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CLINICAL STUDY PROTOCOL

OTX015_108/MK-8628-003

EUDRACT NUMBER: 2014-002680-15

A Phase IB Trial with OTX015/MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Patients with Selected Advanced Solid Tumors

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Date of issue: 19 November, 2015 **Version N°:** *F5.00*

STUDY PROTOCOL AGREEMENT FORM

I, _____, have reviewed this Study Protocol OTX015_108/ MK-8628-003, Final Version F5.00, dated 19 November, 2015, entitled:

A Phase IB Trial with OTX015/MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Patients with Selected Advanced Solid Tumors

I confirm that I have read the above protocol. The information it contains is consistent with the current risk-benefit evaluation of the investigational product.

I understand it, and I agree to conduct the study according to this protocol and to comply with its requirements, subject to scientific, ethical and safety considerations. Specifically, I will work according to the principles of GCP as described in CPMP/ICH/135/95 and 21 CFR parts 50, 54, 56, and 312, and according to applicable local requirements.

I understand that I must keep confidential the information contained in the study documents that I have been or will be provided with.

I understand that, should the decision be made by the Sponsor to terminate prematurely or suspend the study at any time for whatever reason, such a decision will be communicated to me in writing. Should I decide to withdraw from participating in the study I will communicate immediately such a decision in writing to the Sponsor.

Furthermore, by the present, I am committed to enroll the first patient in this study within a month.

SPONSOR: ONCOETHIX	**INVESTIGATOR**
PPD	**Dr.** _____
CRO Representative, Medical Monitor	Principal Investigator
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SYNOPSIS

STUDY TITLE

A Phase IB Trial with OTX015/MK-8628, a Small Molecule Inhibitor of the Bromodomain and Extra-Terminal (BET) Proteins, in Patients with Selected Advanced Solid Tumors

INVESTIGATORS / LOCATIONS

At least 7 centers in Belgium, Canada, France, Spain and Switzerland.

Coordinating investigator: PPD (Canada)

Principal investigators: PPD (Belgium), PPD (France), PPD (Switzerland), PPD (France), PPD (Switzerland), PPD (Spain).

STUDY OBJECTIVES

Primary

- To determine the Maximal Tolerated Dose (MTD) defined as the recommended phase II dose for two distinct regimens of OTX015/MK-8628 administered orally to patients with selected advanced solid tumors

Secondary

- To assess the safety profile of single-agent OTX015/MK-8628
- To characterize pharmacokinetics parameters of OTX015/MK-8628
- To determine the antitumor activity of OTX015/MK-8628 in selected solid tumors

STUDY DESIGN

Open-label, phase I, non-randomized, multicentric study of single-agent OTX015/MK-8628 administered according to two distinct regimens to patients with selected advanced tumors.

The study will be performed in two parts.

Dose Escalation Part

This step is designed to determine the maximum tolerated dose (MTD) in each of the two regimens, which will be evaluated in parallel. Patients will receive oral OTX015/MK-8628 according to:

Regimen 1: continuous, once daily for 21 consecutive days (21-day cycles).

Or

Regimen 2: once daily on days 1 to 7, repeated every three weeks (21-day cycles; 1 week ON/2 weeks OFF).

Patients will be sequentially assigned to Regimen 1 or Regimen 2 according to the next available place and receive OTX015/MK-8628 at escalating doses levels (DL). Cohorts of 3 patients will be treated, and an additional 3 patients will be treated at the first indication of dose-limiting toxicity (DLT). MTD assessment will be based on the tolerability observed during the first 21 days of treatment.

Expansion Part

The efficacy of OTX015/MK-8628 in each of the five indications (i.e., BRD-NUT midline carcinoma, triple negative breast cancer, non-small cell lung cancer harboring a rearrangement ALK gene/fusion protein or KRAS mutation, castrate-resistant prostate cancer, and pancreatic ductal carcinoma) will be assessed in terms of response (RECIST v1.1 or PCWG2) using a selected regimen.

STUDY POPULATION

Inclusion Criteria

Patients must fulfill all of the following requirements to enter the study:

1. Signed informed consent obtained prior to initiation of any study-specific procedures and treatment;

2. 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 patient:
   - NUT midline carcinoma (ectopic expression of NUT protein as determined by IHC and/or detection of BRD-NUT gene translocation as determined by FISH);
   - Triple negative breast cancer defined according to ASCO recommendations (Hammond et al., 2010; Wolff et al., 2007);
   - Non-small cell lung cancer harboring a rearranged ALK gene/fusion protein (FISH or IHC) or KRAS mutation (as defined by any molecular analysis);
   - Castrate-resistant prostate cancer (CRPC);
   - Pancreatic ductal adenocarcinoma;
3. At least one measurable lesion as per RECIST version 1.1., except for CRPC patients who may be enrolled with objective evidence of disease as per Prostate Cancer Clinical Trials Working Group (PCWG2) criteria;
4. Age ≥ 18 years at the time of informed consent;
5. Life expectancy ≥ 3 months;
6. ECOG Performance Status (PS) ≤ 1;
7. Adequate bone marrow reserve, renal and liver function:
   - Absolute neutrophil count ≥ 1.5 x10^9/L,
   - Platelet count ≥ 150 x10^9/L,
   - Hemoglobin ≥ 9 g/dL (blood transfusion ≤ 7 days of screening not permitted),
   - Creatinine clearance ≥ 30 mL/min calculated according to the Cockroft and Gault formula or MDRD formula for patients aged > 65 years,
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤3 x ULN, if alkaline phosphatase (ALP) > 2.5 X ULN, then liver fraction should be ≤ 2.5 X ULN, and total bilirubin ≤ 1.25 x ULN (in case of liver involvement, total bilirubin ≤ 2 x ULN will be allowed),
   - Serum albumin ≥ 2.0 g/dL for NMC, ≥ 3.0 g/dL for NSCLC, CRPC, TNBC and pancreatic cancer
   - INR ≤ 1.5 or INR < 3 for patients treated with antivitamin K;
8. An interval of ≥ 3 weeks since chemotherapy (≥ 6 weeks for nitrosoureas or mitomycin C), immunotherapy, hormone therapy or any other anticancer therapy 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 patients 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. Patients receiving bisphosphonate or denosumab therapy must be on stable doses for at least 4 weeks before initiating study treatment.

Exclusion Criteria

The presence of any of the following criteria excludes a patient from participating in the study:

1. Inability to swallow oral medications or presence of a gastrointestinal disorder (e.g. malabsorption) deemed to jeopardize intestinal absorption of OTX015/MK-8628;
2. Persistent grade >1 clinically significant toxicities related to prior antineoplastic therapies (except for alopecia); stable sensory neuropathy ≤ grade 2 NCI-CTCAE v. 4.0 is accepted.

3. Known primary CNS malignancy or CNS involvement;
4. History of prior or concomitant malignancies (other than excised non-melanoma skin cancer or cured *in situ* cervical carcinoma) within 3 years of study entry;
5. Other serious illness or medical conditions, such as active infection, unresolved bowel obstruction, or psychiatric disorders;
6. Known HIV positivity;
7. Participation in another clinical trial or treatment with any investigational drug within 30 days prior to study entry;
8. Other concomitant anticancer treatment;
9. Concomitant therapy with strong CYP3A4 interfering drugs;
10. Current use of anticoagulants (e.g. warfarin, heparin) at therapeutic levels within 7 days prior to the first dose of OTX015/MK-8628. Low-dose (prophylactic) low molecular weight heparin (LMWH) is permitted;
11. Pregnant or breast-feeding patients, and men and women with childbearing potential not using effective contraception while on study treatment.

STUDY DRUG

Study Drug and Formulation

OTX015/MK-8628 is administered orally. It is provided as size 3 gelatin capsules containing 10 or 20 mg OTX015/MK-8628 (free base) and size 0 gelatin capsules containing 40 mg OTX015/MK-8628 (free base) as a solid molecular dispersion with hypromellose acetate succinate (HPMCAS), mixed with lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate excipients. Capsules should be stored at 2°C to 8°C.

Study Drug Administration

- OTX015/MK-8628 is to be administered *per os* once daily in a fasted state just before breakfast (around 8 a.m. [±2h]), either continuously (Regimen 1) or for 7 consecutive days every 3 weeks (Regimen 2), as a flat dose without adaptation for body weight or surface area.
- A treatment cycle is 3 weeks (21 days).
- Patients participating in pharmacokinetics will be observed for ≥ 8 hours after the first study drug administration to collect PK blood samples and check vital signs, when appropriate.
- Patients should receive the study treatment within 7 days following registration.
- Dosing not performed at the same time (±2h) as on other days will be omitted. Patients are to be instructed that if they vomit or omit their dose in that time frame, it is not to be replaced.

Dose Escalation Scheme

- Up to four OTX015/MK-8628 dose levels (DLs) are planned for each regimen. Patients will be sequentially assigned to Regimen 1 or Regimen 2, according to the next available place.
- The starting dose will be 80 mg *per os* given once daily for Regimen 1, and 100 mg given once daily for 7 days every 3 weeks for Regimen 2.
- DLT assessment in each regimen will be independent and based on tolerability observed during the first 21 days of study treatment.
- The first patient enrolled in a higher DL cohort will not start the study treatment until the last treated patient in the DL immediately below has completed 3 weeks of study treatment.
- If 1/3 patients of a cohort has DLT during cycle 1 (i.e. the first 21 days following study treatment

initiation), up to 3 additional patients will be entered at this DL. If no more than 1/6 evaluable patients has DLT, dose escalation will proceed to the DL immediately above. If more than 1/6 patients (or more than 1/3) has DLT, the DL will be considered to exceed the MTD (see table below).

- Patients not evaluable for DLT (i.e. receiving less than 85% of the intended cumulative dose of the first 21-day cycle period for any reason other than toxicity; <18 days of treatment for Regimen 1, or <6 days of treatment for Regimen 2) and who do not experience DLT will be replaced.

Dose Level	**OTX015 Dose (mg/day)**		**Outcome (#DLT/#Patients)* / Actions to be taken**
	Regimen 1 (continuous)	**Regimen 2** (D1-7, q3w)	
DL 1	80	100	At each DL for each regimen: - If 0 of 3 patients has DLT, escalate dose in next cohort of 3 patients - If 1 of 3 patients has DLT, treat next 3 patients at the same dose level (6 patients total) - **If ≥ 2 of 3 patients has DLT, halt dose escalation** (MTD exceeded) - If 1 of 6 patients has DLT, escalate dose for next cohort of 3 patients - **If ≥ 2 of 6 patients has DLT, halt dose escalation** (MTD exceeded)
DL 2	100	120	
DL 3	120	160	
DL 4	160	200	

* Evaluated during the first 21 days of treatment

DLT Definition

A DLT is defined as any of the following toxicities occurring during the first 21 days of treatment **and considered by the investigator to be related to OTX015/MK-8628**.

Hematologic toxicity

- Any grade 4 hematologic toxicity or febrile neutropenia
- Grade 3 neutropenia with infection
- Grade 3 thrombocytopenia with bleeding or lasting > 7 days

Non-hematologic toxicity

- Any grade 3 or 4 non-hematologic toxicity (regardless of duration) unless it was not optimally managed with supportive care (e.g. grade 3 vomiting not adequately treated according to antiemetic standard of care).
- Any grade 3 or 4 laboratory abnormality, with or without symptoms, lasting > 48 hours.
- Any intolerable grade 2 non-hematologic toxicity resulting in study drug discontinuation or delay > 7 days with or without dose reduction.
- Any of the following liver test abnormalities** (see Appendix 5)
  - ALT or AST > 8 x ULN
  - ALT or AST > 5 x ULN for > 2 weeks
  - ALT or AST > 3 x ULN AND (total bilirubin > 2 x ULN OR INR > 1.5)
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

Other

- Treatment delay > 2 weeks or dose reduction requirement for initiating cycle 2.

**Note: All patients with these liver test abnormalities should be monitored weekly until all abnormalities return to normal or to the baseline state. For patients with isolated total bilirubin increases >2 x ULN or 2 x 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 CRF and in the database. See guidelines on the handling of these events (potential Hy's law cases)

MTD (recommended phase II dose) Definition

The MTD is defined as the dose immediately preceding the DL at which DLTs are observed in ≥ 2 out of 3 to 6 patients; i.e., the DL at which 0 of 3 patients or ≤ 1 of 6 patients experience DLT. The MTD will be determined in each of the two regimens evaluated.

Expansion Part

Once the MTD is established for each regimen with at least 3 patients having received at least 2 evaluable cycles of study drug, the study will be extended with the inclusion of 10 evaluable patients per indication at the MTD. The regimen used in each expansion cohort (i.e., each indication) will be decided by the SMC.

Prophylactic and Concomitant Medications

- No premedication is planned.
- During the study, patients must not receive other investigational drugs, agents or devices, or any other therapy for cancer treatment.
- Drugs given with prophylactic intent are not permitted during cycle 1.
- Patients requiring biphosphonates or denosumab therapy must have been on stable doses for at least 4 weeks prior to study entry. Bisphosphonates or denosumab are permitted from cycle 3.
- Use of anticoagulants (e.g. warfarin, heparin) at curative therapeutic levels within 7 days prior to the study treatment start is not allowed. Preventive low-dose LMWH or antivitamin K (INR < 3) are permitted. INR must be monitored in accordance with local institutional practices.
- For prostate cancer patients, concomitant androgen deprivation therapy with GnRH analogue or antagonist is mandatory unless the patient had previous bilateral orchiectomy as part of his hormone therapy.
- All other medication necessary for the well-being of the patient and which is not expected to interfere with evaluation of the study drug may be given at the investigator's discretion.
- Use of 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)(Appendix 3).

Treatment Adaptation

OTX015/MK-8628 will be interrupted until recovery to ≤ grade 1 or baseline value and the dose reduced or the schedule modified in the event of:

Hematologic toxicity

- Any grade 4 hematologic toxicity or febrile neutropenia
- Grade 3 neutropenia with infection
- Grade 3 thrombocytopenia with bleeding or lasting > 7 days

Non-hematologic toxicity

- Any grade 3 or 4 non-hematologic toxicity (regardless of duration) unless it was not optimally managed with supportive care (e.g. grade 3 vomiting not adequately treated according to antiemetic standard of care).
- Any grade 3 or 4 laboratory abnormality, with or without symptoms, lasting > 48 hours.
- Any intolerable grade 2 non-hematologic toxicity resulting in study drug discontinuation or delay > 7 days with or without dose reduction.

No more than two dose reductions (or schedule modifications) should be implemented, unless the investigator thinks it in the patient's best interests to pursue study treatment with a further dose reduction (an additional dose level), with the Sponsor's agreement.

Dose / Schedule Modifications: Regimen 1		
Initial OTX015 Dose	**1st Modification**	**2nd Modification**
80 mg QD continuously	80 mg QD, 2 weeks ON/ 1 week OFF, q3w	60 mg QD, 2 weeks ON/1 week OFF, q3w
100 mg QD continuously	100 mg QD, 2 weeks ON/1 week OFF, q3w	80 mg QD, 2 weeks ON/1 week OFF, q3w
120 mg QD continuously	120 mg QD, 2 weeks ON/1 week OFF, q3w	100 mg QD, 2 weeks ON/1 week OFF, q3w
160 mg QD continuously	160 mg QD, 2 weeks ON/1 week OFF, q3w	120 mg QD, 2 weeks ON/1 week OFF, q3w

Dose / Schedule Modifications: Regimen 2		
Initial OTX015 Dose	**1st Modification**	**2nd Modification**
100 mg QD, Days 1-7, q3w	80 QD, Days 1-7, q3w	60 QD, Days 1-7, q3w
120 mg QD, Days 1-7, q3w	100 mg QD, Days 1-7, q3w	80 QD, Days 1-7, q3w
160 mg QD, Days 1-7, q3w	120 mg QD, Days 1-7, q3w	100 mg QD, Days 1-7, q3w
200 mg QD, Days 1-7, q3w	160 QD, Days 1-7 q3w	120 mg QD, Days 1-7, q3w

Dosing interruption for > 2 weeks due to toxicity or liver toxicity (see treatment duration for details) will lead to definitive study treatment discontinuation unless the investigator thinks it is in the patient's best interests to pursue study treatment, with the Sponsor's agreement.

Safety Monitoring Committee

An SMC is responsible for making final decisions on stopping dose escalation, further dose escalation, determining the RD and starting cohort expansion enrollment. According to the nature, suspected relationship to study drug, or other clinical considerations, the SMC will make *ad-hoc* decisions, such as replacing non-evaluable patients, adding more patients at the same DL, adding intermediate DLs, exploring additional doses and/or regimens (e.g., if the MTD is not reached at the highest dose), not considering a given DLT as clinically relevant for the determination of the RD, progressing with the dose expansion part, and the regimen to be followed in each indication in the expansion part of the study. Serial assessments of PK results may be taken into account for the determination of the MTD.

The SMC will be composed of the principal investigators of each participating center, the pharmacokinetics specialist, the medical and safety representatives of the Sponsor, and an independent medical expert in oncology drug development. All decisions made by the SMC and their rationale will be recorded in meeting minutes.

Duration of Treatment (per patient)

Treatment will be continued until:

- Disease progression
- Unacceptable toxicity
- Patient withdrawal of consent
- Patient non-compliance
- Treatment interruption > 2 weeks for any reason (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)
- Any of the following liver test abnormalities** (see Appendix 5)
  - ALT or AST > 8 x ULN
  - ALT or AST > 5 x ULN for > 2 weeks
  - ALT or AST > 3 x ULN AND (total bilirubin > 2 x ULN OR INR > 1.5)
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

Duration of Observation

Patients are to be followed up for safety for at least 30 days following the last OTX015/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.

Treatment Compliance

Patients will record daily in a diary, the number of OTX015/MK-8628 capsules swallowed, time of intake, as well as any eventual reactions, including vomiting, and their time of occurrence. At each study visit the hospital pharmacist of the study center will provide the patient with the necessary number of OTX015/MK-8628 capsules until the next visit and retrieve any unused capsules/vials that will be kept until study end for accountability.

ASSESSMENTS

Activity

Disease assessments (RECIST version 1.1 or PCWG2) will be made at baseline (within 4 weeks prior to treatment start). Tumor measurements (using the same method as at baseline) will be made every 2 cycles (q6w) and bone scans every 4 cycles (q12w) until progression. Objective responses must be confirmed at least 4 weeks after first documentation. PCWG2 criteria will be used for CRPC patients.

Safety

Adverse events will be evaluated throughout the study and graded according to the NCI-CTCAE v4.03. A physical examination will be performed and vital signs evaluated before each cycle. Hematology laboratory values will be assessed twice weekly for the first 2 cycles and weekly thereafter, and biochemistry laboratory values will be assessed weekly for the first 2 cycles and every cycle thereafter.

Pharmacokinetics

Pharmacokinetic variables reflecting serum OTX015/MK-8628 exposure will be evaluated in the dose escalation part of the study and in selected patients from the expansion cohort. Six blood samples will be drawn over the first 7 hours of **day 1 of cycle 1, T0** (immediately before OTX015/MK-8628 intake), **T15min** (±5 min), **T1h** (±15min), **T2h** (±15min), **T3h** (±15min), **T7h** (±15min) post-dose.

EVALUATION CRITERIA

Evaluation Populations

Evaluable for DLT: patients who receive at least 85% of the planned dose of study drug (18 days for Regimen 1, or 6 days for Regimen 2) or experience DLT during the first 21-day cycle.

Treated population: patients who receive at least one dose of study drug.

Evaluable for efficacy: patients who receive at least 2 complete cycles (6 weeks) of treatment and have undergone baseline assessment and one on-study tumor assessment, or who discontinue early due to disease progression.

Endpoints

Primary: The number of patients experiencing at least one DLT in cycle 1 (day 1 to 21) for each of the two regimens independently.

Secondary:

Safety: Incidence, severity and relationship of AEs, laboratory abnormalities, SAEs, discontinuations due to AEs, dose adaptations due to AEs, and DLT.

Efficacy: The number of patients with clinical benefit (defined as complete response, partial response or stable disease) and progressive disease based on the best overall response from tumor evaluations performed every 2 cycles, according to RECIST v1.1 or PCWG2, and tumor marker assessment.

Pharmacokinetics: Plasma parameters of OTX015/MK-8628 including C_{max}, C_{min}, T_{max}, AUC $_{[0-\infty]}$, Vd_{ss}, $t_{1/2}$, CL.

Statistical Methods

The dose escalation part of the study is designed to assess the safety of OTX015/MK-8628 in this patient population. The small numbers per cohort are not intended for statistical hypotheses. Treatment decisions will be made by the SMC.

The expansion cohort part will start once the MTD and a regimen are determined. Ten patients will be enrolled per indication to give a total of 50 evaluable patients for efficacy.

Quantitative variables will be summarized using descriptive statistics. Continuous variables will be presented as N, mean and/or median, standard deviation, range. Categorical variables will be presented using frequencies and percentage.

Patient disposition and demographics will be analyzed in all included patients, response will be analyzed in patients evaluable for efficacy, and safety will be analyzed in the treated population with an additional analysis in patients evaluable for DLT for the dose escalation part.

Data will be analyzed according to dose level and regimen for the dose escalation part of the study, and according to indication and/or regimen for the dose expansion part of the study.

Total Number of Patients

Dose escalation part:

Up to 48 patients evaluable for DLT (i.e. up to 24 patients per regimen) will be accrued depending on the number of DLTs encountered. The final sample size will depend on the number of DLTs encountered at each DL, and may be increased if within the two proposed regimens and four planned DLs, MTD is not reached and additional DLs are required.

Expansion cohort part:

Once the MTD is established with at least 3 patients having received at least 2 cycles of study drug, an expansion cohort of up to 50 additional evaluable patients (10 patients per indication) will be enrolled. The regimen used in the expansion cohort will be decided for each indication by the SMC.

STUDY SCHEDULE

Parameter	Pre-study visit (≤2 weeks before treatment)	Day 1 visit every cycle	Twice a week cycles 1+ 2 then weekly	Weekly cycles 1+ 2	Day 1 visit of C3, C5, C7 etc.	Treatment discontinuation visit (35±5 days) after last treatment intake
Informed consent	X					
Eligibility criteria	X					
Demographics, medical history	X					
Diagnosis, prior treatment for malignancy	X					
Physical examination, PS, vital signs[1]	X[1]	X				X
Pregnancy test if child-bearing potential (urine test)	X					
Baseline symptoms and complaints	X					
Concomitant medication	X	X				X
Complete blood count (CBC)[2]	X	X	X			X
INR and Factor VII	X	X		X		X
Serum chemistries[3]	X	X[3]		X[3]		X
Drug dispensation Regimen 1 Regimen 2		QD continuous Days 1-7 q3w				
Adverse events		X				X
CT, MRI, chest X-ray (PA and lateral), bone scan	X[4]				X[4]	X
Tumor markers[5]	X	X				X
PK blood sampling		X[6]				
Other investigations as indicated	X	X		X		X

1) Vital signs include temperature, blood pressure, and pulse; Body weight at each visit and height at baseline only;

2) Hemoglobin, RBC counts, WBC and differential, platelet counts;

3) Minimum: Na, K, Ca, Mg, P, Cl, HCO_3, creatinine, total protein, albumin, glucose, alkaline phosphatase, total bilirubin, AST, ALT, LDH; from cycle 3 on, in the absence of ≥ grade 2 abnormalities, these tests will be performed every cycle, otherwise they are to be done weekly until resolution to baseline levels or < grade 2. All patients with specific liver test abnormalities (see DLT definition) should be monitored weekly until all abnormalities return to normal or to the baseline state. For patients with isolated total bilirubin increases >2 x ULN or 2 x baseline (if elevated at baseline), monitoring should be every 2 weeks until bilirubin returns to normal or to the baseline state;

4) Radiologic exams (CT, MRI, chest X-ray) performed as part of the patient'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) as per RECIST 1.1 or PCWG2 until progression; Bone scans are mandatory in CRPC patients and will be performed every 4 cycles (12 weeks) until progression;

5) As appropriate for tumor type;

6) Pharmacokinetics will be performed in cycle 1 only, during the dose escalation part of the study and in selected patients from the expansion cohorts: **T0** (just before OTX015/MK-8628 intake), then **T15min** (±5 min), **T1h (±15min), T2h (**±15min), **T3h (**±15min), and **T7h** (±15min) post-dose.

ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AL	Acute Leukemia
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
AUC	Area Under The Plasma Concentration Versus Time Curve
BC	Breast Cancer
BET	Bromodomain and Extraterminal
BID	Twice Daily
BRD	Bromodomain
BRDT	BRD Testis-Specific Protein
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CL	Total Plasma Clearance
Cmax	Peak Concentration
Cmin	Residual Concentration
CNS	Central Nervous System
CT-scan	Computerized Tomography scan
CR	Complete Response
CRPC	Castrate-Resistant Prostate Cancer
DCF	Data Correction Form
DILI	Drug Induced Liver Injury
DL	Dose Level
DLT	Dose Limiting Toxicity
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form
EML4	Echinoderm Microtubule-Associated Protein-Like 4
ER	Estrogen Receptor
FISH	Fluorescence In Situ Hybridization
GnRH	Gonadotropin Releasing Hormone
Hb	Hemoglobin
HER2	Human Epidermal Growth Factor Receptor 2
IEC	Independent Ethics Committee
ICF	Informed Consent Form
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board

KRAS	Kirsten Ras
LDH	Lactate Dehydrogenase
LMWH	Low Molecular Weight Heparin
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute -Common Toxicity Criteria for Adverse Events
NMC	NUT Midline Carcinoma
NSCLC	Non-Small Cell Lung Cancer
NUT	Nuclear Protein in Testis
OHM	Other Hematologic Malignancies
OS	Overall Survival
PCWG2	Prostate Cancer Clinical Trials Working Group
PD	Progressive Disease
PFS	Progression-Free Survival
PgR	Progesterone Receptor
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PR	Partial Response
PS	Performance Status
P-TEFb	Positive Transcription Elongation Factor b
QD	Once Daily
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAERF	Serious Adverse Event Report Form
SAR	Suspected Adverse Reaction
SCC	Squamous Cell Carcinoma
SD	Stable Disease
SMC	Safety Monitoring Committee
SUSAR	Serious, Unexpected Suspected Adverse Reaction
$t_{1/2}$	Terminal Half-Life
TEAE	Treatment Emergent Adverse Event
Tmax	Time to Peak Concentration
TNBC	Triple-Negative Breast Cancer
ULN	Upper Limit of Normal
UPN	Unique Patient Number
UPLC-MS/MS	Ultra Performance Liquid Chromatography, with tandem Mass Spectrometry
Vdss	Volume of Distribution At Steady State
WBC	White Blood Cell

1 BACKGROUND

1.1 Bromodomain and Extraterminal (BET) Protein Inhibition

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 (Dang et al., 2009)(Kim et al., 2008). Amplification of MYC is one of the most common genetic alterations observed in cancer genomes (Beroukhim et al., 2010), and the validation of c-MYC as therapeutic target is supported by numerous lines of experimental evidence (Stewart et al., 1984)(Leder et al., 1986)(Harris et al., 1988)(Soucek et al., 2002)(Jain et al., 2002)(Fukazawa et al., 2010). 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 (Darnell, 2002). Considering chromatin as a platform for signal transduction (Schreiber and Bernstein, 2002), the inhibition of MYC transcription and function has been achieved through displacement of chromatin-binding, co-activator proteins, the bromodomains (BRD), using competitive small molecules (Delmore et al., 2011).

BRDs are protein interaction modules that specifically recognize Ɛ-N-acetylated lysine residues (Mujtaba et al., 2002)(Filippakopoulos et al., 2012). 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 (Muller et al., 2011). BRDs are highly sequence diverse but share a conserved fold comprised of a left-handed bundle of four alpha helices (αZ, αA, αB, αC) (Dhalluin et al., 1999). 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 (Filippakopoulos et al., 2012)(Owen et al., 2000). Crystal structures of BET complexes with di-acetylated histone 4-tail peptides showed that the first BRDs of BRD4 and BRDT may accommodate two acetyl-lysines in a single site (Filippakopoulos et al., 2012)(Morinière et al., 2009).

The BET family of BRD proteins, which includes BRD2, BRD3, BRD4, and BRD testis-specific protein (BRDT), are epigenetic reader proteins that bind acetylated lysine residues on histones playing critical roles in cellular proliferation and cell-cycle progression (Dey et al., 2009). BRD4 binds to the positive transcription elongation factor b (P-TEFb), a cyclin-dependent kinase, and stimulates RNA polymerase II-dependent elongation (Yang et al., 2005)(Jang et al., 2005). BRD4 is critical for survival of several diverse tumors due to its function promoting transcription of growth-promoting and anti-apoptotic genes (Filippakopoulos et al., 2010), 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 (Chung et al., 2011) 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 OTX015) [Mitsubishi Tanabe Pharma Corporation. Antitumor agent. WO 2009084693; 2009]. Building on these findings, Bradner and colleagues synthesized a thienotriazolodiazepine, JQ1(Filippakopoulos et al., 2010). 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 (Filippakopoulos et al., 2010)(Nicodeme et al., 2010)(Dawson et al., 2011)(Picaud et al., 2013). 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.

1.2 Overview of Solid Tumor Indications

1.2.1 BRD-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 the most cases, NUT (nuclear protein in testis) on chromosome 15 is fused to BRD4 on chromosome 19 (French et al., 2008), 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, (French, 2012). 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 (French, 2010a).

With a median survival time of 6.7 months (Bauer et al., 2012), 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 (French, 2010b), 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 (Haack et al., 2009). 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 IHC be performed in all poorly differentiated non-cutaneous carcinomas that lack glandular differentiation (French, 2014).

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 progression-free survival (PFS) and overall survival (OS) (Bauer et al., 2012). 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 (French et al., 2008), 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. OTX015, 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% (Noel et al., 2013).

1.2.2 Non-Small Cell Lung Cancer: KRAS Mutated and ALK Positive

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% (Sequist et al., 2011)(Gainor et al., 2013)(Kris et al., 2011). 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. Among NSCLC patients, KRAS mutations have been identified more commonly among Caucasians, smokers (26% versus 6% of never smokers), and patients with adenocarcinoma histology (30% versus 5% with squamous cell carcinoma histology) (Riely et al., 2009)(Riely et al., 2008)(Mao et al., 2010)(Graziano et al., 1999). KRAS mutations are typically mutually exclusive of EGFR mutations, occurring in different patient populations (Riely et al., 2009)(Roberts et al., 2010)(Gainor et al., 2013). The presence of a KRAS mutation appears to have at most a limited effect on OS in patients with early stage NSCLC (Shepherd et al., 2013), although some older data suggested that it was with a worse prognosis (Mascaux et al., 2005). However, in stage IV NSCLC patients, the presence of a KRAS mutation appears to be associated with a worse prognosis. In a controlled phase III trial of maintenance erlotinib, KRAS mutation conferred a shorter time to progression than wild-type patients (HR 1.50, 95%CI: 1.06-2.12) among the 239 patients on the placebo arm. However, the difference in OS was not statistically significant (HR 1.30, 95% CI: 0.90-1.90) (Brugger et al., 2011). 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, $p = 0.048$), while EGFR mutations were associated with longer survival (HR 0.6, $p < 0.001$) (Johnson et al., 2013). Mutant KRAS is a strong activator of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways (Malumbres and Barbacid, 2003), and the inhibition of KRAS-dependent MAPK and PI3K pathways results in MYC dephosphorylation (Sears et al., 2000)(Pelengaris et al., 2002), which contributes to its degradation. Recent studies in NSCLC preclinical models report that the BET bromodomain inhibitor, JQ1, exerts remarkable antitumor activity in NSCLC harboring KRAS mutation but this sensitivity is highly influenced by LKB1 mutation status, as Kras/Lkb1 mutant models are comparatively more resistant. Furthermore, *in vivo* experiments using genetically engineered mouse lung cancer models confirmed that JQ1 prompts tumor regression in mutant Kras mouse lung cancers (Shimamura et al., 2013). In the same report, sensitivity both *in vitro* and *in vivo* was found to be mediated by MYC downregulation.

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 (Shaw and Solomon, 2011). This fusion oncogene rearrangement is transforming both *in vitro* and *in vivo* and defines a distinct clinicopathologic subset of NSCLC.

Tumors that contain the EML4-ALK fusion oncogene or its variants are associated with specific clinical features, including never or light (<10 packet years) smoking history, younger age, and adenocarcinoma with signet ring or acinar histology. ALK gene arrangements are largely mutually exclusive with EGFR or KRAS mutations (Takahashi et al., 2010). Screening for this fusion gene in NSCLC is important, as "ALK-positive" tumors (tumors harboring a rearranged ALK gene/fusion protein) are highly sensitive to therapy with ALK-targeted inhibitors. The oncogenic role of the ALK fusion oncogene provides a potential avenue for therapeutic intervention. Cancer cell lines harboring the EML4-ALK translocation are effectively inhibited by small molecule inhibitors that target the ALK tyrosine kinase (Koivunen et al., 2008). *In vivo*, treatment of EML4-ALK transgenic mice with ALK inhibitors results in tumor regression (Soda et al.,

2008), supporting the notion that ALK-driven lung cancers are "addicted" to the fusion oncogene. ALK gene rearrangements or the resulting fusion proteins may be detected in tumor specimens using fluorescence in situ hybridization (FISH), IHC, and reverse transcription polymerase chain reaction of cDNA (Weickhardt et al., 2013). Nevertheless, the gold standard assay for diagnosing ALK-positive NSCLC is FISH, the only approved test to diagnose ALK positive tumors (Martelli et al., 2009)(Boland et al., 2009)(Shaw et al., 2009)(Perner et al., 2008) while IHC is widely used in Europe to detect ALK rearrangement.

ALK-rearranged tumors depend on ALK for growth and survival and show marked sensitivity to ALK inhibitors such as crizotinib. Among patients with advanced *ALK*-rearranged NSCLC, crizotinib has been associated with response rates of approximately 60% across multiple studies and a median PFS of 8 to 10 months (Camidge et al., 2012)(Shaw et al., 2013). Despite initial response to crizotinib, the majority of patients relapse within 12 months, with the development of resistance (Katayama et al., 2012)(Doebele et al., 2012). Approximately one-third of patients with *ALK*-rearranged NSCLC relapse due to an acquired mutation within the *ALK* tyrosine kinase domain or amplification of the *ALK* fusion gene. In the remaining resistant cases, the *ALK* fusion gene is unchanged, and a variety of resistance mechanisms have been reported (Katayama et al., 2012)(Doebele et al., 2012)(Shaw et al., 2013).Treatment options after the failure of crizotinib are limited and include cytotoxic chemotherapy, palliative radiotherapy, and supportive care.

A recent preclinical report indicates that OTX015 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 (Vazquez et al., 2014). In sensitive NSCLC cell lines, OTX015 results in a rapid and sustained downregulation of c-MYC or N-MYC. In addition, OTX015 exhibits *in vitro* additive activity when combined with crizotinib in ALK positive NSCLC cell lines.

1.2.3 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 ASCO guideline recommendations, breast cancer is considered negative for ER or PgR if less than 1% of tumor cell nuclei are immunoreactive (Hammond et al., 2010), and negative for HER2 if either the IHC score is 0 or 1+, or FISH average gene copy < 4 signals per cell nucleus (Wolff et al., 2007).

TNBC terminology is confusing since it reflects a heterogeneous population (Lehmann et al., 2011) 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 (Sørlie et al., 2001)(Hu et al., 2006). Of these subtypes, which include HER2-enriched, luminal A, luminal B, and basal-like breast cancer, the latter has the poorest prognosis (Perou, 2011). Gene expression analysis demonstrates that the molecular signature of TNBC generally overlaps with basal-like breast cancer, with concordance rates of 70%-90% (Nielsen et al., 2004)(Kreike et al., 2007). However, not all TNBC can be defined as basal-like breast cancer (Perou, 2011)(Prat and Perou, 2011), as a small minority of BLBC patients do in fact, have some ER and HER2 expression. TNBC is also associated with BRCA-related breast cancer, although the incidence of BRCA mutations in TNBC varies from 16% to 42% (Atchley et al., 2008)(Gonzalez-Angulo et al., 2011). Other mechanisms resulting in downregulation of BRCA1/2, including epigenetic alterations and overexpression of BRCA1 inhibitors (Turner et al., 2004)(Miyoshi et al., 2008)(Abd El-Rehim et al., 2005)(Turner et al., 2007), 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 (Haffty et al., 2006)(Kassam et al., 2009)(Onitilo et al., 2009)(Foulkes et al., 2010). In the neoadjuvant setting, TNBC exhibits a better response to chemotherapy compared with non-TNBC (Liedtke et al., 2008). 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) (Haffty et al., 2006)(Dent et al., 2007)(Carey et al., 2006)(Bauer et al., 2007)(Millikan et al., 2008)(Liedtke et al., 2008).

Metastatic TNBC is an aggressive disease that is associated with a high proliferation index (Hugh et al., 2009), visceral and CNS metastases (Liedtke et al., 2008)(Smid et al., 2008)(Heitz et al., 2009), and poor outcome despite treatment. Median survival of advanced TNBC is at best 12 months (Gelmon et al., 2012), 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 (Gelmon et al., 2012). Retrospective evaluations of anti-angiogenic agents have demonstrated encouraging efficacy signals in TNBC, with a doubling of PFS in select trials (O'Shaughnessy et al., 2009)(Brufsky et al., 2012)(O'Shaughnessy et al., 2010)(Miller et al., 2007). However, PFS gains remain modest (~3 months) (Brufsky et al., 2012)(O'Shaughnessy et al., 2010). 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 (Horiuchi et al., 2012). 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 (Shi et al., 2014).

1.2.4 Castrate-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 (Taylor et al., 2010)(Chen et al., 2004)(Visakorpi et al., 1995). Maintenance of AR signaling is the most common resistance mechanism that patients with advanced prostate cancer develop after conventional hormone treatments (Harris et al., 2009). AR amplification, mutation and alternative splicing have all been suggested as potential resistance mechanisms to anti-androgen treatments (Chen et al., 2004)(Taplin et al., 1999)(Sun et al., 2010). Over one half of CRPC patients have at least one of these aberrations in the AR pathway (Grasso et al., 2012).

Despite the success of recently approved therapies targeting AR signaling, such as abiraterone (Stein et al., 2012)(Reid et al., 2010)(de Bono et al., 2011) and second-generation anti-androgen therapy including enzalutamide (Mukherji et al., 2012)(Scher et al., 2012), 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 (Asangani et al., 2014). BRD4 physically interacts with the N-terminal domain of the AR and can be disrupted by the BET inhibitor JQ1 (Delmore et al., 2011)(Filippakopoulos et al., 2010). 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 (Asangani et al., 2014). 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.

1.2.5 Pancreatic Ductal Carcinoma

Pancreatic ductal adenocarcinoma (PDAC) continues to be the leading cause of cancer-related death, in part due to limited efficacy of conventional chemotherapy and few therapeutic options. As such, there is a strong interest in developing inhibitors targeting epigenetic changes, such as targeting BET proteins that bind acetylated histones to regulate gene transcription. Treatment with BET inhibitors decreases PDAC cell growth in collagen (Sahai et al., 2014). Transfection with siRNA against BRD4, which is increased in human PDAC tumors, also decreased PDAC cell growth. Interestingly, BET inhibitors additionally decreased growth in collagen of PDAC cells that have undergone epithelial-to-mesenchymal transition or have become resistant to chemotherapy.

1.3 Development of OTX015

1.3.1 Description of OTX015

OTX015 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 and extraterminal) proteins. The structure is summarized below:

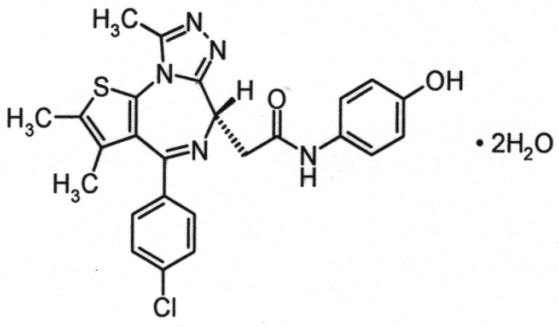
Chemical name: 2-[(6S)-4-(4-Chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo-[4,3-a][1,4]diazepin-6-yl]-N-(4-hydroxyphenyl)acetamide dihydrate

I.N.N.: Not yet issued

Molecular mass: 528.02

Molecular formula: $C_{25}H_{22}ClN_5O_2S \cdot 2H_2O$

Structural formula:



OTX015 is provided as size 3 gelatin capsules containing 10 or 20 mg OTX015 (free base) or size 0 gelatin capsules containing 40 mg OTX015 (free base) as a solid molecular dispersion with hypromellose acetate succinate (HPMCAS), mixed with lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silicone dioxide, and magnesium stearate excipients.

1.3.2 Preclinical Data

1.3.2.1 Pharmacology

In vitro pharmacodynamic studies showed that OTX015 interacts directly with the BET bromodomain proteins BRD2, 3, and 4 with EC50 values ranging from 10 to 19 nM. Competitive inhibition by OTX015 inhibited binding of BRD 2, 3, and 4 to acetylated histone A4 with IC50 values ranging from 92 to 112 nM.

Given the IC50 ~100 nM for OTX015 inhibition of BRD2/3/4 binding to acetylated histone A4, human tumor cell lines were considered to be sensitive to OTX015 if the GI50 was ≤500 nM, as assessed by MTT assays after 72 hours exposure. By these criteria, a wide variety of hematologic malignancy cell lines were sensitive to OTX015, including 4/4 acute lymphoblastic leukemia (ALL) lines, 2/5 acute myeloid leukemia (AML) lines, 15/23 diffuse large B-cell lymphoma (DLBCL) lines, 3/3 splenic marginal zone lymphoma lines, 7/8 anaplastic large T-cell lymphoma (ALCL) lines, and 7/8 multiple myeloma lines; only mantle cell lines were resistant to OTX015 (0/3). Most solid tumor lines were not sensitive to OTX015, though hepatocellular carcinoma (4/5 lines), medulloblastoma (4/4 lines), neuroblastoma (3/4 lines), and ovarian cancer (3/3 lines) were, and the Ty82 midline carcinoma cell line with a BRD-NUT fusion was highly sensitive (GI50 = 40 nM).

Treatment with 500 nM OTX015 induced G1 arrest and apoptosis in leukemia and multiple myeloma cells lines as well as patient-derived primary leukemia and multiple myeloma cells and in a subgroup of ABC-DLBCL lines with mutated MYD88 gene and wild type p53. In other lymphoma lines, OTX015 treatment resulted in G1 arrest and induction of senescence.

Most sensitive cell lines showed downregulation of MYC mRNA as well as putative MYC target genes (CAD, NUC, NPM-ALK). Downregulation was observed after only 1 hour exposure, but recovered within 2 hours after washout.

In selected DLBCL and leukemia cell lines, synergistic or additive effects on cell proliferation were observed when OTX015 was combined with both targeted agents (mTOR inhibitor, BTK inhibitor, HDAC inhibitor, hypomethylating agent, immunomodulator, anti-CD20 monoclonal antibody) and standard chemotherapy agents (bendamustine, cytarabine, daunorubicin, doxorubicin).

In vivo, OTX015 treatment significantly inhibited tumor growth in the Ty82 midline carcinoma model with a BRD4-NUT fusion (79% tumor growth inhibition at 100 mg/kg/day). In the same model, the combination of OTX015 and docetaxel was curative. OTX015 treatment significantly prolonged OS compared with vehicle controls in mice bearing established IMR5/75 MYCN-amplified neuroblastoma or orthotopic U87MG glioblastoma xenografts.

Safety pharmacology studies showed that OTX015 had no effects on general safety assessments at doses up to 10 mg/kg *per os*. OTX015 had no effect on hERG current at concentrations up to 580 nM and no effects on respiration rate, blood pressure, heart rate, and electrocardiogram in anesthetized dogs at doses up to 3 mg/kg intravenously.

1.3.2.2 Pharmacokinetics

Pharmacokinetic measurements following administration of single intravenous doses (in 20% ethanol/20% PEG400) and various solid dispersion oral formulations showed that bioavailability differed with species (lower in rats than in dogs) and with formulation (higher for PVP and HPMCAS solid dispersions than for Eudragit solid dispersions). Toxicokinetic assessments following 28-day and chronic dosing of the PVP solid dispersion formulation to rats and dogs showed no significant difference between genders in either species. Although toxicokinetic analyses showed dose-proportional increases in the 4-week and 52-week

dog studies, more than dose-proportional increases in exposure were observed in the 4-week and 26-week rat studies. Likewise, while no dose accumulation was observed in the 4-week and 52-week dog studies, 1.5- to 2-fold accumulation was observed in the 4-week and 26-week rat studies.

Following a single oral administration of radiolabeled PVP solid dispersion formulation to rats, the highest levels of radioactivity were found in the stomach (and contents), small intestine (and contents), and liver. Excretion was predominantly via feces.

OTX015 was ~95% bound to plasma proteins in rats, dogs, and humans. Over the concentration range from 30 to 300 ng/mL, the distribution ratios into blood cells ranged from 43% to 46% in rats, 29% to 33% in dogs, and 13% to 20% in humans.

From consideration of the chemical structure of OTX015, the primary metabolites expected were an oxidized metabolite and a glucuronic acid conjugate. LC-MS/MS analysis of liver microsomes incubated with OTX015 in the presence of a NADPH regeneration system detected the two expected metabolites in all species, as well as a unique (unidentified) metabolite in humans. Following a single oral administration of radiolabeled OTX015:PVP solid dispersion formulation to rats, both oxidation products and the glucuronide conjugate were observed. Results from incubations with cytochrome P450 isoenzymes suggested that OTX015 is metabolized mainly by CYP3A4 and, to lesser extent, by CYP2C9. Results from incubations with pooled human liver microsomes suggested that OTX015 has a tendency to inhibit CYPs 2A6 and 3A4.

1.3.2.3 Toxicology

The adverse effects of OTX015 were evaluated in 4-week repeated oral dose toxicity studies in rats (dosed at 0, 3, 10, 30 and 60 mg/kg) and dogs (dosed at 0, 1, 3, 10, and 20 mg/kg); 26-week repeated oral dose toxicity studies in rats (dosed at 0, 3, 10, and 30 mg/kg); 13-week repeated oral dose toxicity studies in dogs (dosed at 0, 1, 3, and 10 mg/kg); and 52-week repeated oral dose toxicity studies in dogs (dosed at 0, 0.6, 2, and 6 mg/kg). Studies were conducted using a solid dispersion of 10% or 25% OTX015:PVP, either suspended in water for administration to rats or combined with lactose, corn starch, crystalline cellulose, and calcium carmelose excipient and filled into gelatin capsules for administration to dogs.

Considering results from the 28-day repeated dose and chronic toxicity studies, the main target organ in terms of toxicity is the digestive system, particularly the liver. Other organs which should be monitored are lymphoid tissues, hematopoietic organs, lungs, and the male reproductive organs. Briefly:

- Digestive system: In both rats and dogs, clinical signs of loose stools and diarrhea were accompanied by histopathologic findings of mononuclear cell infiltration of the lamina propria mucosa and degeneration of the epithelium of the small and large intestine. In chronic toxicity studies, abnormal liver function tests were observed in both rats (decreased total protein and albumin) and dogs (increased ALT and AST), accompanied by histologic findings of pigment deposition in perilobular Kupffer cells in the livers of both species and cholestasis and vacuolization of the centrilobular hepatocytes in livers of dogs. Prolonged activated partial prothrombin time (APTT) in both species was observed after 28-day dosing in rats and after both 28-day and chronic dosing in dogs.
- Hematopoietic system: Both rats and dogs showed decreased lymphocytes after 28-day dosing, accompanied by histopathologic findings of depletion of lymphocytes in the spleen and mesenteric and submandibular lymph nodes and myeloid hypoplasia in the bone marrow of femur and sternum. Rats showed decreased red blood cells after both 28-day and chronic dosing, accompanied by histopathologic findings of extramedullary hematopoiesis in the spleen after chronic dosing; however, the decrease in red blood cells (RBC) was of small magnitude and the incidence of extramedullary hematopoiesis in the spleen was consistent with background.

- Lungs: In rats, histopathologic exams showed intra-alveolar foamy macrophages in lungs and bronchus in both sexes after 28-day and chronic dosing; these resolved after 1 month in the 28-day study.
- Reproductive organs in males: In male dogs, histopathologic exams showed tubular degeneration of the testes after both 28-day and chronic dosing and a bilateral decrease in sperm in the epididymides after chronic dosing.

OTX015 showed no genotoxic effects in the standard panel of *in vitro* and *in vivo* tests.

1.3.3 Clinical Data

1.3.3.1 Healthy Volunteer Studies

Three studies in healthy volunteers have been performed:

- Study Y-803-E01 (E01 study) was a double-blind, randomized study to evaluate the safety, tolerability, and pharmacokinetics of single ascending oral doses of 2.5, 5, 10, 20, 40, 80, 120, and 180 mg OTX015 compared with placebo in healthy adults;
- Study Y-803-E02 (E02 study) was an open label, randomized, three-way crossover study to assess the bioavailability of a single oral dose of 20 mg OTX015 in healthy male subjects in a fasted state and before and after food, with at least a 10-day wash-out between doses; and
- Study Y-803-E-04 (E04 study) was a double-blind, placebo-controlled repeat dose study to assess the safety, tolerability, and pharmacokinetics of OTX015 following a single oral dose and once daily oral doses of 10, 20, and 40 mg OTX015 for 10 days in healthy male subjects.

For all three studies, OTX015 was supplied in capsules containing microcrystalline cellulose spheres coated with an ethanolic solution of OTX015, triethyl citrate, aminoalkyl methacrylate copolymer RS, and methacrylic acid copolymer, then spray dried and mixed with talc, magnesium aluminometasilicate, and light anhydrous silicic acid (Eudragit formulation). This formulation was designed to deliver OTX015 to the lower intestine for treatment of inflammatory bowel disease. Bioavailability studies in dogs showed that systemic drug levels following administration of the Eudragit formulation were about 50% of those obtained following administration of the solid dispersion OTX015:PVP formulation used for toxicology studies and the solid dispersion OTX015:HPMCAS formulation planned for use in clinical studies in cancer patients.

All three healthy volunteer studies assessed safety, tolerability, and plasma and urinary pharmacokinetics of OTX015 and its two main metabolites, the glucuronide conjugate and an oxidation product termed M1. Additionally, the single dose studies assessed fecal excretion of OTX015 and the M1 metabolite.

Following administration of single oral doses of OTX015 to fasted subjects, plasma concentrations of OTX015 increased slowly, reaching C_{max} at a median of 4 to 6 hours; thereafter, plasma levels declined slowly for all dose levels, maintaining levels about 50%-60% of C_{max} at 12 hours post-dose and 25% to 30% of C_{max} at 24 hours post-dose. Semi-logarithmic plasma concentration-time curves gave an apparent monophasic decline, with mean $t_{1/2}$ ranging from 12.0 to 16.3 hours for all dose levels. The mean $t_{1/2}$ and median T_{max} were statistically constant. Exposure (C_{max}, AUC_{0-24h}, and $AUC_{0-\infty}$) increased in a dose proportional manner over the range from 2.5 to 80 mg. The mean residence time, Cl, Cl/F, and Vz/F ranged from 17.8 to 21.4 h, from 0.11 to 0.20 L/h, from 28.2 to 54.0 L/h, and from 477.6 to 1159.6 L, respectively.

Mean plasma concentrations of the OTX015 glucuronide conjugate and the M1 metabolite were parallel to those of OTX015 for all dose levels. In C_{max} and AUC, the OTX015 glucuronide conjugate ranged from

50%-73% and from 40%-64% of the OTX015 level, respectively, while the M1 metabolite ranged from 3%-5% and from 3%-6% of the OTX015 level, respectively.

Pharmacokinetic assessments during 10-day repeated dosing showed that steady-state was achieved after 24 hours of dosing at each dose level. Geometric mean pre-dose (trough) plasma concentrations at steady state ranged from 3.9 to 4.9 ng/mL for the 10 mg dose, from 5.9 to 8.5 ng/mL for the 20 mg dose, and from 13.6 to 22.4 ng/mL for the 40 mg dose; for each dose level the pre-dose plasma concentrations were constant. Statistical analysis of the first and last dose across all dose levels showed $t_{1/2}$, MRT, CL/F, and Vz/F to be independent of dose, with no differences between the first and last dose. Interestingly, the mean C_{max} of 52-66 ng/mL achieved with 40 mg repeated dosing was equivalent to approximately 100 nM, an active concentration against hematologic malignancies in *in vitro* experiments.

Pharmacokinetic assessments from the food effect study showed that intake of a high-fat breakfast after and before administration decreased plasma OTX015 concentration: C_{max} by 45% and 47%, AUC_{0-24h} by 35% and 38%, and $AUC_{0-\infty}$ by 20% and 27%, respectively, compared to the fasted state. The T_{max} of OTX015 was prolonged by food intake after and before administration, from 6h (fasted state) to 9h and 10h, respectively, while the MRT was constant for all dosing conditions.

Overall, OTX015 was well tolerated. No severe or serious adverse events (AEs) were reported. The most frequent AEs, occurring in ≥3% of subjects receiving OTX015, were headache (17% of subjects), abdominal pain/discomfort (15%), diarrhea/loose stools (8%), constipation (4%), myalgia (4%), back pain (3%), and paresthesia (3%). With the exception of one transient moderate headache, all of these events were both transient and mild. The most frequent AEs among subjects receiving OTX015 also occurred with similar frequency among subjects receiving placebo, i.e., headache (17% of subjects), diarrhea/loose stools (17%), and abdominal pain/discomfort (13%), suggesting the involvement of formulation excipients rather than the active pharmaceutical ingredient.

1.3.3.2 Patients with Advanced Hematologic Malignancies

Study OTX015_104, an open label phase I dose-finding and pharmacokinetic study in patients with advanced hematologic malignancies was initiated in January 2013 and is ongoing at the time of preparation of the current protocol. Dose escalation is being performed using a conventional 3+3 design. Cohorts of patients with acute leukemias (AL) and patients with other hematologic malignancies (OHM) are being evaluated independently for the determination of the maximum tolerated dose (MTD). Once the MTD has been determined, cohort expansion will be performed.

OTX015 is supplied in size 3 gelatin capsules containing 10 or 20 mg OTX015 as a solid molecular dispersion of OTX015 and hypromellose acetate succinate (HPMCAS) mixed with lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate excipients. Bioavailability studies in dogs showed 4 to 5-fold increased bioavailability for this formulation compared with the Eudragit formulation used in the healthy volunteer studies. OTX015 is administered daily, once daily (QD) or twice daily (BID). AL patients receive a discontinuous schedule (14 days on, 7 days off), and OHM patients receive a continuous schedule. Alternative schedules are currently being evaluated. A cycle is 3-weeks.

Dose escalation, DLT determination, cohort expansion and patient safety are assessed by a Safety Monitoring Committee (SMC).

Patient Disposition

As of June 9, 2014, 64 patients (31 with AL and 33 with OHM) were enrolled. Amongst them 49 (26 with AL and 23 with OHM) were evaluable for DLT assessment at the time of the current protocol (10 non-evaluable patients, 4 too early, and one not yet treated were not assessable for DLTs).

Table 1: Patient disposition (N=64) in the hematologic malignancy trial

	Subset (schedule)	Dose level 1 10 mg QD	Dose level 2 20 mg QD	Dose level 3 40 mg QD	Dose level 4 80 mg QD	Dose level 4 BID 40 mg x2	Dose level 5 120 mg QD	Dose level 6 160 mg QD	Total
Patients enrolled	**AL** (2 weeks, q3w)	3	3	4	3	8	3	4	31
	AL (continuously)	0	0	0	0	0	3	0	
	OHM (continuously)	5	3	4	4	6	7	0	
	OHM (2 weeks, q3w)	0	0	0	0	0	2	0	33
	OHM (5 days a week)	0	0	0		0	2	0	
Patients Treated	**AL**	3	3	4	3	8	6	3	30
	OHM	5	3	4	4	6	11		33
Patients evaluable for DLT*	**AL**	3	3	3	3	6	6	2	26
	OHM	3	3	3	3	5	6	-	23
Patients with DLT	**AL**	0	0	0	0	0	0	2	2
	OHM	0	0	0	0	3	3	-	6

AL: acute leukemia; **OHM:** other hematologic malignancies
*Patients receiving at least 19 of the first 21 days treatment

Key demographic and clinical characteristics of treated patients are summarized below by dose level and patient subset (AL vs OHM).

Table 2: Patient characteristics by dose level (N=64)

Dose	10 mg QD N=8	20 mg QD N=6	40 mg QD N=8	80 mg QD N=7	40 mg BID N=14	120 mg QD N=17	160 mg QD N=4	Total N=64
Median Age in years (range)	67.5 (40-79)	68 (32-83)	72.5 (62-80)	68 (49-73)	64.5 (33-85)	65 (19-80)	65 (62-75)	**68 (19-85)**
Gender M/F	7/1	2/4	4/4	4/3	8/6	13/4	4/0	**42/22**
PS 0-1/2	6/2	5/1	7/1	6/1	12/2	16/1	4/0	**56/8**
Treated conditions								
AML	3	2	4	2	8	6	3	**28**
ALL	-	1	-	1	-	-		**2**
HR-MDS	-	-	-	-	-	-	1	**1**
DLBCL	3	1	-	2	2	8	-	**16**
Lymphoma other*	1	-	2	1	1	3	-	**8**
MM	1	2	2	1	3	-	-	**9**
Previous systemic therapies								
Median N lines (range)	3.5 (1-7)	2.5 (1-5)	2.5 (1-8)	3.0 (2-5)	3.0 (2-8)	3.0 (1-7)	2.5 (2-3)	**3.0 (1-8)**
ASCT/aSCT	2/1	0/1	2/0	2/0	3/0	1/2	0/0	**10/4**

ALL: acute lymphoblastic lymphoma; **AML:** acute myeloid leukemia; **aSCT:** allogeneic stem cell transplantation; **ASCT:** autologous stem cell transplantation; **DLBCL:** diffuse large B-cell lymphoma; **FL:** follicular lymphoma; **HR-MDS**: high-risk myelodysplastic syndrome; **MM:** multiple myeloma; **MCL:** mantle cell lymphoma; **PTCL:** peripheral T-cell lymphoma; **PS:** ECOG performance status

*FL: 2; MCL: 1; PTCL (NOS): 2; lymphoplasmacytic lymphoma: 1; Burkitt's lymphoma: 1

Table 3: Patient characteristics by hematologic subset (N=64)

Dose	AL (N=31)	OHM (N=33)
Age in years, median (range)	70 (19-85)	67 (27-83)
Male/female, N	20/11	22/11
ECOG PS (0-1 / 2), N	29/2	27/6
Treated Conditions		
AML	28	-
De novo/secondary + post-therapy	15/13	-
NPM1 mut/MLL rearrangement/EVI1+/ JAK2 mut	6/1/0/1*	-
ALL	2	-
HR-MDS	1	-
DLBCL	-	16
Other lymphomas	-	8
Multiple myeloma	-	9
Previous Systemic Therapies		
Number of lines, median (range)	2 (1-4)	4 (2-8)
Auto SCT/allo SCT	0/4	10/0

ALL: acute lymphoblastic lymphoma; **AML:** acute myeloid leukemia; **HR-MDS**: high-risk myelodysplastic syndrome; **NPM1**, nucleophosmin-positive,
* Presence of JAK2 mut in AML cells unknown

Dose Escalation and Schedule Adaptation

Acute leukemia cohort

No DLT was observed from a dose of **10 mg QD through 80 mg QD**. Based on preclinical data with OTX015 (and published results for the OTX015 analog JQ1) suggesting a higher efficacy with a BID schedule and residual plasma concentrations at 24 hours, below the *in vitro* active concentrations in patients treated at 80 mg QD, it was decided to proceed to DL4 of 40 mg BID, and to allow AL patients who had tolerated at least one cycle of treatment with an intermittent schedule (14 days ON/7 days OFF) to switch to a continuous treatment schedule.

No DLT was reported in the 6 evaluable patients enrolled and treated at **DL4 of 40 mg BID**. The SMC decided to proceed with dose escalation. Due to the potential risk of severe liver injury by doubling the dose, the decision was to escalated cautiously using a Fibonacci-like dose escalation model with a smaller dose increment using a once daily schedule rather than the BID schedule, as had already been implemented in the OHM patient cohort (see below).

Three patients have been enrolled so far at **DL5 120 mg QD 14/21**, none of whom experienced DLT in Cycle 1. The SMC therefore decided to proceed to DL6 (160 mg QD 14/21). In addition the SMC decided to evaluate a continuous administration schedule (21/21) at 120 mg QD (DL5) from the first cycle.

Amongst four patients enrolled at **DL6 (160 mg QD 14/21)**, two experienced DLT (grade 3 diarrhea and grade 3 asthenia with anorexia, respectively). Thus DL6 could be considered exceeding the MTD.

Three patients have been enrolled at **DL5 (120 mg QD 21/21)**. None have presented DLT to date.

Other hematologic malignancies cohort

No DLT was observed from a dose of **10 mg QD through 80 mg QD**. it was decided to proceed to DL4 of 40 mg BID based on preclinical data with OTX015 (and published results for the OTX015 analog JQ1) suggesting a higher efficacy with a BID schedule and residual plasma concentrations at 24 hours, below the *in vitro* active concentrations in patients treated at 80 mg QD.

Three of five evaluable patients treated at **DL4 of 40 mg BID**, experienced DLTs (grade 3-4 thrombocytopenia), and this DL was considered exceeding the MTD. A schedule dependency was suspected and it was decided to continue dose escalation with the QD schedule only. Nevertheless a Fibonacci-like escalation model was chosen out of caution, with a 1.5-fold dose increment.

Three patients were initially treated at **DL5 of 120 mg QD**. The first patient (with bone marrow involvement and baseline grade 1 thrombocytopenia) experienced a DLT (grade 3 thrombocytopenia on Day 8 with gastrointestinal bleeding). Four additional patients have been enrolled, one of whom experienced DLT (grade 4 thrombocytopenia on Day 15). Finally, another initially deemed not evaluable had repeated dose interruptions and dose reduction due to grade 3 hyponatremia, associated with grade 3 thrombocytopenia and was retrospectively considered as having DLT. Thus, three patients out of seven experienced DLT with this dose and schedule which exceeds the MTD.

The SMC of April 24th therefore decided to add 3 patients at DL4 (80 mg QD) to confirm its tolerability, since only three OHM patients had been treated without DLT at this DL. Furthermore, it was decided to explore alternative discontinuous schedules at **DL5 (120 mg QD): 14 days ON/7 days OFF (14/21)** and **5 days ON/2 days OFF every week (5/7)**.

Safety Findings

Extent of Exposure

The number of treatment cycles, dose reductions, dose interruptions, and reasons for treatment discontinuation for the 63 treated patients is summarized in Table 3 and Table 4 below.

The majority of patients (63%) discontinued OTX015 treatment due to disease progression, and among the 52 patients who could have received at least 3 cycles (i.e., more than 9 weeks elapsed between study treatment initiation and the cut-off date of the present report), 17 (33%) had received more than 3 cycles (median 5.0; range 4-14+).

Study treatment was interrupted for more than one day in 15 patients due to related AEs, 9 with grade 3-4 thrombocytopenia, two with grade 4 neutropenia, and one each with aminotransferase elevation, coagulation factor VII decrease and fever of unknown origin, aggravation of diabetes mellitus, and grade 3 hyponatremia.

Table 4: Patient exposure in treated acute leukemia patients (N=30)

Dose	10 mg QD 14/21 N=3	20 mg QD 14/21 N=3	40 mg QD 14/21 N=4	80 mg QD 14/21 N=3	40 mg BID 14/21 N=8	120 mg QD 14/21 N= 3	120 mg QD 21/21 N=3	160 mg QD 14/21 N=3*	Total N=30*
Median (range) # cycles	6 (1-7)	3 (2-4)	3 (1-14+)	5 (1-5)	2 (<1-8)	2 (2-3)	2+ (2-3+)	2+ (1+-3+)	**2 (<1-14+)**
Dose reduction	0	0	0	0	0	0	0	2	**2**
Intrapatient dose escalation	1 (20 mg)	0	1 (120 mg)	0	0	0	0	0	**2**
Dose interruption > 1 day	2 (unrelated)	1 (unrelated)	2 (1 unrelated)	0	1	0	0	0	**6**
Reason for study treatment discontinuation									
Tumor progression	2	3	1	3	5	3	0	0	**17**
Consent withdrawal	1	0	1		1	0	0	0	**3**
Deterioration general condition	0	0	1	0	0	0	0	0	**1**
No further benefit	0	0	0	0	1	0	0	0	**1**
Early death (unrel)	0	0	0	0	1	0	1	0	**2**
Treatment ongoing	0	0	1	0	0	0	2	3	**6**

*One additional patient (AL cohort, DL6, 160 mg QD 14 / 21) was enrolled but not yet treated due to leukemia-related sepsis

Table 5: Patient exposure in treated OHM patients (N=33)

Dose	10 mg QD 21/21 N=5	20 mg QD 21/21 N=3	40 mg QD 21/21 N=4	80 mg QD 21/21 N=4	40 mg BID 21/21 N=6	120 mg QD 21/21 N= 7	120 mg QD 14/21 N=2	120 mg QD 5/7 N=2	Total N=33
Median (range) N cycles	3 (<1-8)	2 (2-2)	3 (2-10)	3 (1-10+)	1.5 (1-2)	3+ (1-5+)	Too early	Too early	**2 (<1-10+)**
Dose reduction	0	0	1 (unrelated)	0	0	3	Too early	Too early	**4**
Intrapatient dose escalation	1 (20 mg)	0	1 (80 mg)	1 (120 mg 5/7)	0	0	Too early	Too early	**3**
Dose interruption > 1 day	2 (1 unrelated)	0	2 (1 unrelated)	2	4	5	Too early	1 (unrelated)	**16**
Reason for study treatment discontinuation									
Tumor progression	5	3	3	3	3	6	0	0	**23**
Unrelated AE	0	0	1	0	0	0	0	0	**1**
ASCT in PR	0	0	0	0	0	1	0	0	**1**
Treatment ongoing	0	0	0	1	0	3	2	2	**8**

Six AML patients, initially treated with a discontinuous (14/21) schedule, switched to a continuous schedule, which is being explored in AL patients from Cycle 1 at 120 mg.

Adverse Events (AEs)

Treatment emergent AEs at least possibly related to study medication are summarized in **Table 4**. Of 62 patients treated and evaluable for safety to date, 48 (21 AL, 27 OHM) experienced a total of 145 treatment-emergent AEs. Among them, 39 patients (13 AL, 26 OHM) experienced 101 AEs considered to be at least possibly related to OTX015.

In OHM patients, for whom hematologic toxicity is evaluable (AL patients have baseline pancytopenia), **thrombocytopenia** appears the most common toxicity and is dose limiting (**Table 4**). It occurred in 69% (22/32) of evaluable patients regardless of severity or dose.

Thrombocytopenia incidence and severity increased with dose and is possibly schedule dependent: Only 2 out of 8 OHM patients treated at DL 40 or 80 mg QD experienced grade 4 thrombocytopenia versus 10/13 treated at DL 40 mg BID or 120 mg QD. Moreover, despite the same total daily dose, one of four evaluable patients treated at 80 mg QD experienced grade 4 thrombocytopenia, versus five of six patients treated at 40 mg BID.

Table 6: AL patients with TEAEs possibly/probably related to OTX015 (N=30 evaluable patients)

	Any Grade								Grade 3-4 AE							
Dose (mg) Schedule 14/21 unless otherwise specified	**10 N=3**	**20 N=3**	**40 N=4**	**80 N=3**	**40x2 N=8**	**120 N=3**	**120 21/21 N=3**	**160 N=3**	**10 N=3**	**20 N=3**	**40 N=4**	**80 N=3**	**40x2 N=8**	**120 N=3**	**120 21/21 N=3**	**160 N=3**
N pt with AE	**0**	**0**	**1**	**0**	**4**	**2**	**3**	**3**	**0**	**0**	**0**	**0**	**1**	**0**	**1**	**2**
Non-blastic aplasia	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
Hyperglycemia	0	0	1§	0	1	1§	0	0	0	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	2	1	2	2	0	0	0	0	0	0	0	1
Dysgueusia	0	0	0	0	2	1	0	0	0	0	0	0	0	0	0	0
Nausea	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0
Anorexia	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	1
Abdominal pain	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0
FUO	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Factor VII ↓	0	0	1	0	1	1	2	1	0	0	0	0	0	0	0	0
Direct bilirubin ↑	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0
Aminotransferases ↑	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0

Thrombocytopenia and neutropenia are not assessable in AL patients
FUO: fever of unknown origin
§ patient with preexisting diabetes

Table 7: OHM patients with TEAEs possibly/probably related to OTX015 (N=32 evaluable patients*)

	Any Grade								Grade 3-4 AE							
Dose (mg) Schedule 21/21 unless otherwise specified	**10 N=5**	**20 N=3**	**40 N=4**	**80 N=4**	**40x2 N=6**	**120 N=7**	**120 14/21 N=1**	**120 5/7 N=2**	**10 N=5**	**20 N=3**	**40 N=4**	**80 N=4**	**40x2 N=6**	**120 N=7**	**120 14/21 N=1**	**120 5/7 N=2**
N pt with AE	**2**	**2**	**4**	**4**	**6**	**7**	**0**	**1**	**1**	**0**	**3**	**3**	**6**	**6**	**0**	**0**
Thrombocytopenia	0	2	2	4	6	7	0	1	0	0	2	3	6	5	0	0
Neutropenia	1	0	0	0	0	2	0	0	1	0	0	0	0	2	0	0
Hyperglycemia	0	0	2[§]	2 (1[§])	1	3 (1[§])	0	0	0	0	1	0	0	0	0	0
Diarrhea	0	0	2	0	2	4	0	10	0	0	1	0	0	0	0	0
Vomiting	0	0	2	0	1		0	0	0	0	0	0	1	0	0	0
Dysgueusia	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0
Nausea	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	
Bowel movements	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Anorexia	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Abdominal pain	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Skin rash	1	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0
Factor VII ↓	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
Direct bilirubin ↑	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Hypomagnesemia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Hyponatremia	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	0
Weight loss	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Dizziness	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Headache	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0

Thrombocytopenia and neutropenia are assessable only in patients with OHM.
§ patient with preexisting diabetes
* One patient had just started treatment on the cut-off date and was not included in the AE analysis

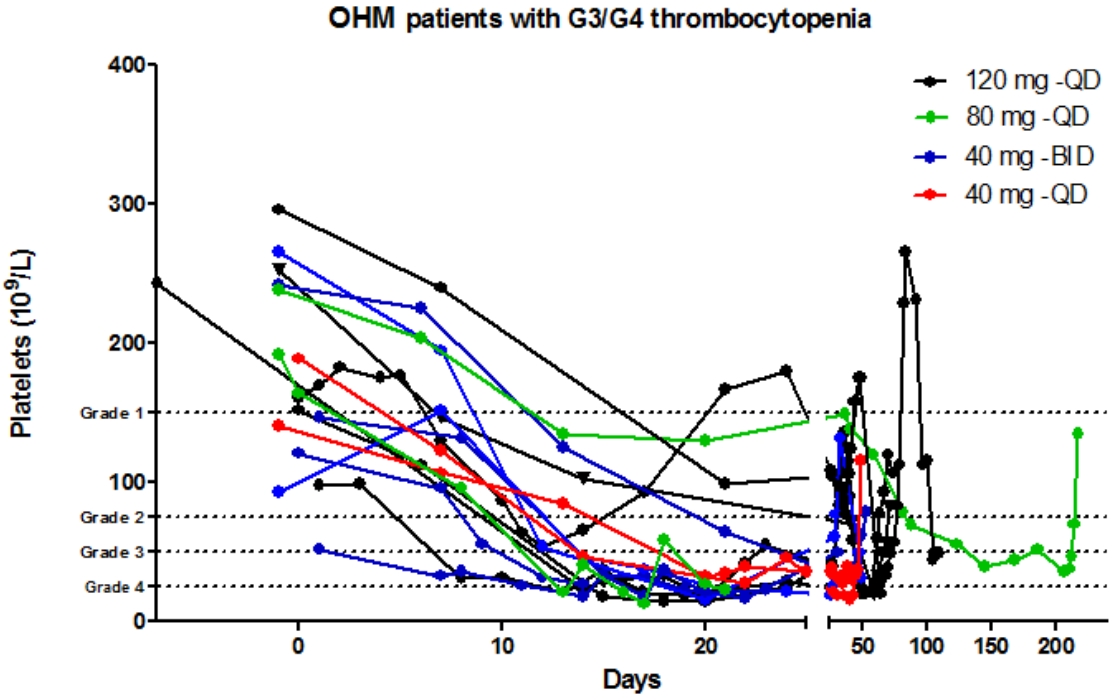
Grade 3-4 thrombocytopenia occurred in 16 (50%) evaluable patients, including 9 with grade 4 (28%). Characteristics of grade 3-4 thrombocytopenia are shown in Figure 1**.**

Two of these 16 patients only had "anecdotal" grade 3; one patient experienced grade 3 toxicity for the first time during the 7th cycle, whereas this patient had been treated continuously at 80 mg QD. A second patient experienced one day of grade 3 thrombocytopenia, which resolved without treatment interruption.

Among the 14 remaining patients with clinically significant grade 3-4 thrombocytopenia, ten had nadir occurring around 3 weeks after study treatment initiation, while 4 patients had earlier nadir.

Recovery to grade < 3 was usually rapid after treatment interruption/discontinuation (i.e., within 10 days), with the exception of 4 patients.

Figure 1: Platelets counts versus time in patients with grade 3-4 thrombocytopenia



Six of the 10 OHM patients with grade 4 thrombocytopenia had previous high dose chemotherapy with autologous stem cell transplantation (ASCT) and/or known bone marrow involvement. Furthermore, platelet counts at baseline, even in the normal range, could predict severe thrombocytopenia. Prior ASCT, bone marrow involvement and baseline platelet count are probably non-independent factors that all reflect bone marrow reserves. Their potential predictive role will be further evaluated and should be clarified.

The mechanism of action of OTX015-induced thrombocytopenia may be complex and will be explored systematically.

Of note, most clinically relevant and treatment-limiting thrombocytopenia in the OHM cohort has been observed at DLs and schedules considered as exceeding the MTD.

Pharmacokinetic Findings

PK showed dose-proportional increases in exposure (C_{max} and AUC) from 10 mg to 120 mg QD, (see Figure 2). T_{max} occurred between 1 and 4 hours (for the oral formulation used in this study T_{max} is expected between 1 to 3 hours, but limited sampling points precluded more accurate assessment of T and C_{max}). Mean clearance was 9.9 (range, 6-12) L/h, mean volume of distribution was 68 L, and mean terminal half-life was 4.7 (range, 3.2-5.7) hours. Preliminary population PK analysis suggests that interpatient variability may be explained by lean body mass and/or body weight. These parameters appear to play a role in clearance variation, as patients with higher lean body mass display increased clearance and volume of distribution.

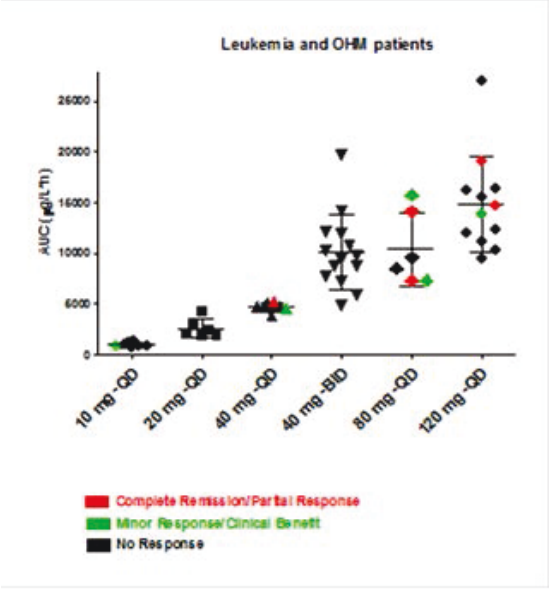
Table 8: Mean (range) PK parameters (N=47)

Dose	N pts	C_{max} Cy1D1 (nM)	Trough (pre-dose) Cy1D8 (nM)	AUC_{0-24h} Cy1 D1 (µg•h/L)
DL1 10 mg QD	**8**	**267** (121 - 424)	**46** (18 - 81)	**962** (648 - 1,349)
DL 2 20 mg QD	**6**	**560** (357 - 844)	**103** (84 - 127)	**2,592** (1,809 - 4,223)
DL3 40 mg QD	**8**	**1,274** (663 - 3,029)	**230** (53 - 897)	**4,722** (3,951 - 5,292)
DL4 80 mg QD	**7**	**2,539** (1,085 - 4,593)	**424** (152 - 1331)	**10,420** (7,229 -1 5,760)
DL4 BID 40 mg x 2	**13**	**1,128** (699 - 1,810)	**638** (269 - 924)	**10,540** (5,898-19,720)
DL5 120 mg QD	**13**	**2,383** (1,412 - 4,055)	**764** (194 - 2,016)	**14,815*** (9,522 - 26,953)

*AUC calculated on 12 patients only

The BID schedule was explored to maintain or increase trough concentrations, while not increasing C_{max}. This goal was achieved, as trough concentrations were significantly higher with the BID schedule, compared to the QD schedule, with the same daily dose, while similar exposures were obtained. Likewise, trough concentrations at DL5 (120 mg) QD achieved similar or higher trough concentration than 40 mg BID. Since both dose/schedule exceed the MTD for OHM patients, it is tempting to assume that thrombocytopenia is related to continuous high trough concentration.

Figure 2: Individual AUC_{0-24h} versus Dose Level



Clinical Activity

Among 20 AML patients and 19 lymphoma patients evaluable for efficacy, evidence of clinical activity has been observed in 11 patients (5 with AML and 6 with lymphoma) (**Table 6**).

While clinical activity does not clearly appear to be dose-dependent for leukemia patients, there may be a trend for a dose response in DLBCL patients.

Table 9: Patients with evidence of clinical activity

Dose (mg)	AL	OHM
10 QD	AML secondary to JAK2 *mut* PV PPD	-
20 QD	-	-
40 QD	AML post chemotherapy PPD **CR**	FL PPD
80 QD	AML (NPM1+) secondary to MDS PPD **CRi** AML secondary to MDS PPD	LPL PPD DLBCL PPD **PR**
40 BID	AML (NPM1+/flt3 *mut*) *de novo* PPD	
120 QD	-	DLBCL PPD **PR** DLBCL PPD **PR** DLBCL PPD

AML: acute myelogenous leukemia; **JAK2:** Janus Kinase 2; **PV:** polycythemia Vera; **MDS:** myelodysplastic syndrome; **NPM1**: nucleophosmine; **FL:** follicular lymphoma; **LPL:** lymphoplasmacytic lymphoma; **DLBCL:** diffuse large B-cell lymphoma; **CR:** complete remission; **CRi:** complete remission with incomplete recovery; **PR:** partial response.

Five of these patients met standard response criteria:

- One patient PPD with post-treatment AML (fludarabine, cyclophosphamide and rituximab) given for previous Waldenström disease in remission, with normal karyotype, no MLL translocation, and over-expression of WT1 as the sole molecular abnormality, who was treated at 40 mg QD had decreased bone marrow blasts (from 94% at baseline to 59%) at the end of Cycle 1, then disappearance of peripheral blood blasts (from 0.84 x 10^9/L at baseline to complete clearance) at the end of Cycle 2, followed by clinically significant hematologic improvement during Cycles 2 to 4, with absolute neutrophil counts rising from 0.05 x 10^9/L at baseline to 3.1 x 10^9/L at Cycle 4 and platelet counts rising from grade 4 with transfusion dependence at baseline to 112 x 10^9/L at the end of Cycle 4 without further transfusion need from mid-Cycle 2. This patient refused to undergo the Day 43 myelogram, but accepted at the end of Cycle 4, which showed 2% blasts in a normal rich bone marrow. This case meets the criteria for complete remission (CR). The patient remained in CR until Cycle 12, then relapsed (CR duration 5 months). PPD is now being rechallenged with substantial dose increase (120 mg) in Cycles 13 and 14 (ongoing). The results of this dose escalation rechallenge are pending.
- One patient PPD with AML secondary to myelodysplastic, syndrome, NMP1+ without flt3-ITD or mutation, who was treated at 80 mg QD had disappearance of bone marrow blasts on Day 22 (from 85% in a rich marrow at baseline to 0 in a poor marrow), confirmed on Day 43 (<1% of blasts). The ratio NPM1 mutated gene/abl in bone marrow shifted from 1.937% at baseline to 0.039% on Day 22. This patient had a slow increase in neutrophil counts from Cycle 2 Day 8, up to complete recovery > 1.5 x 10^9/L around Cycle 3 Day 15, without platelet count improvement, but decreased platelet transfusion needs, while red blood cell transfusions were no longer required. These findings meet the criteria for CR with incomplete recovery (CRi). This patient relapsed at the end of Cycle 5.
- One patient PPD with DLBCL secondary to Hodgkin's lymphoma who was treated at 80 mg QD experienced rapid improvement at Cycle 1 Day 8 with decrease (and almost complete radiologic clearance) of pleural effusion and improvement of dyspnea without new pleural paracenthesis at the beginning of Cycle 2. This patient also showed a 50% decrease of supraclavicular, mediastinal and iliac lymph node. Both CT-scan and PET-scan at the end of Cycle 2 confirmed a PR. PR was further confirmed in successive tumor assessment until PPD 9th cycle, with major clinical benefit (autonomous and oxygen independent). Tumor progression was seen at Cycle 9, and the patient is currently being rechallenged at 120 mg QD (5/7).

- One patients PPD with DLBCL treated at 120 mg (21/21), experienced a minor response (-41% tumor shrinkage) of mediastinal target lymph nodes and partial metabolic response (SUV 8.5→3.3) at the end of Cy 2 which reached PR criteria (-70% tumor shrinkage) at the end of Cy 4. This young patient was withdrawn from study at the end of Cycle 5 in preparation of intensification with ASCT followed by aSCT, because the magnitude of tumor shrinkage achieved with OTX015 is the highest ever observed during previous therapies.
- One patient PPD with DLBCL treated at 120 mg (21/21), experienced PR at CT-scan with complete metabolic response (these criteria meet complete remission criteria) of abdominal lymph nodes. In addition, B-symptoms (night sweats) were completely cleared on therapy. This patient is ongoing at Cycle 5.

An additional six patients, although not fulfilling standard response criteria, had significant clinical evidence of activity, with clinical benefit in two of them.

- One patient PPD with AML secondary to JAK2 mutated polycythemia vera who was treated at 10 mg QD had a regular decrease of high baseline peripheral blasts counts (from 11 x 10^9/L to complete clearance) and late decrease in bone marrow blasts (from 82% to 21%) without improvement of cytopenias, before disease progression after 6 cycles.
- One patient PPD with cutaneous follicular lymphoma being treated at 40 mg QD experienced complete relief of a severe disease-related pruritus, previously refractory to symptomatic therapies. Tumor assessment with CT-scan at Cycle 5 showed minor tumor shrinkage of 32% not meeting criteria of PR. Treatment was discontinued after PPD 10^{th} cycle, due to severe unrelated corneal ulcer (patient with previous cornea graft).
- One patient PPD with AML secondary to myelodysplastic syndrome who was treated at 80 mg QD had hyperleukocytosis (19.7 x 10^9/L at study entry), rapidly increasing to 27.8 x 10^9/L on Day 12, necessitating two courses of hydroxyurea during Cycles 1 and 2. At the end of Cycle 2 white blood cells were 2.0 x 10^9/L with 51% blasts and bone marrow showed 87% blasts. However, OTX015 treatment was pursued without need for hydroxyurea from Cycle 3. At the end of Cycle 3, peripheral blood blasts were cleared and bone marrow blasts were 8%. During Cycle 4, neutrophil count slowly increased up to 1.2 x 10^9/L (starting from 0.4 x 10^9/L at baseline) and bone marrow blast infiltration was 12%. The patient remained dependent on platelet transfusion. At Cycle 5, disease progressed with recurrence of neutropenia, peripheral blasts and bone marrow infiltration with 89% blasts and the patient went off study.
- One patient PPD with lymphoplasmacytic lymphoma and Waldenström magroglobulinemia who was treated at 80 mg QD experienced a 50% decrease in size and SUV at PET-scan at the end of Cycle 2 and a decrease of size of target lymph nodes on a CT-scan, which did not meet the criteria for PR. This patient had disappearance of B-symptoms, but progressed at the end of PPD 5^{th} cycle. The IgM M-component was not measured at the time of response.
- One patient PPD with AML (NMP1+/flt3 mutated) treated at 40 mg BID (14/21) experienced resolution of painful gum hypertrophy from Cycle 1. PPD remained stable over 8 cycles, but without hydroxyurea that was needed prior to study entry. During PPD 7^{th} cycle, PPD ANC increased to normal values, while blasts increased concomitantly. The patient needed hydroxyurea again, experienced aplasia again and PPD The meaning of this ANC increase without blast decrease remains elusive.
- One patient PPD with DLBCL was treated at 120 mg (21/21) and experienced minor response (-18% tumor shrinkage) of a large retroperitoneal mass compressing the vena cava inferior with lumbar pain and lower limb edema. As a result, tumor-related symptoms resolved. This patient is ongoing in Cycle 5 and will have a second tumor assessment.

Finally, two AML patients PPD treated at 10 mg QD subsequently increased to 20 mg QD and PPD treated at 40 mg QD) had stable disease for 7 and 5 cycles, respectively, which was quite unusual after relapse.

1.4 Rationale for the Current Study

In the present study, adult patients with selected advanced solid tumors with the potential to respond to BET inhibition including NMC, NSCLC with RAS mutations or ALK rearrangement, TNBC, CRPC, and PDAC, will receive OTX015 orally using a 3+3 dose escalation scheme to determine the RD for phase II studies for two different administration regimens.

OTX015, a pan-BET bromodomain inhibitor, shows activity in several preclinical hematologic and somatic cancer models. Meaningful antitumor activity has also been reported in patients with heavily pretreated hematological malignancies in the ongoing phase I clinical study treated with OTX015. 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 OTX015, 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, OTX015 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. OTX015 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.

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 OTX015 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, OTX015 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.

PDAC continues to be the leading cause of cancer-related death in part due to limited efficacy of conventional chemotherapy. PDAC cell proliferation in collagen decreased in the presence of BET inhibitors and with transfection with siRNA against BRD4, which is increased in human PDAC tumors, including in cells that had undergone epithelial-to-mesenchymal transition or were resistant to chemotherapy, making OTX015 a potential drug in this pathology.

Preliminary data, from an ongoing phase I clinical trial in advanced hematologic malignancies, show that OTX015 is well tolerated from 10 mg to 120 mg QD (days 1-14, q3w) in AL patients, with no DLT

observed. The dose of 160 mg QD (days 1-14, q3w) may exceed the MTD with 2 out of 3 patients experiencing non-hematologic DLTs (grade 3 diarrhea and grade 3 asthenia, respectively) and will soon be assessed by the SMC. A 120 mg QD (continuous) has been explored concurrently and one patient may have experienced non-blastic aplasia, needing further assessment in three more patients.

For OHM patients, thrombocytopenia emerged as a DLT at 40 mg BID and 120 mg QD (continuous), with 11/13 patients experiencing grade 3-4 thrombocytopenia, including 9 with grade 4 thrombocytopenia leading to treatment interruption. Both of these dose levels/schedules exceed the MTD. Higher trough concentrations achieved with both dose/ schedule may be at least partly responsible for the higher frequency and severity of thrombocytopenia. Other parameters may influence the occurrence and severity of thrombocytopenia, such as bone marrow reserve, estimated by previous ASCT, baseline platelet counts and/or bone marrow involvement.

Evidence of clinically significant antitumor activity has been observed at non-toxic doses in AL patients (including one sustained CR at 40 mg QD and one CRi at 80 mg QD) and also in lymphoma patients (including 3 sustained PRs at 80 mg and 120 mg QD), as well as at the toxic dose of 120 mg QD (continuously).

Optimization of dose and schedule are ongoing before initiating expansion cohorts. In AL, additional patients are being enrolled at 120 mg QD (continuously) and 120 mg QD (days 1-14, q3w), while shorter administration with 160 mg (e.g. Days 1-7, q3w) may be decided by the SMC. In OHM patients, three schedules are being explored simultaneously with additional patients at 80 mg QD (continuously), 120 mg QD (Days 1-14, q3w) and 120 mg QD (5days a week every week). A discontinuous schedule may be necessary to allow prolonged treatment.

1.4.1 Rationale for the Trial Design

The purpose of this trial is to determine the MTD of OTX015 for further phase II trials in patients with selected solid tumors that might benefit from BET inhibition, in order to optimize the dose and schedule in this patient population with non-compromised bone marrow (i.e., without high-dose chemotherapy and autologous stem cell transplantation or bone marrow involvement), which is expected to be higher than the MTD of patients with hematologic malignancies, as well as to generate safety and pharmacokinetic data in this population. Antitumor effects over single and multiple cycles of two different administration regimens will be explored using a 3+3 dose escalation scheme based on DLT assessment, and a cohort expansion.

1.4.2 Justification for the Regimens and Starting Dose

Regimen 1: Daily continuous

A starting dose of 80 mg OTX015 administered orally once daily on a continuous basis will be used based on the following considerations:

1) The 80 mg dose was given safely in the ongoing phase I trial in patients with advanced hematologic malignancies (Study OTX015_104).
2) Patients with solid tumors (without compromised bone marrow) are expected to tolerate higher OTX015 doses better than those with hematologic malignancies; thus their MTD is predicted to be higher.
3) A single daily dose of 80 mg was chosen instead of a 40 mg BID schedule in light of preliminary results from the phase I study in hematologic malignancies suggesting a degree of schedule-dependency, with higher rates of grade 3-4 thrombocytopenia with the BID schedule, which was dose-limiting in patients with hematologic malignancies other than leukemia.

Regimen 2: Days 1-7, every 21 days

A starting dose of 100 mg OTX015 administered orally once daily for 7 consecutive days, repeated every 3 weeks will be explored in an attempt to determine if discontinuous drug administration can reduce:

1) The incidence and severity of thrombocytopenia which appears to be the most common toxicity of OTX015 in patients with hematologic malignancies, emerging at ≥ 80 mg daily continuous dose after nearly 2 weeks of treatment exposure (grade 3-4 thrombocytopenia occurred in 50% of patients with 28% having a grade 4), with an incidence/severity appearing to increase with dose suggesting a possible schedule-dependency.
2) Given that in the ongoing phase I study in patients with advanced hematologic malignancies, severe thrombocytopenia tends to occur after approximately 2 weeks of continuous treatment, and that furthermore a recovery interval of approximately 10 days is required for severe thrombocytopenia to return to lower grades, a discontinuous regimen may be required to allow re-treatment every 3 weeks. This is important to take into account for future combination clinical studies.

These two regimens (with or without recovery period) will be tested in parallel, i.e., Regimen 1 (daily continuous dosing) and Regimen 2 (7 days every 21 days). This will allow selection of the optimal regimen for further studies in terms of balance between tolerability, pharmacokinetics and antitumor activity.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To determine the Maximal Tolerated Dose (MTD) defined as the recommended phase II dose for two distinct regimens of OTX015/MK-8628 administered orally to patients with selected advanced solid tumors.

2.2 Secondary Objectives

- To assess the safety profile of single-agent OTX015/MK-8628
- To characterize pharmacokinetics parameters of OTX015/MK-8628
- To determine the antitumor activity of OTX015/MK-8628 in selected solid tumors

3 STUDY DESIGN, DURATION AND DATES

3.1 Study Design

This is an open-label, multicentric, international, non-randomized phase I trial with dose optimization of single-agent OTX015/MK-8628 administered *per os* in patients with selected advanced tumors (NMC, TNBC, NSCLC, CRPC and PDAC).

The study will be performed in two parts. In the first part a dose escalation study will be performed evaluating two regimens in parallel to establish the MTD in each of the selected indications. In the second part, the efficacy of OTX015/MK-8628 will be evaluated in expansion cohorts of each of the five indications using a selected regimen. Patients will be included in at least seven centers worldwide.

The two regimens evaluated in parallel in the dose escalation part are:

Regimen 1: continuous, once daily for 21 consecutive days (21-day cycles), at a starting dose of 80 mg/day.

Regimen 2: once daily on days 1 to 7, repeated every 3 weeks (21-day cycles; 1 week ON/2 weeks OFF), at a starting dose of 100 mg/day.

A sequential accrual design with standard dose escalation is used. Patients will be included in the next available regimen.

Up to four dose levels will be evaluated for each regimen.

Regimen 1: 80, 100, 120 and 160 mg/day, continuous, 21-day cycles

Regimen 2: 100, 120, 160 and 200 mg/day, 1 week ON/2 weeks OFF, 21-day cycles

Patients will undergo a dose and/or schedule modification in the event of toxicity.

Three patients will be enrolled per dose level, and up to three additional patients at the first occurrence of a DLT (see Section 5.2.4) during the first 21 days of treatment. Up to 48 patients evaluable for DLT will be enrolled in the dose escalation part (24 for each regimen).

The MTD will be the dose level at which fewer than one-third of the patients experience DLT during the first 21 days, and is defined as the DL at which 0 out of 3 patients or 1 out of 6 patients experiences DLT, with the next higher DL having at least 2 out of 3 to 6 patients having DLT.

Once the MTD is established for each regimen and at least 3 patients have received at least two evaluable cycles of study drug at the MTD, an expansion step will be initiated to assess the efficacy of OTX015/MK-

8628 in these populations, as measured by clinical benefit (CR, PR or SD, according to RECIST v1.1 or PCWG2). Up to 50 evaluable patients (10 per indication) will be accrued in the expansion phase.

3.2 Independent Safety and Data Monitoring Committee

The SMC will be composed of the principal investigators of each participating center, the pharmacokinetics (PK) specialist, medical and safety representatives of the Sponsor and an independent expert in the field of oncology early drug development (see Appendix 4). All decisions made by the SMC and their rationale will be recorded.

The SMC will be responsible for the following decisions:

- Proceeding to the next higher DL or stopping dose escalation
- Adding patients at a given DL
- Determining the MTD and closing patient enrollment in that dose level and regimen
- Progressing with the dose expansion part
- Selecting the regimen to be followed in each indication in the expansion part of the study
- Performing optional study parts
- Making decisions aimed at improving participating patients' safety.

In addition, according to the nature, suspected relationship to study drug, or other clinical considerations, the SMC will make *ad-hoc* decisions, such as replacing non-evaluable patients, adding more patients at the same DL, adding intermediate DLs, exploring additional doses and/or regimens (e.g., if the MTD is not reached at the highest dose), or not considering a given DLT as clinically relevant for the determination of the MTD. PK results will be forwarded to the SMC as they become available and will be taken into account for the determination of the MTD, notably if no DLT occurs.

3.3 Study Duration and Dates

Patients will begin treatment within a week after registration, followed by the treatment period (3-week cycles), and a follow-up period of at least 2 treatment cycles after the last patient has started treatment.

Study period: patients are on the study from the time of Informed Consent Form (ICF) signature until the last visit or death, whichever comes first.

Treatment period: the time from the initiation of study therapy until the last study drug intake, plus a 30 day safety observation period during which OTX015/MK-8628-related TEAEs are reported.

End of study: the study is considered completed after the last patient has been evaluated for efficacy with a follow-up of at least 2 cycles.

The duration of this study will depend on the number of DLTs encountered in each regimen, the number of dose levels explored in each regimen and the rate of accrual in each of the five expansion cohorts.

The study will be closed after the last visit of the last patient still on study.

4 SELECTION OF PATIENTS

4.1 Number of Patients

The study will be carried out in two steps.

The dose escalation step will explore up to four OTX015/MK-8628 DLs using two regimens to determine the MTD in each regimen. Up to 48 patients evaluable for DLT (i.e. up to 24 patients per regimen) will be accrued depending on the number of DLTs encountered.

Up to 50 additional patients will be included in five expansion cohorts (10 patients per indication).

Overall, the total number of patients expected to be accrued in this study is up to 98 evaluable patients. The final sample size will depend on the number of DLTs encountered at each DL in each regimen, and may be increased if the MTD is not reached for either of the two proposed regimens with the four planned DLs, and additional DLs are required.

4.2 Inclusion Criteria

Patients must fulfill all of the following requirements to enter the study:

1. Signed informed consent obtained prior to initiation of any study-specific procedures and treatment;
2. 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 patient:
   - NUT midline carcinoma (ectopic expression of NUT protein as determined by IHC and/or detection of BRD-NUT gene translocation as determined by FISH);
   - Triple negative breast cancer defined according to ASCO recommendations (Hammond et al., 2010; Wolff et al., 2007);
   - Non-small cell lung cancer harboring a rearranged ALK gene/fusion protein (FISH or IHC) or KRAS mutation (as defined by any molecular analysis);
   - Castrate-resistant prostate cancer (CRPC);
   - Pancreatic ductal adenocarcinoma;
3. At least one measurable lesion as per RECIST version 1.1., except for CRPC patients who may be enrolled with objective evidence of disease as per Prostate Cancer Clinical Trials Working Group (PCWG2) criteria;
4. Age ≥ 18 years at the time of informed consent;
5. Life expectancy ≥ 3 months;
6. ECOG Performance Status (PS) ≤ 1;
7. Adequate bone marrow reserve, renal and liver function:
   - Absolute neutrophil count ≥ 1.5 x10^9/L,
   - Platelet count ≥ 150 x10^9/L,
   - Hemoglobin ≥ 9 g/dL (blood transfusion ≤ 7 days of screening not permitted),
   - Creatinine clearance ≥ 30 mL/min calculated according to the Cockroft and Gault formula or MDRD formula for patients aged > 65 years,
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) < 3 x ULN, if alkaline phosphatase (ALP) > 2.5 X ULN, then liver fraction should be ≤ 2.5 X ULN, and total bilirubin ≤ 1.25 x ULN (in case of liver involvement, total bilirubin ≤ 2 x ULN will be allowed),
   - Serum albumin ≥ 2.0 g/dL for NMC , ≥ 3.0 g/dL for NSCLC, CRPC, TNBC and pancreatic cancer
   - INR ≤ 1.5 or INR < 3 for patients treated with antivitamin K;

8. An interval of ≥ 3 weeks since chemotherapy (≥ 6 weeks for nitrosoureas or mitomycin C), immunotherapy, hormone therapy or any other anticancer therapy 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 patients 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. Patients receiving bisphosphonate or denosumab therapy must be on stable doses for at least 4 weeks before initiating study treatment.

4.3 Exclusion Criteria

The presence of any of the following criteria excludes a patient from participating in the study:

1. Inability to swallow oral medications or presence of a gastrointestinal disorder (e.g. malabsorption) deemed to jeopardize intestinal absorption of OTX015/MK-8628;
2. Persistent grade >1 clinically significant toxicities related to prior antineoplastic therapies (except for alopecia); stable sensory neuropathy ≤ grade 2 NCI-CTCAE v. 4.0 is accepted.
3. Known primary CNS malignancy or CNS involvement;
4. History of prior or concomitant malignancies (other than excised non-melanoma skin cancer or cured *in situ* cervical carcinoma) within 3 years of study entry;
5. Other serious illness or medical conditions, such as active infection, unresolved bowel obstruction, or psychiatric disorders;
6. Known HIV positivity;
7. Participation in another clinical trial or treatment with any investigational drug within 30 days prior to study entry;
8. Other concomitant anticancer treatment;
9. Concomitant therapy with strong CYP3A4 interfering drugs;
10. Current use of anticoagulants (e.g. warfarin, heparin) at therapeutic levels within 7 days prior to the first dose of OTX015/MK-8628. Low-dose (prophylactic) low molecular weight heparin (LMWH) is permitted;
11. Pregnant or breast-feeding patients, and men and women with childbearing potential not using effective contraception while on study treatment.

Any waiver of these inclusion and exclusion criteria should be exceptional and justified and must be approved by the investigator and the Sponsor on a case-by-case basis prior to enrolling the patient. This must be documented by both the Sponsor and the investigator.

4.4 Patients of Reproductive Potential

The patient must not be pregnant or breast-feeding at inclusion in the study. Absence of pregnancy must be demonstrated by urine testing unless there is proven menopause (age ≥ 50 years and last menarche ≥ 3 years, or documented menopausal sex hormone profile, or surgical castration) prior to exposure to the investigational product or any study procedure with potential risk to the fetus.

Female patients must not become pregnant or start breast-feeding during the study, and women of childbearing potential (i.e. without proven menopause, see above) must use a medically effective contraception during the study and within 6 months after the last study medication intake, as must male patients with a sexual partner of childbearing potential.

5 STUDY TREATMENT

5.1 Formulation and Manufacturer

Drug code	OTX015/MK-8628 (investigational agent)
INN	Not yet issued
Formulation	OTX015/MK-8628 is provided in gelatin capsules as a solid molecular dispersion as follows: 10 mg capsules (white, size 3): OTX015/MK-8628 free base (10 mg), hypromellose acetate succinate (HPMCAS; 10 mg), lactose monohydrate (85 mg), microcrystalline cellulose (70 mg), croscarmellose sodium (10 mg), colloidal silicon dioxide (2.5 mg), and magnesium stearate excipients (2.5 mg). 20 mg capsules (green, size 3): OTX015/MK-8628 free base (20 mg), HPMCAS (20 mg), lactose monohydrate (74 mg), microcrystalline cellulose (61 mg), croscarmellose sodium (10 mg), colloidal silicon dioxide (2.5 mg), and magnesium stearate excipients (2.5 mg). 40 mg capsules (white, size 0): OTX015/MK-8628 free base (40 mg), HPMCAS (40 mg), lactose monohydrate (196 mg), microcrystalline cellulose (162 mg), croscarmellose sodium (25 mg), colloidal silicon dioxide (6 mg), and magnesium stearate excipients (6 mg).
Storage	Capsules should be stored at +2 to +8°C (refrigerated)
Manufacturers	Agere Pharmaceuticals Inc. 62925 NE 18th Street, Bend, Oregon 97701, USA Merck Sharp & Dohme Limited Hertford Road, Hoddesdon, Hertfordshire, EN11 9BU , United Kingdom

5.2 Dosage Schedule

5.2.1 Prophylactic Medication Regimen

No systematic premedication will be given at least during the first cycle, however low dose prophylactic low molecular weight heparin (LMWH) is permitted throughout the study, including cycle 1.

5.2.2 Schedule

OTX015/MK-8628 is to be administered *per os* once daily in a fasted state with a little water just before breakfast (around 8 a.m. [±2h]). Flat doses will be used with no adjustment for BSA or weight.

Two regimens will be evaluated; OTX015/MK-8628 will be administered either continuously (Regimen 1) or for 1 week ON/2 weeks OFF (Regimen 2). 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 associated with the previous cycle.

Patients should receive study treatment within 7 days following registration.

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

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

5.2.3 Dose Escalation

Two regimens will be evaluated with four planned OTX015/MK-8628 dose levels for each. Patients will be sequentially assigned to Regimen 1 or Regimen 2, according to the next available place.

The starting dose will be 80 mg *per os* given once daily for Regimen 1, and 100 mg *per os* given once daily for 7 days every 3 weeks for Regimen 2 (1 week ON/2 weeks OFF).

Dose escalation will be performed independently in each regimen, according to 3+3 cohort design with 3 or 6 patients per cohort. The criteria for dose escalation are based on the occurrence of DLT. DLT assessment will be performed during the first 21 days of study treatment for each patient during the dose escalation phase of the study.

If none of the first 3 evaluable patients treated at a given DL experience DLT during cycle 1 (i.e., the first 21 days following study treatment initiation), dose escalation will proceed to the next highest DL.

If 1 out of 3 patients of a cohort has DLT during cycle 1, up to 3 additional patients will be entered at this DL. If no more than 1 of 6 evaluable patients has DLT, dose escalation will proceed to the DL immediately above. If more than 1 of 6 patients (or more than 1 of 3) has DLT, the DL will be considered to exceed the MTD (see table below).

The first patient enrolled in a higher DL cohort will not start the study treatment until the last treated patient in the DL immediately below has completed one cycle of study treatment (21 days following study treatment initiation).

Patients 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 for Regimen 1, or <6 days of treatment for Regimen 2) and who do not experience DLT will be replaced.

Table 10: OTX015/MK-8628 Dose Escalation Scheme

Dose Level	**OTX015 Dose (mg/day)**		**Outcome (#DLT/#Patients)* / Actions to be taken**
	Regimen 1 (continuous)	**Regimen 2** (D1-7, q3w)	
DL 1	80	100	At each DL for each regimen: - If 0 of 3 patients has DLT, escalate dose in next cohort of 3 patients - If 1 of 3 patients has DLT, treat next 3 patients at the same dose level (6 patients total) - **If ≥ 2 of 3 patients has DLT, halt dose escalation** (MTD exceeded) - If 1 of 6 patients has DLT, escalate dose for next cohort of 3 patients - **If ≥ 2 of 6 patients has DLT, halt dose escalation** (MTD exceeded)
DL 2	100	120	
DL 3	120	160	
DL 4	160	200	

* Evaluated during the first 21 days of treatment

Patients will receive OTX015/MK-8628 at the DL they were assigned at entry throughout the study, or at a reduced dose according to toxicity encountered.

5.2.4 Dose Limiting Toxicity

DLT is defined as any of the following toxicities occurring during the first 21 days of treatment and **considered by the investigator to be related to OTX015/MK-8628**.

Hematologic toxicity

- Any grade 4 hematologic toxicity or febrile neutropenia
- Grade 3 neutropenia with infection
- Grade 3 thrombocytopenia with bleeding or lasting > 7 days

Non-hematologic toxicity

- Any grade 3 or 4 non-hematologic toxicity (regardless of duration) unless it was not optimally managed with supportive care (e.g. grade 3 vomiting not adequately treated according to antiemetic standard of care).
- Any grade 3 or 4 laboratory abnormality, with or without symptoms, lasting > 48 hours.
- Any intolerable grade 2 non-hematologic toxicity resulting in study drug discontinuation or delay > 7 days with or without dose reduction.
- Any of the following liver test abnormalities** (see Appendix 5)
  - ALT or AST > 8 x ULN
  - ALT or AST > 5 x ULN for > 2 weeks
  - ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN OR INR > 1.5)
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

Other

- Treatment delay > 2 weeks or dose reduction requirement for initiating cycle 2.

**Note: All patients with these liver test abnormalities should be monitored weekly until all abnormalities return to normal or to the baseline state. For patients with isolated total bilirubin increases >2 x ULN or 2 x 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 in the CRF and in the database. See guidelines on the handling of these events (potential Hy's law cases)(Appendix 5).

DLTs must be reported immediately to the Sponsor using a Serious Adverse Event Report Form (SAERF) with the reason for seriousness "other important medical event" if there is no other reason for seriousness.

5.2.5 Maximum Tolerated Dose

The MTD (recommended phase II dose) is defined as the dose immediately preceding the DL at which DLTs are observed in ≥ 2 out of 3 to 6 patients, i.e., the DL at which 0 of 3 patients or ≤ 1 of 6 patients experience DLT.

The MTD will be determined in each of the two regimens evaluated.

5.2.6 Expansion Cohort

Once the MTD is established for each regimen with at least 3 patients having received at least 2 evaluable cycles of study drug, the study will be extended with the inclusion of 10 evaluable patients per indication at the MTD. The regimen used in each expansion cohort (i.e., each indication) will be decided by the SMC.

5.2.7 Dose Adaptation

OTX015/MK-8628 will be interrupted until recovery to ≤ grade 1 or baseline value in the event of any of the following toxicities:

Hematologic toxicity

- Any grade 4 hematologic toxicity or febrile neutropenia
- Grade 3 neutropenia with infection
- Grade 3 thrombocytopenia with bleeding or lasting > 7 days

Non-hematologic toxicity

- Any grade 3 or 4 non-hematologic toxicity (regardless of duration) unless it was not optimally managed with supportive care (e.g. grade 3 vomiting not adequately treated according to antiemetic standard of care).
- Any grade 3 or 4 laboratory abnormality, with or without symptoms, lasting > 48 hours.
- Any intolerable grade 2 non-hematologic toxicity resulting in study drug discontinuation or delay > 7 days with or without dose reduction.

After recovery from toxicity, the dose will be resumed as follows and detailed in Table 11:

- For Regimen 1, the continuous schedule will be initially modified to a discontinuous schedule, then with a dose reduction for the second modification.
- For Regimen 2, two consecutive dose reductions may be implemented.

Table 11: OTX015/MK-8628 Dose / Schedule Modifications

Dose / Schedule Modifications: Regimen 1		
Initial OTX015 Dose	**1st Modification**	**2nd Modification**
80 mg QD continuously	80 mg QD, 2 weeks ON/ 1 week OFF, q3w	60 mg QD, 2 weeks ON/1 week OFF, q3w
100 mg QD continuously	100 mg QD, 2 weeks ON/1 week OFF, q3w	80 mg QD, 2 weeks ON/1 week OFF, q3w
120 mg QD continuously	120 mg QD, 2 weeks ON/1 week OFF, q3w	100 mg QD, 2 weeks ON/1 week OFF, q3w
160 mg QD continuously	160 mg QD, 2 weeks ON/1 week OFF, q3w	120 mg QD, 2 weeks ON/1 week OFF, q3w
Dose / Schedule Modifications: Regimen 2		
Initial OTX015 Dose	**1st Modification**	**2nd Modification**
100 mg QD, Days 1-7, q3w	80 QD, Days 1-7, q3w	60 QD, Days 1-7, q3w
120 mg QD, Days 1-7, q3w	100 mg QD, Days 1-7, q3w	80 QD, Days 1-7, q3w
160 mg QD, Days 1-7, q3w	120 mg QD, Days 1-7, q3w	100 mg QD, Days 1-7, q3w
200 mg QD, Days 1-7, q3w	160 QD, Days 1-7 q3w	120 mg QD, Days 1-7, q3w

No more than two dose reductions (or schedule modifications) should be implemented unless the investigator thinks it in the patient'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 or liver toxicity (see Section 5.3 for details) will lead to definitive study treatment discontinuation, unless the investigator thinks it in the patient's best interests to pursue study treatment, with the Sponsor's agreement.

5.2.8 Supportive Care Guidelines for Study Treatment Toxicity

Toxicity will be managed by the investigator according to the local standard of care. Supportive treatment must be reported in the concomitant medication section of the eCRF.

Handling of hepatotoxicity for potential DILI will be managed according to the treatment guidelines outlined in Appendix 5.

5.2.9 Potential Phototoxicity

No phototoxicity studies have been performed in humans to date. However as OTX015/MK-8628 absorbs light in the range of 290 and 400 nm with a molar extinction coefficient (MEC) of >1000 L/mol.cm, it is recommended that patients avoid sun and UV exposure until results of phototoxicity studies are available.

5.3 Treatment Duration

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

- Disease progression
- Unacceptable toxicity
- Patient withdrawal of consent
- Patient non-compliance
- Treatment interruption for > 2 weeks for any reason (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)
- Any of the following liver test abnormalities** (see Appendix 5)
  - ALT or AST > 8 x ULN
  - ALT or AST > 5 x ULN for > 2 weeks
  - ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN OR INR > 1.5)
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

However, in case of investigator's perceived benefit for the patient, 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 patient'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 patient must be followed up to establish whether the reason was a TEAE, 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 patients who receive the investigational product but who do not complete the study according to protocol.

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

5.4 Treatment Assignment

All patients must be registered prior to treatment start. After verifying that the patient meets eligibility criteria and has signed the Informed Consent Form, the investigator will request a patient number by faxing/e-mailing the Patient's Registration Form to:

PPD

Medical Monitor, Oncology Therapeutic Development (OTD)

Fax: PPD

Phone: PPD

Mobile: PPD

E-mail: PPD

The Patient's Registration Form (provided separately) contains the following information necessary to determine eligibility:

1. Institution name
2. Sender's name
3. Principal investigator's name
4. Patient's identification (first letter of first, middle and last name)
5. Patient's age and gender
6. ECOG performance status
7. Planned date of treatment
8. Date when informed consent was obtained
9. Verification of selected inclusion and exclusion criteria including hematologic and biochemistry results and dates examinations were performed
10. Prior anticancer therapies and dates of last therapies
11. Comorbidities and tumor-related symptoms present at screening

After validation and signature by the CRO's Medical Monitor, the registration form will be returned to the investigator, with or without inclusion agreement.

For patients not included, the reason for inclusion refusal will be specified.

For included patients, the dose level and regimen allocated will be specified on the form, along with a unique patient number (UPN). Included patients will receive a UPN only when treatment is about to be started, which must be within 7 days after registration.

The UPN will consist of 5 digits (2 for the center and 3 for the patient, by increasing order of inclusion) and will be recorded on the eCRF. The next consecutive number will be assigned. Once a number has been assigned, it must not be used again.

5.5 Packaging and Labeling

The investigational product OTX015/MK-8628 is manufactured by Agere Pharmaceuticals, Inc. or Merck Sharp & Dohme Limited and packaged by Packaging Coordinators, Inc. It will be supplied as size 3 gelatin capsules containing 10 or 20 mg of OTX015/MK-8628 or size 0 gelatin capsules containing 40 mg OTX015/MK-8628, in bottles of 21 capsules. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

5.6 Supplies and Accountability

The pharmacist of the investigational center will inventory and acknowledge receipt of all shipments of the investigational medicinal product which must be kept in a locked area with restricted access. It must be stored and handled in accordance with the manufacturer's instructions and temperature traceability is required.

At each study visit, the hospital pharmacist will provide patients with the adequate number of OTX015/MK-8628 capsules to ensure continuous study treatment until the next visit. The study drug must be used only as directed in the protocol and must be dispensed only to patients enrolled in this study.

The pharmacist will also keep accurate records of the quantities of the investigational product dispensed, used, and returned by each patient. The Sponsor's study monitor will periodically check the supplies of investigational product held by the pharmacist to verify accountability of all investigational product used. The Sponsor will verify that a final report of drug accountability to the unit dose level is prepared and maintained in the Pharmacy Study File. At the conclusion of the study, all unused investigational product and all medication containers will be destroyed by the pharmacist after final accountability by the study monitor and drug accountability has been reviewed and reconciled by the Sponsor and the Sponsor has authorized destruction or return. A certificate of destruction will be provided by the pharmacist to the Sponsor. Alternatively, study medication may be returned to the clinical supply distributor after notification to OTD and OncoEthix. All delivery records must be reconciled with usage records and destroyed or returned. It is essential that all study drugs be accounted for by the site's pharmacist, and that discrepancies are explained and documented.

Complete instructions and contact information for ordering clinical supplies will be supplied in the Investigator File.

5.7 Compliance

Administration of the investigational product will be supervised by the investigator. Any delegation of this responsibility must follow Section 12.2.

In practice, on study visit days study nurses will supervise the intake of the appropriate OTX01/MK-86285 dose, explaining to patients 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, OTX015/MK-8628 will be taken at home. The patient will note the number of capsules taken, the time of administration, as well as any reactions including the date/time in a specific patient's diary.

When a patient 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.

6 PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

6.1 Medical Conditions

Additional illnesses, independent of the treated condition, present at the time informed consent is given or within 4 weeks prior to first study treatment administration must be documented in the eCRF. Relevant past illnesses (including other cancers) must also be documented in the section "Prior and Concomitant Conditions" of the eCRF.

Medical conditions first occurring or detected during the study or worsening of a concomitant illness during the study, are to be considered TEAEs and must be documented in the "Adverse Events" section of the eCRF.

6.2 Medications

All treatments taken by patients 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 (G-CSF, EPO etc.) after cycle 1.
- For CRPC patients, 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 patient 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 or antivitamin K (INR < 3); INR must be monitored in accordance with local institutional practices. Patients 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). A list is provided in Appendix 3, however since this list is not comprehensive, the investigator should use his/her medical judgment when a patient presents with a medication not on the list or call the Sponsor Medical Expert for clarification.
- Current use of anticoagulants (e.g. warfarin, heparin) at curative therapeutic levels within 7 days prior to the first dose of OTX015/MK-8628, with the exception of prophylactic low-dose LMWH or antivitamin K (INR < 3).

7 STUDY PROCEDURES AND SCHEDULE

7.1 Pre-Study Screening Visit

Each candidate patient will be examined before starting the study to determine eligibility for participation. This must be done within 2 weeks prior to the first study treatment administration, except for radiologic assessment which can have been performed up to 4 weeks prior to study start. The following investigations will be performed:

- Informed consent: obtain written patient informed consent prior to any specific study procedure
- Verification of eligibility criteria
- Demographics, medical history, including non-cancer medical history, and concurrent illnesses
- Diagnosis and prior treatment for malignancy (a confirmatory diagnosis of NUT midline carcinoma or NSCLC at screening is not required)
- Physical examination, PS (Appendix 1), vital signs (temperature, blood pressure, pulse), body weight, height
- Pregnancy test if child-bearing potential (urine test)
- Baseline symptoms and complaints
- Complete blood count (CBC), including hemoglobin, RBC counts, WBC and differential, platelet counts
- INR, Factor VII
- Serum chemistries: Na, K, Ca, Mg, P, Cl, HCO3, creatinine, total protein, albumin, glucose, alkaline phosphatase, total bilirubin, AST, ALT, LDH
- Tumor evaluation: physical examination, CT, MRI, and/or chest X-ray (PA and lateral), as indicated by the patient's diagnosis. A bone scan is mandatory for CRPC patients.
- Serum tumor markers, according to indication (PSA, CA19-9, CA15-3, CEA, etc.); as far as possible, subsequent measures must be made in the same laboratory
- Concomitant medications

7.2 Evaluations During Study Treatment

Visit: Day 1 of each cycle

For cycle 1, patients participating in pharmacokinetics will be observed for ≥ 8 hours after the first study drug administration to collect PK blood samples and check vital signs, when appropriate.

- Physical examination, PS, vital signs, body weight
- CBC
- INR, Factor VII
- Serum chemistries: all patients with specific liver test abnormalities (see Section 5.2.4) should be monitored weekly until all abnormalities return to normal or to the baseline state. For patients with isolated total bilirubin increases >2 x ULN or 2 x baseline (if elevated at baseline), monitoring should be every 2 weeks until bilirubin returns to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped.
- Concomitant medications
- Adverse events
- Tumor markers, as appropriate for tumor type; as far as possible, measures must be made in the same laboratory
- Dispensing of study drug (adequate quantity until day 1 visit of next cycle)
- **Day 1 of cycle 1 only**: PK blood sampling in patients included in the dose escalation part of the study and selected patients from the expansion cohort (see Section 10 for full PK details): T0 (just before OTX015/MK-8628 intake), T15min (±5 min) post-dose, T1h (±15 min) post-dose, T2h (±15min) post-dose, T3h (±15min) post-dose, and T7h (±15min) post-dose, post-dose
- **Day 1 of every 2nd cycle (C3, C5, C7, etc.; i.e., every 6 weeks):** Tumor imaging (CT, MRI, and/or chest X-ray, as indicated) and response assessment
- **Day 1 every 4th cycle (C5, C9, C13 etc.; i.e., every 3 months):** Bone scan for CRPC patients

Twice a week for cycles 1 and 2 then weekly thereafter

- CBC

Weekly for cycles 1 and 2

- Serum chemistries; from cycle 3 on, in the absence of ≥ grade 2 abnormalities these tests will be performed every cycle; otherwise they are to be done weekly until resolution to baseline levels or < grade 2.
- INR, Factor VII

7.3 End of Treatment Visit and Follow-Up

After the last treatment administration, patients will be followed up for safety for 30 days and then until resolution of any TEAEs for which a relationship to OTX015/MK-8628 cannot definitely be excluded (or categorized as sequelae).

A visit will be performed 35 days (±5 days) after the last OTX015/MK-8628 intake, including the following:

- Physical examination, PS, vital signs, body weight

- CBC
- INR, Factor VII
- Serum chemistries
- Concomitant medications
- Adverse events
- Tumor imaging
- Tumor markers

The last patient will be followed-up for at least two cycles after treatment initiation to allow for evaluation of efficacy.

8 ASSESSMENT OF SAFETY

In emergency situations, the investigator should immediately contact a Sponsor representative at the telephone number or email address given on the title page of this protocol.

Patients will be monitored for signs and symptoms of AEs throughout the study by a qualified oncologist, with experience in clinical research. All AEs will be reported in the eCRF, including seriousness, NCI-CTCAE v4.03 grade severity, causal relationship to the study medication, and action taken. The first concern will be the safety of the study participant.

Incidence, severity and relationship of AEs and laboratory abnormalities, SAEs, discontinuations and dose adaptations due to AEs will be recorded.

8.1 Clinical Safety

Clinical and physical examinations, as well as vital signs evaluation, will be performed. Patient data will be analyzed for evidence of cumulative toxicity with repeated cycles of therapy.

TEAEs and signs and symptoms of disease observed by the investigator (preferably by the same physician for a same patient) or reported by patients to the study nurses will be recorded and graded according to NCI-CTCAE version 4.03, accessible via internet [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf]. It is crucial that all events, including those considered not related to the study drug are reported in the eCRF.

8.2 Laboratory Measurements

Any laboratory abnormality assessed as related, probably related, or possibly related must be reported as a TEAE in the eCRF. Clinically significant laboratory values must be reported as TEAEs in the eCRF. Clinically significant laboratory results are those which have clinical consequences (i.e. need treatment or corrective measures, result in study drug dose reduction, delay or discontinuation, hospitalization, prolongation of hospitalization, or death, are life-threatening, are reported as an SAE whatever the reason, or are considered a toxicity of the treatment). The seriousness, the action taken regarding study medication and patient participation in the study, relation to study medication and the most likely cause, must be recorded.

8.3 Definitions (21 CFR§312.32)

- **Adverse event (AE)** means any untoward medical occurrence associated with use of a drug in humans, whether or not considered drug related. The term **treatment emergent adverse event** [TEAE] covers any

unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study. Surgical or other procedures themselves are not TEAEs. The condition for which the surgery/other procedure is required, is a TEAE, if it occurs or is detected during the study period. Planned surgical or other procedures planned/permitted by the study protocol and the condition(s) leading to these measures are not TEAEs, if the condition(s) was (were) known before the start of study treatment. In the latter case the condition should be reported as medical history.

- **Adverse drug reaction (ADR)** means an AE caused by the drug.
- **Suspected adverse reaction (SAR)** means any AE for which there is a reasonable possibility that the drug caused the AE. A "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than an ADR, and include:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;
  - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
  - An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.
- **Serious adverse event (SAE)** or **serious suspected adverse reaction (SSAR)** is an event that, in the view of either the investigator or Sponsor, results in any of the following outcomes:
  - Death occurring on study or within 30 days after the last administration of study drug (regardless of relationship to study treatment) or within any interval if related to the study drug. Although death may occur as a result of the disease, all deaths occurring within 30 days of the last administration of study drug must be managed as SAEs and reported as such;
  - A life-threatening AE;
  - Inpatient hospitalization or prolongation of existing hospitalization;
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
  - A congenital anomaly/birth defect.

  In addition, medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient's safety or may require intervention to prevent one of the outcomes listed in the definition above should also usually be considered serious. Examples of such events include overdose even without complications, or an AE requiring intensive treatment without hospitalization. A diagnosis of a new cancer type during the course of a treatment should be considered as medically important. In addition, any pregnancy diagnosed in a female patient on treatment with the investigational product or in the partner of a male patient on treatment with the investigational product must be reported to the Sponsor immediately. The List of Critical Terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List, provided in the "Instructions for completing the 'Serious Adverse Event/Expedited Report from a Clinical Trial' form") should be used as guidance for AEs that may be considered serious because they are medically important.

  For the purpose of the dose-finding part of this study, any suspected DLT occurring during the dose escalation part will be considered as medically important and reported as an SAE even if it does not meet other criteria for seriousness. In the latter case, the reason for seriousness will be "other important medical event".

- **Life-threatening AE** or **life-threatening SAR** is an AE that, in the view of either the investigator or Sponsor, places the patient at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- **Unexpected AE or unexpected SAR** is an AE or SAR that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected", as used in this definition, also refers to AEs or SARs that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacologic properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.4 Documentation

All TEAEs occurring during the course of the study, whether or not considered related to the study drug or to underlying disease, must be individually recorded in the eCRF, including the nature of the event, date and time of onset (where appropriate), duration of effect, action taken, seriousness, severity, and relationship to study medication. Any consequent change to the dosage schedule or corrective therapy should be recorded.

Every attempt should be made to describe the TEAE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All patients who experience a TEAE, regardless of the relationship to study treatment, must be monitored to determine the outcome. The clinical course of the AE will be followed up even after the end of the period of observation for related TEAEs, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the AE result in death, a post-mortem examination should be considered as far as possible.

After last study treatment administration, patients will be observed for **at least 30 days** to document any late side effects and until resolution in cases of TEAEs for which a relationship to OTX015/MK-8628 cannot definitely be excluded.

AEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment. If resolved, details are to be recorded in the eCRF. If an AE worsens in frequency of attacks/symptoms or in severity, a new record of the event must be started (i.e., distinct AE reports are required for differing frequencies and/or severity of the same event to enable comprehensive safety reports and later analysis).

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, must be reported under "concomitant procedures" in the eCRF and not as an AE. The medical condition for which the procedure was performed must be reported.

8.5 Grade and Severity

All AEs, whether or not they are considered related to the study drug, must be graded using the NCI Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. The worst grade is to be documented.

AE grades usually reflect their severity, with grade 1 meaning "mild", grade 2 meaning "moderate", grade 3 meaning "severe", grade 4 meaning "life-threatening" and grade 5 meaning "fatal".

The term "severity" is used to describe the **intensity** of an AE; the event itself, however, may be of relatively minor clinical significance (e.g., 'severe' headache). This is **not** the same as "serious". Seriousness of AEs is based on the outcome/action of an AE and usually is associated with events that pose a threat to a patient's life or functioning.

Intensity of the AE will be evaluated using the following criteria:

- **Mild:** The patient is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the patient and of little clinical significance. The event is not expected to have any effects on the patient's overall health or wellbeing.
- **Moderate:** The patient has discomfort enough to cause interference with or change in usual activities. The event is of some concern to the patient's health or wellbeing and may require medical intervention and/or close follow-up.
- **Severe:** The AE interferes considerably with the patient's usual activities. The event is of definite concern to the patient and/or poses substantial risk to the patient's health or wellbeing. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life-threatening. Hospitalization and treatment may be required.

8.6 Relationship to Study Treatment

All TEAEs occurring during treatment with an investigational agent may be related to the investigational agent. All TEAEs, regardless of the supposed relationship to study treatment, must therefore be collected. However, the investigator often has arguments to think that a TEAE is or is not related to the study treatment. Albeit subjective, and susceptible to be challenged, the assessment of relationship to study treatment is an important role of the investigator. Thus, the investigators should decide, based on their knowledge and medical expertise, whether, in their opinion, an AE is "reasonably related" or "unlikely related" to the study treatment (or to study specific procedures).

8.7 SAE Reporting

SAEs and other AEs that fulfill a reason for expedited reporting to Pharmacovigilance (overdose and pregnancy) must be documented on a Serious Adverse Event Report Form (SAERF) at the time the SAE is detected. This form must be completed and sent within 24 hours or at the latest on the following working day to the Sponsor's Pharmacovigilance representative:

Oncology Therapeutic Development (OTD)

Tel: PPD
Fax: PPD
E-mail: PPD

The SAERF and guidelines for completing it are provided in the Investigator Study File. The Sponsor is responsible for ensuring that all legal reporting requirements are met.

The initial report must be as complete as possible, including details of the current illness and AE(s), and an assessment of the causal relationship between the event(s) and the investigational product.

Information not available at the time of the initial report (e.g., an AE end date or laboratory values received after the report) must be documented on a follow-up SAERF.

8.8 Period of Observation

For the purposes of this study, the period of observation for collection of AEs extends from the start of treatment with the investigational product until the end of study treatment period, 30 days after the last study drug administration, except for TEAEs for which a relationship to OTX015/MK-8628 cannot definitely be excluded, which must be reported during follow-up until resolution or change of causality from related to non-related or initiation of further antitumor therapy.

If the investigator detects an SAE after the end of the period of observation, and considers the event possibly related to prior study treatment, he/she should contact the Sponsor to determine how the AE should be documented and reported.

8.9 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 patient registration, any ECI, or follow up to an ECI, that occurs to any patient must be reported within 24 hours to the Sponsor if it causes the patient 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, or a procedure.

For the time period beginning at patient registration 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 data entry guidelines.

1. An elevated AST or ALT lab value that is ≥3X ULN and an elevated total bilirubin lab value that is ≥2X ULN and, at the same time, an alkaline phosphatase lab value that is < 2X ULN, as determined by 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 Appendix 5 and the Investigator Brochure section on discussion and guidance for investigator.
2. An elevated total bilirubin lab value that is ≥ 2X ULN.
3. Any of the following liver test abnormalities are observed (see also Appendix 5):
   - 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%)

   **All patients with these liver test abnormalities should be followed weekly until all abnormalities return to normal or to the baseline state. 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 Appendix 5 for guidelines on the handling of events of ALT or AST >3 x ULN AND total bilirubin >2 x ULN or INR>1.5 (potential Hy's law cases).

9 EFFICACY ASSESSMENTS

Efficacy will be measured in terms of tumor response, according to either RECIST, or PCWG2 for CRPC patients. Tumor markers will also be assessed; CEA (for NSCLC), CA19-9 and CEA (for PDAC), PSA (for CRPC), CA15-3 (TNBC), and other nonspecific tumor markers as appropriate. Tumor measurements are to be made every 6 weeks and bone scans will be performed every 12 weeks until progressive disease is observed.

9.1 RECIST

Tumor lesions will be assessed throughout the study according to RECIST criteria (version 1.1) (Eisenhauer et al., 2009). 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.

9.1.1 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.).

9.1.2 Evaluation of Lesions

Table 12: 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). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. 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 13: 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. *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.

9.1.3 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 14.

Table 14: Overall response in patients 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 patient are available. Table 15 below summarizes the best overall tumor response.

Table 15: 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 patient 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.

Patients 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.

9.2 PCWG2

For CRPC patients, PSA response rates will be measured according to the PCWG2 criteria (Scher et al., 2008). RECIST v1.1 is used to assess soft tissue disease (Eisenhauer et al., 2009). Progression of bone disease is defined using PCWG2 criteria, namely a confirmed increase of at least two new lesions on a bone scan.

9.2.1 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 (Fleming et al., 2006).

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 patient using a waterfall plot (Seidman et al., 1992). 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.

9.2.2 Measurable 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.

9.2.3 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 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 16: The Prostate Cancer Clinical Trials Working Group (PCWG2) Response Criteria

Variable	**PCWG2 Criteria** (Scher et al., 2008)
PSA	**For control/relieve/eliminate end points:** 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 **Progression:** **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) 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% Recording the duration of PSA decline of little value **No decline from baseline:** PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	**For control/relieve/eliminate end points:** Use RECIST with caveats Only report changes in lymph nodes that were ≥ 2 cm in diameter at baseline Record changes in nodal and visceral soft tissue sites separately Record complete elimination of disease at any site separately Confirm favorable change with second scan Record changes using waterfall plot **For delay/prevent end points:** Use RECIST criteria for progression, with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later Note that for some treatments, a lesion may increase in size before it decreases
Bone	**For control/relieve eliminate end points:** Record outcome as new lesions or no new lesions First scheduled reassessment: No new lesions: continue therapy New lesions: perform a confirmatory scan 6 or more weeks later Confirmatory scan: No new lesions: continue therapy Additional new lesions: progression Subsequent scheduled reassessments: No new lesions: continue New lesions: progression **For prevent/delay end points (progression):** 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 The date of progression is the date of the first scan that shows the change

PSA, prostate-specific antigen

10 PHARMACOKINETICS ASSESSMENTS

10.1 Sample collection

PK sampling will be performed in all patients enrolled in the dose escalation phase and selected patients from the expansion cohort.

A plasma sampling schedule including a total of 6 time-points over the first 7 hours of **day 1 of cycle 1** will be performed to characterize the PK profile of OTX015 (C_{max}, C_{min}, T_{max}, AUC $_{[0-\infty]}$, Vd_{ss}, $t_{1/2}$, and CL), as follows: **T0** (immediately before OTX015/MK-8628 intake), **T15min** (±5 min), **T1h** (±15min), **T2h** (±15min), **T3h** (±15min), **T7h** (±15min) post-dose.

Blood samples of 3.0 mL will be collected in EDTA tubes, inverted a few times to mix the anticoagulant and then processed as soon as possible (within 15 min). Samples will be centrifuged at 1500 g (4,000 rpm for a 14-15 cm centrifuge) at +4°C for 10 minutes. Plasma will be immediately aliquoted and stored in airtight stoppered polypropylene tubes at -20°C.

In total, six blood samples of 3.0 mL each will be collected, i.e. approximately 18 mL of blood will be drawn per patient from a peripheral venous access for PK analysis.

Blood samples must be sent as soon as possible to the laboratory for analysis, to allow for availability of results at the SMC meeting. If two patients in the same center are treated at the same time or a few days apart, samples of these two patients should be sent together.

All samples will be labeled with:

- Sponsor and Protocol Number
- UPN and patient initials
- Sample number with actual date and time of collection

All samples must be shipped at -20°C to:

PPD

Laboratoire de Pharmacologie
Institut Curie (Hôpital René Huguenin)
35, rue Dailly
92210 Saint-Cloud, France
Phone: PPD
Fax: PPD

PPD

PPD

10.2 Assay Method and Parameters Analyzed

Plasma concentrations of OTX015/MK-8628 will be measured using Ultra Performance Liquid Chromatography with tandem Mass Spectrometry detection (UPLC-MS/MS).

The following parameters will be determined: Trough (C_{min}) and peak (C_{max}) concentrations, T_{max}, AUC$_{[0-\infty]}$, Vd_{ss}, $t_{1/2}$, steady state, total clearance (CL).

Descriptive statistics will be used to summarize PK parameters with mean, standard deviation (SD), coefficient of variation (CV) and ranges. Analyses will be carried out using the nonlinear mixed effect modeling software program Monolix version 3.2s (http://wfn.software.monolix.org).

PK data for OTX015/MK-8628 will be interpreted in terms of safety findings and compared with historical data.

11 STATISTICAL CONSIDERATIONS

11.1 Statistical Design and Sample Size

The exploratory part of the study is designed to assess the safety of OTX015/MK-8628 in patients with advanced or metastatic solid tumors. The small numbers per cohort are not intended for statistical hypotheses. Treatment decisions will be made by the SMC. The expansion cohort part will start once the MTD and a regimen are determined.

In the dose escalation part, up to 48 patients evaluable for DLT (i.e. up to 24 patients per regimen) will be accrued depending on the number of DLTs encountered. Once the MTD is established with at least 3 patients having received at least 2 cycles of study drug, an expansion cohort of up to 50 additional evaluable patients (10 patients per indication) will be enrolled. The regimens used in the expansion cohort will be decided for each indication by the SMC.

The final sample size will depend on the number of DLTs encountered at each DL and in each regimen, and may be increased if within the two proposed regimens and four planned DLs, the MTD is not reached and additional DLs are required.

11.2 Study Endpoints

Primary: The number of patients experiencing at least one DLT in cycle 1 (day 1 to 21) for each of the two regimens independently.

Secondary:

Safety: Incidence, severity and relationship of AEs, laboratory abnormalities, SAEs, discontinuations due to AEs, dose adaptations due to AEs, and DLT.

Efficacy: The number of patients with clinical benefit (defined as complete response, partial response or stable disease) and progressive disease based on the best overall response from tumor evaluations performed every 2 cycles, according to RECIST v1.1 or PCWG2, and tumor marker assessment.

Pharmacokinetics: Plasma parameters of OTX015/MK-8628 including C_{max}, C_{min}, T_{max}, $AUC_{[0-\infty]}$, Vd_{ss}, $t_{1/2}$, CL.

11.3 Analysis Populations

- **Evaluable for DLT:** patients who receive at least 85% of the planned dose of study drug (18 days for Regimen 1, or 6 days for Regimen 2) or experience DLT during the first 21-day cycle.
- **Treated population:** patients who receive at least one dose of study drug.
- **Evaluable for efficacy:** patients who receive at least 2 complete cycles (6 weeks) of treatment and have undergone baseline assessment and one on-study tumor assessment, or who discontinue early due to disease progression.

11.4 Statistical Methods

Quantitative variables will be summarized using descriptive statistics; continuous variables will be presented as N, mean and/or median, standard deviation, range, and categorical variables will be presented using frequencies and percentage. For CRPC patients, waterfall plots for percent change from baseline at 12 weeks, as well as maximal change at any time will be prepared.

Patient disposition and demographics will be analyzed in all included patients, safety will be analyzed in the treated population with an additional analysis in patients evaluable for DLT for the dose escalation part, and response will be analyzed in patients evaluable for efficacy.

AEs will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be tabulated by System Organ Class and Preferred Term. Laboratory values outside normal limits will be summarized using the NCI-CTCAE version 4.03. Concomitant medications will be coded according to the WHO Drug Dictionary.

Data will be presented by dose level and regimen for the dose escalation part, by indication and/or regimen for the dose expansion part of the study. No imputations for missing data will be made.

A Statistical Analytical Plan (SAP) will be finalized prior to analysis. Any deviations from the statistical methods in the study protocol will be described and justified in the SAP and in the statistical report.

Pharmacokinetics will be analyzed and reported separately, as described in Section 10.

11.5 Interim Analysis

No formal interim analysis is planned.

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

12 ETHICAL AND LEGAL ASPECTS

12.1 Good Clinical Practice

This clinical study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), as defined in ICH Guidance E6: *Good Clinical Practice: Consolidated Guidance*, in agreement with the Declaration of Helsinki and applicable federal and local regulatory requirements.

12.2 Delegation of Investigator Duties

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he/she has delegated significant trial-related duties.

12.3 Patient Information and Informed Consent

Before being enrolled in the clinical study, patients must give written informed consent to participate in the study.

A Patient Information Leaflet (PIL), including an Informed Consent Form (ICF) (provided separately) will be given to each patient screened in the study. This document contains all the information required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The master document (in English) is also translated into the national language(s) and in terms that are understandable to any patient. In addition to the document, the investigator should provide oral information and answer to patient's questions. Patients should have an adequate time for thought and to ask questions and should not sign the ICF when it is first given to them.

The patient's consent must be confirmed by their dated signature and the name and dated signature of the principal investigator or sub-investigator conducting the informed consent discussions.

A copy of the signed consent document must be given to the patient. The original signed consent document will be retained in the Investigator Study File.

The investigator will not undertake any measure specifically required for the clinical study until valid consent has been obtained.

12.4 Confidentiality

Patient names will not be supplied to the Sponsor. Only the UPN and initials will be recorded in the eCRF. If the patient name appears on any document (e.g., laboratory report), it must be eliminated on the copy of the document supplied to the Sponsor. Study findings stored on a computer will be kept in accordance with local data protection laws. Patients will be informed that representatives of the Sponsor, independent ethics committee (IEC)/ institutional review board (IRB), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The investigator will maintain a patient identification list (UPN with the corresponding patient name) to enable records to be identified.

12.5 Approval of the Clinical Study Protocol and Amendments

Before the start of the study, the clinical study protocol, PIL/ICF, and any other appropriate documents will be submitted to the IEC/IRB and to the national Health Authorities, in accordance with local legal requirements.

Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

The IEC/IRB and the authorities must be informed of all administrative changes and any important finding that could modify the risk of exposed patients. They also must be informed or their authorization obtained for all subsequent amended protocols, in accordance with local legal requirements.
The investigator must keep a record of all communication with the IEC/IRB and the Health Authorities.

12.6 Ongoing Information for IEC/ IRB and Health Authorities

The Sponsor must submit the following to all investigators, the IEC/IRB and Health Authorities:

- Information on serious or unexpected AEs from any investigational site, as soon as possible.
- Expedited safety reports according to regulations.
- Periodic reports on the study progress.

12.7 Study Closure

The study must be closed at the site on completion. Furthermore, the Sponsor or the investigator has the right to close a study site at any time.

Study materials must be returned, disposed of or retained as directed by the Sponsor.

12.8 Record Retention

Study documents should be retained by the investigator for at least 15 years. Beyond this period, the investigator still must obtain approval in writing from the Sponsor before destruction of any records.

The documents to be retained include:

- Original signed ICFs for all patients
- Patient identification code list, screening log and enrollment log
- Record of all communications between the investigator and the IEC/IRB
- Composition of the IEC/IRB
- Record of all communications between the investigator and Sponsor (or CRO)
- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of CRFs and of documentation of corrections on data correction forms (DCF) for all patients
- Investigational product accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (patient medical records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH E6 Guideline for Good Clinical Practice (Essential Documents for the Conduct of a Clinical Trial)

12.9 Liability and Insurance

Liability and insurance provisions for this study are given in separate agreements.

The Sponsor has taken out an insurance covering their civil responsibility.

The Sponsor, OncoEthix, is a company established outside the European Union. As such, they have empowered the Contract Research Organization (CRO) OTD (Oncology Therapeutic Development) SARL, 100 rue Martre, 92110 Clichy, France, to represent them in the European Union.

12.10 Financial Disclosure

Before the start of the study, the investigator will disclose to the Sponsor any proprietary or financial interests he or she might hold in the investigational products or the Sponsor company as outlined in the financial disclosure form provided by the Sponsor. The investigator agrees to update this information in case of significant changes during the study or within one year of its completion. The investigator also agrees that, where required by law or regulation, the Sponsor may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

Similar information will be provided by each sub-investigator to whom the investigator delegates significant study related responsibilities.

13 STUDY MONITORING AND AUDITING

Monitoring and auditing procedures developed or endorsed by the Sponsor will be followed, in order to comply with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured.

13.1 Monitoring and Source Data Verification

Monitoring will be done by personal visits from representatives of the Sponsor (study clinical research assistant and medical monitor) who will check the eCRFs for completeness and clarity, and crosscheck them with source documents. In addition to the monitoring visits, frequent communications (letter, telephone, e-mail and fax), by the study monitors will ensure that the investigation is conducted according to protocol design and regulatory requirements.

Study close-out will be performed by the study monitor upon closure of the study.

13.2 On-Site Audits/Inspections

An external auditor, appointed by the Sponsor, or the EC/IRBs, as well as inspectors, appointed by domestic and foreign regulatory authorities, may request access to all source documents, case report forms, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that patient names are obliterated on the copies to ensure confidentiality.

14 DOCUMENTATION AND USE OF STUDY FINDINGS

14.1 Documentation of Study Findings

An eCRF will be used.

All protocol-required information collected during the study must be entered by the investigator, or designated representative, in the eCRF. Details of eCRF completion and correction will be explained to the investigator. If the investigator authorizes other persons to make entries in the eCRFs, the names, positions, signatures, and initials of these persons must be supplied to the Sponsor.

The investigator, or designated representative, should complete the eCRF pages as soon as possible after data are collected, preferably on the same day that a study patient is seen for an examination, treatment, or

any other study procedure and at the latest before the next monitoring visit. An explanation should be given for all missing data.

A source data location list will be prepared prior to study start. This list will be filed in both the Trial Master File and the Investigator Study File and updated as necessary.

The completed eCRFs must be reviewed and signed by the investigator named in the clinical study protocol or by a designated co-investigator.

All errors detected after the monitoring visit will be queried using DCFs. The Sponsor will answer the question and/or correct errors in the DCF duly signed and dated. Original DCFs will be collected by the Sponsor's study monitor, while a copy will be kept by the investigator and recorded in the Investigator Study File with the corresponding eCRFs.

A copy of the eCRF will be printed and filed in the Trial Master File. The Sponsor will retain the originals of all eCRFs. The investigator will retain a copy of all completed eCRF pages and DCFs.

14.2 Confidentiality/Use of Study Findings

All information concerning the product as well as any matter concerning the operation of the Sponsor, such as clinical indications for the drug, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained.

The Sponsor has full ownership of the original eCRFs completed as part of the study.

By signing the clinical study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The Sponsor will ensure that a clinical study report on the study is prepared.

All materials, documents and information supplied by the Sponsor to the investigator, and all materials, documents and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the Sponsor. Subject to obligations of confidentiality, the investigator reserves the right to publish only the results of the work performed pursuant to this protocol, provided, however, that the investigator provides an authorized representative of the Sponsor with a copy of any proposed publication for review and comment at least 45 days in advance of its submission for publication. In addition, if requested, the investigator will withhold publication an additional 90 days to allow for filing a patent application or taking such other measures as Sponsor deems appropriate to establish and preserve its proprietary rights.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol.

15 REFERENCES

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16 APPENDICES

16.1 Appendix 1: ECOG Performance Status

ECOG	Characteristics
0	Normal activity
1	Symptoms of disease, but ambulatory and able to carry out activities of daily living
2	Out of bed more than 50% of the time, occasionally needs assistance
3	In bed more than 50% of the time, needs nursing care
4	Bed ridden, may need hospitalization

16.2 Appendix 2: Calculation of renal clearance

Patients 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)**

Patients 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/

16.3 Appendix 3: 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 **s**trong inducer decreases the AUC of a substrate for a given CYP by ≥ 80%.

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

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

1. Preparation-dependent

16.4 Appendix 4: Safety Monitoring Committee Composition and Charter

The study will be reviewed on an ongoing basis by an SMC composed of the principal clinical investigators (or a sub-investigator delegated by the principal investigator), the study PK specialist, Sponsor representatives and an independent medical expert in oncology drug development.

Name	Institution/Company	Position	Sponsor Representative
PPD	PPD	Coordinating Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Principal Investigator	NO
		Pharmacokineticist	NO
	OTD, Clichy, France	Medical Monitor	YES (CRO)
	Merck, USA	Medical Monitor	YES
	Merck, USA	Drug Safety	YES
	PPD	Independent Expert	NO

Curriculum vitae are provided in the Trial Master File.

Safety Monitoring Committee Charter

- The SMC will meet on a regular basis (physically or through teleconference), every 8 weeks, as soon as possible after the full clinical data sets of a cohort of 3 patients over their first 21 days of treatment (cycle 1) have been collected. PK data from at least day 1 of these 3 patients must be available for the meeting.
- After examination of the clinical and PK data and discussion, the SMC will make any necessary decisions to ensure/improve patients' safety, and in particular the following:
  1. Validate DLTs
  2. Replace non-evaluable patients
  3. Proceed to the DL immediately above
  4. Add more patients at the same DL
  5. Stop dose escalation and expand a DL
  6. Decide on the regimen to be used for each tumor indication expansion cohort
  7. Add intermediate unplanned DLs
  8. Exploring additional doses and/or regimens (e.g., if the MTD is not reached at the highest dose)
  9. Recommend systematic premedication/supportive care for common toxicities
  10. Establish the MTD
  11. Discuss the relevance of the MTD for further studies taking into account on PK and PD results
  12. Recommend initiation of optional study parts (schedule optimization, cohort expansion, etc.)
- The minutes of the meetings will be written by the designed secretary (the Sponsor's safety officer by default) within a week, approved and signed by all attendees. The minutes of all meetings will be archived in the Trial Master File.
- In addition, the SMC could be met in case of exceptional circumstance, justifying immediate decision to ensure patients' safety. If it is not possible to hold a meeting or teleconference of the whole SMC, at least the Independent Expert will meet with the Sponsor's representatives.
- In addition, the Independent Expert will review all CIOMs forms released by the Safety Officer before they are sent to the Health Authorities, EC/IRB and investigators.

16.5 Appendix 5: Guidance for Potential Drug-Induced Liver Injury (DILI)

16.5.1 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.

16.5.2 Introduction

Hepatotoxicity is injury or damage to the liver that may be associated with impaired liver function (Navarro and Senior 2006). 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 (Björnsson and Olsson 2005). 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).

As stated in the United States Food and Drug Administration (FDA) "Guidance for Industry - Drug-Induced Liver Injury: Premarketing Clinical Evaluation"; 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) (Zimmerman 1978, 1999). This became known as "Hy's Law". This document describes the recommended process for monitoring and evaluation of patients 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 CRFs and complete pertinent adverse experience fields as outlined in the Data Entry Guidelines (DEGs).

16.5.3 Close Observation Recommendations

The following steps should be taken when a patient 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**.

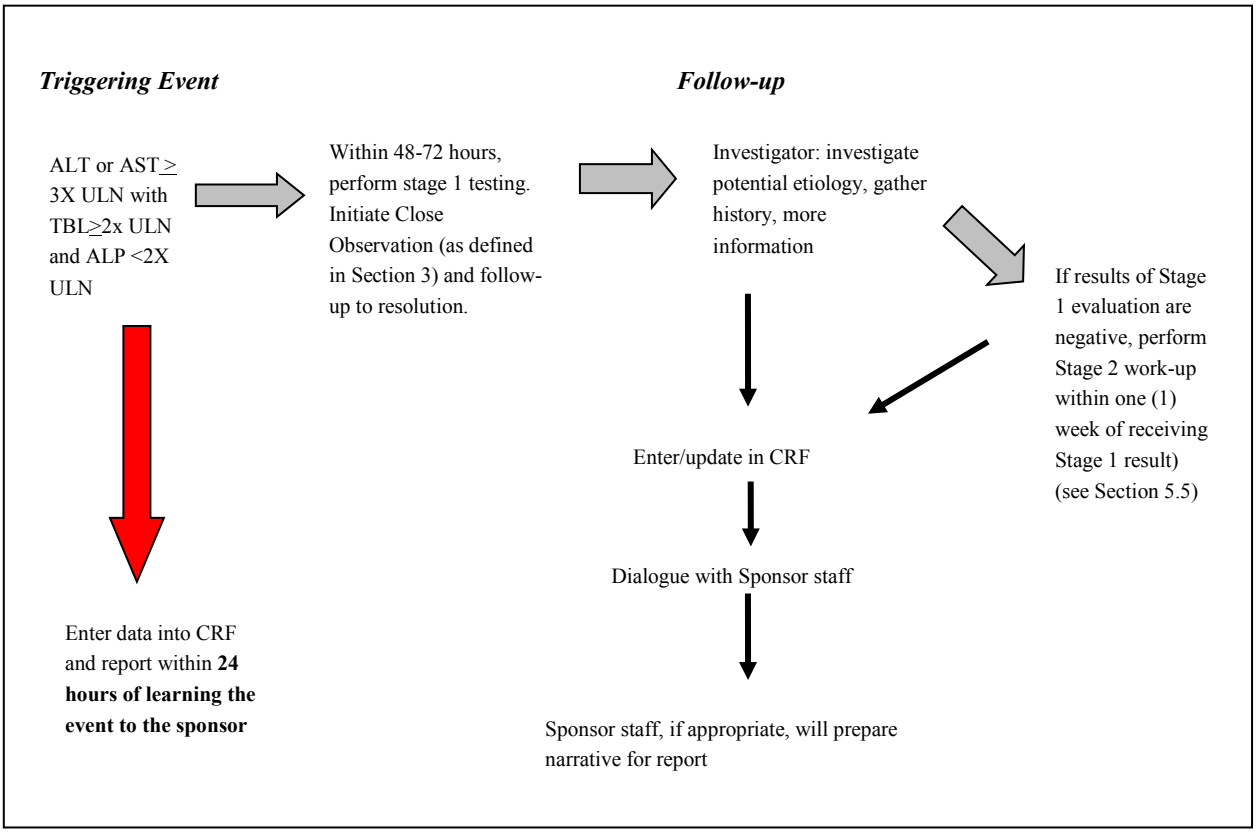
Close observation is defined as follows:

- 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 patient is asymptomatic.
    - For patients 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 16.5).
- 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 16.5 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 16.5.5 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.

16.5.4 Hepatic Assessment Flow Chart

Hepatic Assessment Flow Chart



16.5.5 Factors to Consider in Assessing Potential DILI

When there is a potential DILI, it is important to thoroughly assess the patient'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.

16.5.5.1 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 patient re-challenged with study medication?

16.5.5.2 Treatment

Record any concomitant treatments.

16.5.5.3 Signs and Symptoms (associated with the potential DILI event)

Does the patient have a concomitant illness? Does the patient currently exhibit signs or symptoms of hepatitis/DILI? What are the patient'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

16.5.5.4 Confounding Variables

What are the relevant medical history and findings? What is the differential diagnosis? What risk factors does the patient 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 patient 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
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

16.5.5.5 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 patient 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/ischemic 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 patient 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 patient 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.

16.5.5.6 Potential diagnosis

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

16.5.5.7 Overall clinical impression

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

16.5.5.8 Treatment plan

What is the plan for treatment and follow-up?

16.5.6 Contacts

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

- PPD (OTD)
- PPD (Merck)

16.5.7 References

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