitaxel to subjects with a serum total bilirubin >2 x ULN.

For further guidance on the administration of paclitaxel reference should be made to the paclitaxel prescribing information.

5.3.4. Docetaxel

5.3.4.1. Formulation/Packaging/Storage

A commercial preparation of docetaxel will be used and should be stored and prepared according to manufacurer's instructions.

Refer to the pharmacy manual/site investigational product manual for guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.4.2. Dose and Administration

Docetaxel should be administered as a 60 minute infusion (±10 minutes) at a dose level of 60 - 75 mg/m^2, given continually in 21 day cycles. All subjects should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (eg, 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Complete blood count (CBC), bilirubin, AST or ALT, and alkaline phosphatase values should be obtained prior to initiating each cycle of docetaxel. Docetaxel should not be administered if: 1) bilirubin is >ULN or 2) ALT and/or AST are >1.5 x ULN AND alkaline phosphatase is >2.5 x ULN. Docetaxel should not be administered to subjects with baseline neutrophil counts of less than 1500 cells/mm^3.

Subjects should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported, even following corticosteroid premedication. Severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive therapy. Subjects with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel, which should be permanently discontinued.

Hypersensitivity reactions may occur within a few minutes following initiation of docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required.

Severe fluid retention can occur following docetaxel administration and subjects with pre-existing effusions should be closely monitored from the first dose for possible exacerbations.

Docetaxel has been associated with the ocular disorders of cystoid macular edema. As such, it is important to monitor eye symptoms while subjects are dosed on these drugs; also it is important to advise subjects of the risk associated with wearing contact lenses and developing keratitis while on study.

Close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

Following the first dose only of docetaxel combination therapy (on Cycle 1 Day 1) subjects will remain in the clinic for 2 hours after completion of administration, in order to assess any acute toxicity.

5.3.4.3. Overdose

Any dose of docetaxel administered in excess of that specified in this protocol is considered to be an overdose. There is no known antidote for docetaxel overdosage. In case of overdosage, the subject should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include: bone marrow suppression, peripheral neurotoxicity, and mucositis. Subjects should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

In two reports of overdose, one patient received 150 mg/m^2 and the other received 200 mg/m^2 as 1-hour infusions. Both patients experienced severe neutropenia, mild asthenia, cutaneous reactions, and mild paresthesia, and recovered without incident.

Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose.

5.3.4.4. Dose Modification for Adverse Reactions

If an episode of febrile neutropenia, prolonged neutropenia, or neutropenic infection occurs despite G-CSF use, the docetaxel dose should be reduced from 75 mg/m^2 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the docetaxel dose should be reduced from 60 mg/m^2 to

45 mg/m^2. In case of Grade 4 thrombocytopenia the docetaxel dose should be reduced from 75 mg/m^2 to 60 mg/m^2. Subjects should not be retreated with subsequent cycles of docetaxel until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level >100,000 cells/mm^3. Subjects who develop ≥Grade 3 peripheral neuropathy should have treatment discontinued entirely.

Further information on the management of docetaxel related toxicities is contained within the docetaxel prescribing information.

5.3.5. Cetuximab

5.3.5.1. Formulation/Packaging/Storage

A commercial preparation of cetuximab will be used and should be stored and prepared according to manufacurer's instructions.

Refer to the pharmacy manual/site investigational product manual for guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.5.2. Dose and Administration

Premedication should be given with an H1 antagonist (eg, 50 mg of diphenhydramine) IV 30-60 minutes prior to the first dose; premedication should be administered for subsequent cetuximab doses based upon clinical judgment and presence/severity of prior infusion reactions.

The recommended initial dose is 400 mg/m^2 administered as a 120-minute IV infusion.

The recommended subsequent weekly dose (all other infusions) is 250 mg/m^2 infused over 60 minutes.

Patients should be periodically monitored for hypomagnesemia, hypocalcaemia, and hypokalemia, during and for at least 8 weeks following the completion of cetuximab administration.

Cetuximab has been associated with the ocular disorders of cystoid macular edema and keratitis. As such, it is important to monitor eye symptoms while subjects are dosed on these drugs; also it is important to advise subjects of the risk associated with wearing contact lenses and developing keratitis while on study.

5.3.5.3. Overdose

The maximum single dose of cetuximab administered is 1000 mg/m^2 in one patient and no AEs were reported for this patient.

Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose. There is no specific antidote for cetuximab. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

5.3.5.4. Dose Modification for Adverse Reactions

Infusion reactions have occurred with cetuximab. When an infusion reaction occurs, reduce the infusion rate by 50% for NCI CTC Grade 1 or 2 and non-serious NCI CTC Grade 3 infusion reaction. Immediately and permanently discontinue cetuximab for serious infusion reactions requiring medical intervention and/or hospitalization.

Dermatologic toxicities including aceniform rash occurred in patients receiving cetuximab therapy. Please consult the Table 7 below for cetuximab dose modification for severe acneiform rash.

Table 7. Cetuximab Dose Modification for Severe Acneiform Rash

Severe Acneiform Rash	Cetuximab	Outcome	Cetuximab Dose Modification
1st Occurrence	Delay Infusion for 1-2 Weeks	Improvement	Continue at 250 mg/m^2
		No Improvement	Discontinue Cetuximab
2nd Occurrence	Delay Infusion for 1-2 Weeks	Improvement	Reduce Dose to 200 mg/m^2
		No Improvement	Discontinue Cetuximab
3rd Occurrence	Delay Infusion for 1-2 Weeks	Improvement	Continue at 150 mg/m^2
		No Improvement	Discontinue Cetuximab
4th Occurrence	Discontinue Cetuximab		

Further information on the management of cetuximab related toxicities is contained within the cetuximab prescribing information.

5.4. Criteria for Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. If the subject meets any of the following criteria, then withdrawal from study treatment is mandatory:

- Subject has confirmed PD
- Subject has an intercurrent illness or AE that prevents further administration of both study agents in any cohort
- Subject decides to withdraw from study or becomes pregnant
- Subject is noncompliant with study procedures and/or scheduled evaluations
- Subject requires a prohibited concomitant medication
- Investigator considers withdrawal to be in the best interest of the subject
- The Sponsor requires that the subject withdraw or the Sponsor and/or regulatory authorities terminate the study

Subjects will be treated until disease progression in the absence of unacceptable toxicity (see separate dose management guidelines for toxicity for each agent). If treatment with everolimus, docetaxel, paclitaxel, or cetuximab is discontinued for toxicity, dosing with ibrutinib would continue until disease progression or toxicity.

An End of Treatment (EOT) Visit (Section 8.5) is required for all subjects except for those subjects who have withdrawn full consent (see Sections 9.2 and 9.3)

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1. Concomitant Medications

Concomitant therapies must be recorded from the time of ICF signing until 30 days after the last dose of study drug.

6.1.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of corticosteroid treatment for non–cancer-related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted after discussion with the Medical Monitor.

6.2. Medications to be Used with Caution

6.2.1. CYP3A Inhibitors/Inducers

Ibrutinib

Ibrutinib is metabolized primarily by CYP3A4. Avoid co-administration with strong CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibitio

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 140 mg (for 840 mg/day dose, reduce to 280 mg) for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1.2).
- No dose adjustment is required in combination with mild inhibitors.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix 12. For further information, please refer to the current version of the IB and examples of inhibitors, inducers, and

substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

Everolimus

Avoid the use of strong CYP3A4/P-gp inhibitors (see Appendix 12).

Use caution when co-administered with moderate CYP3A4/P-gp inhibitors (see Appendix 12). If patients require co-administration of a moderate CYP3A4 /P-gp inhibitor, reduce the everolimus dose to 2.5 mg daily. The reduced dose of everolimus is predicted to adjust the area under the curve (AUC) to the range observed without inhibitors. An everolimus dose increase from 2.5 mg to 5 mg may be considered based on patient tolerance. If the moderate inhibitor is discontinued, a washout period of approximately 2-3 days should be allowed before the everolimus dose is increased. If the moderate inhibitor is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/P-gp inhibitor.

Grapefruit, grapefruit juice, and other foods that are known to inhibit cytochrome P450 and P-gp activity may increase everolimus exposures and should be avoided during treatment.

Avoid the use of concomitant strong CYP3A4/P-gp inducers (see Appendix 12). If patients require co-administration of a strong CYP3A4/P-gp inducer, consider doubling the daily dose of everolimus using increments of 5 mg or less. This dose of everolimus is predicted, based data, to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4/P-gp inducers. If the strong inducer is discontinued, consider a washout period of 3-5 days, before the everolimus dose is returned to the dose used prior to initiation of the strong CYP3A4/P-gp inducer.

St. John's Wort (Hypericum perforatum) may decrease everolimus exposure unpredictably and should be avoided.

Docetaxel

Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by CYP3A4.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with docetaxel, close monitoring for toxicity and a docetaxel dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

Paclitaxel

Paclitaxel is a substrate of CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates, inhibitors and inducers of CYP3A4. Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir,

saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

6.2.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib.

6.2.3. QT Prolongation

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

6.2.4. Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries see Section 6.4.

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.3. Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy is prohibited while the subject is receiving study combination therapy.

Corticosteroids for longer than 14 days and/or at doses >20 mg of prednisone or its equivalent are prohibited (with the exception of acute management of infusion reactions, if clinically indicated).

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib.

6.4.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, cystoscopy with biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. Please see Section 3.1 UC cohort 5 for specific biopsy sub-group language.

6.4.2. Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

6.4.3. Emergency Procedures

For emergency procedures, ibrutinib should be held as soon as possible and until the surgical site is reasonably healed, or for at least 7 days after the urgent surgical procedure, whichever is longer.

7. STUDY EVALUATIONS

7.1. Description of Procedures

7.1.1. Assessments

7.1.1.1. Informed Consent

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

7.1.1.2. Confirm Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria (Section 4.2).

7.1.1.3. Medical History and Demographics

The subject's complete history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, dates administered, and responses and duration of response to these treatments, also will be recorded.

7.1.1.4. Prior and Concomitant Medications

All active medications including vitamin supplements, and probiotic use from the signing of ICF or at least 14 days prior to first dose through 30 days after the last dose of study drug will be documented.

7.1.1.5. Adverse Events

The accepted regulatory definition for an AE is provided in Section 11.1.1. All medical occurrences that meet the AE definition must be recorded from the time the ICF is signed until 30 days after the last dose of study drug. Laboratory abnormalities designated clinically significant by the investigator will also be recorded as AEs. Additional important requirements for AE and SAE reporting are explained in Sections 11.1.1 and 11.4.

7.1.1.6. Physical Examination

The complete physical examination should include, at a minimum, the general appearance of the subject, height (Screening only; may use prior height measurement from 30 days prior to Screening if available in source documents), and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system. All physical exams will include a disease-related symptom assessment.

7.1.1.7. Weight

Weight will be recorded per visit schedules listed in Appendix 1, Appendix 3, Appendix 5, Appendix 7, and Appendix 9 until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

7.1.1.8. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature and will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

7.1.1.9. Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG performance index is provided in Appendix 11.

7.1.1.10. Karnofsky Performance Scale (KPS)

The KPS index is provided in Appendix 13.

7.1.2. Laboratory

7.1.2.1. Hematology

Hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Hematology samples will be collected and sent to central laboratory for analysis. In the event that the central lab sample is not evaluable, local lab results will be collected, if available, and entered in the clinical database for response or progression confirmation.

7.1.2.2. Chemistry (serum)

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN)/Urea, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate. Chemistry samples will be collected and sent to central laboratory for analysis. In the event that the central lab sample is not evaluable, local lab results will be collected, if available, and entered in the clinical database for response or progression confirmation.

7.1.2.3. Coagulation Studies

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening using a central laboratory. In the event that the central lab sample is not evaluable, local lab results will be collected, if available, and entered in the clinical database.

7.1.2.4. Hepatitis Serologies

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, and Hepatitis B core antibody and will be evaluated by central laboratory. If Hepatitis B core antibody, Hepatitis B surface antigen or Hepatitis C antibody is positive, then PCR must be performed. PCR needs to be confirmed negative prior to enrollment in subjects who are Hepatitis B core antibody positive, Hepatitis B surface antigen positive or Hepatitis C antibody positive. In the event that the central lab sample is not evaluable, local lab results will be collected, if available, and entered in the clinical database.

7.1.2.5. CRP (UC cohort 5)

Samples will be collected at every cycle on day 1 for central laboratory testing.

7.1.2.6. Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Urinalysis samples will be collected and sent to central laboratory for analysis. In the event that the central lab sample is not evaluable, local lab results will be collected, if available, and entered in the clinical database.

7.1.2.7. Pregnancy Test

Serum or urine pregnancy test will be performed by local laboratory only for women of childbearing potential. Urine pregnancy test will be repeated on Day 1 if screening test was more than 3 days prior to the first dose of study drug. If positive, pregnancy must be ruled out by ultrasound for the subject to be eligible. This test may be performed more frequently if required by local regulatory authorities.

7.1.3. Diagnostics/Procedures

7.1.3.1. ECG

At Screening, a 12-lead ECG will be performed. Clinically significant abnormalities noted at Screening should be included in the medical history.

Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. During any visit in which both ECG and blood draws are performed, ECG should be performed first.

ECGs should be performed if clinically indicated, at any time during the study at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea.

7.1.3.2. CT/MRI

Documented tumor measurement is required using CT/MRI per RECIST 1.1 guidelines. The same method of assessment and the same technique for acquisition of data must be used to characterize each identified and reported lesion at baseline and at follow-up visits.

Pretreatment tumor assessment will be performed within 28 days before the first dose of study drug with a CT or MRI. For pathologies with a high incidence of brain metastasis a pretreatment CT or MRI of the brain to confirm no brain metastasis is required. In the case where CT with contrast is contraindicated, an alternative would be an MRI. Subjects who refuse CT/MRI scans and/or miss more than one scan may be removed from the study following discussion with the medical monitor.

De-identified copies of all scans (including those from screening and any unscheduled scans) must be provided to the Sponsor or designee (eg, central imaging vendor). Scans may be collected for purposes of independent confirmation for cohort 5 if needed for health authority engagement.

7.1.4. Pharmacokinetics/Biomarkers

7.1.4.1. Pharmacokinetics

Plasma samples will be collected in all subjects for each cohort for PK determination for ibrutinib and all coadministered drugs (except for everolimus and cetuximab). Refer to Appendix 2, Appendix 4, Appendix 6, Appendix 8, and Appendix 10 for the PK sampling schedule. All PK samples will be collected and sent to central laboratory. Refer to the laboratory manual for instructions on collecting and processing these samples. On the day of the sampling visit, the clinical staff will instruct the subject to not take a dose before arrival at the clinic. Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each sample is drawn must be recorded using a 24 hour format. The same clock should be used for recording the time of dosing.

7.1.4.2. Biomarkers

Blood, urine, and tissue samples will be collected for pharmacodynamics (PDn) and exploratory investigation of genomic and protein-based biomarkers to predict treatment outcome and mechanisms of resistance.

Additional testing may be performed on stored samples as new methods are developed to further understand the origin, progression, and resistance of cancer and its relationship to the study drug(s). In addition, these samples may be used for research that may lead to the development of

medical products or processes. All leftover samples will be de-identified prior to shipping to a central vendor and will be destroyed no later than 10 years after study completion.

Testing will be performed at a central laboratory.

7.1.4.2.1. Blood Samples for Biomarkers

Blood samples are collected at the time points specified in the Schedule of Assessments to investigate exploratory biomarkers to predict response and mechanism of resistance. Blood samples may be processed for PBMC, plasma and for cell-free DNA for the analysis of gene and protein expression, mutation and PDn biomarkers.

7.1.4.2.2. Urine Samples for Biomarkers

Urine samples for genomic and secreted protein biomarkers will be collected prior to dosing on Day 1 of every cycle for the first 3 cycles, then on Day 1 of every 3rd cycle, or CR, and at EOT.

7.1.4.2.3. Carcinoembryonic Antigen (CEA, CRC only)

Blood samples for CEA levels will be collected and sent to the central lab at Screening and prior to dosing on Day 1 of each cycle for the first 3 cycles, then Day 1 of every 3rd cycle after Cycle 3, or CR, and at EOT for the CRC cohort only.

7.1.4.2.4. Buccal Swab

Subject somatic DNA will be utilized as a comparison for tumor-based genomic analyses including analysis of tumor biopsy, blood, and urine specimens. Buccal swabs will be collected from all subjects prior to dosing on Cycle 1 Day 1.

7.1.4.3. Tumor Biopsy

Fresh tumor biopsy and/or an available archival tumor sample processed as formalin-fixed paraffin embedded (FFPE) will be collected at Screening from all patients. Tumor biopsy samples may be used to analyze whole exome and transcriptome, proteomics and gene expression profiling (GEP) to investigate biomarkers for predictive, prognostic and mechanism of resistance.

7.2. Efficacy Evaluations

All subjects in the study will have their response assessed using the RECIST 1.1 guidelines (Eisenhauer 2009). Grading for best response will be categorized as CR, PR, SD (≥6 weeks), or PD. Additional information can be found in https://www.eortc.be/Recist/documents/RECISTGuidelines.pdf.

7.2.1. Definitions

Response and progression will be evaluated in this study using RECIST 1.1 guidelines (Eisenhauer 2009). Changes in only the longest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 guidelines, with the exception of lymph nodes, where changes in the shortest diameter are utilized.

NOTE: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

7.2.1.1. Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size as follows:

- 10 mm with CT scan with a slice thickness of no greater than 5 mm. If the slice thickness is >5 mm, the minimum size for a measurable lesion is twice the slice thickness.
- 10 mm caliper measurement by clinical exam.
- If the CT slice thickness is >5 mm, the extranodal disease must be ≥ twice the slice thickness.

Lymph nodes can only be considered as target lesions if they are ≥15 mm in the short axis. Although lymph nodes ≥10 mm are considered pathological, they cannot be categorized as target lesions in RECIST 1.1 guidelines.

7.2.1.2. Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm using spiral CT scan or pathological nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable disease.

7.2.1.3. Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at the baseline/screening assessment. Target lesions should be selected on the basis of their size (lesions with the longest diameter or short axis for lymph node) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) or short axis for lymph node for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response. Lesions that have been irradiated cannot be included in the tumor assessment, unless unequivocal tumor progression has been documented in these lesions after radiation therapy.

7.2.1.4. Non-target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at the baseline/screening assessment. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up as 'present', 'absent', or in rare cases 'unequivocal progression'. Recording several lesions involving the same organ as a single item is acceptable.

7.2.1.5. New Lesions

If new lesions appear and there is doubt as to whether a lesion is new or an inflammatory change, follow-up scans are required. If the new lesion is confirmed, as unequivocal (ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to be something other than the tumor by a scan obtained at least 4 weeks after the initial scan), the date of progression is taken to be the date on which the new lesion was first detected. If a lesion reappears after disappearing in a subject with CR, PD is declared. However, if such a lesion behaves in this manner in a subject with SD or PR, it is the change in sum of target disease that defines the response or progression.

A lesion found in a follow-up study in a region that was not scanned at baseline is still considered a new lesion and will indicate PD, if confirmed by a repeat scan obtained at least 4 weeks after the initial scan.

7.2.2. Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

Measurements need not be along the same axis (as measured at baseline), but should always be the longest axis of the lesion (or short axis for lymph node) at that point in time. Measurements do not have to be at the same slice position, provided the measurement is of the same lesion. However, if the initial measurements are in the axial plane, all further measurements of that lesion must remain in the axial plane. Likewise, if the initial measurements are in the coronal plane (this is acceptable), all further measurements of that lesion must be in the coronal plane.

If a lesion disappears, the measurement of that lesion is clearly 0 mm, however, if the lesion remains present, but is too small to measure accurately, a default measurement of 5 mm should be given, regardless of slice thickness. If lymph nodes decrease to <10 mm, these are considered to be disease-free, but remain target lesions. If lesions merge, the long axis of the resulting lesion is measured (or short axis for lymph node) as one lesion in place of the individual lesions. If lesions split, the long axis of each individual lesion (or short axis for lymph node) is added together.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Nodal lesions: If lymph nodes are chosen as target lesions and decrease to normal size (<10 mm), the measurement of the lesion must still be included in the sum of the target lesions. This means that subjects may still meet the criteria for CR even if the sum of target lesions is not zero.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Tumor markers: Tumor markers alone cannot be used to assess response.

Note: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is mandatory to differentiate between response or SD (an effusion may be a side effect of the treatment) and PD.

7.2.3. Response Criteria

7.2.3.1. Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in the short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference 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 must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Note: In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error.	

7.2.3.2. Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions or the appearance of one or more new lesions.
Note: To be considered unequivocal progression on the basis of non-target lesions only, the overall tumor burden must have increased.	

7.2.3.3. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria (Table 8).

Subjects who have signs and symptoms of progression outside of the scheduled assessment, should be evaluated by the investigator and a CT/MRI scan performed to determine if disease progression can be confirmed by RECIST 1.1 criteria.

If a subject shows signs or symptoms of disease progression, the subject may continue study treatment, if judged clinically appropriate by the investigator, until progression is confirmed by radiologic assessment (eg, CT/MRI) according to RECIST 1.1 criteria.

New anticancer therapy should be withheld if clinically appropriate in the absence of confirmation of PD by CT/MRI per RECIST 1.1.

Table 8. Time Point Response: Subject with Target (+/- Non-target) Disease

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

7.2.3.4. Missing Assessments or Inevaluable Lesions

When an imaging assessment is not done or a lesion is not evaluable at a particular time point, the subject is not evaluable (NE) at that time point.

7.3. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the eCRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix 1, Appendix 3, Appendix 5, Appendix 7, and Appendix 9) and PK Sampling Schedules (Appendix 2, Appendix 4, Appendix 6, Appendix 8, and Appendix 10) for the timing and frequency of all sample collections.

8. STUDY PROCEDURES

8.1. Screening Phase

Screening procedures will be performed up to 28 days before Day 1 of Cycle 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. All study tests and procedures should be performed at the study center at which the subject was screened and will be enrolled. After signing the ICF, completing screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. The subject will be screen-failed if not enrolled within the screening window.

8.1.1. Screening Visit

The following procedures will be performed at the Screening Visit within 28 days prior to Day 1 of Cycle 1 unless otherwise noted:

- Obtain signed, written informed consent
- Medical history including demographic information
- Complete physical examination

- Obtain weight
- Obtain vital signs
- ECOG performance status
- Karnofsky performance status (KPS) score
- Obtain 12-lead ECG
- Record concomitant medication history including over-the-counter drugs, vitamins and herbs.
- Imaging by CT/MRI Scan (unless already performed within 28 days prior to anticipated date of Cycle 1 Day 1). Lesions should be measured using RECIST 1.1 criteria.
- Obtain specimens for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Creatinine clearance (Cockcroft-Gault). will be calculated using central lab results.
  - CRP (UC cohort 5)
  - Coagulation panel
  - Hepatitis serologies
  - Serum or urine pregnancy (if female of child bearing age)
  - Carcinoembryonic Antigen (CEA) (for the CRC cohort 4 only)
  - Urinalysis
- Collect fresh tumor biopsy or an available archival tumor sample
- Review of AEs
- Confirm diagnosis of one of the 4 disease cohorts
- Confirm eligibility (per inclusion/exclusion criteria) for enrollment

8.2. Treatment Phase

After eligibility has been confirmed by the Medical Monitor, the subject can be enrolled in the appropriate dose level of the applicable cohort. The subject must start Cycle 1 Day 1 within 7 calendar days of enrollment in the study.

8.2.1. Treatment Visit – Renal Cell Carcinoma (RCC)

8.2.1.1. Cycle 1 Day 1 (C1D1)

Pre-dose

- Complete physical examination
- Obtain weight
- Obtain vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Urine pregnancy test to be repeated if screening test was more than 3 days prior to C1D1
  - Molecular Markers – Blood

- Molecular Markers – Urine
- Buccal Swab
- Pharmacodynamics sample

- Review of AEs and disease-related symptoms, and concomitant medications

Dosing and Post First Dose

- In-clinic administration of ibrutinib
- Dispense ibrutinib
- Administration of everolimus (6 hours ± 15 minutes after ibrutinib administration)
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic and at least 2 hours post everolimus administration
- Dispense everolimus for offsite use and provide study drug compliance instructions

8.2.1.2. Cycle 1 Day 8 (C1D8)

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- Administration of everolimus (6 hours ± 15 minutes after ibrutinib administration)

8.2.1.3. Cycle 1 Day 15 (C1D15)

Pre-dose

- Complete physical examination
- Obtain weight
- ECOG performance status
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- Administration of everolimus (6 hours ± 15 minutes after ibrutinib administration)

8.2.1.4. Cycle 2 Day 1 (C2D1)

Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Molecular Markers – Blood
  - Molecular Markers – Urine
  - Predose pharmacokinetics sample
  - Predose pharmacodynamics sample
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing and Post Dose

- In-clinic administration of ibrutinib
- Administration of everolimus (6 hours ± 15 minutes) after ibrutinib administration)
- Collection of post dose pharmacokinetics and pharmacodynamics samples per Appendix 2
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic
- Dispense ibrutinib and everolimus for offsite use and provide study drug compliance instructions

8.2.1.5. Cycle 2 Day 8 (C2D8)

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- Administration of everolimus (6 hours ± 15 minutes after ibrutinib administration)

8.2.1.6. Cycle 2 Day 15 (C2D15)

Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- Administration of everolimus (6 hours ± 15 minutes after ibrutinib administration)

8.2.1.7. Cycle 3 and Every Subsequent Treatment Cycle Visit Thereafter

Day 1
Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Molecular Markers – Blood (every 3rd cycle after Cycle 3)
  - Molecular Markers – Urine (every 3rd cycle after Cycle 3)
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing and Post Dose

- Administration of ibrutinib
- Administration of everolimus (6 hours ± 15 minutes after ibrutinib administration)

- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic.
- Dispense ibrutinib and everolimus for offsite use and provide study drug compliance instructions

Day 8

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- Administration of everolimus (6 hours ± 15 minutes after ibrutinib administration)

Day 15

Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- Administration of everolimus (6 hours ± 15 minutes after ibrutinib administration)

8.2.2. Treatment Visit – UC Cohort 2

8.2.2.1. Cycle 1 Day 1 (C1D1)

Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Serum or urine pregnancy test to be repeated if screening test was more than 3 days prior to C1D1
  - Molecular Markers – Blood
  - Molecular Markers – Urine
  - Buccal Swab
  - Pharmacodynamics sample
- Review of AEs and disease-related symptoms, and concomitant medications

Dosing and Post First Dose

- Dispense ibrutinib
- In-clinic administration of ibrutinib
- In-clinic infusion of paclitaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic and at least 2 hours post paclitaxel infusion.
- Provide study drug compliance instructions

8.2.2.2. Cycle 1 Day 8 (C1D8)

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- In-clinic infusion of paclitaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)

8.2.2.3. Cycle 1 Day 15 (C1D15)

- Complete physical examination
- Obtain weight
- Vitals signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- In-clinic infusion of paclitaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)

8.2.2.4. Cycle 2 Day 1 (C2D1)

Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Molecular Markers – Blood
  - Molecular Markers – Urine
  - Predose pharmacokinetics sample
  - Predose pharmacodynamics sample
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing and Post Dose

- In-clinic administration of ibrutinib
- In-clinic infusion of paclitaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)
- Collection of post dose pharmacokinetics and pharmacodynamics samples per Appendix 4.
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic.
- Dispense ibrutinib for offsite use and provide study drug compliance instructions

8.2.2.5. Cycle 2 Day 8 (C2D8)

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- In-clinic infusion of paclitaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)

8.2.2.6. Cycle 2 Day 15 (C2D15)

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

- In-clinic infusion of paclitaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)

8.2.2.7. Cycle 3 and Every Subsequent Treatment Cycle Visit Thereafter

Day 1

Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Molecular Markers – Blood (every 3rd cycle after Cycle 3)
  - Molecular Markers – Urine (every 3rd cycle after Cycle 3)
- Review of AEs and disease-related symptoms, and concomitant medications

Dosing and Post Dose

- In-clinic administration of ibrutinib
- In-clinic infusion of paclitaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic
- Dispense ibrutinib for offsite use and provide study drug compliance instructions
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Day 8

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

- In-clinic infusion of paclitaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)

Day 15

Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- In-clinic infusion of paclitaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)

8.2.3. Treatment Visit – Gastric Adenocarcinoma

8.2.3.1. Cycle 1 Day 1 (C1D1)

Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Urine pregnancy test to be repeated if Screening test was more than 3 days prior to C1D1
  - Molecular Markers – Blood
  - Molecular Markers – Urine
  - Buccal Swab
  - Pharmacodynamics sample
- Review of AEs and disease-related symptoms, and concomitant medications

Dosing and Post First Dose

- In-clinic administration of ibrutinib

- Dispense ibrutinib
- In-clinic infusion of docetaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic and at least 2 hours post docetaxel administration
- Provide study drug compliance instructions

8.2.3.2. Cycle 1 Day 8 (C1D8)

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

8.2.3.3. Cycle 1 Day 15 (C1D15)

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

8.2.3.4. Cycle 2 Day 1 (C2D1)

Pre-dose

- Complete physical examination
- Obtain weight

- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Molecular Markers – Blood
  - Molecular Markers – Urine
  - Predose pharmacokinetics sample
  - Pharmacodynamics sample
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing and Post Dose

- In-clinic administration of ibrutinib
- In-clinic infusion of docetaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)
- Collection of post dose pharmacokinetics and pharmacodynamics samples per schedule
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic.
- Dispense ibrutinib for offsite use and provide study drug compliance instructions

8.2.3.5. Cycle 2 Day 8 (C2D8)

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

8.2.3.6. Cycle 2 Day 15 (C2D15)

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status

- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

8.2.3.7. Cycle 3 and Every Subsequent Treatment Cycle Visit Thereafter

Day 1
Pre-dose

- Complete physical examination
- Obtain weight
- ECOG performance status
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Molecular Markers – Blood (every 3rd cycle after Cycle 3)
  - Molecular Markers – Urine (every 3rd cycle after Cycle 3)
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing and Post Dose

- In-clinic administration of ibrutinib
- In-clinic infusion of docetaxel (to start 30 minutes ± 5 minutes after ibrutinib administration)
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic.
- Dispense ibrutinib for offsite use and provide study drug compliance instructions

8.2.4. Treatment Visit – Colorectal Adenocarcinoma (CRC)

8.2.4.1. Cycle 1 Day 1 (C1D1)

Pre-dose

- Complete physical examination
- Obtain weight
- ECOG performance status

- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Serum or urine pregnancy test to be repeated if Screening test was more than 3 days prior to C1D1
  - Molecular Markers – Blood
  - Molecular Markers – Urine
  - CEA
  - Buccal Swab
  - Pharmacodynamics sample
- Review of AEs and disease-related symptoms, and concomitant medications

Dosing and Post First Dose

- Dispense ibrutinib
- In-clinic administration of ibrutinib
- In-clinic infusion of cetuximab (to start 30 minutes ± 5 minutes after ibrutinib administration)
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic and at least 2 hours post cetuximab administration.
- Provide study drug compliance instructions

8.2.4.2. Cycle 1 Day 8 (C1D8)

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- In-clinic administration of cetuximab (to start 30 minutes ± 5 minutes after ibrutinib administration)

8.2.4.3. Cycle 1 Day 15 (C1D15)

- Complete physical examination
- Obtain weight

- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- In-clinic administration of cetuximab (to start 30 minutes ± 5 minutes after ibrutinib administration)

8.2.4.4. Cycle 2 Day 1 (C2D1)

Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Molecular Markers – Blood
  - Molecular Markers – Urine
  - CEA
  - Predose pharmacokinetics sample
  - Predose pharmacodynamics sample
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing and Post Dose

- In-clinic administration of ibrutinib
- In-clinic administration of cetuximab (to start 30 minutes ± 5 minutes after ibrutinib administration)
- Collection of post dose pharmacokinetics and pharmacodynamics samples per schedule
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic.
- Dispense ibrutinib for offsite use and provide study drug compliance instructions

8.2.4.5. Cycle 2 Day 8 (C2D8)

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

8.2.4.6. Cycle 2 Day 15 (C2D15)

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- In-clinic administration of cetuximab (to start 30 minutes ± 5 minutes after ibrutinib administration)

8.2.4.7. Cycle 3 and Every Subsequent Treatment Cycle Visit Thereafter

Day 1
Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology

- Serum Chemistry
- Urinalysis
- Molecular Markers – Blood (every 3rd Cycle after Cycle 3)
- Molecular Markers – Urine (every 3rd Cycle after Cycle 3)
- CEA (every 3rd Cycle after Cycle 3)

- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing and Post Dose

- In-clinic administration of ibrutinib
- In-clinic infusion of cetuximab (to start 30 minutes ± 5 minutes after ibrutinib administration)
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic.
- Dispense ibrutinib for offsite use and provide study drug compliance instructions

Day 8
Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- In-clinic infusion of cetuximab (to start 30 minutes ± 5 minutes after ibrutinib administration)

Day 15
Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry

- Urinalysis

- Review of AEs, disease-related symptoms, and concomitant
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib
- In-clinic infusion of cetuximab (to start 30 minutes ± 5 minutes after ibrutinib administration)

8.2.5. UC Cohort 5:

8.2.5.1. Cycle 1 Day 1 (C1D1)

Pre-dose

- For consenting subjects a biopsy of primary tumor or metastatic lesion should be done at least three days before the first dose of Ibrutinib
- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - CRP
  - Urinalysis
  - Serum or urine pregnancy test to be repeated if screening test was more than 3 days prior to C1D1
  - Molecular Markers – Blood
  - Molecular Markers – Urine
  - Buccal Swab
- Review of AEs and disease-related symptoms, and concomitant medications

Dosing and Post First Dose

- Dispense ibrutinib
- In-clinic administration of ibrutinib
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic and at least 2 hours post ibruitinb administration
- Provide study drug compliance instructions

8.2.5.2. Cycle 1 Day 8 (C1D8)

Pre-dose

- Obtain weight
- Vitals signs

- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

8.2.5.3. Cycle 1 Day 15 (C1D15)

- Complete physical examination
- Obtain weight
- Vitals signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

8.2.5.4. Cycle 2 Day 1 (C2D1)

Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - CRP
  - Urinalysis
  - Molecular Markers – Blood
  - Molecular Markers – Urine
  - Predose ibrutinib pharmacokinetics sample
- Review of AEs and disease-related symptoms, and concomitant medications

- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing and Post Dose

- In-clinic administration of ibrutinib
- Collection of post dose ibrutinib pharmacokinetics samples per Appendix 9 and Appendix 10
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic.
- Dispense ibrutinib for offsite use and provide study drug compliance instructions

8.2.5.5. Cycle 2 Day 8 (C2D8)

Pre-dose

- Obtain weight
- Vitals signs
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Review of AEs and disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

8.2.5.6. Cycle 2 Day 15 (C2D15)

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)

Dosing

- In-clinic administration of ibrutinib

8.2.5.7. Cycle 3 and Every Subsequent Treatment Cycle Visit Thereafter

Day 1
Pre-dose

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum Chemistry
  - CRP
  - Urinalysis
  - Molecular Markers – Blood (every 3rd cycle after Cycle 3)
  - Molecular Markers – Urine (every 3rd cycle after Cycle 3)
- Review of AEs and disease-related symptoms, and concomitant medications

Dosing and Post Dose

- In-clinic administration of ibrutinib
- Review of AEs, disease-related symptoms, and concomitant medications once more before subject leaves the clinic
- Dispense ibrutinib for offsite use and provide study drug compliance instructions
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)
- For consenting subjects: Ont-treatment fresh tumor biopsy should be collected during Cycle 3 anytime from Cycle 3 Day 1 and prior to Cycle 4 Day 1

8.3. Efficacy Evaluations

Efficacy evaluations will be performed per the schedule outlined in Appendix 1, Appendix 3, Appendix 5, Appendix 7, and Appendix 9. The following procedures will be performed in conjunction with standard visits as follows:

- Radiologic exam by CT, or MRI should be performed every 6 weeks until progressive disease, death, withdrawal of consent for further follow up, or lost to follow up, whichever occurs first. Lesions seen on the scans should be measured using RECIST 1.1 criteria.
- A change in neurologic function should be investigated with a head CT or MRI.
- If PD based on RECIST 1.1, optional tumor biopsy

8.4. Fresh Tumor Biopsy for Cohort 5

Fresh paired tumor biopsies will be carried out for 5-10 subjects. Each subject may undergo two biopsies.

- Biopsy 1 (Pre-treatment): Fresh tumor biopsy should be collected 3 days before the first dose of Ibrutinib Cycle 1 dosing.

- Biopsy 2 (On-Treatment): Fresh tumor biopsy should be collected during Cycle 3 anytime from Cycle 3 Day 1 and prior to Cycle 4 Day 1.

Please refer to laboratory manual for storing, packaging, and shipping instructions.

8.5. End-of-Treatment Visit

An EOT Visit should occur 30 days (± 7 days) from the last dose of study drug or prior to the start of a new anticancer treatment whichever occurs first.

The following procedures will be performed at the EOT Visit unless already performed at the previous visit within 14 days:

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status
- Collect blood and urine samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Molecular markers – Blood
  - Molecular markers – Urine
  - CEA (for CRC cohort)
  - If PD based on RECIST 1.1, optional tumor biopsy
- Imaging by CT/MRI with measurement of lesions using RECIST 1.1 criteria (if progression not already confirmed radiologically)
- Review of AEs, disease-related symptoms, and concomitant medications
- Study drug compliance review (review of the study drugs diary and evaluation of contents of the study drug containers from home administration)
- Record any new anticancer therapy if applicable

8.6. Follow-up Phase

Once a subject has completed the EOT Visit they will enter the Follow-Up Phase. Subjects that withdraw from treatment for reasons other than PD will participate in ongoing response follow up.

8.6.1. Response (Efficacy) Follow-up

Subjects who discontinue the study for reasons other than PD will be followed every 6 weeks (±7 days) by clinic visit until PD, death, withdrawal of consent for further follow up, or lost to follow up, whichever occurs first or use of alternative anticancer therapy. During this period, the following procedures will be performed:

- Complete physical examination
- Obtain weight
- Vital signs
- ECOG performance status

- Collect blood samples for the following laboratory tests:
  - Hematology
  - Serum chemistry
  - Urinalysis
- Imaging by CT/MRI (lesions should be measured using RECIST 1.1 criteria)
- Record any new anticancer therapy

8.6.2. Long-term Follow-up

Once subjects progress or start use of alternative anticancer therapy (for subjects who have not withdrawn consent), they will be contacted approximately every 4 weeks (±7 days) by clinic visit or telephone to assess survival and the use of alternative anticancer therapy. Subjects will be contacted until death, subject withdrawal of consent, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Study Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent before the end of study.

9.2. Withdrawal from Study Treatment

Study treatment will be discontinued in the event of any of the following events:

- Progressive disease according to RECIST 1.1 criteria
- Unacceptable toxicity: an intercurrent illness or AE that prevents further administration of both study agents within any cohort
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Study termination by Sponsor
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo an EOT Visit and be followed for progression (if appropriate) and survival.

If a subject shows signs of disease progression on physical examination or laboratory assessment, the subject may continue study treatment, at the discretion of the investigator, until disease progression is confirmed by radiologic assessment (eg, CT/MRI) according to RECIST 1.1 criteria.

9.3. Withdrawal from Study

Withdrawal from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow-up
- Study termination by Sponsor

- Death

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. The measures taken to follow up should be documented.

When a subject withdraws before completing the study, the following information should be documented in the source documents:

- Reason for withdrawal
- Whether the subject withdraws full consent (ie, withdraws consent to treatment and all further contact) or partial consent (ie, withdraws consent to treatment but agrees to participate in follow-up visits)

10. STATISTICAL METHODS AND ANALYSIS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

General Considerations

The Phase 1b portion of this study is performed independently in five separate cohorts defined by the clinical indication; RCC, UC (cohorts 2 and 5), GC, and CRC. All safety and efficacy assessments other than at the RP2D level will be summarized or listed by dose level in each cohort.

The Phase 2 portion of this study is a parallel, unblinded design in five separate cohorts to assess the efficacy and safety of ibrutinib as a single agent or in combination with different anticancer agents depending on clinical indication. All analyses will be performed by individual cohort.

The timing for the analyses for the clinical study report (CSR) will be described in the statistical analysis plan (SAP)

All response assessments in this study are determined by investigator using the RECIST 1.1 criteria (Eisenhauer 2009).

10.1. Subject Information

10.1.1. DLT Evaluable Population

The DLT-evaluable population consists of subjects from Phase 1b who complete at least 21 days of treatment with ibrutinib in combination with the relevant anticancer agent or single agent ibrutinib after the initiation of therapy at the start of Cycle 1, and those who did not complete the DLT observation period and discontinued from study treatment due to a DLT event. The DLT Evaluable Population will be used for DLT assessments. Subjects in cohort 5 may miss up to 2 doses of ibrutinib and remain DLT evaluable.

10.1.2. Safety Population

The Safety Population consists of all subjects treated with at least one dose of any study drug. The Safety Population for ibrutinib consists of all subjects treated with at least one dose of ibrutinib at any dose level, and will be used for the analysis of the safety data.

10.1.3. Efficacy Evaluable Population

The Efficacy Evaluable Population, consisting of eligible subjects treated with at least one dose of ibrutinib at the RP2D level in combination with the relevant anticancer agent or one dose of ibrutinib as a single agent at the RP2D, will be used for the primary analysis of efficacy data.

10.1.4. Additional Analysis Populations

Additional Phase 2 analysis populations, which may be used in sensitivity analyses for primary and secondary efficacy objectives and for analyses of exploratory objectives, will be defined in the SAP.

10.2. Efficacy Endpoints (Phase 2)

10.2.1. Primary Endpoints

- The primary efficacy endpoint is median progression-free survival (PFS) in the RCC cohort 1 and UC cohort 2
- The primary efficacy endpoint is ORR in the GC cohort 3, CRC cohort 4, and UC cohort 5. ORR is the proportion of subjects who achieve a CR or PR by RECIST 1.1 criteria.

10.2.2. Secondary Endpoints

- Disease control rate (DCR) will be determined in each cohort. DCR is defined as the proportion of subjects who achieve a best response of CR, PR, SD $\geq$ 6 weeks in accordance with RECIST 1.1 criteria
- PFS in the GC cohort 3, CRC cohort 4, UC cohort 5
- ORR in the RCC cohort 1 and UC cohort 2
- Overall survival (OS) for each cohort
- DOR for each cohort

10.2.3. Exploratory Endpoints

- [redacted]

10.3. Sample Size Determination

The number of subjects required to be treated with ibrutinib at the RP2D level for the efficacy evaluation is determined for each disease cohort using the following methods.

10.3.1. Renal Cell Carcinoma

The primary endpoint is the median PFS. A sample size of approximately 55 efficacy evaluable subjects will provide 80% power at a 1-sided 0.05 significance level when testing the null hypothesis median PFS ≤4.9 months versus the alternative hypothesis median PFS ≥8.6 months. The 2-sided 90% Brookmeyer-Crowley confidence interval with the log-log-transformed Greenwood variance estimate for the median PFS will be calculated to test the hypotheses. The median PFS for everolimus is assumed to be 4.9 months under the null hypothesis (Motzer 2008, Motzer 2010). The study is designed to detect a 75% increase in median PFS to 8.6 months for ibrutinib in combination with everolimus. With the assumption of an exponential distribution for PFS, the sample size n = 55 to achieve a minimum of 80% power is determined by a simulation method with an enrollment rate of 5 subjects per month and with the data cut time for analysis to be at 6 months following the last subject enrollment.

A single interim analysis for futility will take place when approximately 25 subjects have completed 6 months of follow-up. The time of the interim analysis in terms of the number of included subjects will be further determined in the SAP. The proportion of subjects that are PFS event-free at 6 months will be assessed along with other safety and efficacy data in making the determination if the study should continue. The enrollment may continue while the interim analysis is performed.

10.3.2. Urothelial Carcinoma

10.3.2.1. Cohort 2 (Ibrutinib + Paclitaxel)

The primary endpoint for UC cohort 2 is median PFS. A sample size of approximately 55 efficacy evaluable subjects will provide 80% power at a 1-sided 0.05 significance level when testing the null hypothesis median PFS ≤2.3 months versus the alternative hypothesis median PFS ≥4.1 months. The 2-sided 90% Brookmeyer-Crowley confidence interval with the log-log-transformed Greenwood variance estimate for median PFS will be calculated to test the hypotheses. The median PFS for paclitaxel is assumed to be 2.3 months under the null hypothesis (Yafi 2011b, Vaughn 2002). The study is designed to detect a 78% increase in median PFS to 4.1 months for ibrutinib in combination with paclitaxel. With the assumption of an exponential distribution for PFS, the sample size n = 55 to achieve at a minimum of 80% power is determined by a simulation method with an enrollment rate of 5 subjects per month and with the data cut time for analysis to be at 6 months following the last subject enrollment.

A single interim analysis for futility will take place when approximately 25 subjects have completed 4 months of follow-up. The time of the interim analysis in terms of the number of included subjects will be further determined in the SAP. The proportion of subjects that are PFS event-free at 4 months will be assessed along with other safety and efficacy data in making the determination if the study should continue. The enrollment may continue while the interim analysis is performed.

10.3.2.2. Cohort 5 (Ibrutinib Monotherapy)

The primary endpoint is overall response rate (ORR) for this cohort. A total of up to 27 subjects treated with single-agent ibrutinib are to be enrolled based on Simon's 2-stage design. In stage-1, 13 subjects will be enrolled and if at least one responder is observed, an additional 14 subjects will be enrolled in stage-2. At the end of the study, if there are 4 or more responders, the null hypothesis will be rejected and the study treatment would be considered acceptable for further clinical development.

This Simon's 2-stage minimax design would provide 80% power to test the historical response rate of 5% (null hypothesis) against the target response rate of 20% (alternative hypothesis) at a 1-sided significance level of 0.05.

At the interim analysis, for the stage-1 data, the proportion of responding subjects will be assessed along with other safety and efficacy data in making the determination if the study should continue.

10.3.3. Gastric Adenocarcinoma

A Simon's 2-stage minimax design is selected based on the proportion of subjects having an overall response to study treatment of CR or PR. In this Simon's 2-stage design a total of 39 subjects are to be enrolled in two stages. In stage-1, 21 subjects will be enrolled and if at least 2 subjects are responders, an additional 18 subjects will be enrolled in stage-2. At the end of the study if there are 6 or more responders, then the null hypothesis is rejected and the study treatment would be acceptable for further clinical development.

This Simon's 2-stage design provides at least 80% power to test the historical ORR rate of 7% (null hypothesis) against the target ORR of 20% (alternative hypothesis) at a 1-sided significance level of 0.05.

10.3.4. Colorectal Adenocarcinoma

A Simon's 2-stage minimax design is selected based on the proportion of subjects having an overall response to study treatment of CR or PR. In this Simon's 2-stage design a total of 40 subjects are to be enrolled in two stages. In stage-1, 22 subjects will be enrolled and if at least 3 subjects are responders, an additional 18 subjects will be enrolled in stage-2. At the end of the study if there are 8 or more responders, then the null hypothesis is rejected and the study treatment would be acceptable for further clinical development.

This Simon's 2-stage design provides at least 80% power to test the historical ORR rate of 10% (null hypothesis) against the target ORR of 25% (alternative hypothesis) at a 1-sided significance level of 0.05.

10.4. Efficacy Analyses

10.4.1. Primary Efficacy Endpoint Analyses

The primary efficacy endpoint analysis will be performed on the Efficacy Evaluable Population in each disease cohort.

RCC Cohort 1 and UC Cohort 2

The primary efficacy endpoint is median PFS in RCC cohort 1 and UC cohort 2. The PFS is defined as the time from the date of first dose of study drug until confirmed PD based on investigator assessment, per RECIST 1.1, or death from any cause, whichever occurs first.

For the RCC cohort, the distribution of PFS and the median PFS will be estimated by the Kaplan-Meier method. The null hypothesis that median PFS $\leq$ 4.9 months will be tested against $\geq$ 8.6 months under the alternative hypothesis. The 2-sided 90% Brookmeyer-Crowley confidence interval with the log-log-transformed Greenwood variance estimate for median PFS will be calculated to test the hypotheses. The null hypothesis will be rejected if the confidence interval is above 4.9 month entirely.

The UC cohort 2 will be analyzed in a similar fashion, except that the null hypothesis that median PFS $\leq$2.3 months will be tested against $\geq$4.1 months under the alternative hypothesis.

Subjects who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. Subjects who are progression-free and alive at the time of clinical cut-off, or have unknown status will be censored on the date of the last adequate disease assessment. For subjects without post-baseline disease assessment, PFS will be censored on the date of first dose of study treatment.

GC Cohort 3, CRC Cohort 4, and UC Cohort 5

The primary efficacy endpoint is ORR in the GC, CRC cohorts, and UC cohort 5. ORR is defined as the proportion of subjects having a best overall response of CR or PR.

The analysis of ORR will be performed according to the Simon's 2-stage design using the prespecified stage-2 boundaries described in the Sections 10.3.2.2 through 10.3.4. A final analysis will be performed to provide the ORR with corresponding 2-sided 90% exact binomial CIs.

10.4.2. Secondary Efficacy Endpoint Analyses

The secondary efficacy endpoint analysis will be performed on the Efficacy Evaluable Population in each disease cohort.

10.4.2.1. Disease Control Rate (DCR)

The DCR will be estimated as the proportion of subjects with a best response of CR, PR or SD of length $\geq$6 weeks. The DCR will be calculated by clinical indication with accompanying 2-sided 90% exact binomial CIs.

10.4.2.2. Progression-free Survival (PFS)

PFS is a secondary endpoint for the GC, CRC cohorts, and UC cohort 5. PFS is defined as the time from the date of first dose of study drug until confirmed disease progression based on investigator assessment, per RECIST 1.1, or death from any cause, whichever occurs first. The analysis of PFS will be performed using the Kaplan-Meier methodology. The 2-sided 90% Brookmeyer-Crowley confidence interval with the log-log-transformed Greenwood variance estimate will be provided

for median PFS. The point estimate of the PFS rate at the selected landmark time points will be provided by the Kaplan-Meier method and the corresponding 2-sided 90% confidence interval will be calculated using the log-log-transformed Greenwood variance estimate.

10.4.2.3. Overall Response Rate (ORR) and Duration of Response (DOR)

ORR is a secondary endpoint for RCC and UC cohort 2. The ORR will be estimated as the proportion of subjects with a best response of CR or PR by investigator assessment. The ORR will be calculated by clinical indication with accompanying 2-sided 90% exact binomial CIs.

Duration of Response (DOR) is defined for responders as duration of time from initial response (CR or PR by investigator assessment) to first documentation of disease progression or death from any cause, whichever occurs first. Responders without documentation of disease progression and alive at the data cutoff or with unknown status will be censored the same way as PFS. DOR will be calculated along with its 2-sided 90% confidence interval.

10.4.2.4. Overall Survival (OS)

Overall survival is defined as the time from first dose of study drug to death due to any cause. The analysis of OS will be performed using the Kaplan-Meier methodology, which will provide estimates of median OS survival times and landmark OS survival rates at various timepoints.

10.4.3. Exploratory Efficacy Endpoint Analyses

[redacted]

10.5. Safety Analyses

Analysis of safety data will be conducted using the Safety Population, and all analyses will be performed separately by ibrutinib dose level for each disease cohort.

The safety data to be analyzed include AEs, clinical laboratory test results (hematology and chemistry), and vital signs measurements.

Adverse Events

Adverse event parameters to be evaluated are the type, incidence, and intensity of AEs; the relationship of AEs to study treatment; and the action taken with respect to study treatment due to AEs.

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent period is defined as the period of time from the first dose of study treatment, until the earlier of:

- For cohorts 1-5, 30 days following the last dose of ibrutinib or the companion drugs, whichever occurs later.

AND

- The start date of a new anticancer therapy

The TEAEs are those events that:

- Are not present prior to the treatment-emergent period and occur during the treatment-emergent period
- The onset dates are missing and end dates are during treatment-emergent period
- Are considered related to study drug by the investigator regardless of the start dates of the events, or
- Are present prior to the treatment-emergent period but worsen in severity during the treatment-emergent period or are subsequently considered related to study drug by the investigator

All treatment-emergent AEs will be included in the analysis. For each AE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized. The number and percent of subjects with TEAEs will be summarized according to intensity (CTCAE, v4.03) and drug relationship, as well as categorized by system organ class and preferred term. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, who experience dose reduction to any study drugs due to an AE, or who experience a severe or a SAE.

Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. Laboratory values will be converted to standard international units and will be graded using the NCI CTCAE Version 4.03 for those to which a grade can be applied.

10.6. Pharmacokinetic Analysis

Ibrutinib:

Plasma concentrations of ibrutinib and a major metabolite (PCI-45227) will be determined using a validated analytical method. Other potential metabolites of ibrutinib may be explored.

Ibrutinib and PCI-45227 bioanalytical data will be used in noncompartmental PK analysis. Plasma concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the PK report.

Descriptive statistics will be used to summarize ibrutinib and PCI-45227 concentrations at each sampling time point and PK parameters of ibrutinib and PCI-45227 (including, but not limited to: C_{max}, T_{max}, AUC_{last}, and $t_{1/2}$).

Individual and mean plasma ibrutinib and PCI-45227 concentration time profiles will be plotted.

Ibrutinib data from this study may also be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population-PK analysis using

nonlinear mixed effects models. For the population-PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated. The results of the population-PK analyses (if performed) will be presented in a separate report.

Ibrutinib PK data in this study will be compared to observed/reported concentration data for ibrutinib and/or population PK models to explore the potential for a pharmacokinetic interaction between ibrutinib in combination use with paclitaxel, or docetaxel

Paclitaxel and Docetaxel:

Plasma concentrations of paclitaxel and docetaxel will be determined using a validated analytical method. Bioanalytical data will be analyzed using noncompartmental PK analysis and will be compared to historical data found in the literature.

10.7. Interim Analysis

The interim analyses of efficacy data based on the Efficacy Evaluable Population for each cohort are for futility purposes and not requiring an alpha-level adjustments for the final efficacy analyses. All decisions at the time of the interim analyses will include all available clinical and safety data for that cohort and are not based solely on the efficacy data for the endpoint involved in the interim analysis.

RCC

A single interim analysis for futility will take place when approximately 25 subjects dosed at the RP2D level have completed 6 months of follow-up. The time of the interim analysis in terms of the number of included subjects will be further determined in the SAP. The proportion of subjects that are PFS event-free at 6 months will be assessed along with other safety and efficacy data in making the determination if the study should continue.

UC Cohort 2

A single interim analysis for futility will take place when approximately 25 subjects dosed at the RP2D level have completed 4 months of follow-up. The time of the interim analysis in terms of the number of included subjects will be further determined in the SAP. The proportion of subjects that are PFS event-free at 4 months will be assessed along with other safety and efficacy data in making the determination if the study should continue.

GC, CRC, and UC Cohort 5

The GC, CRC and UC cohort 5 are based on Simon's 2-stage designs involving the ORR endpoint. At the completion of stage 1 the proportion of responding subjects (best response of CR or PR) will be calculated, along with other safety and efficacy data when making the determination if the study should continue into the stage-2

10.8. Dose Level Review Committee (DLRC)

The study will be monitored in accordance with the Sponsor's Pharmacovigilance Committee procedures. Adverse events and SAEs will be reviewed by the Sponsor on an ongoing basis to identify safety concerns.

A DLRC will evaluate the safety data at the completion of the initial Phase 1b portion in each cohort, prior to continuing with enrollment into the Phase 2 portion. Members of this committee will include the medical monitor or designee, a Drug Safety representative, a biostatistician, and at least 2 participating investigators.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

11.1. Adverse Event Definitions and Classifications

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

Progressive disease is not an AE; rather it may be the cause of an AE. The clinical diagnosis that is associated with PD must be reported as all other AEs. “Disease progression” should never be used as an AE term.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the patient and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient through the completion of final study procedures.
- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing Condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.

- **Pre-planned or Elective Hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- **Asymptomatic Treatment Related Lymphocytosis:** This event should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

11.1.2. Serious Adverse Events

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (ie, the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the patient or patient may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the investigator believes that the event is serious, the event will be considered serious.

11.1.3. Severity Criteria (Grade 1-5)

Definitions found in the CTCAE version 4.03 will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

11.1.4. Causality (Attribution)

The investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

11.2. Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the IB/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the IB/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

11.3. Special Reporting Situations

Safety reporting situations on a Sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject/patient exposure to the study drug, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the Serious Adverse Event page of the CRF. If the AE is considered serious, it should be recorded on the AEs eCRF as serious and should be reported on the Serious Adverse Event Report Form.

11.4. Documenting and Reporting of Adverse Events

11.4.1. Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the Adverse Event CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

11.4.2. Adverse Event Reporting Period

All AEs whether serious or non-serious, will be documented in the source documents from the time signed and dated ICF is obtained until 30 days following the last dose of study drug. SAEs will be reported to the Sponsor from the time of ICF signing. Both serious and non-serious AEs will be recorded in the eCRF from the first dose of study drug until 30 days after the last dose of study drug.

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported. (See Section 11.1.1).

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the

relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

All deaths should be reported with the primary cause of death, as death is typically the outcome of the event, not the event itself. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines.

If a death occurs within 30 days after the last dose of study drug, the death must be reported to the Sponsor as a SAE.

11.4.3. Expediting Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results). The contact information (phone, email and fax) for Pharmacyclics Drug Safety can be found on the Serious Adverse Event Report Form and instructions.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities and governing bodies according to the local regulations.

The investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

11.4.4. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days after delivery will be requested.

A female subject must immediately inform the investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the investigator if his partner becomes pregnant from the time of consent to 90 days after the last dose

of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a SAE.

11.4.5. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for OS. If observed, enter data in the corresponding eCRF.

11.4.6. Adverse Events of Special Interest (AESI)

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of awareness.

11.4.6.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AEs of Grade 3 or higher*. Any treatment-emergent SAEs of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v 4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.6 above.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1. Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations

(including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2. Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

The investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (e.g., all advertising materials or materials given to the subject during the study) to the appropriate IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and informed consent form must also be approved by the IRB/REB/IEC before the implementation of changes in this study.

The investigator is responsible for providing the IRB/REB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/REB/IEC must comply with current US regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics or its authorized representative before entering subjects in this study: (1) a copy of the IRB/REB/IEC letter that grants formal approval; and (2) a copy of the IRB/REB/IEC-approved ICF.

12.3. Informed Consent

The ICF and process must comply with the US regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the investigator or his/her designee provides to the subject and the subject's agreement to participate.

The investigator or designee (designee must be listed on the Delegation of Authority log), **must** explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

12.4. Quality Control and Quality Assurance

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and investigators) and with the ICH guidelines on GCP (ICH E6).

12.5. Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 7.1.1.1), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/REBs/IECs. As the study Sponsor, Pharmacyclics will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

12.6. Study Files and Record Retention

The investigator **must** keep a record of **all** subjects who have consented to enroll in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

The investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/REB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosures, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, and documentation of CRF corrections, SAE forms transmitted to Pharmacyclics and notification of SAEs and related reports, source documentation, normal laboratory values, decoding procedures for blinded studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documentation will be retained by the investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The investigator must notify Pharmacyclics and obtain written approval from Pharmacyclics before destroying any clinical study documents or images (e.g., scan, radiograph, ECG tracing) at any time. Should an investigator wish to assign the study records to another party or move them to

another location, advance written notice will be given to Pharmacyclics. Pharmacyclics will inform the investigator of the date that study records may be destroyed or returned to Pharmacyclics.

Pharmacyclics must be notified in advance of, and Pharmacyclics must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Pharmacyclics to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

12.7. Case Report Forms and Record Maintenance

CRFs will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (e.g., physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the CRFs are accurate, complete, legible, and completed within a reasonable period of time. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs exists within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics or its authorized representative for this study. Study staff will be appropriately trained in the use of CRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the CRFs is true by providing electronic signature within the EDC system. After database lock, the investigator will receive a copy of the subject data (eg, paper, CD, or other appropriate media) for archiving at the study site.

12.8. Investigational Study Drug Accountability

Ibrutinib and anticancer agents used must be kept in a locked limited access room. Study drugs must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply a study drug to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

Accountability records for ibrutinib and anticancer agents must be maintained and readily available for inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. Study identification number (PCYC-1128-CA)
2. Subject identification number
3. Lot number(s) of ibrutinib or dispensed for that subject
4. Date and quantity of drug dispensed
5. Any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Pharmacyclics' requirements. If the site cannot meet Pharmacyclics' requirements for disposal/destruction, arrangements will be made between the site and Pharmacyclics or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

12.9. Study Monitoring/Audit Requirements

Representatives of Pharmacyclics or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. If access to the EMR cannot be granted to the monitor, the site must ensure that all certified copies of documents are available during monitoring visits for all screened and enrolled subjects. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/REB/IEC, representatives of Pharmacyclics, its designated agents and authorized employees of the appropriate Regulatory Authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

Pharmacyclics or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

12.10. Investigator Responsibilities

A complete list of investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572, both of which are signed by the investigator before commencement of the study. In summary, the investigator will conduct the study according to the current protocol; will read and understand the IB; will obtain IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/ REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

12.11. Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary, the Sponsor will select qualified investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols and promptly inform investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

12.12. Financial Disclosure

A separate financial agreement will be made between each principal investigator and Pharmacyclics or its authorized representative before the study drug is delivered.

For this study, each investigator and sub-investigator (as designated on the Form FDA1572) will provide a personally signed Financial Disclosure Form in accordance with § 21 CFR 54. Each investigator will notify Pharmacyclics or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

12.13. Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the investigator/designee will be provided.

The ICF will include a description of treatment in the event of a study related injury and handling of the costs associated therewith, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

12.14. Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/REB/IEC and required site approval must be received by Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on any change in risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign each revised ICF confirming their willingness to remain in the trial.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the Investigator and Pharmacyclics.

12.15. Publication of Study Results

Pharmacyclics may use the results of this clinical study in registration documents for Regulatory Authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics sufficient time to make appropriate comments before submission for publication.

In most cases, the investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The Medical Monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted in accordance with current standards for authorship as recorded in professional conference and journal submission instructions.

12.16. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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14. APPENDICES

Appendix 1. Schedule of Assessments – Renal Cell Carcinoma (RCC) – Ibrutinib and Everolimus – Cohort 1

		Treatment Phase[b]									FU Phase		
		Cycle 1			Cycle 2			Cycle 3 through Treatment d/c			Efficacy Evaluations	EOT	Response (Efficacy) FU[n]	Long-term FU
RCC	Screening Phase	D1	D8	D15	D1	D8	D15	D1	D8	D15	Every 6 weeks	30 days after treatment d/c	Every 6 weeks	Every 4 weeks
Visit Window	-28 days	N/A	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d	±7d	±7d	±7d
Informed consent	X													
Confirmation of eligibility criteria	X													
Medical history	X													
Physical examination (including disease-related symptom assessment)	X	X		X	X		X	X		X		X	X	
Weight	X	X	X	X	X	X	X	X	X	X		X	X	
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X		X	X	
ECOG Performance Status	X	X		X	X		X	X		X		X	X	
KPS score	X													
Concomitant medications[c]	X	X	X	X	X	X	X	X	X	X		X		
AEs[d]	X	X[e]	X	X	X	X	X	X	X	X		X		
12-lead ECG[f]	X	If clinically indicated (e.g., subjects with palpitations, lightheadedness)												
Laboratory:														
Hematology	X	X	X	X	X	X	X	X	X	X		X	X	
Serum Chemistry	X	X	X	X	X	X	X	X	X	X		X	X	
Coagulation panel	X													
Hepatitis serologies[g]	X													
Creatinine clearance (Cockcroft-Gault)	X													
Urinalysis	X	X	X	X	X	X	X	X	X	X		X	X	
Pregnancy Test[h]	X	X[h]												
Disease Assessment:														
CT / MRI scan[i]	X[i]										X[i]	X[i]	X[i]	
Pharmacokinetics/Biomarkers														
Pharmacokinetics (PK)[j]					X[j]									
Pharmacodynamics (PDn)[j, k]		X[k]			X[j]									
Molecular markers – blood [l]		X			X			X [l]				X		
Molecular markers- urine [l]		X			X			X [l]				X		
Buccal Swab		X												
Tumor biopsy [m]	X													
Study Drug Administration														
In-clinic administration of ibrutinib		X	X	X	X	X	X	X	X	X				
Administration of everolimus[o]		X	X	X	X	X	X	X	X	X				
Dispense ibrutinib		X			X			X						
Dispense Everolimus		X			X			X						
Study drug compliance review		X	X	X	X	X	X	X	X	X		X		
Survival and subsequent anticancer therapy												X	X	X

a. Vital signs will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

b. All assessments are to be performed prior to dosing unless otherwise specified.

c. Continuous from the signing of ICF or 14 days prior to the first dose of study drug (whichever is greater) through 30 days after the last dose of study drug.

d. AEs are reported from the time the subject signs the ICF until 30 days following last dose of study drug. All new malignant tumors are to be reported as AEs through Long Term Follow-up for OS.

e. Cycle 1 Day 1 ONLY: Assessment of AEs for 2 hours post everolimus administration. At the discretion of the investigator, subject may leave clinic 2 hours post everolimus administration.

f. At Screening, 12-lead ECGs will be recorded. Abnormalities noted at Screening should be included in the medical history.

g. Hepatitis serologies evaluated by central laboratory. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR must be performed and must be negative prior to enrollment.

h. Serum or urine pregnancy test will be required at Screening (within 3 days of Day 1) for women of childbearing potential. The test must be repeated prior to first dose if not performed within 3 days of C1D1. The test will be performed locally.

i. Measurements of lesions using RECIST 1.1 criteria is required where CT/MRI was obtained.

j. Predose and postdose PK and PDn samples will be collected per the schedule in Appendix 2.

k. Predose PDn sample will be collected on C1D1.

l. Blood and urine samples for biomarkers will be collected prior to dosing on Day1 for the first 3 cycles and then Day 1of every 3rd cycle thereafter until RECIST 1.1 documented disease progression, CR or EOT.

m. Archival tumor biopsy tissue will be collected when available or optional fresh tumor will be collected on consenting subjects at Screening and upon documented disease progression. Fresh tumor biopsy at Screening must be performed 7 days prior to enrollment.

n. Subjects who are withdrawn for reasons other than RECIST 1.1 determined progression will continue to have normally scheduled clinical and radiological disease assessments (CT/MRI) until disease progression is documented, death, withdrawal of consent for further follow up, or lost to follow up, whichever occurs first

o. Everolimus 10 mg PO qd should be administered 6 hours (± 15 minutes) after ibrutinib.

Appendix 2. C2D1: Pharmacokinetics and Pharmacodynamics Sampling Schedule – Renal Cell Carcinoma (RCC) Cohort 1[c]

Cycle	Study Day	Predose	Time after ibrutinib Dosing[a]			
			1 h ± 15 min	2 h ± 15 min	4 h ± 15 min	6 h ± 15 min
2	1	X[b]	X	X	X	X

a. Record actual time of sample collection.

b. PK and PDn samples collected 24 hours (± 2 hours) after previous ibrutinib dose and prior to ibrutinib dosing on Cycle 2 Day 1, which is also prior to everolimus administration since ibrutinib is dosed 6 hours before everolimus dosing.

c. PK samples will be collected in all cohort 1 subjects for ibrutinib PK determination only.

Appendix 3. Schedule of Assessments – Urothelial Carcinoma – Ibrutinib and Paclitaxel – Cohort 2

		Treatment Phase[b]										FU Phase		
		Cycle 1			Cycle 2			Cycle 3 through Treatment d/c			Efficacy Evaluations	EOT	Response (Efficacy) FU[n]	Long-term FU
Urothelial Carcinoma	Screening Phase	D1	D8	D15	D1	D8	D15	D1	D8	D15	Every 6 weeks	30 days after treatment d/c	Every 6 weeks	Every 4 weeks
Visit Window	-28 days	N/A	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d	±7d	±7d	±7d
Informed consent	X													
Confirmation of eligibility criteria	X													
Medical history	X													
Physical examination (including disease-related symptom assessment)	X	X		X	X		X	X		X		X	X	
Weight	X	X	X	X	X	X	X	X	X	X		X	X	
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X		X	X	
ECOG Performance Status	X	X		X	X		X	X		X		X	X	
KPS score	X													
Concomitant medications[c]	X	X	X	X	X	X	X	X	X	X		X		
AEs[d]	X	X[e]	X	X	X	X	X	X	X	X		X		
12-lead ECG[f]	X	If clinically indicated (e.g., subjects with palpitations, lightheadedness)												
Laboratory:														
Hematology	X	X	X	X	X	X	X	X	X	X		X	X	
Serum Chemistry	X	X	X	X	X	X	X	X	X	X		X	X	
Coagulation panel	X													
Hepatitis serologies[g]	X													
Creatinine clearance (Cockcroft-Gault)	X													
Urinalysis	X	X	X	X	X	X	X	X	X	X		X	X	
Pregnancy Test[h]	X	X[h]												
Disease Assessment:														
CT / MRI scan[i]	X[i]										X[i]	X[i]	X[i]	
Pharmacokinetics/Biomarkers														
Pharmacokinetics (PK)[j]					X[j]									
Pharmacodynamics (PDn)[j, k]		X[k]			X[j]									
Molecular markers – blood[l]		X			X			X[l]				X		
Molecular markers- urine[l]		X			X			X[l]				X		
Buccal Swab		X												
Tumor biopsy[m]	X													
Study Drug Administration														
In-clinic administration of ibrutinib		X	X	X	X	X	X	X	X	X				
In-clinic administration of paclitaxel[o]		X	X	X	X	X	X	X	X	X				
Dispense ibrutinib		X			X			X						
Study drug compliance review		X	X	X	X	X	X	X	X	X		X		
Survival and subsequent anticancer therapy												X	X	X

a. Vital signs will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

b. All assessments are to be performed prior to dosing unless otherwise specified.

c. Continuous from the signing of ICF or 14 days prior to the first dose of study drug (whichever is greater) through 30 days after the last dose of study drug.

d. AEs are reported from the time the subject signs the ICF until 30 days following last dose of study drug. All new malignant tumors are to be reported as AEs through Long Term Follow-up for OS.

e. Cycle 1 Day 1 ONLY: Assessment of AEs for 2 hours post paclitaxel infusion. At the discretion of the investigator, subject may leave clinic 2 hours post paclitaxel infusion.

f. At Screening, 12-lead ECGs will be recorded. Abnormalities noted at Screening should be included in the medical history.

g. Hepatitis serologies evaluated by central laboratory. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR must be performed and must be negative prior to enrollment.

h. Serum or urine pregnancy test will be required at Screening (within 3 days of Day 1) for women of childbearing potential. The test must be repeated prior to first dose if not performed within 3 days of C1D1. The test will be performed locally.

i. Measurements of lesions using RECIST 1.1 criteria is required where CT/MRI was obtained.

j. Predose and postdose PK and PDn samples will be collected per the schedule in Appendix 4

k. Predose PDn sample will be collected on C1D1.

l. Blood and urine samples for biomarkers will be collected prior to dosing on Day1 for the first 3 cycles and then Day 1of every 3rd cycle thereafter until RECIST 1.1 documented disease progression or CR and at EOT.

m. Archival tumor biopsy tissue will be collected when available or optional fresh tumor will be collected on consenting subjects at Screening and upon documented disease progression. Fresh tumor biopsy at Screening must be performed 7 days prior to enrollment.

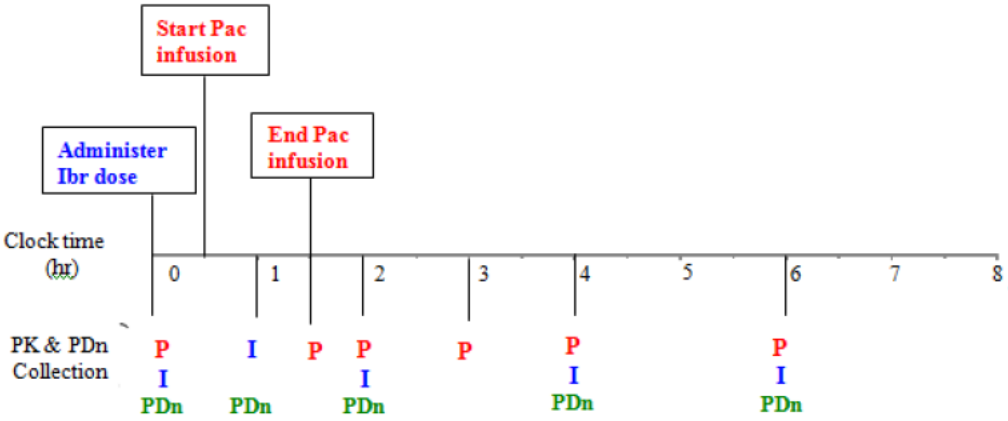
n. Subjects who are withdrawn for reasons other than RECIST 1.1 determined progression will continue to have normally scheduled clinical and radiological disease assessments (CT/MRI) until disease progression is documented, death, withdrawal of consent for further follow up, or lost to follow up, whichever occurs first.

o. Paclitaxel 80 mg/m^2 IV qweek infusion should start 30 minutes hours (± 5 minutes) after ibrutinib.

Appendix 4. C2D1: Pharmacokinetics and Pharmacodynamics Sampling Schedule and Scheme – Urothelial Carcinoma - Cohort 2[d]

Study Cycle & Day	Time Points	Ibrutinib	Paclitaxel	PDn
Cycle 2 Day 1	Predose [a]	X	X	X
	Drug Administration/Infusion (Time 0)	Drug Administration	Start Infusion[b]	
	Infusion (Time 1 hr)		End of Infusion X[c]	
	0.5 hr post end of infusion (±15 min)		X	
	1.0 hr post dose (±15 min)	X		X
	1.5 hr post end of infusion (±15 min)		X	
	2.0 hr post dose (±15 min)	X		X
	2.5 hr post end of infusion (±15 min)		X	
	4.0 hr post dose (±15 min)	X		X
	4.5 hr post end of infusion (±15 min)		X	
	6.0 hr post dose (±15 min)	X		X

a. Predose samples should be collected prior to the administration of any drug
b. Paclitaxel start of infusion is 30 min after ibrutinib dosing
c. End of infusion samples for paclitaxel should be collected within 5 minutes before the infusion is stopped
d. PK samples will be collected in all cohort 2 subjects for **ibrutinib** and **paclitaxel** PK determination



- All PKs and PDn at time 0 must be collected prior to dosing with any drug
- End of infusion PK samples collected within 5 minutes before the infusion is stopped
- PK collection times within 6-hour window
  - Paclitaxel (Pac, P): up to 4.5 hours post infusion (6 time points)
  - Ibrutinib (Ibr, I): up to 6 hours post dose (5 time points)
- PDn collection times (PDn) up to 6 hours post dose (5 time points)
- Total number of blood draws: 7

Appendix 5. Schedule of Assessments – Gastric Adenocarcinoma – Ibrutinib and Docetaxel – Cohort 3

		Treatment Phase[b]								FU Phase		
		Cycle 1			Cycle 2			Cycle 3 through Treatment d/c	Efficacy Evaluations	EOT	Response FU[n]	Long-term FU
Gastric Adenocarcinoma	Screening Phase	D1	D8	D15	D1	D8	D15	D1	Every 6 weeks	30 days after treatment d/c	Every 6 weeks	Every 4 weeks
Visit Window	-28 days	N/A	±2d	±2d	±2d	±2d	±2d	±2d	±7d	±7d	±7d	±7d
Informed consent	X											
Confirmation of eligibility criteria	X											
Medical history	X											
Physical examination (including disease-related symptom assessment)	X	X		X	X		X	X		X	X	
Weight	X	X	X	X	X	X	X	X		X	X	
Vital Signs[a]	X	X	X	X	X	X	X	X		X	X	
ECOG Performance Status	X	X		X	X		X	X		X	X	
KPS score	X											
Concomitant medications[c]	X	X	X	X	X	X	X	X		X		
AEs[d]	X	X[e]	X	X	X	X	X	X		X		
12-lead ECG[f]	X	If clinically indicated (e.g., subjects with palpitations, lightheadedness)										
Laboratory:												
Hematology	X	X	X	X	X	X	X	X		X	X	
Serum Chemistry	X	X	X	X	X	X	X	X		X	X	
Coagulation panel	X											
Hepatitis serologies[g]	X											
Creatinine clearance (Cockcroft-Gault)	X											
Urinalysis	X	X	X	X	X	X	X	X		X	X	
Pregnancy Test[h]	X	X[h]										
Disease Assessment:												
CT / MRI scan[i]	X[i]								X[i]	X[i]	X[i]	
Pharmacokinetics/Biomarkers												
Pharmacokinetics (PK)[j]					X[j]							
Pharmacodynamics (PDn)[j, k]		X[k]			X[j]							
Molecular markers – blood [l]		X			X			X [l]		X		
Molecular markers- urine [l]		X			X			X [l]		X		
Buccal Swab		X										
Tumor biopsy [m]	X											
Study Drug Administration												
In-clinic administration of ibrutinib		X	X	X	X	X	X	X				
In-clinic administration of docetaxel[o]		X			X			X				
Dispense ibrutinib		X			X			X				
Study drug compliance review		X	X	X	X	X	X	X		X		
Survival and subsequent anticancer therapy										X	X	X

a. Vital signs will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

b. All assessments are to be performed prior to dosing unless otherwise specified.

c. Continuous from the signing of ICF or 14 days prior to the first dose of study drug (whichever is greater) through 30 days after the last dose of study drug.

d. AEs are reported from the time the subject signs the ICF until 30 days following last dose of study drug. All new malignant tumors are to be reported as AEs through Long Term Follow-up for OS.

e. Cycle 1 Day 1 ONLY: Assessment of AEs for 2 hours post docetaxel infusion. At the discretion of the investigator, subject may leave clinic 2 hours post completion of docetaxel infusion.

f. At Screening, 12-lead ECGs will be recorded. Abnormalities noted at Screening should be included in the medical history.

g. Hepatitis serologies evaluated by central laboratory. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR must be performed and must be negative prior to enrollment.

h. Serum or urine pregnancy test will be required at Screening (within 3 days of Day 1) for women of childbearing potential. The test must be repeated prior to first dose if not performed within 3 days of C1D1. The test will be performed locally.

i. Measurements of lesions using RECIST 1.1 criteria is required where CT/MRI was obtained.

j. Predose and postdose PK and PDn samples will be collected per the schedule in Appendix 6.

k. Predose PDn sample will be collected on C1D1.

l. Blood and urine samples for biomarkers will be collected prior to dosing on Day1 for the first 3 cycles and then Day 1 of every 3rd cycle thereafter until RECIST 1.1 documented disease progression or CR and at EOT.

m. Archival tumor biopsy tissue will be collected when available or optional fresh tumor will be collected on consenting subjects at Screening and upon documented disease progression. Fresh tumor biopsy at Screening must be performed 7 days prior to enrollment.

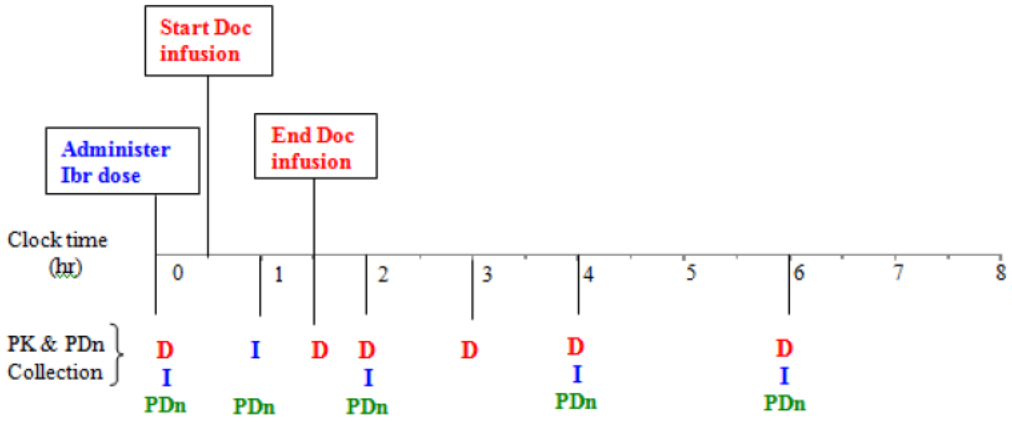
n. Subjects who are withdrawn for reasons other than RECIST 1.1 determined progression will continue to have normally scheduled clinical and radiological disease assessments (CT/MRI) until disease progression is documented, death, withdrawal of consent for further follow up, or lost to follow up, whichever occurs first

o. Docetaxel (75 mg/m^2 IV q 3weeks) infusion should start 30 minutes hours (± 5 minutes) after ibrutinib.

Appendix 6. C2D1: Pharmacokinetics and Pharmacodynamics Sampling Schedule and Scheme – Gastric Adenocarcinoma - Cohort 3[d]

Study Cycle & Day	Time Points	Ibrutinib	Docetaxel	PDn
Cycle 2 Day 1	Predose [a]	X	X	X
	Drug Administration/Infusion (Time 0)	Drug Administration	Start Infusion[b]	
	Infusion (Time 1 hr)		End of Infusion X[c]	
	0.5 hr post end of infusion (±15 min)		X	
	1.0 hr post dose (±15 min)	X		X
	1.5 hr post end of infusion (±15 min)		X	
	2.0 hr post dose (±15 min)	X		X
	2.5 hr post end of infusion (±15 min)		X	
	4.0 hr post dose (±15 min)	X		X
	4.5 hr post end of infusion (±15 min)		X	
	6.0 hr post dose (±15 min)	X		X

[a] Predose samples should be collected prior to the administration of any drug
[b] Docetaxel start of infusion is 30 min after ibrutinib dosing
[c] End of infusion samples for docetaxel should be collected within 5 minutes before the infusion is stopped
[d] PK samples will be collected in all cohort 3 subjects for ibrutinib and docetaxel PK determination



- All PKs at time 0 must be collected prior to dosing with any drug
- End of infusion PK samples collected within 5 minutes before the infusion is stopped
- PK collection times within 6-hour window
  - Docetaxel (Doc, D): up to 4.5 hours post infusion (6 time points)
  - Ibrutinib (Ibr, I): up to 6 hours post dose (5 time points)
- PDn collection times (PDn) up to 6 hours post dose (5 time points)
- Total number of blood draws: 7

Appendix 7. Schedule of Assessments – Colorectal Adenocarcinoma (CRC) – ibrutinib and cetuximab – Cohort 4

		Treatment Phase[b]										FU Phase		
		Cycle 1			Cycle 2			Cycle 3 through Treatment d/c			Efficacy Evaluations	EOT	Response (Efficacy) FU[a]	Long-term FU
CRC	Screening Phase	D1	D8	D15	D1	D8	D15	D1	D8	D15	Every 6 weeks	30 days after treatment d/c	Every 6 weeks	Every 4 weeks
Visit Window	-28 days	N/A	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d	±7d	±7d	±7d
Informed consent	X													
Confirmation of eligibility criteria	X													
Medical history	X													
Physical examination (including disease-related symptom assessment)	X	X		X	X		X	X		X		X	X	
Weight	X	X	X	X	X	X	X	X	X	X		X	X	
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X		X	X	
ECOG Performance Status	X	X		X	X		X	X		X		X	X	
KPS score	X													
Concomitant medications[c]	X	X	X	X	X	X	X	X	X	X		X		
AEs[d]	X	X[e]	X	X	X	X	X	X	X	X		X		
12-lead ECG[f]	X	If clinically indicated (e g , subjects with palpitations, lightheadedness)												
Laboratory:														
Hematology	X	X	X	X	X	X	X	X	X	X		X	X	
Serum Chemistry	X	X	X	X	X	X	X	X	X	X		X	X	
Coagulation panel	X													
Hepatitis serologies[g]	X													
Creatinine clearance (Cockcroft-Gault)	X													
Urinalysis	X	X	X	X	X	X	X	X	X	X		X	X	
Pregnancy Test[h]	X	X[h]												
Disease Assessment:														
CT / MRI scan[i]	X[i]										X[i]	X[i]	X[i]	
Pharmacokinetics/Biomarkers														
Pharmacokinetics (PK)[j]					X[j]									
Pharmacodynamics (PDn)[j, k]		X[k]			X[j]									
Molecular markers – blood [l]		X			X			X [l]				X		
Molecular markers- urine [l]		X			X			X [l]				X		
Buccal Swab		X												
CEA	X[p]	X[p]			X[p]			X[p]				X[p]		
Tumor biopsy [m]	X													
Study Drug Administration														
In-clinic administration of ibrutinib		X	X	X	X	X	X	X	X	X				
In-clinic administration of cetuximab[o]		X	X	X	X	X	X	X	X	X				
Dispense ibrutinib		X			X			X						
Study drug compliance review		X	X	X	X	X	X	X	X	X		X		
Survival and subsequent anticancer therapy												X	X	X

a. Vital signs will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

b. All assessments are to be performed prior to dosing unless otherwise specified.

c. Continuous from the signing of ICF or 14 days prior to the first dose of study drug (whichever is greater) through 30 days after the last dose of study drug.

d. AEs are reported from the time the subject signs the ICF until 30 days following last dose of study drug. All new malignant tumors are to be reported as AEs through Long Term Follow-up for OS.

e. Cycle 1 Day 1 ONLY: Assessment of AEs for 2 hours post cetuximab infusion. At the discretion of the investigator, subject may leave clinic 2 hours post cetuximab infusion.

f. At Screening, 12-lead ECGs will be recorded. Abnormalities noted at Screening should be included in the medical history.

g. Hepatitis serologies evaluated by central laboratory. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR must be performed and must be negative prior to enrollment.

h. Serum or urine pregnancy test will be required at Screening (within 3 days of Day 1) for women of childbearing potential. The test must be repeated prior to first dose if not performed within 3 days of C1D1. The test will be performed locally.

i. Measurements of lesions using RECIST 1.1 criteria is required where CT/MRI was obtained.

j. Predose and postdose PK and PDn samples will be collected per the schedule in Appendix 8.

k. Predose PDn sample will be collected on C1D1.

l. Blood and urine samples for biomarkers will be collected prior to dosing on Day1 for the first 3 cycles and then Day 1 of every 3rd cycle, thereafter until RECIST 1.1 documented disease progression or CR and at EOT.

m. Archival tumor biopsy tissue will be collected when available or optional fresh tumor will be collected on consenting subjects at Screening and upon documented disease progression. Fresh tumor biopsy at Screening must be performed 7 days prior to enrollment.

n. Subjects who are withdrawn for reasons other than RECIST 1.1 determined progression will continue to have normally scheduled clinical and radiological disease assessments (CT/MRI) until disease progression is documented, death, withdrawal of consent for further follow up, or lost to follow up, whichever occurs first.

o. Cetuximab (C1D1- 400 mg/m^2 over120-minutes; after that-250 mg/m^2 over 60 minutes) infusion should start 30 minutes hours (± 5 minutes) after ibrutinib.

p. CEA will be collected at Screening, prior to dosing on Day1 for the first 3 cycles and then Day 1of every 3rd cycle thereafter until RECIST 1.1 documented disease progression or CR and at EOT.

Appendix 8. C2D1: Pharmacokinetics and Pharmacodynamics Sampling Schedule – Colorectal Adenocarcinoma (CRC) - Cohort 4[c]

			Time after ibrutinib Dosing[a]			
Cycle	Study Day	Predose	1h ± 15 min	2 h ± 15 min	4 h ± 15 min	6 h ± 15 min
2	1	X[b]	X	X	X	X

a. Record actual time of sample collection.

b. PK and PDn samples collected 24 hours (± 2 hours) after previous ibrutinib dose and prior to ibrutinib dosing on Cycle 2 Day 1.

PK samples will be collected in all cohort 4 subjects for **ibrutinib** PK determination only.

Appendix 9. Schedule of Assessments – Urothelial Carcinoma – Ibrutinib Single Agent – Cohort 5

Urothelial Carcinoma	Screening Phase	Treatment Phase[b]								FU Phase	
		Cycle 1				Cycle 2			Cycle 3 through Treatment d/c	Efficacy Evaluations	EOT	Long-term FU
		D-3 OR Earlier	D1	D8	D15	D1	D8	D15	D1	Every 6 weeks	30 days after treatment d/c	Every 4 weeks
Visit Window	**-28 days**		**N/A**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±7d**	**±7d**	**±7d**
Informed consent	X											
Confirmation of eligibility criteria	X											
Medical history	X											
Physical examination (including disease-related symptom assessment)	X		X		X	X		X	X		X	
Weight	X		X	X	X	X	X	X	X		X	
Vital Signs[a]	X		X	X	X	X	X	X	X		X	
ECOG Performance Status	X		X		X	X		X	X		X	
KPS score	X											
Concomitant medications[c]	X		X	X	X	X	X	X	X		X	
AEs[d]	X		X	X	X	X	X	X	X		X	
12-lead ECG[f]	X											
Laboratory												
Hematology	X		X	X	X	X	X	X	X		X	
Serum Chemistry	X		X	X	X	X	X	X	X		X	
Coagulation panel	X											
Hepatitis serologies[g]	X											
Creatinine clearance (Cockcroft-Gault)	X											
CRP[o]			X[o]			X[o]			X[o]			
Urinalysis	X		X	X	X	X	X	X	X		X	
Pregnancy Test[h]	X		X[h]									
Disease Assessment												
CT / MRI scan[i]	X[i]									X[i]	X[i]	
Pharmacokinetics/Biomarkers												
Pharmacokinetics (PK)[j]						X[j]						
Molecular markers – blood[k]			X			X			X[k]		X	
Molecular markers- urine[k]			X			X			X[k]		X	
Buccal Swab			X									
Tumor biopsy[l, m, n]	X[l]	X[m]							X[n]			
Study Drug Administration												
In-clinic administration of ibrutinib			X	X	X	X	X	X				
Dispense ibrutinib			X			X			X			
Study drug compliance review			X	X	X	X	X	X	X		X	
Survival and subsequent anticancer therapy											X	X

a. Vital signs will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

b. All assessments are to be performed prior to dosing unless otherwise specified.

c. Continuous from the signing of ICF or 14 days prior to the first dose of study drug (whichever is greater) through 30 days after the last dose of study drug.

d. AEs are reported from the time the subject signs the ICF until 30 days following last dose of study drug. All new malignant tumors are to be reported as AEs through Long Term Follow-up for OS.

f. At Screening, 12-lead ECGs will be recorded. Abnormalities noted at Screening should be included in the medical history.

g. Hepatitis serologies evaluated by central laboratory. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR must be performed and must be negative prior to enrollment.

h. Serum or urine pregnancy test will be required at Screening (within 3 days of Day 1) for women of childbearing potential. The test must be repeated prior to first dose if not performed within 3 days of C1D1. The test will be performed locally.

i. Measurements of lesions using RECIST 1.1 criteria is required where CT/MRI was obtained.

j. Predose and postdose ibrutinib PK samples will be collected per the schedule in Appendix 10

k. Blood and urine samples for biomarkers will be collected prior to dosing on Day1 for the first 3 cycles and then Day 1 of every 3rd cycle thereafter until RECIST 1.1 documented disease progression or CR and at EOT.

l. Archival tumor biopsy tissue will be collected when available or optional fresh tumor will be collected on consenting subjects at Screening and upon documented disease progression. Fresh tumor biopsy at Screening must be performed 7 days prior to enrollment.

m. Applies to subjects enrolled in the paired-biopsy subgroup only. Pre-treatment fresh tumor biopsy for 5-10 subjects. Cycle 1 dosing should be after ~3 days post biopsy.

n. Applies to subjects enrolled in the paired-biopsy subgroup only. On- treatment fresh tumor biopsy should be collected during Cycle 3 anytime from Cycle 3 Day 1 and prior to Cycle 4 Day 1.

o. C-Reactive Protein will be collected on Day 1 of all cycles.

Appendix 10. C2D1: Pharmacokinetics Sampling Schedule and Scheme – Urothelial Carcinoma (Cohort 5)

Study Cycle & Day	Time Points	brutinib (Cohort 5)
Cycle 2 Day 1	Predose [a]	X
	Drug Administration	Drug Administration
	1.0 hr post dose (±15 min)	X
	2.0 hr post dose (±15 min)	X
	4.0 hr post dose (±15 min)	X
	6.0 hr post dose (±15 min)	X

a. Predose samples should be collected prior to the administration of any drug.

Appendix 11. ECOG Performance Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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Appendix 12. Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors or inducers with ibrutinib. Further information's can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

Appendix 13. Karnofsky Perfomance Scale Index

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
	40	Disabled; requires special care and assistance.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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