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| **Official Protocol Title:** | A Phase IB Dose Exploration Trial with MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Subjects with Selected Advanced Solid Tumors |
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**SPONSOR:**
Oncoethix GmbH, a wholly owned subsidiary of Merck Sharp & Dohme Corp.
(hereafter referred to as the Sponsor or Merck)

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**TITLE:**

A Phase IB Dose Exploration Trial with MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Subjects with Selected Advanced Solid Tumors

**IND NUMBER:** 123,715
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## SUMMARY OF CHANGES

**PRIMARY REASON(S) FOR THIS AMENDMENT:**

| Section Number (s) | Section Title(s) | Description of Change (s) | Rationale |
|---|---|---|---|
| 1.0<br>2.1;<br>2.2;<br>5.2;<br>5.2.1.3;<br>5.2.1.4;<br>5.2.1.6;<br>5.3;<br>6.0;<br>8.1;<br>8.9 | Trial Summary;<br>Trial Design;<br>Trial Diagram;<br>Trail Treatment(s);<br>NMC Cohort (Part B);<br>Dose Limiting Toxicity;<br>Dose Adaptation;<br>Randomization or Treatment Allocation;<br>Trial Flow Chart;<br>Statistical Analysis Plan Summary;<br>Sample Size and Power Calculation | An additional cohort of up to 30 NMC subjects has been added for treatment in a parallel cohort (Part B). NMC subjects enrolled in Part B will be treated at one dose level below the current dose level from the dose escalation part of the study (Part A). | To allow access to treatment for patients with this rare and aggressive cancer when treatment slots are unavailable in the dose escalation part of the study (Part A), while assessing safety, tolerability, pharmacokinetic/ pharmacodynamic parameters , anti-tumor activity and any additional scientific data. Priority for treatment allocation will be to enroll into Part A of the study (Dose Escalation). If there are no slots available in Part A at the time the NMC subject is identified, the subject will be enrolled and allocated to treatment in Part B (NMC Cohort). |

**ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:**

| Section Number (s) | Section Title (s) | Description of Change (s) | Rationale |
|---|---|---|---|
| 1.0 | Trial Summary | Revised withdrawal criteria of treatment interruption for > 2 weeks to be due to toxicity, as opposed to due to any reason. | Text updated to align with subject withdrawal criteria outlined in Section 5.8. |
| 4.1.3 | MK-8628 – Ongoing Clinical Trials in Advanced Solid Tumors | Updated the data reported in this section from this ongoing study to include up to date enrollment and response figures. | Updated the data reported in this section from this ongoing study to include up to date enrollment and response figures. |
| 5.1.2 | Inclusion criteria | Removed the guideline for allowing inclusion of subjects with an INR of <3 if being treated with anti-vitamin K therapy. | The use of anti-vitamin K therapy is prohibited on study, so this criterion is not applicable. |
| 5.1.2 | Inclusion criteria | Added an exception to allow NMC patients included with an interval of ≥ 2 weeks since chemotherapy, as opposed to the standard 3 week interval. | Due to the high risk for rapid disease progression in this indication, and provided any previously administered therapies meet the remaining criteria for wash-out in terms of half-lives, shortening the standard window can provide a faster time to treatment for subjects with this rare and aggressive cancer. |
| 5.1.3 | Exclusion criteria | Added language clarifying that subjects with treated and stable CNS metastases are eligible. | Text added for clarity. |

## 1.0 TRIAL SUMMARY

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|---|---|
| Abbreviated Title | MK-8628 Solid Tumor Trial |
| Sponsor Product Identifiers | MK-8628 |
| Trial Phase | Ib |
| Clinical Indication | Treatment of subjects with selected advanced solid tumors, including NUT midline carcinoma (NMC), non-small-cell lung cancer (NSCLC), triple negative breast cancer (TNBC) and castration-resistant prostate cancer (CRPC). |
| Trial Type | Interventional |
| Type of control | No treatment control |
| Route of administration | Oral |
| Trial Blinding | Unblinded Open-label |
| Treatment Groups | Part A: Dose Escalation<br>MK-8628 20 mg, twice a day, continuous, 21 consecutive days/cycle;<br>MK-8628 30 mg, twice a day, continuous, 21 consecutive days/cycle;<br>MK-8628 40 mg, twice a day, continuous, 21 consecutive days/cycle<br>Part B: NMC Cohort<br>MK-8628 10 mg, twice a day, continuous, 21 consecutive days/cycle;<br>MK-8628 20 mg, twice a day, continuous, 21 consecutive days/cycle;<br>MK-8628 30 mg, twice a day, continuous, 21 consecutive days/cycle;<br>MK-8628 40 mg, twice a day, continuous, 21 consecutive days/cycle |
| Number of trial subjects | Approximately a maximum of 72 subjects will be enrolled. |
| Estimated duration of trial | The Sponsor estimates that the trial will require approximately 2 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit. |
| Duration of Participation | Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of up to 2 weeks, eligible subjects will receive treatment according to their assigned regimen and dose level in 3-week dosing cycles. Treatment with MK-8628 will continue until documented disease progression, unacceptable toxicity, subject withdrawal of consent, subject non-compliance with trial treatment or procedure requirements, treatment interruption > 2 weeks for toxicity (except in the event of perceived benefit, with Sponsor agreement), recurrence of dose limiting toxicity (DLT) despite dose reduction (except in the event of perceived benefit, with Sponsor agreement), or by the investigators decision to withdraw the subject. After the end of treatment, subjects are to be followed up for safety for at least 30 days following the last MK-8628 dosing and until recovery or stabilization of all related toxicities. Tumor measurements are to be made every 6 weeks and bone scans will be performed every 12 weeks until progressive disease is observed. |

A list of abbreviations used in this document can be found in Section 12.10.

## 2.0 TRIAL DESIGN

### 2.1 Trial Design

This is an open-label, multicenter, international, non-randomized phase Ib trial with dose exploration of single-agent MK-8628 (formally known as OTX015) administered orally in subjects with selected advanced solid tumors (NMC, NSCLC, TNBC and CRPC), to be conducted in conformance with Good Clinical Practices (GCP).

The study will be conducted in two parallel parts: The primary objective will be evaluated in a dose escalation study (Part A), and additional NMC subjects will be treated in a parallel cohort (Part B).

Part A: Dose Escalation:

This dose escalation study will evaluate a twice-daily (BID) dosing regimen to establish the recommended phase II dose (RP2D). Subjects will be included in at least nine centers worldwide.

Dose administration will be continuous for 21 consecutive days per cycle (21-day cycles) at a starting dose of 20 mg BID.

A 6+8 two-stage design is used, offering a fast approach with continuous dose-limiting toxicity (DLT) rate monitoring via a modified toxicity probability index (Ji design) [1]. Up to three dose levels (DL) will be evaluated: 20, 30 and 40 mg BID, continuous, 21-day cycles.

Up to 14 subjects will be enrolled per DL, depending on the occurrence of DLT (see Sections 5.2.1.2 and 5.2.1.4) during the first 21 days of treatment. Thus up to 42 subjects evaluable for DLT will be enrolled in Part A.

Subjects will undergo a dose and/or schedule modification in the event of toxicity (see Section 5.2.1.6 and 5.6.1.1).

The RP2D will be selected based on a multi-faceted decision taking into account safety, tolerability, early efficacy signal, pharmacokinetic (PK) exposure and pharmacodynamic (PD) markers. The primary endpoint driving dose selection is the DLT rate, with weight given to the highest DL tolerated (<25% DLT rate) (see Section 5.2.1.5).

Part B: NMC Cohort:

An additional cohort of NMC subjects will be treated in a parallel study. This study will only include NMC subjects. The primary purpose of this part of the study is to allow access to treatment for patients with this rare and aggressive cancer when treatment slots are unavailable in Part A (Dose Escalation), while assessing safety, tolerability, pharmacokinetic/pharmacodynamic parameters, anti-tumor activity and any additional scientific data. Priority for treatment allocation will be to enroll into Part A of the study (Dose Escalation). If there are no slots available in Part A at the time the NMC subject is identified, the subject will be enrolled and allocated to treatment in Part B (NMC Cohort).

As in Part A, dose administration will be continuous for 21 consecutive days per cycle (21-day cycles). NMC subjects enrolled in Part B will be treated at one dose level below the current dose level from the dose escalation study in Part A. Therefore, a starting dose of 10 mg BID will be administered, and up to four dose levels will be evaluated: 10, 20, 30 and 40 mg BID, continuous, 21-day cycles. Once the RP2D is established, newly enrolled NMC subjects in Part B may be treated at the RP2D.

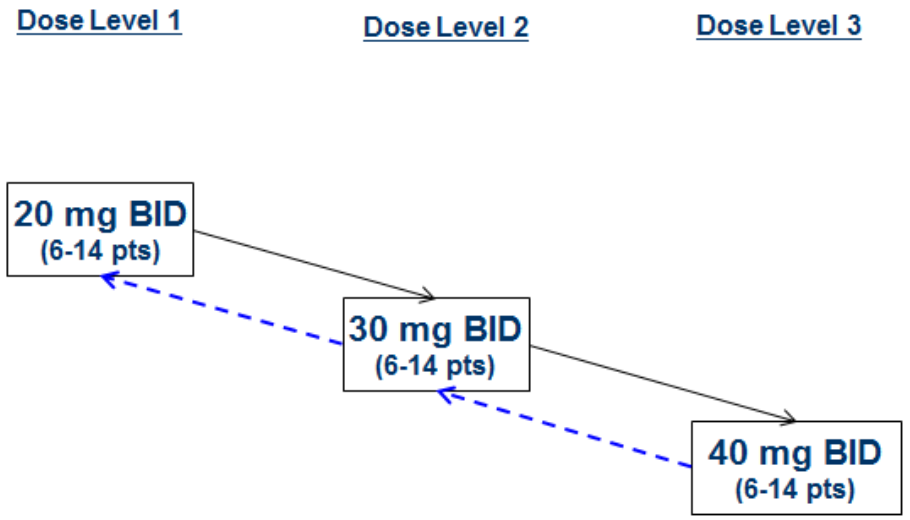
Subjects will undergo a dose and/or schedule modification in the event of toxicity (see Section 5.2.1.6 and 5.6.1.1).

Up to 30 NMC subjects will be enrolled in Part B.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

## 2.2 Trial Diagram

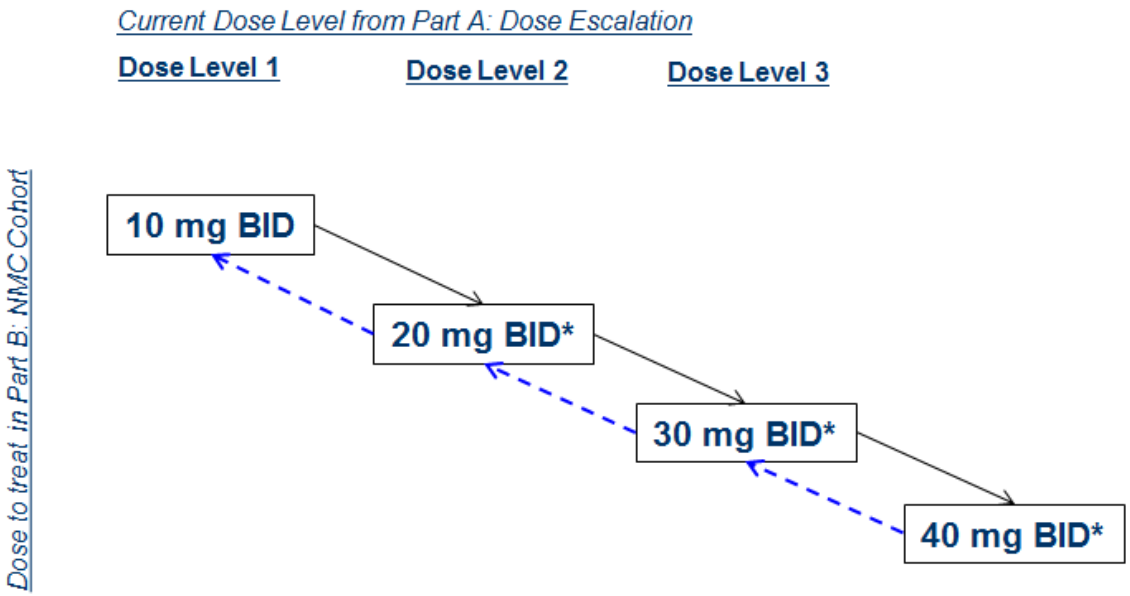
The trial design for Part A of the study is depicted in Figure 1.




*Ji Y, Wang SJ. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol. 2013;31(14):1785-91.*

Figure 1: Dose Escalation Scheme

The trial design for Part B of the study is depicted in Figure 2.




*NMC subjects enrolled in Part B will be treated at one dose level below the current dose level from the dose escalation study in Part A. A maximum of 30 NMC subjects will be enrolled in Part B.*
**Once the RP2D is established, newly enrolled NMC subjects in Part B may be treated at the RP2D.*

Figure 2: NMC Cohort Dosing Scheme

## 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

Objectives for this trial are to be evaluated for single-agent MK-8628 administered orally to subjects with selected solid tumors (NMC, NSCLC, TNBC or CRPC) as follows:

### 3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To determine the recommended phase II dose (RP2D).

### 3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To assess the safety and tolerability.

(2) **Objective**: To characterize pharmacokinetic (see Section 4.2.3.2) and pharmacodynamic (see Section 4.2.3.3) parameters.

(3) **Objective**: To evaluate antitumor activity using objective response rate (ORR), duration of response (DOR) and disease control rate (DCR) by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or Prostate Cancer Clinical Trials Working Group (PCWG2) as assessed by investigator radiologic review.

### 3.3 Other Objectives (Exploratory)

(1) Objective: Evaluate antitumor activity using progression-free survival (PFS) by RECIST v1.1 or PCWG2 as assessed by investigator radiologic review, and overall survival (OS).

(2) Objective: Explore the relationship between genomic variation and response to the treatment(s) administered. Variation across the human genome (germline and tumor) will be analyzed for association with clinical data collected in this study.

## 4.0 BACKGROUND & RATIONALE

### 4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-8628.

#### 4.1.1 Pharmaceutical and Therapeutic Background

MK-8628 is a synthetic small molecule targeted to bromodomains (BRD) 2, 3 and 4 of the tandem-BRD-containing family of transcriptional regulators known as the BET (bromodomain extraterminal) proteins.

In cancer, pathologic activation of c-MYC plays a central role in disease pathogenesis, by the coordinated upregulation of a transcriptional program influencing cell division, metastatic adaptation and survival [2][3]. Amplification of MYC is one of the most common genetic alterations observed in cancer genomes [4], and the validation of c-MYC as therapeutic target is supported by numerous lines of experimental evidence [5][6][7][8][9][10]. Nevertheless, despite the central importance of MYC in cancer pathogenesis, conventional approaches toward its direct inhibition have not proven successful. The absence of a clear ligand-binding domain is a formidable obstacle to direct inhibition, a challenging feature shared by many compelling transcriptional targets in cancer [11]. Considering chromatin as a platform for signal transduction [12], the inhibition of MYC transcription and function has been achieved through displacement of chromatin-binding, co-activator proteins, the BRDs, using competitive small molecules [13].

BRDs are protein interaction modules that specifically recognize Ɛ-N-acetylated lysine residues [14][15]. BRDs are common in nuclear proteins that regulate gene transcription and chromatin organization and play a key function of recruiting these protein complexes to acetylated chromatin. Dysfunction of BRD-containing proteins has been linked to the development of diverse diseases, and in particular to the development of cancer [16]. BRDs are highly sequence diverse but share a conserved fold comprised of a left-handed bundle of four alpha helices (αZ, αA, αB, αC) [17]. The acetyl-lysine side chain is typically anchored by a hydrogen bond to a conserved asparagine residue and has water-mediated interactions with a conserved tyrosine [15][18]. Crystal structures of BET complexes with di-acetylated histone 4-tail peptides showed that the first BRDs of BRD4 and BRD testis-specific protein (BRDT) may accommodate two acetyl-lysines in a single site [15][19].

The BET family of BRD proteins, which includes BRD2, BRD3, BRD4, and BRDT, are epigenetic reader proteins that bind acetylated lysine residues on histones playing critical roles in cellular proliferation and cell-cycle progression [20]. BRD4 binds to the positive

transcription elongation factor b (P-TEFb), a cyclin-dependent kinase, and stimulates ribonucleic acid (RNA) polymerase II-dependent elongation [21][22]. BRD4 is critical for survival of several diverse tumors due to its function promoting transcription of growth-promoting and anti-apoptotic genes [23], which has prompted the development of potent and selective protein interaction inhibitors targeting BET BRDs.

The biological action of BET proteins occurs through a protein-protein interaction (BET protein binding to an acetylated histone protein) and, as such, this biochemical activity has historically possessed poor tractability for small molecule drug discovery identification. The identification by Chung and colleagues [24] of potent, selective BET inhibitors was not the result an oncology drug discovery effort to "drug" the BRD4 protein to target NMC, but rather was fortuitous, being the result a high-throughput screen to identify molecules for potential use in atherosclerosis (apolipoprotein A1 upregulation). In independent studies during the same time period, Mitsubishi Tanabe scientists reported the discovery and development of thienotriazolodiazepine as a BET inhibitor (including MK-8628) [Mitsubishi Tanabe Pharma Corporation. Antitumor agent. WO 2009084693; 2009]. Building on these findings, Bradner and colleagues synthesized a thienotriazolodiazepine, JQ1 [23]. The initial presumption of low tractability of the BET proteins has proven not to be the case, as multiple researchers have identified other potent, selective BET inhibitors with substantially different chemical structures [23][25][26][27]. The crystal structures of these small molecule inhibitors bound to BRD4 illustrate that the binding pocket, which also binds acetyl-lysine, is small, deep, and hydrophobic.

#### 4.1.1.1 NUT Midline Carcinoma

NUT midline carcinoma (NMC) is an aggressive subtype of squamous cell carcinoma (SCC) defined by chromosomal rearrangement of the gene nuclear protein in testis (NUT). In most cases, NUT on chromosome 15 is fused to BRD4 on chromosome 19 [28], providing the first indication of a link between BRDs and cancer. Human BRD4 was first identified as a result of its involvement in NMC. A minor NMC subset has alternative rearrangements that create BRD3-NUT fusion genes. These genetic rearrangements of the BRD3 and BRD4 loci in which in-frame chimeric proteins of the N-terminal BRDs of BRD3 or BRD4 with NUT, give rise to a uniformly fatal SCC subtype, [29]. The somatic alteration defining NMC is a t(15;19)(q14;p13.1) chromosomal translocation that results in a fusion protein between the BET proteins BRD3 or BRD4 and the nuclear protein NUT [30].

With a median survival time of 6.7 months [31], NMC is far more aggressive than typical non-cutaneous SCC. The lack of effective treatments means a diagnosis of NMC comes with substantial clinical challenges. NMC has no organ or tissue of origin and can occur anywhere but most commonly along the midline, with typical sites being the head, neck and mediastinum. However, cases arising in the bladder, pancreas, adrenal gland, kidney and salivary gland have been described [32], challenging the notion that this is strictly a midline neoplasm. Although rare, the true incidence of NMC is still unknown because it is frequently confused with common forms of SCC that arise most often in the aero-digestive tract; NMC is still undoubtedly underdiagnosed.

The key to the diagnosis of NMC is a high index of suspicion coupled with molecular testing. Given that NUT expression is restricted to the testes, the tumor can be diagnosed with virtually 100% specificity by immunohistochemistry (IHC) for NUT protein expression [33].

Because NMC cannot be diagnosed by morphology alone, and occurs in many organs and across a wide range of ages (from neonates to the elderly), it is recommended that testing for NUT expression by immunohistochemistry (IHC) be performed in all poorly differentiated non-cutaneous carcinomas that lack glandular differentiation [34].

The optimal treatment for patients with NMC is unclear. Although a number of therapeutic regimens have been used, the overall effectiveness of chemotherapy is questionable. In the series by Bauer et al., gross total resection was associated with improved survival, both PFS and OS [31]. Intriguingly, these tumors seem to respond well to early administration of radiotherapy.

Given that the disruption of complexes containing BRD proteins is a critical facet of NMC pathogenesis and that that these proteins are key oncogenic drivers for this cancer [28], it was hypothesized that an agent that would block the biological activity of BRD4-NUT and/or BRD3-NUT may be an effective therapy for NMC. Recent laboratory studies have suggested that the NUT fusion protein results in aberrant histone acetylation and blockade of differentiation. Efforts have been made to develop targeted therapeutic approaches such as direct acting inhibitors of the BRD3 and BRD4 bromodomains. MK-8628, an orally bioavailable small molecule inhibitor of BRD2, BRD3 and BRD4 has been shown to inhibit the growth of Ty82 BRD-NUT carcinoma in nude mice by 79% [35].

#### 4.1.1.2 Non-Small Cell Lung Cancer

Approximately 50%-60% of NSCLC patients have at least one identifiable driver mutation, with the most common mutations being the Kirsten ras (KRAS) gene (24%-27%) and the epidermal growth factor receptor (EGFR) gene (13%-22%), with translocations involving anaplastic lymphoma kinase (ALK) in another 5%-6% [36][37][38]. Several additional mutations have been identified.

KRAS, like other RAS family of oncogenes, encodes a guanine triphosphate-binding protein involved in cellular growth, differentiation, and apoptosis by interacting with multiple effectors. KRAS mutations are typically mutually exclusive of EGFR mutations, occurring in different patient populations [37][39][40]. In a retrospective series of 1036 patients, multivariate analysis demonstrated that the presence of a KRAS mutation was associated with a shorter OS (HR 1.21, $p = 0.048$) [41]. Mutant KRAS is a strong activator of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways [42], and the inhibition of KRAS-dependent MAPK and PI3K pathways results in MYC dephosphorylation [43][44], which contributes to its degradation. In support of MYC as a therapeutic target in NSCLC, Soucek et al. reported regression of KRAS-induced lung adenocarcinoma upon systemic expression of a dominant-negative MYC inhibitory peptide (OMOMYC) [45]. Furthermore, in vivo experiments using a similar KRAS-induced cancer model confirmed that the BET bromodomain inhibitor, JQ1, prompts tumor regression in mutant KRAS mouse lung cancers [46]. In the same report, preclinical models showed that JQ1 exerts anti-proliferative activity in a diverse panel of NSCLC cell lines with different mutational profiles [46]. This study suggested that KRAS-mutant NSCLC harboring a concurrent liver kinase B1 (LKB1) loss-of-function mutation is comparatively more resistant. However, meta-analyses examining co-mutation rates in non-small cell lung cancer find that $\leq$5% of patients carry *both* KRAS activating and the LKB1 inactivating mutations [47].

A subgroup of NSCLC patients have tumors containing an inversion in chromosome 2 that juxtaposes the 5' end of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the 3' end of the ALK gene, resulting in the novel fusion oncogene EML4-ALK [48]. This fusion oncogene rearrangement is transforming both in vitro and in vivo and defines a distinct clinicopathologic subset of NSCLC.

A recent preclinical report indicates that MK-8628 is broadly active in both EMLA4-ALK positive and negative NSCLC cell lines, and its sensitivity is not correlated to basal levels of BRDs, c-MYC, N-MYC, BCL2 or p21 [49]. In sensitive NSCLC cell lines, MK-8628 results in a rapid and sustained downregulation of c-MYC or N-MYC. In addition, MK-8628 exhibits in vitro additive activity when combined with crizotinib in ALK positive NSCLC cell lines. Preclinical studies relying on genetic or pharmacologic disruption of either MYC or BET protein function point toward a broad potential of MK-8628 to impair NSCLC tumor growth across a range of genetically diverse backgrounds.

#### 4.1.1.3 Triple-Negative Breast Cancer

Triple negative breast cancer (TNBC) is a distinct subset of breast cancer defined by the lack of IHC expression of the estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor 2 (HER2), accounting for approximately 15%-20% of breast cancer patients. According to the American Society of Clinical Oncology (ASCO) guideline recommendations, breast cancer is considered negative for ER or PgR if less than 1% of tumor cell nuclei are immunoreactive [50], and negative for HER2 if either the IHC score is 0 or 1+, or Fluorescence In Situ Hybridization (FISH) average gene copy < 4 signals per cell nucleus [51].

TNBC terminology is confusing since it reflects a heterogeneous population [52] with a more complex molecular transcriptome than is suggested by the triple-negative IHC expression. Classification of breast tumors by their gene expression signature revealed distinct subtypes with important implications for outcome [53][54]. Of these subtypes, which include HER2-enriched, luminal A, luminal B, and basal-like breast cancer (BLBC), the latter has the poorest prognosis [55]. Gene expression analysis demonstrates that the molecular signature of TNBC generally overlaps with basal-like breast cancer, with concordance rates of 70%-90% [56][57]. However, not all TNBC can be defined as basal-like breast cancer [55][58], as a small minority of BLBC patients do in fact, have some ER and HER2 expression. TNBC is also associated with Breast Cancer gene (BRCA)-related breast cancer, although the incidence of BRCA mutations in TNBC varies from 16% to 42% [59][60]. Other mechanisms resulting in downregulation of BRCA1/2, including epigenetic alterations and overexpression of BRCA1 inhibitors [61][62][63][64], are also associated with TNBC and likely contribute to aneuploidy and genomic instability characteristics of this subgroup.

Chemotherapy remains the core option for TNBC patients. However, treatment with cytotoxic chemotherapy produces mixed results and has a variable impact on long-term prognosis [65][66][67][68]. In the neoadjuvant setting, TNBC exhibits a better response to chemotherapy compared with non-TNBC [69]. Patients who do not respond well to preoperative chemotherapy have a high risk of relapse within the first 2 years and worse OS (3-year survival, 68% versus 94% pathological complete response non-responders versus responders) [65][70][71][72][73].

Metastatic TNBC is an aggressive disease that is associated with a high proliferation index [74], visceral and central nervous system (CNS) metastases [69][75][76], and poor outcome despite treatment. Median survival of advanced TNBC is at best 12 months [77], much shorter than the duration of survival seen in other subtypes of advanced breast cancer. The most dramatic improvements in survival are associated with targeted therapy. However, TNBC trials of targeted therapy as single agents or in combination with chemotherapy, despite a strong biological rationale in many cases, have been less promising, resulting in modest gains in PFS and no gains in OS [77]. Retrospective evaluations of anti-angiogenic agents have demonstrated encouraging efficacy signals in TNBC, with a doubling of PFS in select trials [78][79][80][81]. However, PFS gains remain modest (~3 months) [79][80]. Therefore, identification of more active therapies for TNBC patients remains an important clinical challenge.

MYC expression was found to be disproportionally elevated in TNBC, and in primary tumors, MYC signaling did not predict response to neoadjuvant conventional chemotherapy but was associated with shortened disease-free survival [82]. Furthermore, a recent report on TNBC indicates that the interaction with BRD4 is critical for the oncogenic function of Twist, a key activator of epithelial-mesenchymal transition. In addition, pharmacologic inhibition of the Twist-BRD4 association reduces invasion, cancer stem cell-like properties, and tumorigenicity of TNBC cells [83].

#### 4.1.1.4 Castration-Resistant Prostate Adenocarcinoma

Patients who develop metastatic castration-resistant prostate cancer (CRPC) invariably succumb to the disease. Progression to CRPC after androgen deprivation therapy is predominantly driven by deregulated androgen receptor (AR) signaling [84][85][86]. Maintenance of AR signaling is the most common resistance mechanism that patients with advanced prostate cancer develop after conventional hormone treatments [87]. AR amplification, mutation and alternative splicing have all been suggested as potential resistance mechanisms to anti-androgen treatments [85][88][89]. Over one half of CRPC patients have at least one of these aberrations in the AR pathway [90].

Despite the success of recently approved therapies targeting AR signaling, such as abiraterone [91][92][93] and second-generation anti-androgen therapy including enzalutamide [94][95], durable responses are limited, presumably owing to acquired resistance.

Recent preclinical studies showed that AR-signaling-competent human CRPC cell lines are preferentially sensitive to BET bromodomain inhibition [96]. BRD4 physically interacts with the N-terminal domain of the AR and can be disrupted by the BET inhibitor JQ1 [13][23]. Like the direct AR antagonist enzalutamide, JQ1 disrupted AR recruitment to target gene loci. By contrast with enzalutamide, JQ1 functions downstream of AR, and more potently abrogated BRD4 localization to AR target loci and AR-mediated gene transcription, including induction of the TMPRSS2-ERG gene fusion and its oncogenic activity [96]. Furthermore, in vivo, BET bromodomain inhibition was found to be more efficacious than direct AR antagonism in CRPC xenograft mouse models. As BET inhibitors function downstream of AR, these compounds may be effective in the context of AR-mediated resistance, including compensatory mechanisms involving related steroid hormone receptors that are also likely to require BET bromodomain functioning.

### 4.1.2 MK-8628 Metabolism – Cytochrome P450 Interactions

Results from MK-8628 incubations either with individual recombinant cytochrome P450 (CYP) or with human microsomes and chemical inhibitors to individual CYPs show MK-8628 was metabolized to the mono-hydroxylated metabolite mainly by CYP3A4 and to a lesser extent by CYP2C9 and potentially by CYP2C19, which will need to be confirmed. Results from incubations with individual uridine diphosphate (UDP) glucuronosyltransferase(s) (UGT) showed that MK-8628 can be glucuronidated mainly by UGT1A7 and, to a lesser extent, by UGT1A1, 1A10, 1A3, 1A8, and 1A9. MK-8628 inhibits CYP2A6 and 3A4 turnover of probe substrates in microsomes with half maximal inhibitory concentration ($IC_{50}$) values that were >10 µM. At 10 µM MK-8628, the inhibition of CYP2A6 and CYP3A4 were 30% and 39%, respectively. MK-8628 has a high apparent permeability ($P_{app}$ ≥21 x $10^{-6}$ cm/s apical-to-basal) across cell monolayers and is a phosphoglycolate phosphatase (P-gP) substrate. The involvement of several enzymes in the metabolism of MK-8628 reduces concerns for victim drug-drug interaction (DDI). The inhibition of CYP2A6 and particularly CYP3A4 raises concerns that MK-8628 could be a perpetrator in a DDI with co-administered drugs whose clearance is primarily mediated by these enzymes.

### 4.1.3 MK-8628 – Ongoing Clinical Trials in Advanced Solid Tumors

Study MK-8628-P003 (previously known as OTX015_108), a Phase Ib study in subjects with selected advanced solid tumors (NMC, NSCLC with either rearranged *ALK* or *KRAS* mutation, and CRPC) was started (first subject enrolled) on 05 November 2014. The main objective of this study was to determine the recommended Phase II dose, with a dose escalation of once-daily dosing regimens assessed. A total of 46 subjects were treated as of October 2016. Two out of five NMC subjects treated at Dose Level (DL) 1 on the continuous regimen (80 mg once daily [QD], 21/21 days) achieved objective responses (2 confirmed partial responses [PRs]). The preliminary recommended dose / schedule for phase 2 studies in solid tumors was 80 mg/day continuous dosing. Following dose escalation, an expansion cohort was authorized to enroll and treat 6 additional NMC patients at this dose level. As of October 2016, one patient remains ongoing from this cohort and is currently being treated in Cycle 17, with a confirmed PR in Cycle 10. At DL1, four DLTs were observed in 4 out of 16 subjects treated according to the continuous regimen (80 mg QD, 21/21 days), consisting of two prolonged grade 3 thrombocytopenia lasting more than 7 days, 1 grade 4 thrombocytopenia and 1 grade 3 hyperbilirubinemia/transaminitis lasting more than 48 hours. No DLT was observed in 13 subjects treated according to the intermittent regimen (i.e., 100 mg QD, 7/21 days). At DL2, two DLTs have been observed in 2 out of 4 subjects treated according to the continuous regimen (100 mg QD, 21/21 days) consisting of one grade 4 thrombocytopenia, and one case of a treatment interruption for > 7 days due to grade 2 nausea/anorexia that did not fulfill the DLT definition, but was considered as a DLT by the investigator. No DLT was observed in 3 subjects treated according to the intermittent regimen (i.e. 120 mg QD, 7/21 days). At DL3, 160 mg QD, 7/21 days, no DLTs were observed in 6 subjects treated.

By literature survey, several mechanisms can be invoked to explain an observation of clinical hyperbilirubinemia including competitive inhibition of transporters/enzymes involved in the disposition of bilirubin and/or its conjugates. Preliminary results of in vitro experiments

using parent compound only suggest that MK-8628 can weakly inhibit OATP1B1 ($IC_{50}$ > 5 μM), OATP1B3 ($IC_{50}$ = 3 μM), and BSEP ($IC_{50}$ > 10 μM) in a concentration-dependent manner, while no concentration-dependent inhibition of MRP2 or MRP3 has been observed. In addition, MK-8628 can weakly inhibit UGT1A1 ($IC_{50}$ = 10 μM), the primary enzyme involved in the conjugation of bilirubin. Feasibility assessments of future experiments to elucidate the mechanism of clinical hyperbilirubinemia are ongoing.

Additionally, prior to opening Study MK-8628-P003, MK-8628 was provided for compassionate use treatment of patients with BRD-NUT midline carcinoma at one clinical center. A total of 5 patients were treated at a dose of 80 mg QD continuously for at least 21 days. Two of these patients achieved dramatic objective responses (2 complete responses [CRs]).

Additional details can be found in the Investigator's Brochure (IB).

## 4.2 Rationale

### 4.2.1 Rationale for the Trial and Selected Subject Population

In the present study, adult subjects with selected advanced solid tumors with the potential to respond to BET inhibition (NMC, NSCLC, TNBC and CRPC) will receive MK-8628 orally to determine the recommended dose (RD) for phase II studies. Two QD evaluations were evaluated in parallel in a previous study. This study will focus on the evaluation of a BID regimen.

MK-8628, a pan-BET bromodomain inhibitor, shows activity in several preclinical hematologic and somatic cancer models. Meaningful antitumor activity has also been reported in subjects with heavily pretreated hematological malignancies in the ongoing phase I clinical study treated with MK-8628. Accumulating studies reveal the critical roles of BET bromodomains in cancer development. The first clue linking BRD4 with cancer was identification of the BRD4-NUT fusion oncogene which was recognized as an important mechanism in NMC. Besides the chromosomal rearrangement-induced NMC, other studies have also indicated that BRDs may contribute to cancer development through different mechanisms. Knockdown of BRD4 exhibited a robust antileukemic activity against AML in vitro and in vivo. Other recent studies with small molecule inhibitors of the BET proteins revealed the critical role of BRD4 in the development of several hematopoietic and somatic cancers. Accordingly, small molecule inhibitors targeting BET, such as MK-8628, have been proven to be a promising drug for cancer therapy.

Mutant KRAS is a strong activator of the MAPK and PI3K pathways, and the inhibition of KRAS-dependent MAPK and PI3K pathways results in the dephosphorylation of MYC which contributes to its degradation. Recent studies in NSCLC preclinical models reported that the BET bromodomain inhibitors, MK-8628 and its analog JQ1, exert remarkable antitumor activity in NSCLC harboring KRAS mutation. However, the concurrent mutation in KRAS and LKB1 genes abrogates effects of these BET inhibitors. Furthermore, in vivo experiments using genetically engineered mouse lung cancer models confirmed that JQ1 prompts tumor regression in mutant Kras mouse lung cancers, and sensitivity both in vitro and in vivo was found to be mediated by MYC downregulation. MK-8628 is also broadly active in several NSCLC cell lines harboring EML4-ALK gene fusion supporting its further

clinical development in patients with either KRAS mutated or ALK positive NSCLC. In order to explore the clinical implications of inducing changes in expressions of various intracellular pathways by disrupting the complexes containing BRD as a result of treatment on BET inhibitors like MK-8628, this study has adopted to not restrict the study population to only RAS mutated or ALK positive patients, but rather to allow all comers for NSCLC.

MYC expression was found to be disproportionally elevated in TNBC, and in primary tumors, MYC signaling was associated with shortened disease-free survival. A recent report on TNBC indicates that the interaction with BRD4 is critical for the oncogenic function of Twist, a key activator of epithelial-mesenchymal transition. In addition pharmacologic inhibition of the Twist-BRD4 association reduces invasion, cancer stem cell-like properties, and tumorigenicity of TNBC cells highlighting the use of MK-8628 in this poor prognosis tumor.

In CRPC, the BET inhibitor JQ1 disrupts AR recruitment to target gene loci and functions downstream of AR, and abrogated BRD4 localization to AR target loci and AR-mediated gene transcription. In addition, in vivo, BET bromodomain inhibition was found to be more efficient than direct AR antagonism in CRPC xenograft mouse models. As BET inhibition functions downstream of AR, MK-8628 may be effective in the context of AR-mediated resistance, including compensatory mechanisms involving related steroid hormone receptors that are also likely to require BET bromodomain function.

As of 30-June-2015, no pediatric patients have been treated with MK-8628. Based on the age of rats used in the toxicology studies (~5 weeks at study initiation which is equivalent to 10 to 12 years in humans for overall development of the central nervous system and reproductive systems), the current toxicology data supports treatment with MK-8628 in children 10 years of age and older. Additionally, a model-based extrapolation of adult pharmacokinetic data was conducted to provide the basis for initial dosing of MK-8628 in an expanded patient population to include adolescents ≥15 years of age. The pharmacokinetic model developed for this purpose utilized 941 concentration-time samples from adult subjects enrolled on protocols MK-8628-P001, MK-8628-P002, and MK-8628-P003 with doses from 10 mg to 160 mg. The adult subjects in the model development dataset encompassed a wide range of body weight, from 44.5 kg to 127 kg. The 50th percentile weight for a 15 year old adolescent falls within this range based on the weight-for-age growth charts published by the Centers for Disease Control and Prevention (56 kg for 15 year old male/ 52 kg for female) [97]. Parameter scaling for MK-8628 apparent oral clearance (CL/F) and volume of distribution (V/F) was performed by standard weight-based allometric principles and for both CL/F and V/F, the estimated exponents were ~0.4, suggesting minimal influence of weight on MK-8628 pharmacokinetic disposition from 44.5 to 127 kg.

Simulations from the final pharmacokinetic model were conducted at the proposed 20 mg, 30 mg and 40mg BID dose for both a typical weight adult (72 kg) and 50th percentile for a 15 year old adolescent. Based on these projections, substantial overlap in steady-state trough concentration (e.g. Day 8 $C_{min}$) is predicted for adolescents 15 years of age and older compared to a typical weight adult. The typical simulated trough concentrations for pediatric body weight in the range of 52 to 56 kg fall below the observed levels attained at the 120 mg QD dose in adults. Together, these results support the use of the same flat dosing approach for subjects ≥15 years of age as that used in the adult population.

Taken together, preclinical data and results from the ongoing Phase I hematologic study provide the rationale for investigating MK-8628 in selected solid tumors.

### 4.2.2 Rationale for Dose Selection/Regimen/Escalation

Preliminary results are available from the current solid tumor Phase I study (MK-8628-003, previously known as OTX015_108) (see Section 4.1.3). As of January 2016, 47 patients were enrolled and 46 patients have been treated with doses ranging from 80 mg to 160 mg QD at both continuous and discontinuous regimens. The preliminary recommended dose / schedule for phase 2 studies in solid tumors was 80 mg/day continuous dosing. An expansion cohort was authorized to enroll and treat 6 additional NMC patients at this dose level. As of August 2016, one patient remains ongoing from this cohort and is currently being treated in Cycle 14, with a confirmed PR in Cycle 10.

In the previous hematologic Phase I study (MK-8628-001, previously known as OTX015_104), a dose escalation was completed and preliminary results of the cohort expansion are available. As of June 2015, a total of 87 subjects had been included in the dose escalation part in the two cohorts (acute leukemia [AL] and other hematologic malignancies [OHM]), and a further 49 subjects had been included in three dose expansion cohorts. A QD schedule was evaluated at all levels (up to 160 mg) and a 40 mg BID schedule was also evaluated.

The preliminary RD for the QD schedule was 80 mg QD, with a 14 days ON/7 days OFF schedule for both the OHM and the AL cohorts. The main dose limiting toxicities reported are thrombocytopenia, fatigue, gastrointestinal toxicities, as well as asymptomatic bilirubin increases and Factor VII decreases.DLT of thrombocytopenia was the prevalently observed adverse event (AE) in the OHM cohort, occurring above 40 mg QD. At DL4, thrombocytopenia was more frequent at 40 mg BID with a higher incidence of thrombocytopenia compared to the equivalent total dose per day given as QD, i.e., 5/6 subjects vs. 2/7 subjects, respectively - making the dose of 40 mg BID unacceptable in hematological malignancies with >33% of DLT in this cohort. Based on preliminary results from the ongoing solid tumor Phase I study (MK-8628-003), patients with solid tumors (without compromised bone marrow) are expected to tolerate higher MK8628 doses than those with hematologic malignancies; thus their maximum tolerated dose is predicted to be higher. Therefore, 40 mg BID is included as the highest dose level for evaluation in this study.

Preliminary clinical activity has been observed at a range of dose levels, including objective responses at 40 mg QD (1 CR), 80 mg (complete response with incomplete blood count recovery [CRi]) and 160 mg (CR) in the AL cohort and at 80 mg QD (1 PR) and 120 mg (2 CR) in DLBCL subjects.

A total of 49 subjects had been treated in the expansion cohorts with non-continuous dosing at 80 mg QD, 14 days ON/7 days OFF: 16 acute myeloid leukemia (AML) post-myelodysplastic syndrome (MDS) subjects, 18 AML non-MDS related (i.e. de novo, secondary to chemotherapy or myeloproliferative disorder [MPD]) subjects, and 15 diffuse large B-cell lymphoma (DLBCL) subjects. The expansion cohort demonstrated that at 80 mg QD, 14 days ON/7 days OFF was reasonably well tolerated with no DLTs reported. However, one subject with AML had grade 3 asthenia, deemed not related by the investigator

after clarification (related to aspergilliosis), and one subject with AML had a dose reduction due to poor tolerance (asthenia, anorexia, dysgueusia G2).

In the dose expansion cohort, one PR has been reported to date in a DLBCL subject along with evidence of clinical activity not yet meeting standard response criteria in some ongoing subjects (decrease in bone marrow blasts in five AML subjects and decreased lymph node lesions in two DLBCL subjects)

#### 4.2.2.1 Starting Dose for This Trial

Data are now emerging on how to better dose epigenetic therapies, including more frequent dosing that avoids undesirable effects mediated by higher concentrations and resultant enhanced broad inhibition of the targeted genes. The limited number objective responses in the dose expansion cohorts in the hematologic malignancies study where MK-8628 was given in a discontinuous manner (i.e. 14 days ON/7 days OFF) raises the question of whether there is a need for continuous and sustained target inhibition. On the basis of several translational and clinical studies, low, prolonged drug exposure is becoming the hallmark of successful epigenetic modulation [98]. Notable epigenetic agents where this phenomenon is observed include Food and Drug Administration (FDA) approved Deoxyribonucleic acid (DNA) methyltransferase (DNMT) inhibitors such as 5-azacitidine and decitabine [99]. Clinical development of these agents was initially hindered because early trials used higher, infrequent doses that proved to be substantially toxic to subjects (likely because of off-target epigenetic modulation). Lower, continuous dosing was found to markedly decrease treatment-related AEs and enhance targeted effects on DNMTs because the concentrations are maintained at a level where cytotoxic effects are not the prevailing mode of action. The available data support the notion that maintaining concentrations that avoid immediate cytotoxic effects but engage the target in a continuous fashion allows for reprogramming of the tumor cells that can alter disease biology in a durable, clinically meaningful manner [98].

Therefore, to maintain or sustain target inhibition with MK-8628 and mitigate daily fluctuations in systemic concentrations, a more frequent dosing schedule will be evaluated in this protocol using BID dosing. The hypothesis underlying this approach is that a higher $C_{trough}$ achieved with lower, more frequent dosing may be needed to disrupt super-enhancer driven oncogene expression (e.g., Myc, Bcl-2) over longer periods of time in order to induce antitumor activity [100]. Enhanced preclinical efficacy seen with the BET inhibitor JQ1 and MK-8628 with more frequent dosing (BID versus QD) seen in preclinical evaluations [100] is likely attributable to the ability of these powerful gene expression enhancers to quickly restore oncogene expression once the compound exposure wanes. Considering the short half-life for MK-8628 of ~5-6 hours, BID dosing has the potential to maintain sustained target engagement at a lower dose (i.e. lower $C_{max}$ could help avoid off-target toxicities).

Based on available PK data and results suggesting MK-8628 exhibits dose proportional exposure and a half-life much shorter than either a 12-hour or 24-hour dosing interval, a $C_{trough}$ 12 hours after BID dosing will more than likely result in significantly higher concentrations than a $C_{trough}$ of double the same dose at 24 hours (~4 cumulative half-lives). For example, the MK-8628 PK results from both cohorts combined shown in Figure 3 demonstrate that a 40 mg BID dose attains significantly higher $C_{trough}$ than a similar daily

dose of 80 mg QD. In the absence of a clear understanding of target engagement at different doses and an appropriate efficacious dose, total daily doses up to 80 mg administered as BID (i.e., max of 40 mg BID) or additional dose schedules will be evaluated with the hypothesis that more frequent dosing may improve efficacy.

Because epigenetic reprogramming can take longer to become apparent than the actions of traditional chemotherapies, a continuous prolonged course of treatment may be required for efficacy evaluation. Balancing this against risk (thrombocytopenia) and tolerability issues (as seen in the initial dose escalation), a lower, more frequent BID dosing schedule will be explored primarily for Proof of Concept (POC).

In Figure 3 below, PK comparison of QD versus BID in the combined dose escalation cohorts suggests that $C_{trough}$ or time above threshold could underlie hematologic toxicity and potentially efficacy of MK-8628. PK data suggest no difference in total exposure (top graph). Median daily area under the plasma concentration versus time curve (AUC) of 40 mg BID is similar to 80 mg QD. However, there is a large difference in median trough concentration (bottom graph).

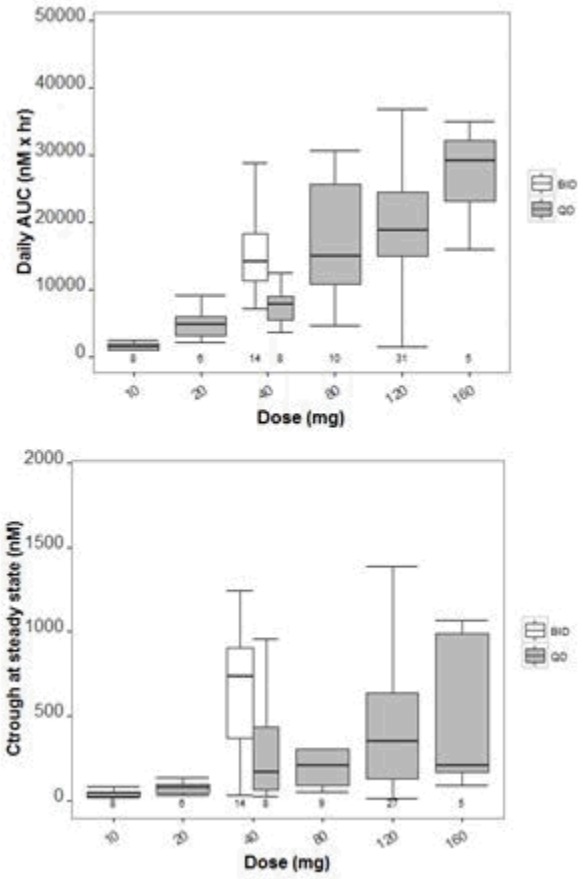



Figure 3: PK comparison of QD versus BID

#### 4.2.2.2 Maximum Dose/Exposure for This Trial

The maximum dose for the BID regimen in this study will be the highest dose level tolerated (<25% DLT rate).

#### 4.2.2.3 Rationale for Dose Interval and Trial Design

The purpose of this trial is to determine the recommended phase II dose (RP2D) of MK-8628 for further trials in subjects with selected solid tumors that might benefit from BET inhibition. The RP2D of BID administration regimens will be explored using a 6+8 two-stage design which offers a fast approach with continuous DLT rate monitoring via a modified toxicity probability index (Ji design).

### 4.2.3 Rationale for Endpoints

#### 4.2.3.1 Safety Endpoints

##### 4.2.3.1.1 Primary Safety Endpoint:

A primary objective of this trial is to determine the recommended phase II dose (RP2D) of MK-8628. Selecting the RP2D will involve a multi-faceted decision taking into account safety, tolerability, early efficacy signal, PK exposure and PD markers. The primary endpoint driving dose selection is the DLT rate, with weight given to the highest DL tolerated (<25% DLT rate). All other facets will be considered supportive. It is important to note that dose selection in this study aims to assess a RP2D *range*, with other factors aside from those mentioned above, such as target engagement, contributing to refining the dose selection for phase 2. This will be further evaluated in subsequent clinical investigations in either monotherapy or combination trials.

##### 4.2.3.1.2 Secondary Safety Endpoints

A secondary objective of this trial is to determine the safety and tolerability of MK-8628 across subjects with selected advanced solid tumors (NMC, NSCLC, TNBC and CRPC) included in this trial. Safety will be assessed in subjects who have received MK-8628 by determining the RP2D and quantifying and grading reported AEs using Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Attribution to drug, time-of-onset, duration of the event, resolution, and any concomitant medications administered will be recorded. AEs to be analyzed include but are not limited to all AEs, events of clinical interest (ECI), serious adverse events (SAE), fatal SAEs, and laboratory changes.

#### 4.2.3.2 Pharmacokinetic Endpoints

Plasma parameters of MK-8628 as appropriate and according to analyses performed (non-compartmental or nonlinear mixed effect modelling) will be determined and may include trough ($C_{min}$) and peak ($C_{max}$) concentrations, time to peak concentration ($T_{max}$), $AUC_{[0-\infty]}$, volume of distribution at steady state ($Vd_{ss}$), terminal half-life ($t_{1/2}$), steady state, and total clearance (CL). PK data for MK-8628 will be interpreted in terms of safety findings and compared with historical data. Incidence and severity of AEs along with PK parameters will be analyzed in relation to the most pertinent biomarker(s), if any.

#### 4.2.3.3 Pharmacodynamic Endpoints

Inhibition of BET proteins by MK-8628 leads to alterations in the transcription of messenger RNA (mRNA) at loci most sensitive to disruption of BET activity. These are considered target genes. Changes in expression, measured via mRNA, of prespecified target genes* will be used as PD biomarkers to assess target engagement of BET proteins by MK-8628. (*Note: the following non-exhaustive list of target genes may be considered for testing: *Bcl2*, *IL7R*, and *MYC* as down-regulated target genes; *CSRNP2*, *HEXIM1*, and *HIST1H2BK* as up-regulated target genes.) A range of PD biomarkers will be explored in surrogate samples from all subjects treated, using appropriate assays to establish target engagement. Rather than rely on gene expression changes in cancer cells, these PD biomarkers will be based on current PD knowledge from translational studies of mouse and human whole blood (e.g. Figure 4 below). Using RNA extracted from whole blood samples collected both prior to and following administration of MK-8628, messenger RNA transcript profiling may be performed to assess gene expression and evaluate whether changes in specific genes or sets of genes may represent a PD biomarker of response. Potential limitations of this assay include patient-to-patient variability and a small effect size of induction or repression upon treatment with MK-8628. Due to these limitations, the PD endpoint is considered to be qualitative given the assay may not be able to differentiate target engagement between the MK-8628 doses examined in this study.

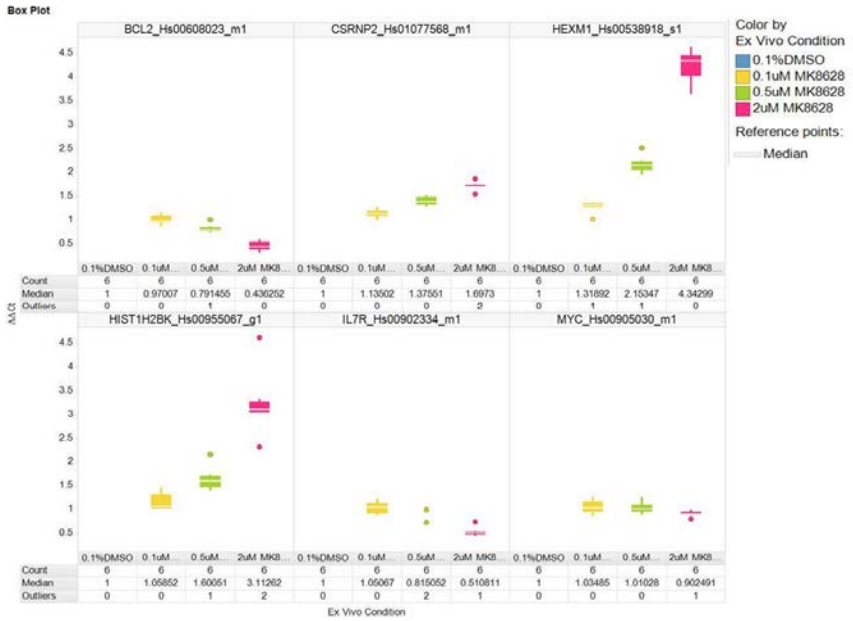



Figure 4: Dose-dependent changes in BET protein target gene expression

*Dose-dependent changes in BET protein target gene expression in human whole blood ex vivo. Whole blood from 6 normal healthy volunteers was treated with either vehicle (0.1% dimethyl sulfoxide [DMSO]) or increasing concentrations of MK-8628. After 4 hours, whole blood was lysed (PAXgene tube) and mRNA extracted for quantitative polymerase chain reaction (qPCR) analysis of candidate BET target genes. Data were normalized (Δcycle threshold [Ct]) by peptidylpropyl isomerase B (PPIB) and plotted for all six individuals as change in ΔCt.*

#### 4.2.3.4 Efficacy Endpoints

##### 4.2.3.4.1 Secondary Efficacy Endpoints: RECIST or PCWG -based Response Rate

A secondary efficacy objective of this trial is to evaluate the anti-tumor activity of MK-8628 in subjects with selected advanced solid tumors (NMC, NSCLC, TNBC and CRPC). Secondary efficacy endpoints include (1) ORR, defined as the percentage of subjects who have achieved confirmed complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (see Section 12.8) or Prostate Cancer Clinical Trials Working Group (PCWG2) (see Section 12.9), as assessed by investigator radiologic review; (2) DOR, defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first; and (3) DCR, defined as the percentage of subjects who have achieved stable disease or confirmed complete response (CR) or confirmed partial response (PR) according to RECIST v1.1 or PCWG2, by the investigator review

##### 4.2.3.4.2 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include (1) PFS, defined as the time from allocation to the first documented disease progression according to RECIST v1.1 or PCWG2 as assessed by investigator radiologic review, or death due to any cause, whichever occurs first, and (2) OS.

#### 4.2.3.5 Planned Exploratory Biomarker Research

**Planned Genetic Analysis**

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

#### 4.2.3.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational

material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

### 4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

## 5.0 METHODOLOGY

### 5.1 Entry Criteria

#### 5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with non-small cell lung cancer, triple negative breast cancer or castration-resistant prostate cancer of at least 18 years of age, and male/female subjects with NUT midline carcinoma of at least 16 years of age will be enrolled in this trial.

#### 5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have signed informed consent/assent prior to initiation of any study-specific procedures and treatment. For study subjects who are legal minors, the parent or legal guardian must also sign the consent/assent form. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical research.
2. Have histologically or cytologically confirmed diagnosis of one of the following advanced or metastatic solid tumors for which standard therapy either does not exist or has proven ineffective, intolerable or inacceptable for the subject:
    a) NUT midline carcinoma (NMC)(ectopic expression of NUT protein as determined by IHC and/or detection of BRD-NUT gene translocation as determined by FISH)
    b) Non-small cell lung cancer (NSCLC): all comers without gene rearrangement or mutational restrictions
    c) Triple negative breast cancer (TNBC) defined according to ASCO recommendations [50][51]
    d) Castration-resistant prostate cancer (CRPC)
3. Have at least one measurable lesion as per RECIST version 1.1., except for CRPC subjects who may be enrolled with objective evidence of disease as per Prostate Cancer Clinical Trials Working Group (PCWG2) criteria.

4. For NSCLC, TNBC and CRPC subjects, be age ≥ 18 years at the time of informed consent; for NMC subjects, be age ≥ 16 years at the time of informed consent.
5. Have a life expectancy ≥ 3 months.
6. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 1.
7. Demonstrate adequate organ function (adequate bone marrow reserve, renal and liver function) as defined in Table 1. (Note: All screening labs should be performed within 10 days of treatment initiation).

Table 1: Adequate Organ Function Laboratory Values

| System | Laboratory Value |
|---|---|
| **Hematological** | |
| Absolute neutrophil count (ANC) | ≥ 1.5 x$10^9$/L |
| Platelets | ≥ 150 x$10^9$/L |
| Hemoglobin | ≥ 9.0 g/dL<br>*Note: subject must not have had a blood transfusion within 7 days of screening in meeting this criteria |
| **Renal** | |
| Creatinine clearance | ≥ 30 mL/min calculated according to the Cockroft and Gault formula or Modification of Diet in Renal Disease (MDRD) formula for subjects aged > 65 years (see Section 12.5) |
| **Hepatic** | |
| Total bilirubin | ≤ 1.25 X upper limit of normal (ULN) **OR**<br>In case of liver involvement, ≤ 2 x ULN will be allowed |
| Aspartate aminotransferase (AST) (SGOT) and alanine aminotransferase (ALT) (SGPT) | < 3 X ULN |
| Alkaline Phosphatase | If > 2.5 X ULN, then liver fraction should be ≤ 2.5 X ULN |
| **Chemistry** | |
| Serum albumin | For NSCLC, CRPC and TNBC:<br>≥ 3.0 g/dL |
| | For NMC:<br>≥ 2.0 g/dL |
| **Coagulation** | |
| International Normalized Ratio (INR) | ≤ 1.5 |

8. Have an interval of ≥ 3 weeks (or ≥ 2 weeks for NMC patients) since chemotherapy (≥ 6 weeks for nitrosoureas or mitomycin C), immunotherapy, hormone therapy or any other anticancer therapy (including investigational) or surgical intervention resection, or ≥ 3 half-lives for monoclonal antibodies, or ≥ 5 half-lives for other non-cytotoxic agents (whichever is longer).

9. CRPC subjects must maintain ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) analogue, antagonist or orchiectomy providing serum testosterone is < 50 ng/dL (<1.7 nmol/L).
10. Subjects receiving bisphosphonate or denosumab therapy must be on stable doses for at least 4 weeks before initiating study treatment
11. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
12. Female subjects of childbearing potential should be willing to use an adequate method of contraception as outlined in section 5.7.3– Contraception, for the course of the study through 90 days after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
13. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.3 – Contraception, starting with the first dose of trial treatment through 90 days after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

### 5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has inability to swallow oral medications or presence of a gastrointestinal disorder (e.g. malabsorption) deemed to jeopardize intestinal absorption of MK-8628.
2. Has persistent grade >1 clinically significant toxicities related to prior antineoplastic therapies (except for alopecia); stable sensory neuropathy ≤ grade 2 National Cancer Institute (NCI)-CTCAE v. 4.0 is accepted.
3. Has known primary CNS malignancy or symptomatic or untreated CNS metastases. Treated and stable CNS metastases are allowed.
4. Has a history of prior or concomitant malignancies (other than excised non-melanoma skin cancer or cured *in situ* cervical carcinoma) within 3 years of signing informed consent.
5. Has other serious illness or medical condition, such as active infection, unresolved bowel obstruction, psychiatric disorders, or cerebrovascular accident (within 1 year of study entry).
6. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
7. Has known active Hepatitis B (e.g. hepatitis B surface antigen [HBsAg] reactive) or Hepatitis C (e.g. hepatitis C viral [HCV] RNA [qualitative] is detected).
8. Has any of the following cardiac-related conditions:
    a. Congestive heart failure or angina pectoris (except if medically controlled)
    b. Previous history of myocardial infarction (within 1 year of study entry)

c. Uncontrolled hypertension (defined as systolic blood pressure > 140 mmHg, and/or diastolic blood pressure > 90 mmHg, and not adequately managed by anti-hypertensive medication)

d. Uncontrolled arrhythmias

9. Has participated in another clinical trial or treatment with any investigational drug (excluding anticancer treatments) within 30 days prior to study entry.
10. Has other concomitant anticancer treatment, except the use of anti-androgens in CRPC subjects.
11. Has concomitant therapy with strong CYP3A4 inhibitors or inducers.
12. Is currently using therapeutic anticoagulation (e.g. warfarin, heparin, etc.) (Must be stopped at least 7 days prior to the first dose of MK-8628). Low-dose low molecular weight heparin (LMWH) is permitted.
13. Has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might expose the subject to risk by participating in the trial, confound the results of the trial, or interfere with the subject's participation for the full duration of the trial.
14. Is pregnant or breast-feeding.

## 5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 2 and Table 3.

Table 2: Trial Treatments – Part A: Dose Escalation

| Drug | Dose/Potency | Dose Frequency | Route of Administration | Regimen/Treatment Period |
|---|---|---|---|---|
| MK-8628 | 20 mg | BID | Oral | Continuous / 21 days per cycle |
| MK-8628 | 30 mg | BID | Oral | Continuous / 21 days per cycle |
| MK-8628 | 40 mg | BID | Oral | Continuous / 21 days per cycle |

Table 3: Trial Treatments – Part B: NMC Cohort

| Drug | Dose/Potency | Dose Frequency | Route of Administration | Regimen/Treatment Period |
|---|---|---|---|---|
| MK-8628 | 10 mg | BID | Oral | Continuous / 21 days per cycle |
| MK-8628 | 20 mg | BID | Oral | Continuous / 21 days per cycle |
| MK-8628 | 30 mg | BID | Oral | Continuous / 21 days per cycle |
| MK-8628 | 40 mg | BID | Oral | Continuous / 21 days per cycle |

The first dose of trial treatment will be administered at the trial site in the morning of the Cycle 1 Day 1 Visit, and then again in the evening. Subsequent dosing will be performed twice daily either at the trial site on scheduled Visit days, or by the subject (i.e., unsupervised at his/her home), at approximately the same times each day.

All supplies indicated in Table 2 and Table 3 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

### 5.2.1 Dose Selection/Modification

#### 5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

#### 5.2.1.2 Dose Escalation (Part A)

A twice daily (BID) dose escalation will be performed using a 6+8 two-stage design with continuous DLT rate monitoring via a modified toxicity probability index (mTPI) (Ji design), targeting a maximum 25% DLT rate [1].

Starting from 20 mg BID, up to three planned dose levels may be evaluated: 20 mg BID, 30 mg BID 40 mg BID (all continuous daily). See Table 4 and Table 5 for the dose escalation scheme.

Table 4: Dose Escalation Scheme

| **Dose Level (DL)** | **MK-8628 (mg/dose)** **BID Regimen** (continuous) | **Outcome (#DLT/#Subjects)* / Actions to be taken** |
|---|---|---|
| DL 1 | 20 | **At each DL**:<br>- Escalate/de-escalate per DLT rate observed using mTPI Table (Table 5) |
| DL 2 | 30 | |
| DL 3 | 40 | |

* Evaluated during the first 21 days of treatment

Table 5: Modified Toxicity Probability Interval (mTPI) Design

| | **Number of subjects treated at current dose** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Number of toxicities** | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 0 | E | E | E | E | E | E | E | E | E |
| 1 | S | E | E | E | E | E | E | E | E |
| 2 | S | S | S | S | S | S | S | S | E |
| 3 | D | S | S | S | S | S | S | S | S |
| 4 | DU | DU | DU | D | S | S | S | S | S |
| 5 | DU | DU | DU | DU | DU | D | S | S | S |
| 6 | DU | DU | DU | DU | DU | DU | DU | DU | D |
| 7 | | DU | DU | DU | DU | DU | DU | DU | DU |
| 8 | | | DU | DU | DU | DU | DU | DU | DU |
| 9 | | | | DU | DU | DU | DU | DU | DU |
| 10 | | | | | DU | DU | DU | DU | DU |
| 11 | | | | | | DU | DU | DU | DU |
| 12 | | | | | | | DU | DU | DU |
| 13 | | | | | | | | DU | DU |
| 14 | | | | | | | | | DU |

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target toxicity rate = 25%

Subjects may be enrolled continuously, such that the number of subjects who are enrolled but are not yet fully evaluable for DLT assessment may not exceed the number of remaining subjects who are at risk of developing a DLT before the dose would be considered unacceptably toxic. If 0 out of the first 6 subjects in a given dose level develop a DLT, then the dose can escalate to the next level without further expansion. If 3 subjects out of the first 6 subjects develop a DLT, the dose will be de-escalated to the next lower dose level. If ≥4 out of the first 6 subjects develop a DLT, this indicates an unacceptable toxicity. If 1 to 2 out of the first 6 subjects of a given dose level develop a DLT, expand the current dose level according to Table 5 by continuing enrollment as follows. As stated above, the number of subjects who are enrolled at that dose but are not yet fully evaluable for DLT assessment may not exceed the number of remaining subjects who are at risk of developing a DLT before the dose would be considered unacceptably toxic (denoted as DU in Table 5). For example, if 2/7 subjects have experienced a DLT at a given dose level, no more than an additional 3 subjects should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 of the additional subjects experience a DLT (i.e., 5/10 subjects with DLT in Table 5). To find out how many more subjects can be enrolled, one can count steps in diagonal direction (down and to the right) from the cell (7 subjects, 2 toxicities) to the first cell marked DU.

De-escalation (D) or unacceptable (DU) at the starting dose level (DL1) indicates stopping of the trial. Escalation (E) at the highest dose level (DL3) indicates staying at that level. Note that while 25% has been the target toxicity rate used to generate the guidelines in Table 5, the observed rate of subjects with DLT at the RP2D may be slightly above or below 25%.

Subjects not evaluable for DLT (i.e. receiving less than 85% of the intended cumulative dose in Cycle 1 for any reason other than toxicity; <18 days of treatment) and who do not experience DLT will be replaced.

Subjects will receive MK-8628 at the DL they were assigned at entry throughout the study, or at a reduced dose according to toxicity encountered. Subjects will undergo a dose and/or schedule modification in the event of toxicity (see Section 5.2.1.6 and 5.6.1.1).

#### 5.2.1.3 NMC Cohort (Part B)

An additional cohort of NMC subjects will be treated in a parallel study. This study will only include NMC subjects. Priority for treatment allocation will be to enroll into Part A of the study (Dose Escalation). If there are no slots available in Part A at the time the NMC subject is identified, the subject will be enrolled and allocated to treatment in Part B (NMC Cohort).

As in Part A, dose administration will be continuous for 21 consecutive days per cycle (21-day cycles). NMC subjects enrolled in Part B will be treated at one dose level below the current dose level from the dose escalation study in Part A. Therefore, a starting dose of 10 mg BID will be administered, and up to four dose levels will be evaluated: 10, 20, 30 and 40 mg BID, continuous, 21-day cycles. Once the RP2D is established, newly enrolled NMC subjects in Part B may be treated at the RP2D. See Table 6 for the dosing scheme for the NMC Cohort study.

Table 6: Dosing Scheme for NMC Cohort

| Dose Level (DL) | Current Dose Level from Part A: Dose Escalation | Dose to Treat in Part B: NMC Cohort |
|---|---|---|
| DL1 | 20 mg BID, continuous | 10 mg BID, continuous |
| DL2 | 30 mg BID, continuous | 20 mg BID, continuous |
| DL3 | 40 mg BID, continuous | 30 mg BID, continuous |
| RP2D* | N/A | 20, 30 or 40 mg BID, continuous |

*Once the RP2D is established, newly enrolled NMC subjects in Part B may be treated at the RP2D.

Subjects will receive MK-8628 at the DL they were assigned at entry throughout the study, or at a reduced dose according to toxicity encountered. Subjects will undergo a dose and/or schedule modification in the event of toxicity (see Section 5.2.1.6 and 5.6.1.1).

#### 5.2.1.4 Dose Limiting Toxicity

For the dose escalation part of this study (Part A), a DLT is defined as any of the following toxicities occurring during the first cycle of treatment (21 days) for each dose level. See Section 5.9 for rules on replacement of subjects in the DLT period.

The occurrence of any of the following toxicities during Cycle 1, **if assessed by the investigator to be possibly, probably or definitely related to MK-8628**, will be considered a DLT**:**

Hematologic toxicity

- Grade 4 hematologic toxicity lasting ≥ 7 days, except thrombocytopenia
  - Grade 4 thrombocytopenia of any duration
  - Grade 3 thrombocytopenia is a DLT if associated with bleeding
- Febrile neutropenia Grade 3 or Grade 4

Non-hematologic toxicity

- Grade 4 non-hematologic toxicity (not laboratory)
- Grade 3 non-hematologic toxicity (not laboratory) lasting > 3 days despite optimal supportive care. Grade 3 nausea, vomiting or diarrhea will be considered a DLT if lasting more than 3 days despite optimal supportive care.
- Any Grade 3 or 4 non-hematologic laboratory abnormality, if:
  - medical intervention is required, or
  - the abnormality leads to hospitalization, or
  - the abnormality persists for > 1 week
- Any of the following liver test abnormalities are observed (see also Section 12.7):
  - ALT or AST > 8X ULN
  - ALT or AST > 5X ULN for more than 2 weeks
  - ALT or AST > 3X ULN **AND** (total bilirubin > 2X ULN **OR** INR > 1.5)
  - ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%), unless the investigator assesses the rash or fatigue to be related to MK-8628 and not related to liver impairment, with Sponsor's agreement

Other

- Any drug-related AE which caused the subject to discontinue treatment during Cycle 1
- Any study drug-related toxicity resulting in a subject missing ≥ 20% of planned doses during Cycle 1.
- Any treatment-related toxicity which causes a greater than 2 week delay in initiation of Cycle 2.
- Grade 5 toxicity

DLTs must be reported within 24 hours to the Sponsor as Events of Clinical Interest (see Section 7.2.3.2). If the event also meets the criteria for seriousness, follow the reporting guidelines for Serious Adverse Events (SAEs) outlined in Section 7.2.3.1.

### 5.2.1.5 Recommended Phase II Dose

The recommended phase II dose (RP2D) will be determined based on a multi-faceted decision taking into account safety, tolerability, early efficacy signal, PK exposure and PD markers. The primary endpoint driving dose selection is the DLT rate, with weight given to the highest DL tolerated (<25% DLT rate). All other facets will be considered supportive. It is important to note that dose selection in this study aims to assess a RP2D *range*, with other factors aside from those mentioned above, such as target engagement, contributing to refining the dose selection for phase 2. This will be further evaluated in subsequent clinical investigations in either monotherapy or combination trials.

### 5.2.1.6 Dose Adaptation

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events. MK-8628 will be withheld for drug related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 7 below. If a dose of MK-8628 is withheld for toxicity, then subjects may resume dosing with MK-8628 if that is appropriate at their next scheduled appointment or when toxicity has improved as described below.

Table 7: Dose Modification Guidelines for Drug-Related Adverse Events

| Toxicity | Grade | Hold Treatment (Y/N) | Timing for restarting treatment | Dose/Schedule for restarting treatment | Criteria for discontinuation after consultation with Sponsor |
|---|---|---|---|---|---|
| Hematologic toxicity | 1, 2 | No | N/A | N/A | N/A |
| | 3<br><br>associated neutropenia with infection; or thrombocytopenia with bleeding or lasting > 7 days | Yes | Toxicity resolves to Grade 0-1, or to baseline | Resume treatment at next lower dose level (Table 8) | Toxicity does not resolve within 2 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event* |
| | 4<br><br>or febrile neutropenia | Yes | Toxicity resolves to Grade 0-1, or to baseline | Resume treatment at next lower dose level (Table 8) | Toxicity does not resolve within 2 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event* |
| Non-Hematologic | 1, 2 | No | N/A | N/A | N/A |

| Toxicity | Grade | Hold Treatment (Y/N) | Timing for restarting treatment | Dose/Schedule for restarting treatment | Criteria for discontinuation after consultation with Sponsor |
|---|---|---|---|---|---|
| Laboratory Abnormalities | 3, 4<br><br>With or without symptoms lasting > 48 hours | Consider holding<br><br>Hold treatment for total bilirubin increases >2X ULN or 2X baseline (if elevated at baseline) and/or AST or ALT ≥ 5X ULN | Toxicity resolves to Grade 0-1, or to baseline | Laboratory abnormalities resolve within 1 week: treat vat same dose and schedule<br><br>Laboratory abnormalities do not resolve within 1 week: may consider resuming treatment at next lower dose level (Table 8) | Toxicity does not resolve within 2 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event* |
| Non-Hematologic toxicity<br><br>Note: Exception to be treated similar to Grade 1 toxicity<br>• Grade 2 alopecia<br>• Grade 2 fatigue | 1 | No | N/A | N/A | N/A |
| | 2<br><br>Any intolerable G2 non-hematologic toxicity lasting >7 days with or without dose reduction | Consider holding for persistent symptoms | Toxicity resolves to Grade 0-1 or baseline | Clinical AE resolves within 2 weeks: treat at same dose and schedule<br><br>Clinical AE does not resolve within 2 weeks: may consider resuming treatment at next lower dose level (Table 8) | Dose is interrupted for > 2 weeks. |
| | 3, 4<br><br>Unless not optimally treated with supportive care (e.g. Grade 3 vomiting not adequately treated according to anti-emetic standard of care) | Yes | Toxicity resolves to Grade 0-1 or baseline | Resume treatment at next lower dose level (Table 8) | Toxicity does not resolve within 2 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event* |

After recovery from toxicity, treatment will be resumed at the next lower dose level (Table 8). For subjects treated at DL1 (20 mg BID), 10 mg BID will be evaluated.

Table 8: MK-8628 Dose and Schedule Modifications

| Dose Level (DL) | Initial Dose | 1st Modification |
|---|---|---|
| DL 1 | 20 mg BID continuous | 10 mg BID continuous |
| DL 2 | 30 mg BID continuous | 20 mg BID continuous |
| DL 3 | 40 mg BID continuous | 30 mg BID continuous |

Note: Dose modification for 10 mg BID continuous will only include dose interruption and no further reduction is allowed.
For subjects enrolled in Part B of the study (NMC Cohort), the same guidelines for dose modifications should be followed.

No more than one dose reduction should be implemented unless the investigator thinks it in the subject's best interests to pursue study treatment with further dose reduction (additional dose reduction by one dose level), with the Sponsor's agreement.

Dosing interruption for > 2 weeks due to toxicity will lead to definitive study treatment discontinuation, unless the investigator thinks it in the subject's best interests to pursue study treatment, with the Sponsor's agreement.

### 5.2.2 Timing of Dose Administration

MK-8628 is to be administered orally with water in a fasted state, and as part of a BID regimen (twice daily, approximately 12±2 hours apart). The definition of a fasted state is that subjects should not have food for 1 hour before or 3 hours after study drug administration.

Dosing not performed at the same time (±2h) as on other days will be skipped. Subjects are to be instructed that if they vomit or skip their dose in that time frame, it is not to be replaced.

Capsules must not be opened or chewed.

A treatment cycle is 21 days (3 weeks). The subsequent cycle will begin on day 22 or after recovery from any AEs to baseline or Grade < 2 associated with the previous cycle.

Subjects should receive study treatment within 3 days following registration.

Details of the exact dose and time of administration will be documented in a validated subject diary and reported in the electronic case report form (eCRF).

#### 5.2.2.1 Premedication

No systematic premedication will be given at least during the first cycle. See Section 5.5.1 for a list of allowed and prohibited medications

### 5.2.3 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

### 5.3 Randomization or Treatment Allocation

Cohort management and treatment allocation will occur centrally using an interactive web response system (IWRS). Subjects will be allocated to treatment by non-random assignment based on the open dosing cohort and number of available slots at the time of registration.

For NMC subjects, priority for treatment allocation will be to enroll into Part A of the study (Dose Escalation). If there are no slots available in Part A at the time the NMC subject is identified, the subject will be enrolled and allocated to treatment in Part B (NMC Cohort).

### 5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

### 5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

#### 5.5.1 Medications

All treatments taken by subjects at study entry or within 4 weeks or 5 half-lives prior to initiating treatment (whichever is longer) or at any time during the study, in addition to the investigational product are considered concomitant medications and must be documented in the eCRF.

No premedication is planned.

**Allowed:**

- Supportive treatment of symptoms/AEs or standard treatment of concomitant conditions, including corticosteroids, aspirin, transfusion support, and antibiotics,
- Growth factors (Granulocyte-colony stimulating factor [G-CSF], erythropoietin [EPO] etc.) after cycle 1.
- For CRPC subjects, maintenance treatment with ongoing androgen deprivation therapy with a gonadotropin releasing hormone (GnRH) analogue or antagonist is mandatory providing serum testosterone is < 50 ng/dL (<1.7 nmol/L), unless the subject had previous bilateral orchiectomy as part of his hormone therapy.
- Chemotherapy, hormone therapy or any other anticancer therapy or surgical intervention resection performed ≥ 3 weeks prior to study start (≥ 6 weeks for nitrosoureas or mitomycin C) or ≥ 3 half-lives for monoclonal antibodies or ≥ 5 half-lives for other non-cytotoxic agents (whichever is longer). Palliative radiation therapy (for analgesia) is authorized only if the irradiated field does not include target lesions.

- Bisphosphonates or denosumab given at stable doses for ≥ 4 weeks prior to study start. Bisphosphonates or denosumab are permitted from cycle 3.
- Prophylactic low-dose LMWH, as defined by local institutional practices; INR must be monitored in accordance with local institutional practices. Subjects who develop venous thromboembolic events during study requiring therapeutic levels of LMWH must be closely monitored for their platelet counts.

**Not allowed:**

- Other concurrent investigational drugs, agents or devices or any other therapy for cancer treatment.
- Any drugs given with a prophylactic intent during the first cycle.
- Concurrent treatment with strong CYP3A4 interfering drugs/substances is not permitted. The concomitant use of other CYP3A4 interfering drugs or any CYP2A6 interfering drug is allowed provided a careful follow-up of laboratory results that may be influenced by the concomitant agent is performed (e.g. INR if the concomitant agent is an anticoagulant, blood cell counts if the concomitant drug is hematotoxic must be followed up more frequently than required by the protocol).

  Note: CYP3A4 inhibitors/inducers/substrates are listed in Section 12.6. Since this list is not comprehensive, the investigator should use his/her medical judgment when a subject presents with a medication not on the list or call the Sponsor Clinical Director for clarification.
- Use of therapeutic anticoagulation (e.g. warfarin, heparin, etc.). Must be stopped at least 7 days prior to the first dose of MK-8628.

### 5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

#### 5.6.1 Supportive Care Guidelines

Toxicities will be managed by the investigator according to the local standard of care, except where noted in this protocol. Supportive treatment must be reported in the concomitant medication section of the eCRF.

##### 5.6.1.1 General Guidelines for Clinically Significant Toxicities

General guidelines regarding management and dose reduction for adverse events that are considered by the investigator to be related to study treatment are provided in Section 5.2.1.6. All adverse events should be monitored closely, with supportive care provided according to institutional standards.

#### 5.6.1.2 Hepatic Laboratory Abnormalities

All trial subjects with liver test abnormalities should be monitored weekly until all abnormalities return to normal or to the baseline state. For subjects with isolated total bilirubin increases >2X ULN or 2X baseline (if elevated at baseline), monitoring should be every 2 weeks until bilirubin returns to normal or to the baseline state. Drug induced liver injury (DILI) may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. See Section 12.7 for guidelines on the handling of these events (potential Hy's law cases).

### 5.7 Diet/Activity/Other Considerations

#### 5.7.1 Diet

Subjects must avoid drinking grapefruit juice while on study, as this is a CYP3A4 inhibitor and is therefore not permitted.

Subjects should otherwise maintain a normal diet, except when required to fast prior to MK-8628 administration (Section 5.2.2), or unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

#### 5.7.2 Potential Phototoxicity

No phototoxicity studies have been performed in humans to date. However as MK-8628 absorbs light in the range of 290 and 400 nm with a molar extinction coefficient (MEC) of >1000 $L \cdot mol^{-1} \cdot cm^{-1}$, it is recommended that subjects avoid sun and ultraviolet (UV) exposure until the results of phototoxicity studies are available.

#### 5.7.3 Contraception

MK-8628 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-8628 has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug MK-8628 and for 90 days after the last dose of study drug. Subjects must comply with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's sole male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study treatment [Day 1] for oral contraception) throughout the study period up to 90 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Monthly pregnancy testing is recommended per local standards if applicable.

**For countries (e.g., Sweden and Norway) or sites that follow the Clinical Trial Facilitation Group (CTFG) guidance, please use the following**:

MK-8628 may have adverse effects on a fetus in utero. Furthermore, it is not known if it may have transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breastfeeding women may only be enrolled if they are willing to follow the CTFG Guidance (Final Version 2014-09-15, Sections 4.1 and 4.2) for highly effective birth control as outlined below, or are considered to be highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Subjects should start using birth control from study Visit 1 throughout the study period up to 90 days after the last dose of study therapy.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 7.2.2 – Reporting of Pregnancy and Lactation to the Sponsor. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

### 5.7.4 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-8628, the subject will immediately be discontinued from trial treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the SPONSOR without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the SPONSOR. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the SPONSOR and followed as described above and in Section 7.2.2.

### 5.7.5 Use in Nursing Women

It is unknown whether MK-8628 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

## 5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Subjects will continue study treatment until any of the following events at which point it will be definitively discontinued:

- Disease progression
- Unacceptable toxicity
- Subject withdrawal of consent
- Subject non-compliance
- Treatment interruption for > 2 weeks for toxicity (except in the event of perceived benefit, with Sponsor agreement)
- Recurrence of DLT despite dose reduction (except in the event of perceived benefit, with Sponsor agreement)

However, in case of investigator's perceived benefit for the subject, treatment continuation can be considered with dose reduction despite delay/interruption > 2 weeks or reoccurrence of a DLT with the same intensity after one dose reduction. The perceived benefit of the investigator is defined by 1) any objective tumor response, or 2) any tumor shrinkage not meeting standard response criteria, but which could improve with additional treatment, or 3)

any symptomatic improvement, which, in the investigator's opinion, could not be achieved by other means. If, in the cases described above, DLT recurs with the same intensity despite one dose reduction, a second dose reduction may be considered. The decision should be discussed with the Sponsor, but the final decision must be made by the investigator.

In all cases, the reason for and date of study treatment discontinuation must be recorded in the eCRF and source documented in the subject's medical records. As far as possible, there should be only one reason for treatment discontinuation. If there are several (e.g. concomitant progressive disease and toxicity), the primary one must be reported. The subject must be followed up to establish whether the reason was an AE, and if so, this must be reported as such.

As far as possible, all examinations scheduled for the final study day must be performed for all subjects who receive the investigational product but who do not complete the study according to protocol.

The investigator must make every effort to contact subjects lost to follow-up, especially when a subject is treated in another non-study center.

### 5.9 Subject Replacement Strategy

Subjects not evaluable for DLT (i.e. receiving less than 85% of the intended cumulative dose in Cycle 1 for any reason other than toxicity; <18 days of treatment) and who do not experience DLT will be replaced.

A subject who discontinues from the trial for any other reason will not be replaced.

### 5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

### 5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Incidence or severity of adverse drug reactions in this or other trials suggest a potential health hazard to subjects;
2. Quality or quantity of data recording is inaccurate or incomplete;
3. Poor adherence to protocol and regulatory requirements;
4. Plans to modify or discontinue the development of the study drug

In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

## 6.0 TRIAL FLOW CHART

Subjects enrolled into both Part A (Dose Escalation) and Part B (NMC Cohort) will follow the same visit schedule and procedures outlined in the trial flow chart below:

| | **Screening Phase** | **Treatment Phase[q] Cycle = 21 days** | | | | | | | | | **End of Treatment** | **Post Treatment Phase** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Pre-study / Screening (Visit 1) | Cycle 1 and 2 | | | | | | Cycle 3 and beyond | | | Treatment Discontinuation Visit | Safety Follow Up Visit | Follow Up Visits[a] |
| Cycle Day: | | 1 | 4 | 8 | 11 | 15 | 18 | 1 | 8[j] | 15[j] | Date of discontinuation | 30 days post last treatment | Every 6 weeks post treatment discontinuation |
| Scheduling Window Days: | -14 to -1 | | ±1 | ±3 | ±3 | ±3 | ±3 | | ±3 | ±3 | | +5 | ±3 |
| **Administrative Procedures** | | | | | | | | | | | | | |
| Informed Consent[b] | X | | | | | | | | | | | | |
| Informed Consent for Future Biomedical Research | X | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | |
| Subject Identification Card | X | | | | | | | | | | | | |
| Demographics, Medical History | X | | | | | | | | | | | | |
| Concomitant Medication Review | X | X | X | X | X | X | X | X | X | X | X | X | |
| Diagnosis & prior treatments for malignancy | X | | | | | | | | | | | | |
| Baseline symptoms & complaints | X | | | | | | | | | | | | |
| **MK-8628 Administration/Dispensing** | | | | | | | | | | | | | |
| MK-8628 Administration/Dispensing | | BID Continuously[c], at assigned dose level; Study drug will be dispensed on or prior to Day 1 of each Cycle. | | | | | | | | | | | |
| **Clinical Procedures/Assessments** | | | | | | | | | | | | | |
| Full Physical Examination | X | X | | | | | | X | | | | X | |

| | **Screening Phase** | **Treatment Phase[q] Cycle = 21 days** | | | | | | | | | **End of Treatment** | **Post Treatment Phase** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Cycle/Title: | Pre-study / Screening (Visit 1) | Cycle 1 and 2 | | | | | | Cycle 3 and beyond | | | Treatment Discontinuation Visit | Safety Follow Up Visit | Follow Up Visits[a] |
| Cycle Day: | | 1 | 4 | 8 | 11 | 15 | 18 | 1 | 8[j] | 15[j] | Date of discontinuation | 30 days post last treatment | Every 6 weeks post treatment discontinuation |
| Scheduling Window Days: | -14 to -1 | | ±1 | ±3 | ±3 | ±3 | ±3 | | ±3 | ±3 | | +5 | ±3 |
| ECOG Performance Status (PS) | X | X | | | | | | | | | | X | |
| Height | X | | | | | | | | | | | | |
| Vital Signs (heart rate, blood pressure, temperature, and weight) | X | X | X | X | X | X | X | X | X[j] | X[j] | | X | |
| 12-Lead Electrocardiogram (ECG) | X | X[d] | | | | | | X[d] | | | | X | |
| CT, MRI, chest X-ray (posterior-anterior and lateral) | X[e] | | | | | | | X[e] | | | | X[a,e] | X[a,e] |
| Bone scan (CRPC subjects) | X[f] | | | | | | | X[f] | | | | X[a,f] | X[a,f] |
| Adverse Events Monitoring | | X | X | X | X | X | X | X | X | X | X | X[g] | X[g] |
| **Laboratory Procedures/Assessments** | | | | | | | | | | | | | |
| Complete Blood Count (CBC)[h] | X[i] | X[i] | X | X | X | X | X | X[h] | X[h,j] | X[h,j] | | X | |
| Serum Chemistry[h] | X[i] | X[i] | | X | | X | | X[h] | X[h,j] | X[h,j] | | X | |
| PT (INR), aPTT and Factor VII | X | X[i] | | X | | X | | | | | | | |
| Urinalysis | X | | | | | | | | | | | | |
| Urine Pregnancy Test – if applicable[k] | X | | | | | | | | | | | | |
| Tumor markers[l] | X[l] | X[l] | | | | | | X | | | | X[l] | X[l] |
| PK Blood (Plasma) Sampling | | X[m] | | X[n] | | X[n] | | | | | | | |
| PD Blood Sampling | | X[o] | | X[o] | | | | | | | | | |
| Blood for Genetic Analysis[p] | | X | | | | | | | | | | | |

a. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging[e,f] * every 6 weeks ±3 days until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. *Note: This includes bone scans for CRPC subjects every 12 weeks ±3 days. If subjects have stable disease, partial response, or complete response, they should continue on this assessment schedule. The timing for these assessments should continue the same imaging schedule from the treatment phase; Imaging, and if applicable, bone scans, should occur at any time where there is clinical suspicion of progression;
b. For study subjects who are legal minors, the parent or legal guardian must also sign the consent/assent form;
c. MK-8628 is to be administered orally with water in a fasted state, and as part of a BID regimen (twice daily, approximately 12±2 hours apart). Dosing not performed at the same time (±2h) as on other days will be skipped. Subjects are to be instructed that if they vomit or skip their dose in that time frame, it is not to be replaced;
d. On Cycle 1 Day 1, conduct 12-lead ECG immediately before intake of the morning study dose, then again 1 and 2 hours after the intake of the morning study dose. Conduct additional 12-lead ECGs immediately before the morning intake on Day 1 of odd subsequent cycles (e.g. Cycle 3, 5, 7 etc.);
e. Radiologic exams (CT, MRI, chest X-ray) performed as part of the subject's standard follow-up within 4 weeks prior to the first treatment cycle, are acceptable. Radiologic assessment will be performed every 2 cycles (6 weeks) (± 3 days) as per RECIST 1.1 or PCWG2 until progression, by calendar date starting from Cycle 1 Day 1 (not adjusted for cycle or treatment days). Scans used for tumor measurements may be requested for central review;
f. Bone scans are mandatory in CRPC subjects and will be performed every 4 cycles (12 weeks) (± 3 days) until progression, by calendar date starting from Cycle 1 Day 1 (not adjusted for cycle or treatment days). Scans used may be requested for central review;
g. Record all AEs occurring within 30 days after the last dose of trial treatment regardless when the Treatment Discontinuation Visit occurs. After 30 days, any drug related AE regardless of seriousness occurring outside of any reporting timeframes must be reported;
h. From Cycle 3 on, in the absence of ≥ grade 2 abnormalities, these tests will be performed every cycle on Day 1, otherwise they are to be done weekly until resolution to baseline levels or < grade 2;
i. Screening CBC and serum chemistry measurements must be taken within 7 days of the first dose of study treatment; All laboratory assessments (e.g. CBC, serum chemistry, PT [INR], aPTT, Factor VII, and PSA [if applicable]) on Cycle 1 Day 1 must be taken prior to the first dose;
j. From Cycle 3 on, in the absence of ≥ grade 2 abnormalities requiring weekly CBC and serum chemistry measurements, these visits may be conducted via a documented telephone contact with the Investigator or Sub-Investigator. Adverse events and concomitant medications will be reviewed; blood tests and vital signs will not be required;
k. For women of reproductive potential, urine pregnancy test must be confirmed negative within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The subject must be excluded in the event of a positive or borderline-positive serum test result;
l. As appropriate for tumor type; For CRPC subjects, Prostate Specific Antigen (PSA) measurements are mandatory, and will be performed at screening, and then on Day 1 of every cycle starting with Cycle 2;;
m. Pharmacokinetics will be performed in cycle 1 only. Samples will be collected immediately prior to the first dose (T0) on day 1, 20min±5min, 1h±10min, 2h15min±10min, 3h15min±10min, 8h+1h, and 12h±2h post-dose (immediately before the second daily dose on day 1);
n. Steady-state PK blood samples will be collected on days 8 (±1 days) and 15 (±2 days) of cycle 1, and day 1 of cycle 2 (day 22, ±3 days), prior to the morning drug intake;
o. PD blood samples will be collected immediately prior to the first dose on day 1, 3h15min±10min, 8h±1h and 12h±2h post-dose, and immediately prior to the first dose on day 8 only;
p. Blood for Genetic Analysis samples should be collected prior to the first dose only at Cycle 1 Day 1. Details for collection can be found in Section 7.1.3.3.
q. During the treatment phase, the assessment schedule for scheduled visits, collection of blood for labs, and other study procedures should be held/delayed to correspond with any dose hold – in other words, study visits and assessments coincide with the dosing calendar (cycle/treatment day), not the actual calendar. There is one notable exception to this – radiologic scans for tumor assessments (including bone scans and PSA measurements) should be conducted every 6 weeks (or 12 weeks for bone scan/PSA) by calendar date starting from Cycle 1 Day 1.

# 7.0 TRIAL PROCEDURES

## 7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

### 7.1.1 Administrative Procedures

#### 7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

##### 7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

#### 7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

### 7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

### 7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

### 7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any previously diagnosed conditions that are considered clinically significant by the Investigator. A detailed medical history must be documented, including non-cancer medical history and concurrent illnesses.

Diagnosis and prior treatments for malignancies will be documented (a confirmatory diagnosis of NUT midline carcinoma or NSCLC at screening is not required).

### 7.1.1.5 Prior and Concomitant Medications Review

#### 7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 4 weeks or 5 half-lives before first dose of trial medication.

#### 7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

#### 7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

#### 7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. This unique number is termed a randomization number throughout the protocol for operational purposes. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

#### 7.1.1.8 Trial Compliance (Medication)

Administration of the investigational product will be supervised by the investigator. Any delegation of this responsibility must be documented.

In practice, on study visit days study nurses will supervise the intake of the appropriate MK-8628 dose, explaining to subjects the exact number of capsules they should take. Nurses will document in the eCRF the administration, the dose, the time of administration, as well as any immediate reactions at the time of intake.

For non-visit days, MK-8628 will be taken at home. The subject will note the number of capsules taken, the time of administration, as well as any reactions including the date/time in a specific subject's diary.

When a subject attends a study visit, he/she will bring any unused capsules and their diary. According to the center procedures, the diary will be used to complete the eCRF treatment administration section, either directly as a Source Document or as an aid for completing the nurse's notes which will be used as a Source Document.

Interruptions from the protocol specified treatment for > 2 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

### 7.1.2 Clinical Procedures/Assessments

#### 7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0. Toxicities will be characterized in terms including seriousness, causality, toxicity grading and action taken with regard to trial treatment.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

#### 7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant findings should be recorded as medical history. Starting with Cycle 1, perform a full physical exam prior to trial administration on Day 1 of each cycle. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs. Perform a final physical exam during the post-treatment follow-up period.

#### 7.1.2.3 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or designee will assess the ECOG status (see Section 12.4) at screening, prior to trial administration on Day 1 of each cycle, and during the post-treatment follow-up period.

#### 7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to trial administration on Day 1 of each cycle, and during the post-treatment follow-up period as specified in the Trial Flow Chart. Vital signs include heart rate, blood pressure, body temperature and weight. Height will be measured at screening only.

#### 7.1.2.5 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures at screening. Clinically significant abnormal findings should be recorded as medical history.

On Cycle 1 Day 1, conduct 12-lead ECGs immediately before intake of the morning study dose, then again 1 and 2 hours after the intake of the morning study dose. Conduct additional 12-lead ECGs immediately before the morning intake on Day 1 of odd subsequent cycles (e.g. Cycle 3, 5, 7 etc.).

#### 7.1.2.6 Tumor Imaging and/or Bone Scan

##### 7.1.2.6.1 CT, MRI and/or Chest X-Ray

For tumor evaluation, a CT, MRI and/or chest X-ray (posterior-anterior and lateral) will be performed every 6 weeks (± 3 days) by calendar date starting from Cycle 1 Day 1 (not adjusted for cycle or treatment days). These assessments will be performed on approximately Day 1 of every 2nd cycle (C3, C5, C7, etc.), as clinically indicated by the subjects diagnosis. Scans used may be requested for central review. Effort should be made to maintain the same imaging modality throughout the study.

In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks ±3 days until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. If subjects have stable disease, partial response, or complete response, they should continue on this every 6 weeks ±3 days assessment schedule. The timing for these assessments should continue the same imaging schedule from the treatment phase. Imaging should occur at any time where there is clinical suspicion of progression.

##### 7.1.2.6.2 Bone Scan

A bone scan is mandatory for CRPC subjects, and will be performed every 12 weeks (± 3 days) by calendar date starting from Cycle 1 Day 1 (not adjusted for cycle or treatment days). These assessments will be performed on approximately Day 1 of every 4th cycle (C5, C9, C13 etc.). Scans used may be requested for central review. Effort should be made to maintain the same imaging modality throughout the study.

In CRPC subjects who discontinue study therapy without documented disease progression, every effort should be made to continue these bone scans every 12 weeks ±3 days until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. If subjects have stable disease, partial response, or complete response, they should continue on this every 12 weeks ±3 days assessment schedule. The timing for these assessments should continue the same imaging schedule from the treatment phase. Bone scans should occur at any time where there is clinical suspicion of progression.

##### 7.1.2.6.3 Assessment of Disease

Tumor lesions will be assessed throughout the study according to RECIST criteria (version 1.1) [101] (see Section 12.8). Any tumor shrinkage, in terms of percentage of tumor regression, will be reported even if it does not meet RECIST criteria for response. While RECIST criteria (version 1.1) do not require confirmation of objective response in clinical studies where response rate is not the study primary endpoint, as a convincing proof-of-concept of antitumor activity, efforts should be made to confirm objective response at least 4 weeks apart.

For CRPC subjects, PSA response rates will be measured according to the PCWG2 criteria [102] (see Section 12.9). RECIST v1.1 is used to assess soft tissue disease [101]. Progression

of bone disease is defined using PCWG2 criteria, namely a confirmed increase of at least two new lesions on a bone scan.

### 7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

#### 7.1.3.1 Laboratory Safety and Other Evaluations (Hematology, Chemistry, Coagulation and Other)

Laboratory tests for hematology, chemistry, coagulation and other are specified in Table 9. These tests are to be performed locally per institutional standards.

Table 9: Laboratory Tests

| Hematology | Chemistry | Urinalysis[b] | Other |
|---|---|---|---|
| Hematocrit | Albumin | Blood | Serum β-human chorionic gonadotropin (β-hCG)[a] |
| Hemoglobin | Alkaline phosphatase | Glucose | Urine pregnancy test[a] |
| Platelet count | Alanine aminotransferase (ALT) | Protein | Prothrombin Time (PT) (INR)[d] |
| White Blood Cell (total and differential) | Aspartate aminotransferase (AST) | Specific gravity | Activated Partial Thromboplastin Time (aPTT)[d] |
| Red Blood Cell Count | Carbon dioxide ($CO_2$ or bicarbonate)[b] | Microscopic exam, if abnormal results are noted | Factor VII |
| | Calcium | | PSA[e] |
| | Chloride | | |
| | Creatinine[c] | | |
| | Glucose | | |
| | Phosphorus | | |
| | Potassium | | |
| | Sodium | | |
| | Total Bilirubin | | |
| | Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal | | |
| | Total protein | | |
| | Blood Urea Nitrogen or Urea | | |
| | Uric acid | | |

[a] Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
[b] If these tests are not done per local institutional standards as part of standard of care in a geographical region then these tests do not need to be performed.
[c.] For subjects with a baseline calculated creatinine clearance below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed.

| Hematology | Chemistry | Urinalysis[b] | Other |
|---|---|---|---|
| [d] Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.<br>[e] CRPC subjects only. | | | |

#### 7.1.3.1.1 Urine or Serum β-hCG

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, will be tested for pregnancy via a urine test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. These tests are to be performed locally per institutional standards. The subject must be excluded in the event of a positive or borderline-positive serum test result.

### 7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

#### 7.1.3.2.1 PK Sample Collection (Plasma)

Samples will be collected on day 1 and three additional steady-state trough concentrations will be collected 1, 2 and 3 weeks after the first treatment intake.

The timing of the PK sample collections is as follows (see also Table 10 below). Seven blood samples will be collected on **Day 1 of Cycle 1**: immediately prior to the first dose (**T0**) and **20 min**±5min, **1h**±10min, **2h15min**±10min, **3h15min**±10min, **8h**±1h, and **12h**±2h (immediately before the second daily dose on day 1). Subjects will remain in clinic or be hospitalized for a minimum of 12±2 hours for PK sampling on day 1.

In addition, a single blood sample will be collected from all subjects immediately before drug intake on **days 8** (±1 days), **15** (±2 days), **and 22** (±3 days) to evaluate steady-state trough concentrations. Note: On these three days, it is critical that the subject withhold the morning dose until after the PK sample is collected in the clinic. Every effort should be made to collect the sample approximately 12 h after the previous evening dose. The timing of the previous dose should be recorded.

Table 10: PK Sample Collection Timing

| PK Sample # | Visit | Time of collection |
|---|---|---|
| 1 | Cycle 1 Day 1 | T0: Pre-morning dose |
| 2 | Cycle 1 Day 1 | 20 min ±5 min post-morning dose |
| 3 | Cycle 1 Day 1 | 1 hr ±10 min post-morning dose |
| 4 | Cycle 1 Day 1 | 2 hr 15 min ±10 min post-morning dose |
| 5 | Cycle 1 Day 1 | 3 hr 15 min ±10 min post-morning dose |
| 6 | Cycle 1 Day 1 | 8 hr ±1 hr post-morning dose |
| 7 | Cycle 1 Day 1 | 12 hr ±2 hr post-morning dose |
| 8 | Cycle 1 Day 8 | Pre-morning dose |
| 9 | Cycle 1 Day 15 | Pre-morning dose |
| 10 | Cycle 1 Day 22 *(Cycle 2 Day 1)* | Pre-morning dose |

In total, ten blood samples of 3.0 mL each will be collected, i.e. approximately 30 mL of blood will be drawn per subject treated in the BID regimen from a peripheral venous access for PK analysis.

Sample collection, storage and shipment instructions for plasma samples will be provided in the Procedure Manual.

#### 7.1.3.2.2 PK Assay Method and Parameters Analyzed

Plasma concentrations of MK-8628 will be measured using chromatography coupled with mass spectrometry detection.

The following parameters will be determined as appropriate, and may include trough ($C_{min}$) and peak ($C_{max}$) concentrations, $T_{max}$, AUC[0-∞], $Vd_{ss}$, t1/2, steady state, total clearance (CL) if non-compartmental analysis is performed.

PK data for MK-8628 will be interpreted in terms of safety/efficacy findings.

#### 7.1.3.2.3 PD Sample Collection

A range of PD biomarkers (based on current PD knowledge) will be explored in all subjects treated, using appropriate assays.

The timing of the PD sample collections is as follows (see also Table 11 below), and timing of collections should align with the collection of the PK samples at the same timepoints described in Table 11 PD biomarkers will be analyzed in peripheral blood. Four blood samples will be collected on **Day 1 of Cycle 1**: immediately prior to the first dose (**T0**) and **3h15min**±10min, **8h**±1h, and **12h**±2h (immediately before the second daily dose on day 1). In addition, a single blood sample will be collected from all subjects immediately before drug intake on **day 8** (±1 day)(same day as PK sample collection).

Table 11: PD Sample Collection Timing

| PD Sample # | Visit | Time of collection |
|---|---|---|
| 1 | Cycle 1 Day 1 | T0: Pre-morning dose |
| 2 | Cycle 1 Day 1 | 3 hr 15 min ±10 min post-morning dose |
| 3 | Cycle 1 Day 1 | 8 hr ±1 hr post-morning dose |
| 4 | Cycle 1 Day 1 | 12 hr ±2 hr post-morning dose |
| 5 | Cycle 1 Day 8 | Pre-morning dose |

#### 7.1.3.2.4 Serum Tumor Markers

Serum tumor markers, according to indication, will be measured; as far as possible, subsequent measures must be made in the same laboratory. These tests are to be performed locally per institutional standards. For CRPC subjects, the PSA measurements are mandatory, and will be performed at screening, and then on Day 1 of every cycle starting with Cycle 2. For other indications, the following non-exhaustive list of indication-specific tumor markers may be optionally considered for testing: CEA, CA 15-3, or CA 27.29 for Breast cancer, etc.

#### 7.1.3.3 Planned Genetic Analysis Sample Collection

This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage and shipment instructions for plasma samples will be provided in the Procedure Manual.

#### 7.1.3.4 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research.

### 7.1.4 Other Procedures

#### 7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Treatment Discontinuation Visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

##### 7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox PPD and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

#### 7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

#### 7.1.4.3 Domiciling

Subjects will report to the clinical research unit (CRU) the morning of the scheduled day of trial drug administration in Cycle 1 and remain in the unit for a minimum of 12±2 hours post-dose to collect PK blood samples and check vital signs, when appropriate. It is recommended, but not required, that subjects be admitted overnight for this first treatment day (Cycle 1 Day 1), and at the discretion of the investigator, subjects may be requested to remain in the CRU longer.

#### 7.1.4.4 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for study objectives

See protocol-specified guidance in the Administrative Binder, Procedures Manual and Site Imaging Manual.

### 7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

#### 7.1.5.1 Screening

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

Each candidate subject will be examined before starting the study to determine eligibility for participation as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor. Screening procedures are to be performed within 14 days prior to the first dose of trial treatment except for the following:

- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment.
- Complete blood count and serum chemistry measurements which must be performed within 7 days of the first dose of study treatment.

- Radiologic assessments can be obtained up to 4 weeks prior to the first dose of trial treatment.

Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

#### 7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

#### 7.1.5.3 End of Treatment

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. For each subject, record the date that study treatment is permanently discontinued, along with the reason for treatment discontinuation.

#### 7.1.5.4 Post-Treatment

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures

After the last treatment administration, subjects will be followed up for safety for 30 days and then until resolution of any AEs for which a relationship to MK-8628 cannot definitely be excluded (or categorized as sequelae). A visit will be performed 30 days (+5 days) after the last MK-8628 intake.

In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging* every 6 weeks (±3 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first. *Note: This includes bone scans for CRPC subjects every 12 weeks (±3 days). If subjects have stable disease, partial response, or complete response, they should continue on this assessment schedule. The timing for these assessments should continue the same imaging schedule from the treatment phase. Imaging, and if applicable, bone scans, should occur at any time where there is clinical suspicion of progression.

### 7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

### 7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-8628 by 1 dose in a 24 hour time period (i.e. $\geq$ 3 total doses in 24 hours). No specific information is available on the treatment of overdose of MK-8628. In the event of overdose, MK-8628 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is

reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### 7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 30 days following cessation of Sponsor's product must be reported. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### 7.2.3 Immediate Reporting of Adverse Events to the Sponsor

#### 7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

**Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 12 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

#### 7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).
3. an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal.
4. an elevated AST or ALT lab value that is greater than or equal to 5X the upper limit of normal.

   *Note: For further guidance on the monitoring, treatment and follow-up of any ECI related to potential drug-induced liver injury (DILI), please see Section 12.7.
5. For the purpose of this dose-finding study, any suspected DLT occurring during dose escalation will be considered as medically important and reported as an ECI. If the event also meets the criteria for seriousness, follow the reporting guidelines for Serious Adverse Events (SAEs) outlined in Section 7.2.3.1.

#### 7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

### 7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 12: Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

| | | |
|---|---|---|
| **V4.0 CTCAE Grading** | **Grade 1** | **Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.** |
| | **Grade 2** | **Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.** |
| | **Grade 3** | **Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.** |
| | **Grade 4** | **Life threatening consequences; urgent intervention indicated.** |
| | **Grade 5** | **Death related to AE** |
| **Seriousness** | A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that: | |
| | †**Results in death**; or | |
| | †**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or | |
| | †**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or | |
| | †**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or | |
| | †**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or | |
| | **Is a** new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or** | |
| | **Is an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours. | |
| | **Other important medical events** that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †). | |
| **Duration** | Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units | |
| **Action taken** | Did the adverse event cause the Sponsor's product to be discontinued? | |
| **Relationship to Sponsor's Product** | Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.<br>**The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE): | |
| | **Exposure** | Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen? |
| | **Time Course** | Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)? |
| | **Likely Cause** | Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors |

| | | |
|---|---|---|
| **Relationship to Sponsor's Product (continued)** | **The following components are to be used to assess the relationship between the test drug and the AE: (continued)** | |
| | **Dechallenge** | Was the Sponsor's product discontinued or dose/exposure/frequency reduced?<br>If yes, did the AE resolve or improve?<br>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.<br>(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.) |
| | **Rechallenge** | Was the subject re-exposed to the Sponsor's product in this study?<br>If yes, did the AE recur or worsen?<br>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.<br>(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time).<br>NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL. |
| | **Consistency with Trial Treatment Profile** | Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology? |
| The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements. | | |
| **Record one of the following** | **Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).** | |
| **Yes, there is a reasonable possibility of Sponsor's product relationship.** | There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause. | |
| **No, there is not a reasonable possibility of Sponsor's product relationship** | Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.) | |

### 7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

## 8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to final database lock, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (i.e., separate documents from the sSAP) will be developed to detail other planned analyses (i.e., those specific to the analysis of PK data, and future biomedical research).

### 8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in subsequent sections.

| | |
|---|---|
| **Study Design Overview** | A Phase IB Dose Exploration Trial with MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Subjects with Selected Advanced Solid Tumors |
| **Treatment Assignment** | This is an open label study with dose level specific cohorts. |
| **Analysis Populations** | Efficacy: Treatment Full Analysis Set (FAS), which is the same as ASaT<br>Safety: DLT evaluable, and All Subjects as Treated (ASaT) |
| **Primary Endpoint(s)** | Proportion of subjects experiencing at least one DLT in cycle 1 (day 1 to 21) |
| **Secondary Endpoints** | ORR, DOR and DCR based on the best overall response from tumor evaluations performed every 2 cycles, according to RECIST v1.1 or PCWG2 as assessed by investigator radiologic review. |
| **Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses** | ORR and DCR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval). |
| **Statistical Methods for Key Safety Analyses** | Counts and percentage of DLT will be provided. 80% Bayesian credible interval for DLT rate will be estimated based on a prior distribution of Beta(1,1). |
| **Interim Analyses** | During the dose escalation phase, regular assessment of data from the most recent cohort of subjects evaluable for DLT will be performed. |
| **Multiplicity** | This is an estimation study and no multiplicity adjustment will be implemented |
| **Sample Size and Power** | The study is designed to assess the safety of MK-8628 in subjects with advanced or metastatic solid tumors. The small numbers per cohort are not intended for statistical hypotheses.<br>Up to 72 evaluable subjects (up to 6-14 per three dose levels in the dose escalation part [Part A] and up to 30 in the NMC cohort [Part B]) will be included. The final sample size will depend on the number of subjects experiencing DLTs at each DL, and may be increased if the RP2D is not reached and additional DLs are required. |

## 8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This trial is being conducted as an open-label study with dose level-specific cohorts.

## 8.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.0.

There are no statistical hypotheses for this study.

## 8.4 Analysis Endpoints

### 8.4.1 Safety Endpoints

The primary safety objective of this trial is to estimate Proportion of subjects experiencing at least one DLT in cycle 1 (day 1 to 21) for each of the dose level-specific cohorts.

Other safety endpoints include Incidence, severity and relationship of AEs, laboratory abnormalities, SAEs, discontinuations due to AEs, dose adaptations due to AEs.

### 8.4.2 Efficacy/Pharmacokinetics/Pharmacodynamics Endpoints

Secondary endpoints are presented below:

**Objective Response Rate (ORR)**: is defined as the percentage of subjects who have achieved confirmed complete response (CR) or partial response (PR) according to RECIST v1.1 or PCWG2 as assessed by investigator radiologic review.

**Duration of Response (DOR)**: is defined as the time interval between the date of the first confirmed response (CR/PR) (the response prior to confirmation) and the date of first documented disease progression based upon RECIST v1.1 or PCWG2 as assessed by investigator radiologic review.

**Disease Control Rate (DCR)**: is defined as the percentage of subjects who have achieved stable disease or confirmed complete response (CR) or confirmed partial response (PR) according to RECIST v1.1 or PCWG2 as assessed by investigator radiologic review. Subjects with missing response will be considered not to have achieved disease control.

**Pharmacokinetics**

Plasma parameters of MK-8628 as appropriate and according to analyses performed (non-compartmental or nonlinear mixed effect modelling) (see Section 4.2.3.2).

**Pharmacodynamics**

Incidence and severity of AEs along with PK parameters will be analyzed in relation to the most pertinent biomarker(s), if any (see Section 4.2.3.3).

## 8.5 Analysis Populations

### 8.5.1 Efficacy Analysis Populations

Treatment **Full Analysis Set** (**FAS**), also known as **evaluable for efficacy**: subjects who receive at least one dose of study drug.

### 8.5.2 Safety Analysis Populations

**DLT Evaluable population**: subjects who receive at least 85% of the planned dose of study drug (18 days) or experience DLT during the first 21-day cycle.

The **All Subjects as Treated (ASaT)** population, also known as **treated population**, consisting of subjects who receive at least one dose of study drug, will be used for the analysis of all other safety data in this study.

## 8.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the supplemental SAP. Data will be presented by dose level, and where appropriate by indication. No imputations for missing data will be made.

Pharmacokinetics and pharmacodynamics will be analyzed and reported separately.

### 8.6.1 Statistical Methods for Efficacy Analyses

ORR and DCR with 95% confidence intervals will be estimated using Exact method based on binomial distribution (Clopper-Pearson interval).

DOR will be estimated by Kaplan-Meier method.

### 8.6.2 Statistical Methods for Safety Analyses

Count and percentage of DLT will be provided. 80% Bayesian credible interval for DLT rate will be estimated based on a prior distribution of *Beta*(1,1), with other credible levels considered as clinically needed.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Counts and percentage of AE will be provided. 95% confidence interval for rate of AE of clinical interest will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval).

### 8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

## 8.7 Interim Analyses

During the dose escalation phase, regular assessment of data from the most recent cohort of three subjects of each regimen evaluable for DLT will be performed.

## 8.8 Multiplicity

This is an estimation study and no multiplicity adjustment will be implemented

## 8.9 Sample Size and Power Calculations

The study is designed to assess the safety of MK-8628 in subjects with advanced or metastatic solid tumors. The small numbers per cohort are not intended for statistical hypotheses.

Up to 42 evaluable subjects will be included in the dose escalation cohort (Part A). There will be a maximum of 14 subjects at each of the pre-specified dose levels for DLT evaluation. The final sample size will depend on the number of subjects experiencing DLTs at each dose level, and may be increased if the RP2D is not reached and additional dose levels are required. For ORR, the sample size will be dependent on the number of subjects in each tumor type. Table 13 below provides Bayesian credible interval and confidence interval with different number of events or responses for sample sizes of 6 and 14 to characterize the precision of estimates for DLT rate and ORR, respectively. Up to 30 subjects will be included in the NMC cohort (Part B). Except for DLT, other safety and efficacy endpoints will be reported for each dose level pooling the dose escalation cohort and NMC cohort together.

Table 13: Bayesian credible interval for DLT rate estimate and confidence interval for ORR estimate for different sample sizes and number of events

| Sample Size | Number of Events or Responses | Observed Rate | 80% Bayesian credible interval | 95% Bayesian credible interval | 95% Confidence interval[a] |
|---|---|---|---|---|---|
| 6 | 0 | 0 | (0, 0.205) | (0, 0.348) | (0, 0.459) |
| 6 | 1 | 0.167 | (0.040, 0.391) | (0.013, 0.527) | (0.004, 0.641) |
| 6 | 2 | 0.333 | (0.146, 0.567) | (0.081, 0.685) | (0.043, 0.777) |
| 6 | 3 | 0.500 | (0.279, 0.721) | (0.184, 0.816) | (0.118, 0.882) |
| 14 | 0 | 0 | (0, 0.102) | (0, 0.181) | (0, 0.232) |
| 14 | 1 | 0.071 | (0.014, 0.194) | (0.004, 0.281) | (0.002, 0.339) |
| 14 | 2 | 0.143 | (0.053, 0.283) | (0.027, 0.373) | (0.018, 0.428) |
| 14 | 3 | 0.214 | (0.102, 0.367) | (0.062, 0.456) | (0.047, 0.508) |
| 14 | 4 | 0.286 | (0.156, 0.445) | (0.105, 0.533) | (0.084, 0.581) |
| 14 | 5 | 0.357 | (0.215, 0.519) | (0.154, 0.605) | (0.128, 0.649) |
| 14 | 6 | 0.429 | (0.276, 0.590) | (0.208, 0.672) | (0.177, 0.711) |

a. Confidence intervals were calculated using Exact method based on binomial distribution (Clopper-Pearson interval)

### 8.10 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses and effect of baseline factors may be explored as appropriate.

### 8.11 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

### 8.12 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication. Summary statistics will be provided on Extent of Exposure for ASaT population.

## 9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

### 9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 14.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 14: Product Descriptions

| Product Name & Potency | Dosage Form |
|---|---|
| MK-8628 10 mg | Gelatin capsules (white, size 3) |
| MK-8628 20 mg | Gelatin capsules (green, size 3) |
| MK-8628 40 mg | Gelatin capsules (white, size 0) |

### 9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open label bottles. No kitting is required.

### 9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

### 9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

### 9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

### 9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

## 10.0 ADMINISTRATIVE AND REGULATORY DETAILS

### 10.1 Confidentiality

#### 10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

#### 10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying

worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

### 10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

### 10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

## 10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements.

The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

### 10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last

approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

### 10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as

Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

### 10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

### 10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

### 10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement.

When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

## 11.0 LIST OF REFERENCES

1. Ji, Y., and Wang, S.-J. (2013). Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 31, 1785–1791.
2. Dang, C.V., Le, A., and Gao, P. (2009). MYC-induced cancer cell energy metabolism and therapeutic opportunities. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 15, 6479–6483.
3. Kim, J., Chu, J., Shen, X., Wang, J., and Orkin, S.H. (2008). An extended transcriptional network for pluripotency of embryonic stem cells. Cell 132, 1049–1061.
4. Beroukhim, R., Mermel, C.H., Porter, D., Wei, G., Raychaudhuri, S., Donovan, J., Barretina, J., Boehm, J.S., Dobson, J., Urashima, M., et al. (2010). The landscape of somatic copy-number alteration across human cancers. Nature 463, 899–905.

5. Stewart, T.A., Pattengale, P.K., and Leder, P. (1984). Spontaneous mammary adenocarcinomas in transgenic mice that carry and express MTV/myc fusion genes. Cell 38, 627–637.

6. Leder, A., Pattengale, P.K., Kuo, A., Stewart, T.A., and Leder, P. (1986). Consequences of widespread deregulation of the c-myc gene in transgenic mice: multiple neoplasms and normal development. Cell 45, 485–495.

7. Harris, A.W., Pinkert, C.A., Crawford, M., Langdon, W.Y., Brinster, R.L., and Adams, J.M. (1988). The E mu-myc transgenic mouse. A model for high-incidence spontaneous lymphoma and leukemia of early B cells. J. Exp. Med. 167, 353–371.

8. Soucek, L., Jucker, R., Panacchia, L., Ricordy, R., Tatò, F., and Nasi, S. (2002). Omomyc, a potential Myc dominant negative, enhances Myc-induced apoptosis. Cancer Res. 62, 3507–3510.

9. Jain, M., Arvanitis, C., Chu, K., Dewey, W., Leonhardt, E., Trinh, M., Sundberg, C.D., Bishop, J.M., and Felsher, D.W. (2002). Sustained loss of a neoplastic phenotype by brief inactivation of MYC. Science 297, 102–104.

10. Fukazawa, T., Maeda, Y., Matsuoka, J., Yamatsuji, T., Shigemitsu, K., Morita, I., Faiola, F., Durbin, M.L., Soucek, L., and Naomoto, Y. (2010). Inhibition of Myc effectively targets KRAS mutation-positive lung cancer expressing high levels of Myc. Anticancer Res. 30, 4193–4200.

11. Darnell, J.E. (2002). Transcription factors as targets for cancer therapy. Nat. Rev. Cancer 2, 740–749.

12. Schreiber, S.L., and Bernstein, B.E. (2002). Signaling network model of chromatin. Cell 111, 771–778.

13. Delmore, J.E., Issa, G.C., Lemieux, M.E., Rahl, P.B., Shi, J., Jacobs, H.M., Kastritis, E., Gilpatrick, T., Paranal, R.M., Qi, J., et al. (2011). BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 146, 904–917.

14. Mujtaba, S., He, Y., Zeng, L., Farooq, A., Carlson, J.E., Ott, M., Verdin, E., and Zhou, M.-M. (2002). Structural basis of lysine-acetylated HIV-1 Tat recognition by PCAF bromodomain. Mol. Cell 9, 575–586.

15. Filippakopoulos, P., Picaud, S., Mangos, M., Keates, T., Lambert, J.-P., Barsyte-Lovejoy, D., Felletar, I., Volkmer, R., Müller, S., Pawson, T., et al. (2012). Histone recognition and large-scale structural analysis of the human bromodomain family. Cell 149, 214–231.

16. Muller, S., Filippakopoulos, P., and Knapp, S. (2011). Bromodomains as therapeutic targets. Expert Rev. Mol. Med. 13, e29.

17. Dhalluin, C., Carlson, J.E., Zeng, L., He, C., Aggarwal, A.K., and Zhou, M.M. (1999). Structure and ligand of a histone acetyltransferase bromodomain. Nature 399, 491–496.

18. Owen, D.J., Ornaghi, P., Yang, J.C., Lowe, N., Evans, P.R., Ballario, P., Neuhaus, D., Filetici, P., and Travers, A.A. (2000). The structural basis for the recognition of acetylated histone H4 by the bromodomain of histone acetyltransferase gcn5p. EMBO J. 19, 6141–6149.

19. Morinière, J., Rousseaux, S., Steuerwald, U., Soler-López, M., Curtet, S., Vitte, A.-L., Govin, J., Gaucher, J., Sadoul, K., Hart, D.J., et al. (2009). Cooperative binding of two acetylation marks on a histone tail by a single bromodomain. Nature 461, 664–668.

20. Dey, A., Nishiyama, A., Karpova, T., McNally, J., and Ozato, K. (2009). Brd4 marks select genes on mitotic chromatin and directs postmitotic transcription. Mol. Biol. Cell 20, 4899–4909.

21. Yang, Z., Yik, J.H.N., Chen, R., He, N., Jang, M.K., Ozato, K., and Zhou, Q. (2005). Recruitment of P-TEFb for stimulation of transcriptional elongation by the bromodomain protein Brd4. Mol. Cell 19, 535–545.

22. Jang, M.K., Mochizuki, K., Zhou, M., Jeong, H.-S., Brady, J.N., and Ozato, K. (2005). The bromodomain protein Brd4 is a positive regulatory component of P-TEFb and stimulates RNA polymerase II-dependent transcription. Mol. Cell 19, 523–534.

23. Filippakopoulos, P., Qi, J., Picaud, S., Shen, Y., Smith, W.B., Fedorov, O., Morse, E.M., Keates, T., Hickman, T.T., Felletar, I., et al. (2010). Selective inhibition of BET bromodomains. Nature 468, 1067–1073.

24. Chung, C.-W., Coste, H., White, J.H., Mirguet, O., Wilde, J., Gosmini, R.L., Delves, C., Magny, S.M., Woodward, R., Hughes, S.A., et al. (2011). Discovery and characterization of small molecule inhibitors of the BET family bromodomains. J. Med. Chem. 54, 3827–3838.

25. Nicodeme, E., Jeffrey, K.L., Schaefer, U., Beinke, S., Dewell, S., Chung, C.-W., Chandwani, R., Marazzi, I., Wilson, P., Coste, H., et al. (2010). Suppression of inflammation by a synthetic histone mimic. Nature 468, 1119–1123.

26. Dawson, M.A., Prinjha, R.K., Dittmann, A., Giotopoulos, G., Bantscheff, M., Chan, W.-I., Robson, S.C., Chung, C., Hopf, C., Savitski, M.M., et al. (2011). Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. Nature 478, 529–533.

27. Picaud, S., Da Costa, D., Thanasopoulou, A., Filippakopoulos, P., Fish, P.V., Philpott, M., Fedorov, O., Brennan, P., Bunnage, M.E., Owen, D.R., et al. (2013). PFI-1, a highly selective protein interaction inhibitor, targeting BET Bromodomains. Cancer Res. 73, 3336–3346.

28. French, C.A., Ramirez, C.L., Kolmakova, J., Hickman, T.T., Cameron, M.J., Thyne, M.E., Kutok, J.L., Toretsky, J.A., Tadavarthy, A.K., Kees, U.R., et al. (2008). BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene 27, 2237–2242.

29. French, C.A. (2012). Pathogenesis of NUT midline carcinoma. Annu. Rev. Pathol. 7, 247–265.

30. French, C.A. (2010a). Demystified molecular pathology of NUT midline carcinomas. J. Clin. Pathol. 63, 492–496.

31. Bauer, D.E., Mitchell, C.M., Strait, K.M., Lathan, C.S., Stelow, E.B., Lüer, S.C., Muhammed, S., Evans, A.G., Sholl, L.M., Rosai, J., et al. (2012). Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 18, 5773–5779.

32. French, C.A. (2010b). NUT midline carcinoma. Cancer Genet. Cytogenet. 203, 16–20.

33. Haack, H., Johnson, L.A., Fry, C.J., Crosby, K., Polakiewicz, R.D., Stelow, E.B., Hong, S.-M., Schwartz, B.E., Cameron, M.J., Rubin, M.A., et al. (2009). Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am. J. Surg. Pathol. 33, 984–991.

34. French, C. (2014). NUT midline carcinoma. Nat. Rev. Cancer 14, 149–150.

35. Noel, J.K., Iwata, K., Ooike, S., Sugahara, K., Nakamura, H., and Daibata, M. (2013). Development of the BET bromodomain inhibitor OTX015. Mol. Cancer Ther. 12, Abstract #C244.

36. Sequist, L.V., Heist, R.S., Shaw, A.T., Fidias, P., Rosovsky, R., Temel, J.S., Lennes, I.T., Digumarthy, S., Waltman, B.A., Bast, E., et al. (2011). Implementing multiplexed genotyping of non-small-cell lung cancers into routine clinical practice. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. ESMO 22, 2616–2624.

37. Gainor, J.F., Varghese, A.M., Ou, S.-H.I., Kabraji, S., Awad, M.M., Katayama, R., Pawlak, A., Mino-Kenudson, M., Yeap, B.Y., Riely, G.J., et al. (2013). ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 19, 4273–4281.

38. Kris, M.G., Johnson, B.E., Kwiatkowski, D.J., Iafrate, A.J., Wistuba, I.I., Aronson, S.L., Engelman, J.A., Shyr, Y., Khuri, F.R., Rudin, C.M., et al. (2011). Identification of driver mutations in tumor specimens from 1,000 patients with lung adenocarcinoma: The NCI's Lung Cancer Mutation Consortium (LCMC). J. Clin. Oncol. 29: 2011 (suppl; Abstract #CRA7506).

39. Riely, G.J., Marks, J., and Pao, W. (2009). KRAS mutations in non-small cell lung cancer. Proc. Am. Thorac. Soc. 6, 201–205.

40. Roberts, P.J., Stinchcombe, T.E., Der, C.J., and Socinski, M.A. (2010). Personalized medicine in non-small-cell lung cancer: is KRAS a useful marker in selecting patients for epidermal growth factor receptor-targeted therapy? J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 28, 4769–4777.

41. Johnson, M.L., Sima, C.S., Chaft, J., Paik, P.K., Pao, W., Kris, M.G., Ladanyi, M., and Riely, G.J. (2013). Association of KRAS and EGFR mutations with survival in patients with advanced lung adenocarcinomas. Cancer 119, 356–362.

42. Malumbres, M., and Barbacid, M. (2003). RAS oncogenes: the first 30 years. Nat. Rev. Cancer 3, 459–465.

43. Sears, R., Nuckolls, F., Haura, E., Taya, Y., Tamai, K., and Nevins, J.R. (2000). Multiple Ras-dependent phosphorylation pathways regulate Myc protein stability. Genes Dev. 14, 2501–2514.

44. Pelengaris, S., Khan, M., and Evan, G. (2002). c-MYC: more than just a matter of life and death. Nat. Rev. Cancer 2, 764–776.

45. Soucek, L., Whitfield, J., Martins, C., Finch, A., Murphy, D., Sodir, N., Karnezis, A., Swigart, L., Nasi, S., Evan, G. (2008). Modelling Myc inhibition as a cancer therapy. Nature 455, 679-683.

46. Shimamura, T., Chen, Z., Soucheray, M., Carretero, J., Kikuchi, E., Tchaicha, J.H., Gao, Y., Cheng, K.A., Cohoon, T.J., Qi, J., et al. (2013). Efficacy of BET bromodomain inhibition in Kras-mutant non-small cell lung cancer. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 19, 6183–6192.

47. Dearden, S., Stevens, J., Wu, Y., Blowers, D. (2013). Mutation incidence and coincidence in non small-cell lung cancer: meta analyses by ethnicity and histology (mutMap). Ann. Oncol. 00, 1-6.

48. Shaw, A.T., and Solomon, B. (2011). Targeting anaplastic lymphoma kinase in lung cancer. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 17, 2081–2086.

49. Vazquez, R., Astorgues-Xerri, L., Bekradda, and et al (2014). OTX015, a novel pan BET-BRD inhibitor is active in non-small-cell lung cancer (NSCLC) cell lines bearing the fusion protein EML4-ALK. Proc 105th Annu. Meet. AACR Apr 5-9 San Diego USA Abstr. 5530.

50. Hammond, M.E.H., Hayes, D.F., Dowsett, M., Allred, D.C., Hagerty, K.L., Badve, S., Fitzgibbons, P.L., Francis, G., Goldstein, N.S., Hayes, M., et al. (2010). American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J. Clin. Oncol. 28, 2784–2795.

51. Wolff, A.C., Hammond, M.E.H., Schwartz, J.N., Hagerty, K.L., Allred, D.C., Cote, R.J., Dowsett, M., Fitzgibbons, P.L., Hanna, W.M., Langer, A., et al. (2007). American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J. Clin. Oncol. 25, 118–145.

52. Lehmann, B.D., Bauer, J.A., Chen, X., Sanders, M.E., Chakravarthy, A.B., Shyr, Y., and Pietenpol, J.A. (2011). Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J. Clin. Invest. 121, 2750–2767.

53. Sørlie, T., Perou, C.M., Tibshirani, R., Aas, T., Geisler, S., Johnsen, H., Hastie, T., Eisen, M.B., van de Rijn, M., Jeffrey, S.S., et al. (2001). Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc. Natl. Acad. Sci. U. S. A. 98, 10869–10874.

54. Hu, Z., Fan, C., Oh, D.S., Marron, J.S., He, X., Qaqish, B.F., Livasy, C., Carey, L.A., Reynolds, E., Dressler, L., et al. (2006). The molecular portraits of breast tumors are conserved across microarray platforms. BMC Genomics 7, 96.

55. Perou, C.M. (2011). Molecular stratification of triple-negative breast cancers. The Oncologist 16 Suppl 1, 61–70.

56. Nielsen, T.O., Hsu, F.D., Jensen, K., Cheang, M., Karaca, G., Hu, Z., Hernandez-Boussard, T., Livasy, C., Cowan, D., Dressler, L., et al. (2004). Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin. Cancer Res. 10, 5367–5374.

57. Kreike, B., van Kouwenhove, M., Horlings, H., Weigelt, B., Peterse, H., Bartelink, H., and van de Vijver, M.J. (2007). Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas. Breast Cancer Res. BCR 9, R65.

58. Prat, A., and Perou, C.M. (2011). Deconstructing the molecular portraits of breast cancer. Mol. Oncol. *5*, 5–23

59. Atchley, D.P., Albarracin, C.T., Lopez, A., Valero, V., Amos, C.I., Gonzalez-Angulo, A.M., Hortobagyi, G.N., and Arun, B.K. (2008). Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J. Clin. Oncol. 26, 4282–4288.

60. Gonzalez-Angulo, A.M., Timms, K.M., Liu, S., Chen, H., Litton, J.K., Potter, J., Lanchbury, J.S., Stemke-Hale, K., Hennessy, B.T., Arun, B.K., et al. (2011). Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin. Cancer Res. 17, 1082–1089.

61. Turner, N., Tutt, A., and Ashworth, A. (2004). Hallmarks of "BRCAness" in sporadic cancers. Nat. Rev. Cancer 4, 814–819.

62. Miyoshi, Y., Murase, K., and Oh, K. (2008). Basal-like subtype and BRCA1 dysfunction in breast cancers. Int. J. Clin. Oncol. 13, 395–400.

63. Abd El-Rehim, D.M., Ball, G., Pinder, S.E., Rakha, E., Paish, C., Robertson, J.F.R., Macmillan, D., Blamey, R.W., and Ellis, I.O. (2005). High-throughput protein expression analysis using tissue microarray technology of a large well-characterised series identifies biologically distinct classes of breast cancer confirming recent cDNA expression analyses. Int. J. Cancer 116, 340–350.

64. Turner, N.C., Reis-Filho, J.S., Russell, A.M., Springall, R.J., Ryder, K., Steele, D., Savage, K., Gillett, C.E., Schmitt, F.C., Ashworth, A., et al. (2007). BRCA1 dysfunction in sporadic basal-like breast cancer. Oncogene 26, 2126–2132.

65. Haffty, B.G., Yang, Q., Reiss, M., Kearney, T., Higgins, S.A., Weidhaas, J., Harris, L., Hait, W., and Toppmeyer, D. (2006). Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J. Clin. Oncol. 24, 5652–5657.

66. Kassam, F., Enright, K., Dent, R., Dranitsaris, G., Myers, J., Flynn, C., Fralick, M., Kumar, R., and Clemons, M. (2009). Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin. Breast Cancer 9, 29–33.

67. Onitilo, A.A., Engel, J.M., Greenlee, R.T., and Mukesh, B.N. (2009). Breast cancer subtypes based on ER/PR and Her2 expression: comparison of clinicopathologic features and survival. Clin. Med. Res. 7, 4–13.

68. Foulkes, W.D., Smith, I.E., and Reis-Filho, J.S. (2010). Triple-negative breast cancer. N. Engl. J. Med. 363, 1938–1948.

69. Liedtke, C., Mazouni, C., Hess, K.R., André, F., Tordai, A., Mejia, J.A., Symmans, W.F., Gonzalez-Angulo, A.M., Hennessy, B., Green, M., et al. (2008). Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J. Clin. Oncol. 26, 1275–1281.

70. Dent, R., Trudeau, M., Pritchard, K.I., Hanna, W.M., Kahn, H.K., Sawka, C.A., Lickley, L.A., Rawlinson, E., Sun, P., and Narod, S.A. (2007). Triple-negative breast cancer: clinical features and patterns of recurrence. Clin. Cancer Res. 13, 4429–4434.

71. Carey, L.A., Perou, C.M., Livasy, C.A., Dressler, L.G., Cowan, D., Conway, K., Karaca, G., Troester, M.A., Tse, C.K., Edmiston, S., et al. (2006). Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 295, 2492–2502.

72. Bauer, K.R., Brown, M., Cress, R.D., Parise, C.A., and Caggiano, V. (2007). Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer 109, 1721–1728.

73. Millikan, R.C., Newman, B., Tse, C.-K., Moorman, P.G., Conway, K., Dressler, L.G., Smith, L.V., Labbok, M.H., Geradts, J., Bensen, J.T., et al. (2008). Epidemiology of basal-like breast cancer. Breast Cancer Res. Treat. 109, 123–139.

74. Hugh, J., Hanson, J., Cheang, M.C.U., Nielsen, T.O., Perou, C.M., Dumontet, C., Reed, J., Krajewska, M., Treilleux, I., Rupin, M., et al. (2009). Breast cancer subtypes and response to docetaxel in node-positive breast cancer: use of an immunohistochemical definition in the BCIRG 001 trial. J. Clin. Oncol. 27, 1168–1176.

75. Smid, M., Wang, Y., Zhang, Y., Sieuwerts, A.M., Yu, J., Klijn, J.G.M., Foekens, J.A., and Martens, J.W.M. (2008). Subtypes of breast cancer show preferential site of relapse. Cancer Res. 68, 3108–3114.

76. Heitz, F., Harter, P., Lueck, H.-J., Fissler-Eckhoff, A., Lorenz-Salehi, F., Scheil-Bertram, S., Traut, A., and du Bois, A. (2009). Triple-negative and HER2-overexpressing breast cancers exhibit an elevated risk and an earlier occurrence of cerebral metastases. Eur. J. Cancer 1990 45, 2792–2798.

77. Gelmon, K., Dent, R., Mackey, J.R., Laing, K., McLeod, D., and Verma, S. (2012). Targeting triple-negative breast cancer: optimising therapeutic outcomes. Ann. Oncol. 23, 2223–2234.

78. O'Shaughnessy, J., Dieras, V., Glaspy, J., Brufsky, A., Miller, K., Miles, D., Koralewski, P., Phan, S., and Bhattacharya, S. (2009). Comparison of subgroup analyses of PFS from three Phase III studies of bevacizumab in combination with chemotherapy in patients with HER2-negative metastatic breast cancer (MBC). Cancer Res. 69, Abstract #207.

79. Brufsky, A., Valero, V., Tiangco, B., Dakhil, S., Brize, A., Rugo, H.S., Rivera, R., Duenne, A., Bousfoul, N., and Yardley, D.A. (2012). Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial. Breast Cancer Res. Treat. 133, 1067–1075.

80. O'Shaughnessy, J., Romieu, G., Dieras, V., Byrtek, M., Duenne, A.-A., and Miles, D. (2010). Meta-Analysis of patients with triple-negative breast cancer (TNBC) from three randomized trials of first-line bevacizumab (BV) and chemotherapy treatment for metastatic breast cancer (MBC). Cancer Res. 70, Abstract #P6–12–03.

81. Miller, K., Wang, M., Gralow, J., Dickler, M., Cobleigh, M., Perez, E.A., Shenkier, T., Cella, D., and Davidson, N.E. (2007). Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N. Engl. J. Med. 357, 2666–2676.

82. Horiuchi, D., Kusdra, L., Huskey, N.E., Chandriani, S., Lenburg, M.E., Gonzalez-Angulo, A.M., Creasman, K.J., Bazarov, A.V., Smyth, J.W., Davis, S.E., et al. (2012). MYC pathway activation in triple-negative breast cancer is synthetic lethal with CDK inhibition. J. Exp. Med. 209, 679–696.

83. Shi, J., Wang, Y., Zeng, L., Wu, Y., Deng, J., Zhang, Q., Lin, Y., Li, J., Kang, T., Tao, M., et al. (2014). Disrupting the interaction of BRD4 with diacetylated Twist suppresses tumorigenesis in basal-like breast cancer. Cancer Cell 25, 210–225.

84. Taylor, B.S., Schultz, N., Hieronymus, H., Gopalan, A., Xiao, Y., Carver, B.S., Arora, V.K., Kaushik, P., Cerami, E., Reva, B., et al. (2010). Integrative genomic profiling of human prostate cancer. Cancer Cell 18, 11–22.

85. Chen, C.D., Welsbie, D.S., Tran, C., Baek, S.H., Chen, R., Vessella, R., Rosenfeld, M.G., and Sawyers, C.L. (2004). Molecular determinants of resistance to antiandrogen therapy. Nat. Med. 10, 33–39.

86. Visakorpi, T., Hyytinen, E., Koivisto, P., Tanner, M., Keinänen, R., Palmberg, C., Palotie, A., Tammela, T., Isola, J., and Kallioniemi, O.P. (1995). In vivo amplification of the androgen receptor gene and progression of human prostate cancer. Nat. Genet. 9, 401–406.

87. Harris, W.P., Mostaghel, E.A., Nelson, P.S., and Montgomery, B. (2009). Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. Nat. Clin. Pract. Urol. 6, 76–85.

88. Taplin, M.E., Bubley, G.J., Ko, Y.J., Small, E.J., Upton, M., Rajeshkumar, B., and Balk, S.P. (1999). Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. Cancer Res. 59, 2511–2515.

89. Sun, S., Sprenger, C.C.T., Vessella, R.L., Haugk, K., Soriano, K., Mostaghel, E.A., Page, S.T., Coleman, I.M., Nguyen, H.M., Sun, H., et al. (2010). Castration resistance in human prostate cancer is conferred by a frequently occurring androgen receptor splice variant. J. Clin. Invest. 120, 2715–2730.

90. Grasso, C.S., Wu, Y.-M., Robinson, D.R., Cao, X., Dhanasekaran, S.M., Khan, A.P., Quist, M.J., Jing, X., Lonigro, R.J., Brenner, J.C., et al. (2012). The mutational landscape of lethal castration-resistant prostate cancer. Nature 487, 239–243.

91. Stein, M.N., Goodin, S., and Dipaola, R.S. (2012). Abiraterone in prostate cancer: a new angle to an old problem. Clin. Cancer Res. 18, 1848–1854.

92. Reid, A.H.M., Attard, G., Danila, D.C., Oommen, N.B., Olmos, D., Fong, P.C., Molife, L.R., Hunt, J., Messiou, C., Parker, C., et al. (2010). Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. J. Clin. Oncol. 28, 1489–1495.

93. De Bono, J.S., Logothetis, C.J., Molina, A., Fizazi, K., North, S., Chu, L., Chi, K.N., Jones, R.J., Goodman, O.B., Saad, F., et al. (2011). Abiraterone and increased survival in metastatic prostate cancer. N. Engl. J. Med. 364, 1995–2005.

94. Mukherji, D., Pezaro, C.J., and De-Bono, J.S. (2012). MDV3100 for the treatment of prostate cancer. Expert Opin. Investig. Drugs 21, 227–233.

95. Scher, H.I., Fizazi, K., Saad, F., Taplin, M.-E., Sternberg, C.N., Miller, K., de Wit, R., Mulders, P., Chi, K.N., Shore, N.D., et al. (2012). Increased survival with enzalutamide in prostate cancer after chemotherapy. N. Engl. J. Med. 367, 1187–1197.

96. Asangani, I.A., Dommeti, V.L., Wang, X., Malik, R., Cieslik, M., Yang, R., Escara-Wilke, J., Wilder-Romans, K., Dhanireddy, S., Engelke, C., et al. (2014). Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. Nature 510, 278–282.

97. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11. 2002; 246:1-190.

98. Azad, N., Zahnow, C., Rudin, C., Baylin, S. (2013). The future of epigenetic therapy in solid tumors – lessons from the past. Nature Rev Clin Onco 10, 256-266.

99. Issa, J., Kantarjian, H., Kirkpatrick, P. (2005). Azacitidine. Nature Rev Drug Disc 4, 275-276.

100. Mertz, J., Conery, A., Bryant, B., Sandy, P., Balasubramanian, S., Mele, D., Bergeron, L, Sims III, R. (2011). Targeting MYC dependence in cancer by inhibiting BET bromodomains. PNAS 108:40, 1669-16674.

101. Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*, 228–247.

102. Scher, H.I., Halabi, S., Tannock, I., Morris, M., Sternberg, C.N., Carducci, M.A., Eisenberger, M.A., Higano, C., Bubley, G.J., Dreicer, R., et al. (2008). Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J. Clin. Oncol. *26*, 1148–1159.

# 12.0 APPENDICES

## 12.1 Merck Code of Conduct for Clinical Trials

**Merck***
**Code of Conduct for Clinical Trials**

**I. Introduction**

**A. Purpose**

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

**B. Scope**

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

**II. Scientific Issues**

**A. Trial Conduct**

**1. Trial Design**

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

**2. Site Selection**

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

**3. Site Monitoring/Scientific Integrity**

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

**B. Publication and Authorship**

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

**III. Subject Protection**

**A. IRB/ERC review**

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

**B. Safety**

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

**C. Confidentiality**

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

**D. Genomic Research**

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

**IV. Financial Considerations**

**A. Payments to Investigators**

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

**B. Clinical Research Funding**

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

**C. Funding for Travel and Other Requests**

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

**V. Investigator Commitment**

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

## 12.2 Collection and Management of Specimens for Future Biomedical Research

### 1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

### 2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

### 3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

**4. Confidential Subject Information for Future Biomedical Research**

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

**5. Biorepository Specimen Usage**

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

**6. Withdrawal From Future Biomedical Research**

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox PPD and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

**7. Retention of Specimens**

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

**8. Data Security**

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

**9. Reporting of Future Biomedical Research Data to Subjects**

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

**10. Future Biomedical Research Study Population**

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

**11. Risks Versus Benefits of Future Biomedical Research**

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).']

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

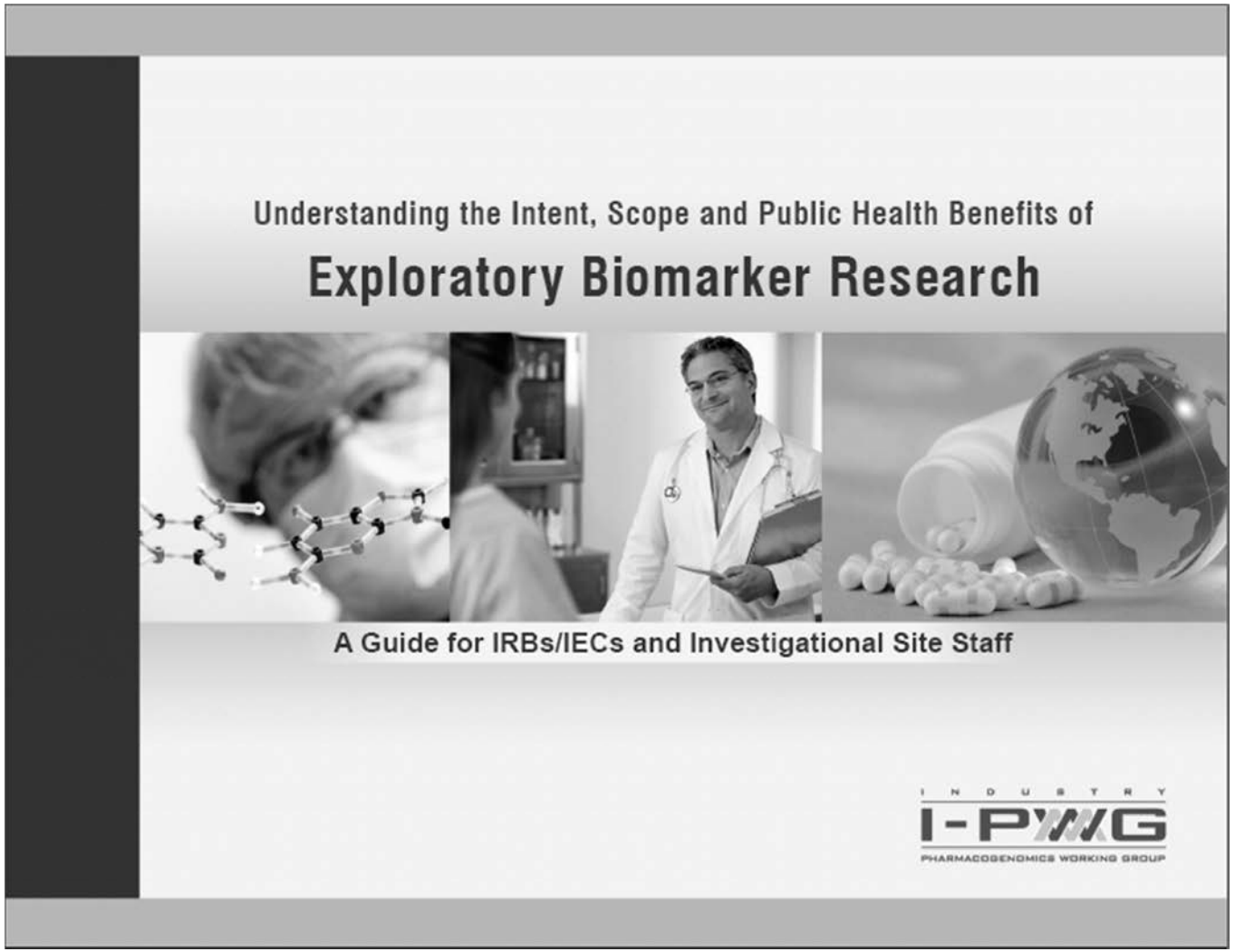
**12. Questions**

Any questions related to the future biomedical research should be e-mailed directly to PPD

**13. References**

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

## 12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff



**This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.**

*Developed by*
*The Industry Pharmacogenomics Working Group (I-PWG)*
***www.i-pwg.org***

## 1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

## 2. Why is Biomarker Research Important?

**Importance to Patients and Public Health**
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

**Importance to Drug Development**
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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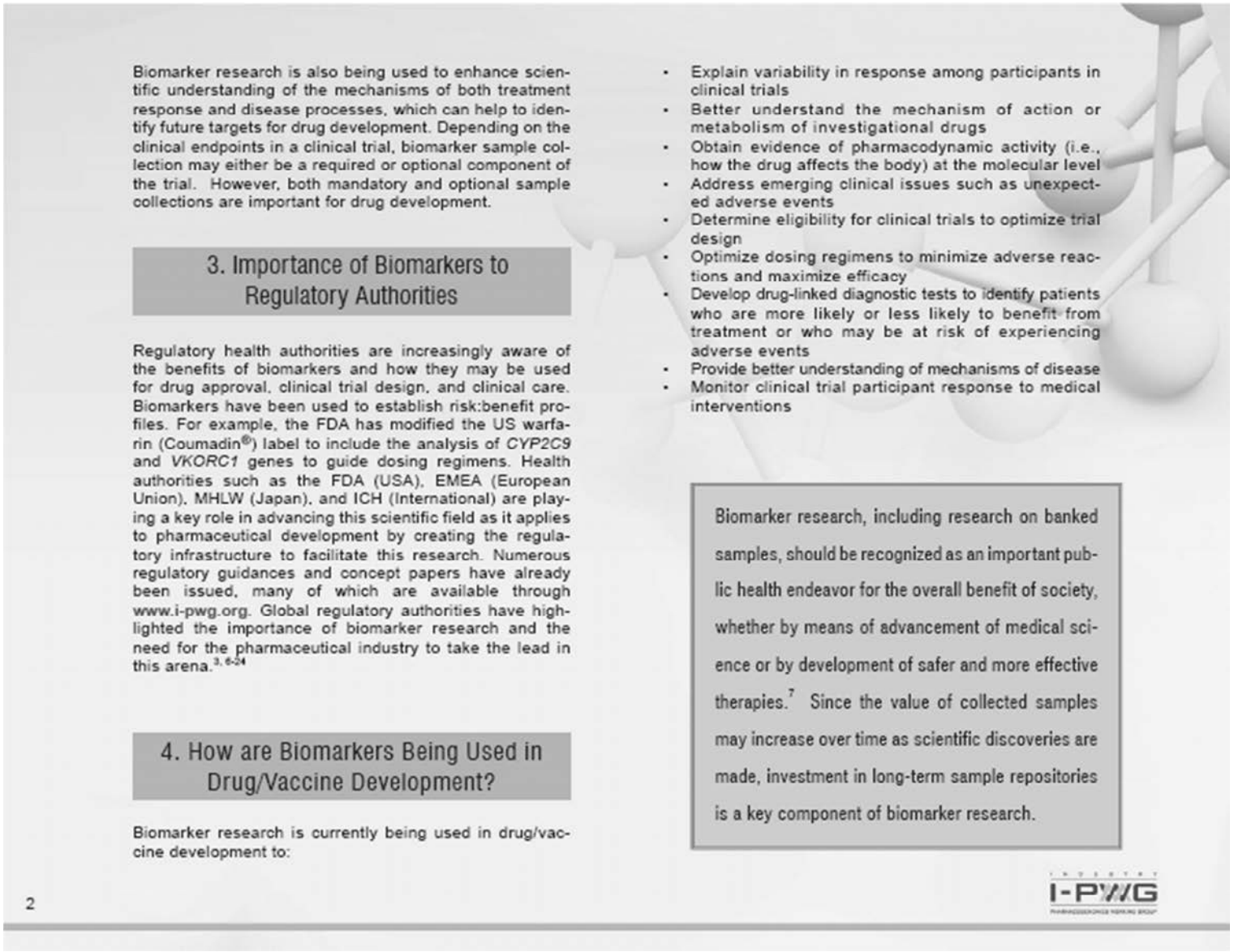
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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## 5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

***Predictive biomarkers (efficacy)*** – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

***Predictive biomarkers (safety)*** – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

***Surrogate biomarkers*** – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

***Prognostic biomarkers*** – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

## 6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

## 7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

### Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

### Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

**The scope of research** – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

**Withdrawal of consent / sample destruction** – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

**The duration of storage** – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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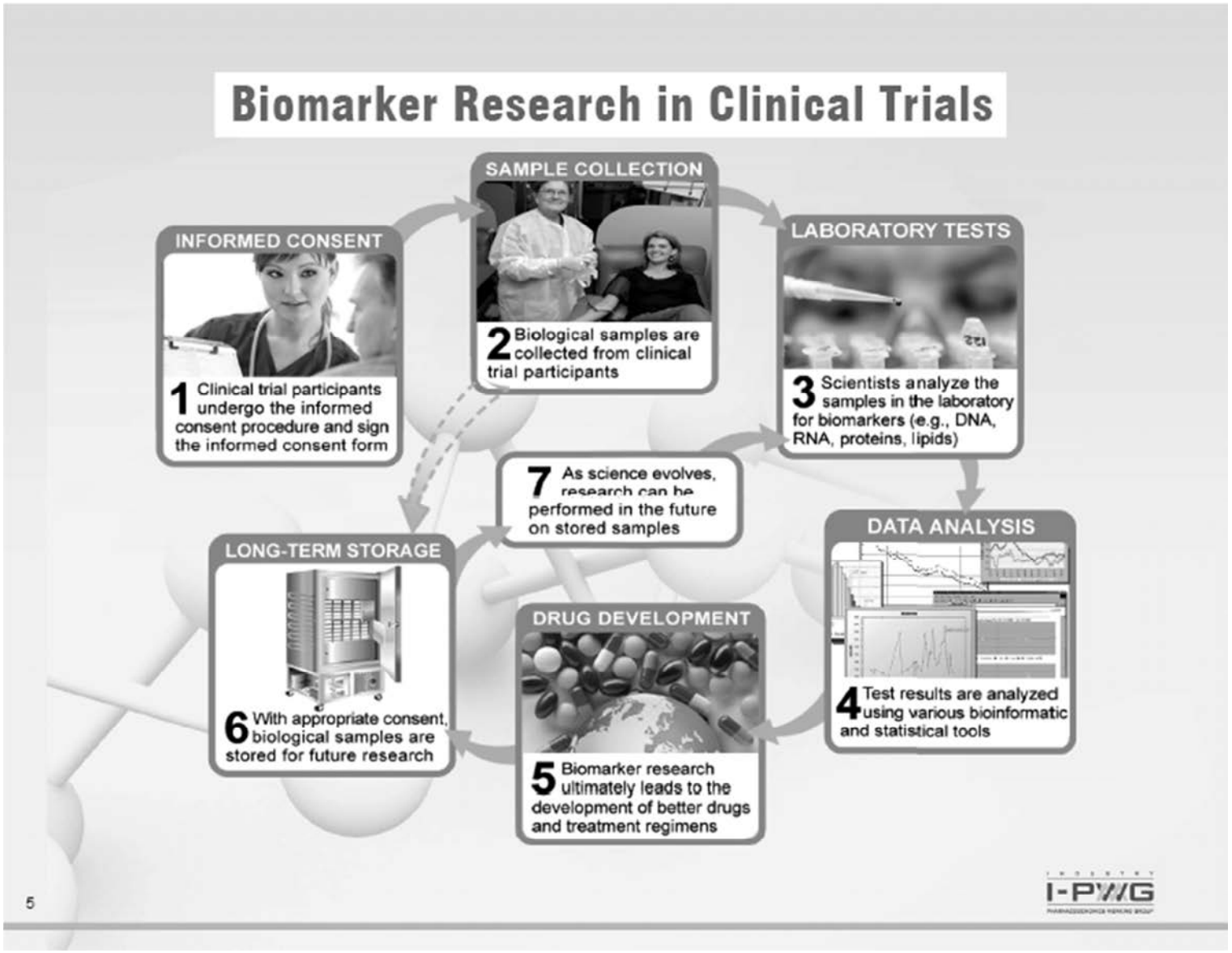
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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## 8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

## 9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

## 10. Benefits and Risks Associated with Biomarker Research

**Benefits**

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

**Risks**

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

## 11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

*"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",*

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

## 12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

## 13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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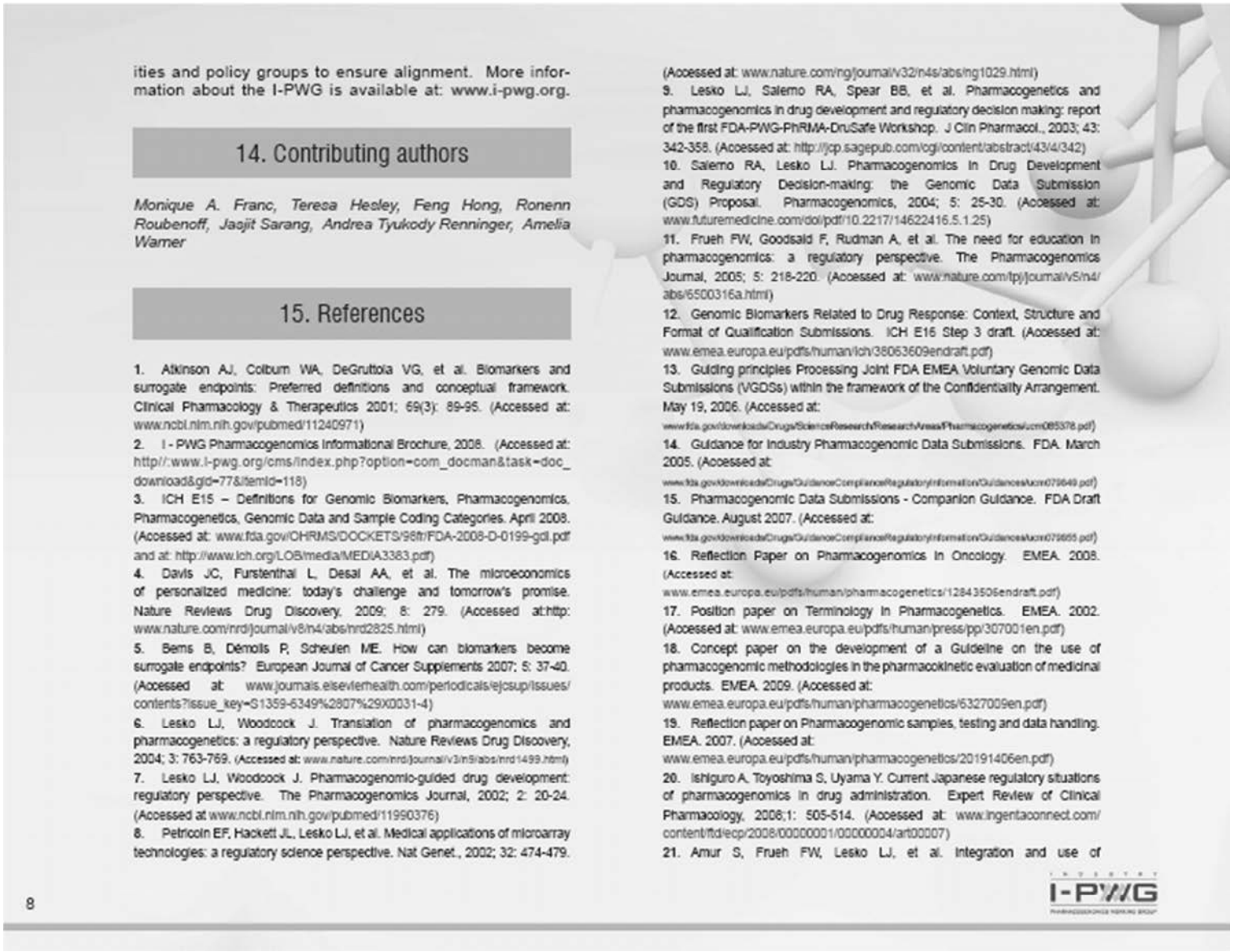

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

## 14. Contributing authors

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## 15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)
3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)
4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)
5. Bems B, Démolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)
6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)
7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)
8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)
9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)
10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)
11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)
12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/38063609endraft.pdf)
13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)
14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf)
15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079855.pdf)
16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)
17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/307001en.pdf)
18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)
20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/ftd/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

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biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)

23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)

24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)

25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

26. International Serious Adverse Event Consortium. (Accessed at: www.saeconsortium.org)

27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)

28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)

29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)

30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)

31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MED/A482.pdf)

32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy, 2004; 3: 440-450.

33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)

34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)

35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)

36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)

37. Genetic Information Nondiscrimination Act. (Accessed at: http://webgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:pu1233.110.pdf)

38. Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf

39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research: Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:284-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)


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## 12.4 ECOG Performance Status

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

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

### 12.5 Calculation of Renal Clearance

Subjects aged < 65 years: **Cockroft &Gault** formula

| |
|---|
| **Male** = 1.25 x **weight (kg)** x (140-**age**) / serum **creatinine (µmol/L)** |
| **Female** = 1.04 x **weight (kg)** x (140-**age**) / serum **creatinine (µmol/L)** |

Subjects aged ≥ 65 years: **MDRD** (Modification of Diet in Renal Disease) formula

| |
|---|
| Male = 186 x (serum **creatinine (µmol/L)** x 0,0113)$^{-1,154}$ x **age**$^{-0,203}$ |
| x 1,21 in subjects with black skin |
| x 0.742 in female |

**Clearance can be calculated using tools available via the internet, e.g.**

http://filfola.fr/medecine/cockroft_MDRD.html

or

http://mdrd.com/

## 12.6 Non-Exhaustive List of Drugs and Substances with the Potential to Interfere with CYP3A4 and CYP2A6

**Strong CYP3A4 interfering agents are prohibited (in bold and underlined).**

A **strong inhibitor** increases the AUC of a substrate for a given CYP by ≥5-fold or > 80% decrease in clearance. A **strong inducer** decreases the AUC of a substrate for a given CYP by ≥ 80%.

| **Strong CYP3A4 inducers** | **Strong CYP3A4 inhibitors** | | **Moderate CYP3A4 inducers** | **Moderate CYP3A4 inhibitors** | |
|---|---|---|---|---|---|
| **avasimibe** | **boceprevir** | **nefazodone** | amobarbital | atazanavir | fluconazole |
| **carbamazepine** | **clarithromycin** | **nelfinavir** | dexamethasone | amiodarone | fosamprenavir |
| **phenytoin** | **conivaptan** | **posaconazole** | efavirenz | amprenavir | imatinib |
| **rifampicin** | **grapefruit juice**[1] | **ritonavir** | felbamate | aprepitant | miconazole |
| **St John's wort**[1] | **indinavir** | **saquinavir** | nevirapine | cimetidine | suboxone |
| | **itraconazole** | **telaprevir** | omeprazole | cyclosporine | verapamil |
| | **ketoconazole** | **telithromycin** | phenobarbital | darunavir | |
| | **lopinavir** | **tipranavir** | pioglitazone | delavirdine | |
| | **mibefradil** | **voriconazole** | primidone | diltiazem | |
| | | | rifabutin | erythromycin | |
| | | | tamoxifen | | |
| | | | troglitazone | | |

| **CYP3A Sensitive substrates** | | | | **CYP3A Substrates with a Narrow Therapeutic Range** | |
|---|---|---|---|---|---|
| alfentanil | dronedarone | lovastatin | simvastatin | alfentanil | fentanyl |
| aprepitant | eletriptan, | lurasidone | sirolimus | astemizole | pimozide |
| budesonide | eplerenone, | maraviroc | tolvaptan | cisapride | quinidine |
| buspirone | everolimus | midazolam | tipranavir | cyclosporine | sirolimus |
| conivaptan | felodipine | nisoldipine | triazolam | dihydroergotamine | tacrolimus |
| darifenacin | indinavir | quetiapine | vardenafil | ergotamine | terfenadine |
| darunavir | fluticasone | saquinavir | | | |
| dasatinib | lopinavir | sildenafil | | | |

| **CYP2A6 inducers** | **CYP2A6 inhibitors** | **Other CYP2A6 substrates** | |
|---|---|---|---|
| phenobarbital | grapefruit juice | coumarin | nicotine |
| rifampicin | ketoconazole | halothane | quinoline |
| | methoxsalen | losigamone | SM-12502 |
| | pilocarpine | methoxyflurane | valproic acid |
| | tranylcypromine | | |

1. Preparation-dependent

## 12.7 Guidance for Potential Drug-Induced Liver Injury (DILI)

### 12.7.1 Purpose

The purpose of this document is to provide guidance to enable the investigator/study coordinator to provide clinical follow-up and systematically gather and report data on potential DILI. The data collected will be used by the Sponsor to create narratives for regulatory agency reporting.

### 12.7.2 Introduction

Hepatotoxicity is injury or damage to the liver that may be associated with impaired liver function [1]. Drug-induced hepatotoxicity is one of the most common causes of termination of drug development, a major reason for refusal of market authorization and for restricted use, and the single most important cause of the withdrawal of market authorization for products [2]. Thus, drug-induced hepatotoxicity is a major concern during the discovery, development to post-authorization phases of the product life cycle (excerpted from Draft Guidance Document, Hepatotoxicity of Health Products, Ministry of Public Health, Canada, December 2010)[3].

As stated in the United States Food and Drug Administration (FDA) "Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation" [4]; hepatocellular injury (usually detected by serum aminotransferase elevations [AT]) can be caused by drugs that rarely, if ever, cause severe DILI (e.g., aspirin, tacrine, statins, and heparin), as well as by drugs that do cause such injury. The frequency of serum AT elevations also is not a good indicator of a potential for severe DILI because drugs such as tacrine (not a cause of severe DILI) can cause AT elevations in as many as 50 percent of patients. Very high levels of observed ATs may be a somewhat better indicator of potential for severe DILI, but the most specific indicator is evidence of altered liver function accompanying or promptly following evidence of hepatocellular injury.

The single clearest (most specific) predictor found to date of a drug's potential for severe hepatotoxicity, is the occurrence of hepatocellular injury (AT elevation) accompanied by increased serum total bilirubin (TBL) not explained by any other cause, such as viral hepatitis or exposure to other hepatotoxins, and without evidence of cholestasis, together with an increased incidence of AT elevations in the overall trial population compared to control. Increased plasma prothrombin time, or its international normalized ratio (INR), a consequence of reduced hepatic production of Vitamin K-dependent clotting factors, is another potentially useful measure of liver function that might suggest the potential for severe liver injury.

Recognition of the importance of altered liver function, in addition to liver injury, began with Hyman Zimmerman's observation that drug-induced hepatocellular injury (i.e., AT elevation) accompanied by jaundice (i.e., TBL elevation) had a poor prognosis, with a 10 to 50 percent mortality from acute liver failure (in pretransplantation days) [5][6]. This became known as "Hy's Law". This document describes the recommended process for monitoring and evaluation of subjects meeting the laboratory criteria for potential DILI defined as:

- an elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- an elevated TBL lab value that is greater than or equal to two times (2X) ULN and
- at the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,

as a result of within-protocol-specific testing or unscheduled testing.

The protocol identifies these laboratory criteria for potential DILI as ECIs. ECIs are selected adverse experiences that must be reported to the Sponsor within 24 hours. The Principal Investigator should record these ECIs on the Adverse Experience Case Report Forms (CRFs) and complete pertinent adverse experience fields as outlined in the Data Entry Guidelines (DEGs).

### 12.7.3 Close Observation Recommendations

The following steps should be taken when a subject is observed to have an elevated AST or ALT lab value that is greater than or equal to 3X ULN and an elevated TBL lab value that is greater than or equal to 2X ULN and, at the same time, an ALP lab value that is less than 2X ULN, as a result of within-protocol-specific testing or unscheduled testing. In addition, close monitoring of *isolated* bilirubin increases greater than 2X ULN will be required.

Initiate **close observation,** defined below, and continue performing **follow-up to resolution.**

**Close observation is defined as follows**:

- Repeat liver enzyme and serum bilirubin tests two (2) or three (3) times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the subject is asymptomatic.
    - For subjects with *isolated* bilirubin elevations greater than 2X ULN, repeat serum bilirubin tests every 2 weeks until the bilirubin returns to normal or baseline.
- Obtain a more detailed history of symptoms and prior or concurrent diseases. (See Section 12.7.5).
- Obtain a history of concomitant medication use (including prescription and nonprescription medications, herbal and other dietary supplements), alcohol use, recreational drug use and special diets. (See Section 12.7.5 for details.)
- Obtain a history of exposure to chemical agents or other environmental toxins.

- Obtain additional history and complete Stage 1 work-up to attempt to rule out other potential causes of the transaminase elevation, including but not limited to the following: acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease. (See Section 12.7.5.5 for details.)
- Consider gastroenterology or hepatology consultation.

**In general, treatment with study therapy should be stopped if the laboratory criteria for potential DILI are met. Please refer to the specific discontinuation criteria in the protocol as appropriate.**

### 12.7.4 Hepatic Assessment Flow Chart

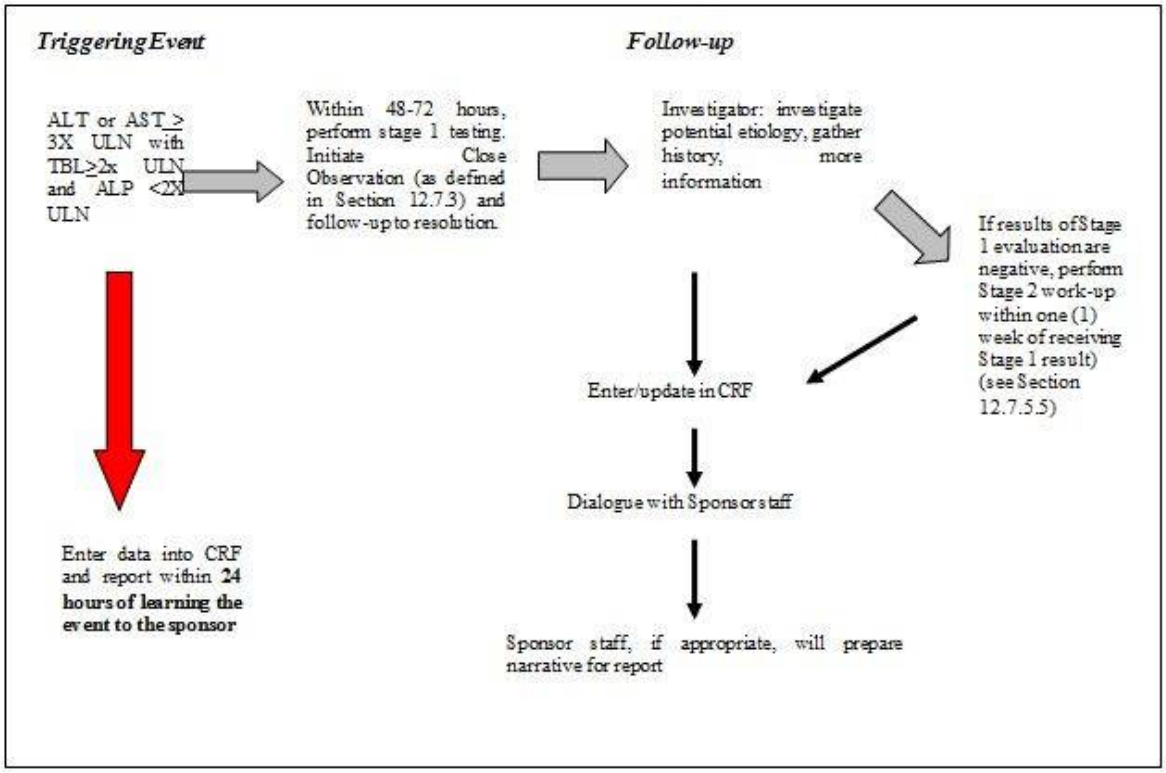


Figure 5: Hepatic Assessment Flow Chart

### 12.7.5 Factors to Consider in Assessing Potential DILI

When there is a potential DILI, it is important to thoroughly assess the subject's history, hepatic risk factors, clinical condition and hepatic function until resolution (normal or baseline levels).

Answers to the following questions should be recorded in source documents and in appropriate CRFs as outlined in the DEGs.

### 12.7.5.1 Study Medication

Considerations should include the following: What was the time interval between administration of study medication and the laboratory abnormality(ies)? What is the status of study medication use: Continuing? Interrupted? Discontinued? Was the subject re-challenged with study medication?

### 12.7.5.2 Treatment

Record any concomitant treatments.

### 12.7.5.3 Signs and Symptoms (associated with the potential DILI event)

Does the subject have a concomitant illness? Does the subject currently exhibit signs or symptoms of hepatitis/DILI? What are the subject's signs and symptoms (see examples below)? What are the pertinent findings from medical history, physical/laboratory examination (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%, hepatomegaly, splenomegaly, etc.) that could suggest DILI?

| Category | Examples of Signs and Symptoms |
|---|---|
| Blood/lymphatic | Eosinophilia, coagulopathy, susceptibility to bleeding/bruising |
| Circulatory | Varicose veins, edema |
| Constitutional | Fever, fatigue, malaise, weight gain, other (identify). |
| Digestive/hepatic | Anorexia, diarrhea, bloody or black stool, light-colored stools, nausea, vomiting, hematemesis, upper quadrant abdominal pain, upper quadrant tenderness, hepatomegaly, jaundice, splenomegaly, ascites, cholestasis |
| Endocrine/reproductive | Loss of libido |
| Integumentary | Rash, pruritus |
| Muscular | Myalgia |
| Nervous | Changes in mental status or level of consciousness |
| Urinary | Dark urine |

### 12.7.5.4 Confounding Variables

What are the relevant medical history and findings? What is the differential diagnosis? What risk factors does the subject have for hepatic injury? (See examples below.) Provide onset of risk factor and duration.

| Category | Examples of Confounding Variables |
|---|---|
| Subject medical history | Autoimmune disorder, cancer, Gilbert's syndrome, obesity, Wilson's disease |
| Substance use/abuse | Alcohol, illegal drugs, illegal intravenous (IV) drugs |
| Prior & Concomitant Medications: Review all non-study medications and therapies, including: over-the-counter (OTC), as well as prescription. Ask the subject to bring products/packaging to site and review contents. | History of recent concomitant acetaminophen (APAP)/paracetamol use, excessive nonsteroidal anti-inflammatory drug (NSAID) intake, use of non-study drug or therapy that can cause liver damage or idiosyncratic adverse drug reactions |
| Herbal and nutritional supplements | Herbal, complementary therapies, and nutritional supplements |
| Adulteration of products | History of previous exposure to the product or a similar product, and information on potential contamination or adulteration of products |

| Category | Examples of Confounding Variables |
|---|---|
| Chemical exposure | Occupational or in other situations |
| Potential exposure to infectious agents | Infectious hepatitis, transfusion, travel, tattoos, sexually transmitted diseases, new sexual partner, shared needles |
| Special Diet | Special diet started since randomization |
| Other | Recent physical trauma, excessive exercise, or other prolonged physical exertion |
| Family history | Autoimmune disorder, cancer, Gilbert's syndrome, Wilson's disease |

### 12.7.5.5 Evaluation algorithm for potential DILI if there are no other clinical reasons

Note: If clear etiology for the laboratory abnormalities has been confirmed, Stage 1 and 2 testing may not be required. In this case, consultation with the Sponsor is recommended.

**Stage 1 work-up should be performed within 48-72 hours:**

- ALT
- AST
- Bilirubin: total, direct, indirect
- Alkaline phosphatase (ALP)
- Prothrombin Time (PT)/international normalized ratio (INR)
- Creatine phosphokinase (CPK)
- Manual eosinophil count (if automated count was elevated)
- Toxicology screen for drugs of abuse (including ethanol) and for acetaminophen/paracetamol level should also be sent. Investigators may order additional toxicology tests as clinically indicated.
- Evaluate subject for the following signs and symptoms: fatigue, nausea, vomiting, right upper quadrant abdominal pain or tenderness, fever, rash.
- Obtain the following additional history and assessment for associated risk/confounding factors:
    - More detailed history of symptoms and prior or concurrent illness
    - Aminotransferase values obtained prior to the study or administration of study medication
    - Alcohol consumption (recent and historical)
    - Acetaminophen (APAP)/paracetamol use
    - New prescription, concomitant, or non-prescription (including herbal and other dietary supplements) medications
    - Unusual foods (e.g. mushrooms) or special diets. Consumption of seasonal foods.
    - Recreational drug use

  - Prior history of liver injury or disease, including but not limited to Gilbert's syndrome, autoimmune disorders, cancer, Wilson's disease, NASH, alcoholic or infectious hepatitis, biliary tract disease, hypoxic/ischaemic hepatopathy
  - Obesity/abdominal adiposity (record weight, height, and waist circumference)
  - Occupational history and history of exposure to chemical agents or other environmental toxins
  - Recent travel (last three [3] years)
  - Transfusion history
- Perform the following required laboratory tests**:**
  - Albumin
  - Eosinophils (percentage and absolute; obtain manual count if automated count is elevated)
  - Viral hepatitis serologies (obtain appropriate consent prior to testing, if required locally)
    - A (IgG, IgM)
    - B (HepBs Ag, Hep Bs Ab, Hep Bc Ab, Hep Be Ag)
    - C (RNA)
    - D (requires concomitant hepatitis B infection)
  - Human Immunodeficiency Virus (HIV) testing (obtain appropriate consent prior to testing, if required locally)
  - Evaluation for autoimmune hepatitis:
    - Serum gamma globulin levels/ serum protein electrophoresis
    - Antinuclear antibody (ANA)
    - Anti-mitochondrial antibody (if ALP or TBL >ULN)
  - If AST/ALT ratio is greater than one (1) with suspicions of increased alcohol intake, perform the following:
    - Gamma-glutamyl transferase (GGT)
- Obtain a right upper quadrant ultrasound

**Stage 2 work-up tests should be drawn within one (1) week of receiving the Stage 1 work-up results and the results of Stage 1 evaluation are negative.**

**Note: A specific test may be performed earlier if the investigator determines that the clinical presentation leads to a certain diagnosis.**

**Stage 2 work-up:**

- Perform the following laboratory tests:
    - Genetic test for Gilbert's disease if there is a suspicious history. Ensure appropriate subject consent is obtained for this test.
    - Viral hepatitis E (IgG and IgM, obtain appropriate consent prior to testing, if required locally)
    - Anti-smooth muscle antibody
    - Anti-liver-kidney microsomal antibody
    - Anti-soluble liver antigen
    - Serologies for the following:
        - Cytomegalovirus (CMV) (IgG, IgM)
        - Epstein-Barr Virus (EBV) (IgG, IgM)
        - Herpes simplex
        - Toxoplasmosis
        - Varicella
        - Parvovirus
    - Ceruloplasmin
    - Serum alpha-1 anti trypsin
    - Genetic test for hemochromatosis. Ensure appropriate subject consent is obtained for this test
    - Iron Studies:
        - serum ferritin,
        - serum iron,
        - total iron binding capacity
- Consider referral to hepatologist/gastroenterologist
- Consider screen for celiac disease and cystic fibrosis if clinically indicated
- If laboratory tests or ultrasound evidence of biliary tract obstruction, consider obtaining Endoscopic Retrograde Cholangiopancreatography (ERCP) or Magnetic Resonance Cholangiopancreatography (MRCP)

If applicable, request copies of hospital discharge summaries, consultation reports, pathology reports, special studies (e.g. imaging or biopsy), etc.

#### 12.7.5.6 Potential diagnosis

What diagnosis do the history, clinical course, and laboratory tests suggest?

#### 12.7.5.7 Overall clinical impression

What are the investigator's overall clinical impressions (e.g., differential diagnosis, potential alternative causes)?

#### 12.7.5.8 Treatment plan

What is the plan for treatment and follow-up?

### 12.7.6 Contacts

If you have any questions, please refer to your Sponsor contact list for the following Merck personnel:

- Clinical Research Associate or Subsidiary Monitor
- Clinical Monitor
- Clinical Scientist

### 12.7.7 References

1. Navarro, VJ and JR Senior, 2006, Drug-Related Hepatotoxicity, N Eng J Med, 354(7):731-9.
2. Björnsson, E and R Olsson, 2005, Outcome and Prognostic Markers in Severe Drug-Induced Liver Disease, Hepatology, 42(2):481-9.
3. Draft Guidance Document, Hepatotoxicity of Health Products, Ministry of Public Health, Canada, December 2010

   http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/consultation/drug-medic/draft_ebauche_hepatotox_guide_ld-eng.pdf
4. FDA Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009

   www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf
5. Zimmerman, HJ, 1978, Drug-Induced Liver Disease, in: Hepatotoxicity, The Adverse Effects of Drugs and Other Chemicals on the Liver, 1st ed., pp. 351-3, Appleton-Century-Crofts, New York.
6. Zimmerman, HJ, 1999, Drug-Induced Liver Disease, in: Hepatotoxicity, The Adverse Effects of Drugs and Other Chemicals on the Liver, 2nd ed., pp. 428-33, Lippincott Williams & Wilkins, Philadelphia.

## 12.8 Response Evaluation Criteria in Solid Tumors (RECIST)

Tumor lesions will be assessed throughout the study according to RECIST criteria (version 1.1) [1]. Any tumor shrinkage, in terms of percentage of tumor regression, will be reported even if it does not meet RECIST criteria for response. While RECIST criteria (version 1.1) do not require confirmation of objective response in clinical studies where response rate is not the study primary endpoint, as a convincing proof-of-concept of antitumor activity, efforts should be made to confirm objective response at least 4 weeks apart.

### 12.8.1 Imaging Technique

To ensure comparability, the baseline and subsequent tumor measurements to assess response should be performed using identical imaging techniques (i.e., preferably the same machine, contrast agent and standard volume of contrast agent, etc.).

### 12.8.2 Evaluation of Lesions

Table 15: Evaluation of response in target lesions

| | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in 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. |
| Progression (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).<br>In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.<br>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. |

Table 16: Evaluation of non-target lesions

| | |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions. 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) and/or maintenance of tumor marker level above the normal limits. |
| Progression (PD) | Unequivocal progression of existing non-target lesions; see Section 4.3.4 of Eisenhauer et al., 2009 for further details.<br>*Note:* the appearance of one or more new lesions is also considered progression. Unequivocal progression of existing non-target lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating investigator (in this circumstance an explanation must be provided)[1]. |

[1]Although clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later by the Medical Monitor.

### 12.8.3 Definition of Best Overall Tumor Response

The best overall response is the best response recorded between the start and the end of treatment, as described below. Overall response is calculated for each assessment time point according to Table 17.

Table 17: Overall response in subjects 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; NE, not evaluable

The best overall response is determined once all data for a given subject are available. Table 18 below summarizes the best overall tumor response.

Table 18: Best overall response

| Overall response First time point | Overall response Subsequent time points | Best overall response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[1] |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| NE | NE | NE |

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable

1. If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/ biopsy) before confirming the complete response status.

### 12.8.4 References

1. Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*, 228–247.

## 12.9 Prostate Cancer Clinical Trials Working Group (PCWG2) Response Criteria

For CRPC subjects, PSA response rates will be measured according to the PCWG2 criteria [1]. RECIST v1.1 is used to assess soft tissue disease [2]. Progression of bone disease is defined using PCWG2 criteria, namely a confirmed increase of at least two new lesions on a bone scan.

### 12.9.1 PSA

**For control/relief/eliminate end points**

The PCWG2 advises against reporting PSA response rates because they are of little value given the uncertain significance of a defined degree of decline from baseline, be it 50% or 30%, and no criterion has been shown prospectively to be a surrogate of clinical benefit [3].

To report PSA-based outcomes, PCWG2 recommends that the percentage of change in PSA from baseline to 12 weeks (or earlier for those who discontinue therapy), as well as the maximum decline in PSA that occurs at any point after treatment be reported for each subject using a waterfall plot [4]. Waterfall plots provide a broader and more sensitive display of data, and are more informative until a validated surrogate of clinical benefit becomes available. PCWG2 recommends that the same waterfall plot be used to illustrate outcomes for noncytotoxic agents. It discourages the use of changes in PSA-doubling time or PSA slope as a primary end point, given that their clinical significance is uncertain, and also recommends avoiding reporting duration of PSA control, as described in PCWG1 guidelines, because its interpretation varies between investigators.

**For delay/prevent end points**

PCWG2 defines PSA progression as the date that a 25% or greater increase and an absolute increase of ≥2 ng/mL from the nadir is documented, which is confirmed by a second value obtained 3 or more weeks later. This will be used to determine both PSA progression and response duration. This recommendation recognizes that variations in progression times might occur simply on the basis of the rate of PSA rise. Where no decline from baseline is documented, PCWG2 defines PSA progression as a 25% increase from the baseline value along with an increase in absolute value of 2 ng/mL or more (rather than 5 ng/mL) after 12 weeks of treatment.

### 12.9.2 Measureable Soft-Tissue Lesions

**For control/relieve/eliminate end points**

PCWG2 accepts with modifications RECIST criteria for evaluating drugs or approaches anticipated to produce tumor regression. The modifications are that changes in nodal and visceral sites be recorded and reported separately, and lymph nodes in the pelvis must measure at least 2 cm in their greatest diameter to be considered target lesions. PCWG2 also recommends that the complete elimination of disease at a particular site be recorded separately. PCWG2 reinforces the recommendation in RECIST that any favorable change should be confirmed using a second follow-up scan. As with changes in PSA, PCWG2 suggests that changes in the size of the target lesions be reported as a waterfall plot to facilitate comparison between studies.

**For prevent/delay end points**

Progression in a nodal or visceral site should also be defined using RECIST, with the recognition that, for some therapies, early unfavorable changes may not accurately reflect disease status. As noted, a lymphocytic infiltration of a tumor mass after successful immunization may result in an enlarged soft-tissue lesion that could be an early indication that the treatment is working. Further, because the effects of some agents (non-cytotoxic) may be delayed, the degree of increase in tumor size at the first 12-week assessment should also be confirmed before it is considered a treatment failure.

### 12.9.3 Bone

Given the frequency of bone involvement in patients with progressive, castration-resistant disease, the decreased emphasis of early changes in PSA, and the increased availability of cytostatic agents, reliable methods to assess changes in bone are of increasing importance. PCWG2 recognizes that standards for using MRI and positron emission tomography (PET) to assess bone metastases are under active investigation, so only radionuclide bone scans are considered here. PCWG2 also recognizes that there are no validated criteria for response on radionuclide bone scan.

**For control/relieve/eliminate end points**

PCWG2 recommends that post-treatment changes be recorded simply as either "no new lesions" or "new lesions." However, progression at the first scheduled assessment should be confirmed on a second scan performed 6 or more weeks later, in the absence of clearly worsening soft-tissue (nodal and visceral) disease or disease-related symptoms. In the rare case where visible lesions disappear, this too should be confirmed at the next scheduled assessment.

**For prevent/delay end points**

Progressing disease on bone scan is considered when a minimum of two new lesions is observed. PCWG1 made the provision that a worsening bone scan on the first follow-up manifests tumor "flare"; PCWG2 does not recommend performing a follow-up bone scan before 12 weeks of treatment unless clinically indicated. At the first 12-week reassessment, defining disease progression requires a confirmatory scan (which shows additional new lesions compared with the first follow-up scan) performed 6 or more weeks later, because lesions visible at the 12-week assessment may represent disease that was not detected on the pretreatment scan. When further progression is documented on the confirmatory scan, the date of progression recorded for the trial, is the date of the first scan that shows the change.

Note that symptoms will not be evaluated in this phase Ib study.

Table 19: The Prostate Cancer Clinical Trials Working Group (PCWG2) Response Criteria

| Variable | PCWG2 Criteria [1] |
|---|---|
| **PSA** | **For control/relieve/eliminate end points:**<br>Record the percent change from baseline (rise or fall) at 12 weeks, and separately, the maximal change (rise or fall) at any time using a waterfall plot<br>**Progression:**<br>**Decline from baseline**: record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend)<br>The requirement of an increase of 5 ng/mL is decreased to 2 ng/mL, and the requirement for a 50% increase is reduced to 25%<br>Recording the duration of PSA decline of little value<br>**No decline from baseline:**<br>PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks |
| **Soft-tissue lesions** | **For control/relieve/eliminate end points:**<br><br>Use RECIST with caveats<br>Only report changes in lymph nodes that were ≥ 2 cm in diameter at baseline<br>Record changes in nodal and visceral soft tissue sites separately<br>Record complete elimination of disease at any site separately<br>Confirm favorable change with second scan<br>Record changes using waterfall plot<br>**For delay/prevent end points:**<br>Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later<br>Note that for some treatments, a lesion may increase in size before it decreases |
| **Bone** | **For control/relieve eliminate end points:**<br>Record outcome as new lesions or no new lesions<br>First scheduled reassessment:<br>No new lesions: continue therapy<br>New lesions: perform a confirmatory scan 6 or more weeks later<br>Confirmatory scan:<br>No new lesions: continue therapy<br>Additional new lesions: progression<br>Subsequent scheduled reassessments:<br>No new lesions: continue<br>New lesions: progression<br>**For prevent/delay end points (progression):**<br>The appearance of ≥ 2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions<br>The date of progression is the date of the first scan that shows the change |

PSA, prostate-specific antigen

### 12.9.4 References

1. Scher, H.I., Halabi, S., Tannock, I., Morris, M., Sternberg, C.N., Carducci, M.A., Eisenberger, M.A., Higano, C., Bubley, G.J., Dreicer, R., et al. (2008). Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J. Clin. Oncol. *26*, 1148–1159.
2. Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer *45*, 228–247.
3. Fleming, M.T., Morris, M.J., Heller, G., and Scher, H.I. (2006). Post-therapy changes in PSA as an outcome measure in prostate cancer clinical trials. Nat. Clin. Pract. Oncol. *3*, 658–667.
4. Seidman, A.D., Scher, H.I., Petrylak, D., Dershaw, D.D., and Curley, T. (1992). Estramustine and vinblastine: use of prostate specific antigen as a clinical trial end point for hormone refractory prostatic cancer. J. Urol. *147*, 931–934.

## 12.10 List of Abbreviations

| | |
|---|---|
| ADL | Activities of daily living |
| AE | Adverse Event |
| AL | Acute Leukemia |
| ALK | Anaplastic Lymphoma Kinase |
| ALT (or SGPT) | Alanine Aminotransferase (serum glutamic-pyruvic transaminase) |
| ALP | Alkaline Phosphatase |
| AML | Acute Myeloid Leukemia |
| ANA | Antinuclear antibody |
| ANC | Absolute neutrophil count |
| APAP | N-Acetyl-p-Aminophenol (acetaminophen) |
| aPTT | Activated Partial Thromboplastin Time |
| AR | Androgen receptor |
| ASaT | All Subjects as Treated |
| ASCO | American Society of Clinical Oncology |
| AST (or SGOT) | Aspartate Aminotransferase (serum glutamic-oxaloacetic transaminase) |
| AT | Aminotransferase(s) |
| AUC | Area Under The Plasma Concentration Versus Time Curve |
| BCL2 | B-cell lymphoma 2 |
| BET | Bromodomain and Extraterminal |
| β-hCG | Serum β-human chorionic gonadotropin |
| BID | Twice Daily |
| BLBC | Basal-like breast cancer |
| BRCA (1 and 2) | Breast cancer genes 1 and 2 |
| BRD | Bromodomain |
| BRD2 | Bromodomain-containing gene 2 |
| BRD3 | Bromodomain-containing gene 3 |
| BRD4 | Bromodomain-containing gene 4 |
| BRDT | BRD Testis-Specific Protein |
| BSEP | Bile salt export pump |
| CA 15-3 | Cancer Antigen 15-3 |
| CA 27.29 | Cancer Antigen 27.29 |
| CBC | Complete Blood Count |
| CEA | Carcinoembryonic Antigen |
| CFR | Code of Federal Regulations |
| CL | Total Plasma Clearance |
| CL/F | Oral clearance |
| cm | centimeter |
| $C_{max}$ | Maximum Concentration |
| $C_{min}$ | Minimum Concentration |
| CMV | Cytomegalovirus |
| CNS | Central Nervous System |
| $CO_2$ | Carbon dioxide |
| CPK | Creatine phosphokinase |
| CRU | Clinical Research Unit |
| Ct | Cycle threshold |
| CT | Computerized Tomography scan |
| $C_{trough}$ | Trough concentration |
| CR | Complete Response |
| CRi | Complete Response with incomplete blood count recovery |
| CRPC | Castration-Resistant Prostate Cancer |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTFG | Clinical Trial Facilitation Group |

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|---|---|
| CYP | Cytochrome P450 enzyme |
| CYP2A6 | Cytochrome P450, family 2, subfamily A, polypeptide 6 |
| CYP2C9 | Cytochrome P450, family 2, subfamily C, polypeptide 9 |
| CYP2C19 | Cytochrome P450, family 2, subfamily C, polypeptide 19 |
| CYP3A4 | Cytochrome P450, family 3, subfamily A, polypeptide 4 |
| D | De-escalate |
| DCR | Disease Control Rate |
| DDI | Drug-drug interaction |
| DILI | Drug-induced liver injury |
| dL | deciliter |
| DL | Dose Level |
| DLBCL | Diffuse large B-cell lymphoma |
| DLT | Dose Limiting Toxicity |
| DMSO | Dimethyl sulfoxide |
| DNA | Deoxyribonucleic acid |
| DNMT | DNA methyltransferase |
| DOR | Duration of Response |
| DU | Dose unacceptably toxic |
| E | Escalate |
| EBV | Epstein-Barr Virus |
| ECG | Electrocardiogram |
| ECI | Events of clinical interest |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EGFR | Epidermal Growth Factor Receptor |
| EML4 | Echinoderm Microtubule-Associated Protein-Like 4 |
| EPO | Erythropoietin |
| ER | Estrogen Receptor |
| ERC | Ethics Review Committee |
| ERCP | Endoscopic Retrograde Cholangiopancreatography |
| ERG | Erythroblast transformation-specific related gene |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act |
| FDAMA | Food and Drug Administration Modernization Act |
| FISH | Fluorescence In Situ Hybridization |
| FSH | Follicle stimulating hormone |
| g | gram |
| GCP | Good Clinical Practices |
| G-CSF | Granulocyte-colony stimulating factor |
| GGT | Gamma-glutamyl transferase |
| GnRH | Gonadotropin Releasing Hormone |
| HBcAb | Hepatitis B core antibody |
| HBeAg | Hepatitis B e antigen |
| HBsAb | Hepatitis B surface antibody |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HER2 | Human Epidermal Growth Factor Receptor 2 |
| HIV | Human immunodeficiency virus |
| hr | hour |
| IB | Investigators Brochure |
| $IC_{50}$ | Half maximal inhibitory concentration |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IgG | Immunoglobulin G |

| | |
|---|---|
| IgM | Immunoglobulin M |
| IHC | Immunohistochemistry |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IUD | Intrauterine device |
| IUS | Intrauterine hormone-releasing system |
| IV | Intravenous |
| IWRS | Interactive Web Response System |
| JQ1 | small-molecule inhibitor of BET bromodomain chromatin-associated proteins |
| kg | kilogram |
| KRAS | Kirsten rat sarcoma viral oncogene homolog |
| L | liter |
| LKB1 | Liver kinase B1 |
| LMWH | Low Molecular Weight Heparin |
| MAPK | Mitogen-activated protein kinase |
| MDRD | Modification of Diet in Renal Disease |
| MDS | Myelodysplastic syndrome |
| MEC | Molar extinction coefficient |
| mg | milligrams |
| mL | milliliter |
| µM | Micromolar |
| mm | millimeter |
| mmHg | Millimeters of mercury |
| MPD | Myeloproliferative disorder |
| MRCP | Magnetic Resonance Cholangiopancreatography |
| MRI | Magnetic Resonance Imaging |
| mRNA | Messenger RNA |
| MRP2 | Multi-drug resistance-associated protein 2 |
| MRP3 | Multi-drug resistance-associated protein 3 |
| mTPI | Modified Toxicity Probability Interval |
| MYC (or c-MYC) | v-myc avian myelocytomatosis viral oncogene homolog |
| NASH | Non-alcoholic steatohepatitis |
| NCI | National Cancer Institute |
| NE | Not evaluable |
| ng | nanogram |
| nmol | nanomole |
| NMC | NUT Midline Carcinoma |
| N-MYC | V-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog |
| NSAID | Nonsteroidal anti-inflammatory drug |
| NSCLC | Non-Small Cell Lung Cancer |
| NUT | Nuclear Protein in Testis |
| OATP1B1 | Organic anion-transporting polypeptide, 1B1 |
| OATP1B3 | Organic anion-transporting polypeptide, 1B3 |
| OHM | Other Hematologic Malignancies |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| p21 | P21/Ras protein |
| $P_{app}$ | Apparent permeability |
| PCWG2 | Prostate Cancer Clinical Trials Working Group |
| PD | Pharmacodynamics |
| PD | Progressive Disease |
| PET | Positron emission tomography |
| PFS | Progression-Free Survival |
| P-gP | Phosphoglycolate phosphatase |
| PgR | Progesterone Receptor |

| | |
|---|---|
| PI3K | Phosphoinositide 3-kinase |
| PK | Pharmacokinetics |
| POC | Proof of concept |
| PPIB | Peptidylpropyl isomerase B |
| PR | Partial Response |
| PS | Performance Status |
| PSA | Prostate Specific Antigen |
| PT | Prothrombin Time |
| P-TEFb | Positive Transcription Elongation Factor b |
| QD | Once Daily |
| OTC | Over the counter |
| qPCR | Quantitative polymerase chain reaction |
| RAS | P21/Ras protein |
| RD | Recommended dose |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| RNA | Ribonucleic acid |
| RP2D | Recommended Phase II Dose |
| S | Stay at current dose |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SCC | Squamous Cell Carcinoma |
| SD | Stable Disease |
| SOP | Standard Operating Procedure |
| sSAP | Supplemental Statistical Analysis Plan |
| $t_{1/2}$ | Terminal Half-Life |
| TBL | Serum total bilirubin |
| Tmax | Time to Peak Concentration |
| TMPRSS2 | Transmembrane protease, serine 2 |
| TNBC | Triple Negative Breast Cancer |
| Ty82 | Human thymic carcinoma cell line |
| UDP | Uridine diphosphate |
| UGT | Uridine diphosphate glucuronosyltransferase |
| UGT1A1 | Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1 |
| UGT1A3 | Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A3 |
| UGT1A7 | Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A7 |
| UGT1A8 | Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A8 |
| UGT1A9 | Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A9 |
| UGT1A10 | Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A10 |
| ULN | Upper Limit of Normal |
| UV | Ultraviolet |
| $Vd_{ss}$ | Volume of Distribution At Steady State |
| V/F | Volume of distribution |

## 13.0 SIGNATURES

### 13.1 Sponsor's Representative

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|---|---|
| TYPED NAME | |
| TITLE | |
| SIGNATURE | |
| DATE SIGNED | |

### 13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

| | |
|---|---|
| TYPED NAME | |
| TITLE | |
| SIGNATURE | |
| DATE SIGNED | |