

EORTC Network of Core Institutions (NOCI)

Cross-tumoral phase 2 clinical trial exploring crizotinib (PF-02341066) in patients with advanced tumors induced by causal alterations of ALK and/or MET ("CREATE")

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Protocol summary

Title of the Study	Cross-tumoral phase 2 clinical trial exploring crizotinib (PF-02341066) in patients with advanced tumors induced by causal alterations of ALK and/or MET ("CREATE")
Objective(s)	<p>Primary objective</p> <ul style="list-style-type: none"> ◆ To study the antitumor activity and safety of crizotinib across predefined tumor types in patients whose tumors are harboring specific alterations in ALK and/or MET <p>Secondary objectives</p> <ul style="list-style-type: none"> ◆ To study the specificity of the kinase inhibitor for tumors in all cohorts by explorative comparison of treatment results in patients with the same disease type with and without alterations in ALK and/or MET pathways (“ALK/MET+” and “ALK/MET-“sub-cohorts). ◆ To investigate sensitive and reliable methodologies for patient screening for such defects, to be potentially cross-validated and further developed by an accredited laboratory in later steps, based on prospectively collected biological material from this trial. ◆ To explore the potential value of selected biomarkers to study the pharmacological effects of crizotinib, to be used later in the context of future trials. ◆ To explore whether molecularly driven, high quality multi-tumor screening Phase 2 trials are feasible in a multi-institutional, multidisciplinary setting, when screening and treatment are performed by EORTC sites(+/- additional selected sites).
Methodology	<p>This is a biomarker-driven multi-tumor single agent Phase 2 trial. The study will assess the efficacy of crizotinib in a variety of tumors with specific alterations in either ALK and/or MET. The patient population will include patients with tumors harboring specific alterations leading to ALK and/or MET activation. The trial will also include patients with the same tumor types without specific ALK or MET alterations. The study population will comprise the following diagnoses:</p> <ol style="list-style-type: none"> 1. Anaplastic large cell lymphoma (ALCL; can be associated with ALK alterations) 2. Inflammatory myofibroblastic tumor (IMFT; can be associated with ALK alterations) 3. Papillary renal cell carcinoma type 1 (PRCC; can be associated with MET alterations) 4. Alveolar soft part sarcoma (ASPS; can be associated with MET alterations) 5. Clear cell sarcoma (CCSA; can be associated with MET alterations) 6. Alveolar rhabdomyosarcoma (ARMS; can be associated with MET and ALK alterations)

<p>Number of patients</p> <p>Number planned (Statistical design)</p> <p>Number analyzed</p>	<p>The study will comprise six tumor-specific cohorts, with two sub-cohorts per tumor type: those with and those without specific pathway alterations. If none of the stopping rules are met, a maximum of 35 eligible and evaluable patients for each of the 6 ALK/MET+ sub-cohorts will be treated but it will not be mandatory to complete the ALK/MET- sub-cohorts (see statistical methods).</p> <p>The number of patients who have to be screened in order to recruit 35 eligible and evaluable patients in the ALK/MET+ sub-cohort depends on the prevalence of the according pathway alterations. In any case, a maximum of 70 eligible and evaluable patients per cohort will be enrolled.</p>
<p>Diagnosis and main criteria for inclusion</p>	<p>Patient enrollment will follow a three steps procedure. Subjects must meet all of the following criteria to be eligible for molecular screening, clinical screening and active enrollment into the trial. Both the general inclusion criteria and the tumor-specific selection criteria must be met to enter a patient.</p> <p>The following criteria are a prerequisite for step 1 registration:</p> <ul style="list-style-type: none"> ◆ Local diagnosis of locally advanced and/or metastatic malignant tumor (anaplastic large cell lymphoma, inflammatory myofibroblastic tumor, papillary renal cell carcinoma type 1, alveolar soft part sarcoma, clear cell sarcoma or alveolar rhabdomyosarcoma) deemed incurable by conventional surgery, radiotherapy, systemic therapy or any other means. Medical history and previous treatment need to meet the disease specific inclusion criteria (3.2). Proven presence of specific ALK and/or MET pathway alteration in tumor tissue is <u>not</u> mandatory for patient registration. ◆ Mandatory availability for shipment of formalin-fixed, paraffin-embedded, tumor-containing, tissue blocks from primary tumor and/or metastatic site. Slides are not accepted. Information on previous histopathology reports and previous molecular analysis will be entered in an electronic CRF, to accompany the tissue samples. ◆ Before patient registration, written informed consent for central collection of tissue block and any other trial-specific procedures must be obtained from the patient according to ICH/GCP, and national/local regulations, allowing for collection storage and analysis of tissue and screening procedures. <p>Histopathology central confirmation for step 2:</p> <ul style="list-style-type: none"> ◆ Confirmation of receipt of tissue block and accompanying required local information, and confirmation that tissue block contains tumor tissue (quality assurance) by central biorepository through EORTC, as well as central pathology confirmation, are required before starting the patient screening (step 3) according to chapter 6.4. <p>All the other inclusion criteria must be met for step 3 enrollment:</p> <ul style="list-style-type: none"> ◆ Measurable disease according to RECIST 1.1 with target lesion of at least 20 mm (or 10 mm on spiral CT scans) and presence of at least one RECIST-measurable lesion outside of a previously radiated field or

	<p>potential palliative irradiation fields.</p> <ul style="list-style-type: none"> ◆ No malignant meningitis or leptomeningeal disease. ◆ Patients with brain metastases are eligible if treated and/or neurologically stable with no ongoing requirement for corticosteroids (off steroids for at least 2 weeks) and not taking contraindicated medications as specified in section 5.6. Absence of spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function. ◆ Any previous systemic anticancer therapy must have been completed at least 4 weeks prior to initiation of study medication. ◆ No treatment with any other investigational drug within the past 4 weeks or within less than 4 half-life times of the investigational drug before treatment with crizotinib (whatever is the longest period). ◆ No prior therapy directly targeting ALK and/or MET, no previous treatment with crizotinib. ◆ Major surgery must have been completed at least 4 weeks prior to initiation of study medication. ◆ Prior palliative radiotherapy must have been completed at least 24 hrs prior to initiation of study medication, and minor surgical procedures must have been completed at least two weeks prior to the initiation of study medication. ◆ Minimum age ≥ 1 year, no upper age limit. ◆ Eastern Cooperative Oncology Group (ECOG) performance status 0-2, or Lansky play scale ≥ 50 for children aged 1 to 12 yo. (Appendix G). ◆ No other previous and active malignancy for the last three years with the exception of non-melanoma skin cancer, localized cervical cancer, localized and presumably cured prostate cancer or adequately treated basal or squamous cell skin carcinoma. ◆ Adequate hematological function: ANC $\geq 1 \times 10^9/L$, platelets $\geq 30 \times 10^9/L$ and hemoglobin ≥ 8 g/dL. <ul style="list-style-type: none"> ◆ Adequate renal function <ul style="list-style-type: none"> ◆ For patients up to 21 years old: <p>The Schwartz formula should be used for Clearance Creatinine [mL/min/1.73 m²= F x Height (cm) x 88.4/creatinine (blood) in $\mu\text{mol/L}$. ClCr of 80-140 mL/min/1.73 m² is considered as normal range</p> <ul style="list-style-type: none"> - F= 0.55 for boys 1-15 yo - F= 0.70 for boys 16-21 yo - F= 0.55 for girls 1-21 yo ◆ For patients 21 years or older: serum creatinine $\leq 2 \times \text{ULN}$. ◆ Adequate liver function: Bilirubin $\leq 1.5 \times \text{ULN}$ unless due to Gilbert's syndrome (status of the disease documented by repeated laboratory values
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	<p>with slight increase in bilirubin without any other known causes). AST and ALT $\leq 2.5 \times$ ULN in the absence of liver metastases and $\leq 5 \times$ UNL if liver function abnormalities are due to the underlying malignancy.</p> <ul style="list-style-type: none"> ◆ No laboratory abnormalities that would impart, in the judgment of the investigator and/or sponsor, excess risk associated with study participation or study drug administration, and which would, therefore, make the patient inappropriate for entry into this trial. ◆ All related adverse events from previous therapies must have recovered to \leq Grade 1 (except alopecia). No persistence of adverse events from prior anti-cancer therapy deemed clinically relevant. ◆ No acute or chronic severe gastrointestinal conditions such as diarrhea or ulcer. Clinically normal cardiac function based on the institutional lower limit of normal LVEF (assessed by MUGA or ECHO) and normal 12 lead ECG. ◆ Within the three months prior to starting study treatment, no myocardial infarction, no severe/unstable angina, no coronary/peripheral artery bypass graft, congestive heart failure or cerebrovascular accident including transient ischemic attack. ◆ No ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥ 2. ◆ No uncontrolled atrial fibrillation of any grade. ◆ Machine-read ECG with QTcF interval ≤ 470 msec. Note: crizotinib should be avoided in patients with congenital long QT syndrome ◆ No history of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis. ◆ No concurrent use of drugs or foods that are known strong CYP3A4 inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice (refer to section 5.6). The topical use of these medications (if appropriate), such as 2% ketoconazole cream, may be allowed. ◆ No concurrent use of drugs that are known potent CYP3A4 inducers, within 12 days prior to first dose of crizotinib including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort (refer to section 5.6). ◆ No use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to pimozide, dihydroergotamine, ergotamine, astemizole, cisapride, and terfenadine (refer to section 5.6). ◆ No other severe acute or chronic medical conditions including severe gastrointestinal conditions such as diarrhea or ulcer) or psychiatric conditions or end stage renal disease on hemodialysis or laboratory abnormalities that would impact, in the judgment of the investigator
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	<p>and/or sponsor, excess risk associated with study participation or study drug administration, and which would, therefore, make the patient inappropriate for study entry.</p> <ul style="list-style-type: none"> ◆ Women of child bearing potential (WOCBP) must have a negative serum pregnancy test prior to the first dose of study treatment. ◆ All patients (male and female) of childbearing/reproductive potential must use adequate birth control measures during the study treatment period and for at least three months after the last study treatment (effective contraception methods are implants, injectable, combined oral contraceptives, IUDs, sexual abstinence and vasectomised partners for female patients). ◆ Female subjects who are breast feeding should discontinue nursing prior to the first dose of study treatment and until three months after the last study treatment. ◆ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial. <p>Disease specific inclusion criteria for patients with anaplastic large cell lymphoma (ALCL)</p> <ul style="list-style-type: none"> ◆ Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or advanced disease. ◆ Patient must have received previous systemic chemotherapy (usually a CHOP-like multidrug combination, if not medically contraindicated, with or without monoclonal antibodies), and may not qualify for further conventional therapy with curative intent. ◆ No pretreatment limitations (including autologous or allogeneic stem cell- or bone marrow transplantation), provided all other patient selection criteria are met. <p>Disease-specific inclusion criteria for patients with inflammatory myofibroblastic tumor (IMFT)</p> <ul style="list-style-type: none"> ◆ Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or metastatic disease. ◆ No mandatory pretreatment. ◆ No pretreatment limitations, provided all other patient selection criteria are met. <p>Disease-specific inclusion criteria for patients with papillary renal cell carcinoma type 1 (PRCC)</p> <ul style="list-style-type: none"> ◆ Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or metastatic disease. ◆ No mandatory pretreatment. ◆ No pretreatment limitations, provided all other patient selection criteria are met.
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<p>Criteria for evaluation</p> <p>Efficacy</p> <p>Safety</p>	<p>Primary endpoint</p> <ul style="list-style-type: none"> ◆ Response rate documented by RECIST 1.1 (with response confirmation) <p>Secondary endpoints</p> <ul style="list-style-type: none"> ◆ Safety (CTAE v 4.0) ◆ Progression free survival ◆ Disease control rate ◆ Overall survival ◆ Duration of response ◆ Correlative research endpoints <p>Adverse events, concomitant medications and laboratory tests</p>
<p>Statistical methods</p>	<p>This study has six cohorts and each cohort has two sub-cohorts: ALK/MET+ and ALK/MET- patients.</p> <p>For each sub-cohort a Simon's optimal two stage design will be implemented. The maximum response probability of an ineffective treatment is $P_0=0.1$, and the minimum response probability of an effective treatment is $P_1=0.3$. The Null Hypothesis (H_0) of this design is: the true response probability of the new treatment is 0.1 or lower. The Alternative Hypothesis is: The true response probability is greater than 0.1. The design is powered to detect a difference of 0.2 (i.e., 0.1 vs. 0.3). Alpha and Beta are 10%.</p> <p>In each sub-cohort, a maximum of 35 eligible and evaluable patients will be treated.</p> <p>For the stage I, 12 eligible and evaluable patients are needed per sub-cohort. If at least 2 patients respond (RECIST 1.1 confirmed CR or PR), the sub-cohort goes into the stage II. For the stage II, a maximum of 35 eligible and evaluable patients per sub-cohort (including the 12 patients from stage I) are enrolled and treated. If at least 6 patients respond, the treatment is deemed successful, otherwise not. The trial will have one result for each of the six sub-cohorts with ALK/MET+ screening. For the ALK/MET- sub-cohorts, if 35 eligible and evaluable patients are recruited, the same criteria as for the ALK/MET+ sub-cohorts will apply.</p> <p>Patient accrual will not be suspended for the stage I analysis. Excess patients enrolled above the total number of 12 are counted as part of stage II.</p> <p>Details about decision rule to be taken for stage I / stage II analysis according to the accrual rate are provided in the statistical consideration section. In addition, an early stopping rule for low prevalence of ALK/MET+ is implemented.</p>

Translational research	Key objectives of the translational research are: <ul style="list-style-type: none">◆ Identification and characterization of the ALK and/or MET status and pathway activation in the different patient cohorts and sub-cohorts of this trial.◆ Explorative correlation of specific molecular changes in tissue and serum that can potentially be used as predictive markers of response to crizotinib. This would potentially allow in the future a better definition of the most sensitive patient population for crizotinib.◆ Development and partial validation of reliable assays for future routine usage.
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1 Background and introduction

1.1 Relevance of ALK/MET inhibition as a step towards personalized cancer care in selected malignancies

1.1.1 Anaplastic large cell lymphoma (ALCL)

ALCL is a rare variant of Non-Hodgkin's lymphoma associated with ALK alterations in 80-90% of cases diagnosed in adolescents and young adults. Stein and Lennert identified in 1985 a unique large cell lymphoma with anaplastic cytology, an unusual sinus growth pattern, and strong expression of the antigen Ki-1. Subsequently, Ki-1 was identified as an activation antigen (now designated CD30) and a member of the tumor necrosis factor receptor family. In the late 1980s and early 1990s, a recurrent chromosomal translocation t(2;5) was described. In 1994, the translocation was cloned and was found to involve a receptor tyrosine kinase called anaplastic lymphoma kinase (ALK) on 2p23 and nucleophosmin (NPM) on 5q35.

Because ALK is not normally expressed in lymphoid tissue, anti-ALK antibodies can be used as a surrogate method for detecting t(2;5). After widespread immunohistochemical analysis with anti-ALK antibodies, ALK+ ALCL was defined as a specific entity that typically affects children and young adults and has a morphologic spectrum that includes small cell and lymphohistiocytic variants. Currently, three distinct T-cell tumors (ALK+ ALCL, ALK- ALCL and primary cutaneous ALCL) are described in the 2008 World Health Organization (WHO) classification. Molecular diagnostics are routinely used to establish this diagnosis.

Patients with ALK+ ALCL generally have a good prognosis with a 77% overall 5-year survival rate. ALK+ ALCLs are known to be highly responsive to cytotoxic drugs. However, relapses occur and require salvage therapy (Ref. 1). Only experimental treatments are available for patients failing standard therapy. Gambacorti-Passerini et al. (Ref. 2) recently reported the treatment results of two patients with relapsed ALK+ ALCL with the ALK/MET inhibitor crizotinib given at a dose of 250 mg twice daily. They observed clinical, radiological and metabolic responses to the experimental agent.

1.1.2 Inflammatory myofibroblastic tumor (IMFT)

IMFT is a distinctive mesenchymal neoplasm characterized by a spindle-cell proliferation with an inflammatory infiltrate. These tumors occur primarily during the first two decades of life and typically arise in the lung, retroperitoneum, or abdominopelvic region. Abdominal tumors may be multifocal. Lesional cells are predominantly myofibroblasts in a myxoid to collagenous stroma admixed with inflammatory cells. Local recurrence may occur after initial surgery, with a low risk of distant metastases, so that IMFTs are considered to be soft tissue tumors of intermediate biologic potential, with only a small fraction behaving aggressively.

Rearrangements involving the ALK locus on chromosome 2p23 have been documented in approximately 50% of IMFTs. ALK aneuploidy has also been described, with a gain in copy number without rearrangement. Among cancers with rearrangement, several fusion partners have been identified that serve to constitutively activate ALK. ALK expression reliably correlates with ALK rearrangement. Distant metastasis occurs primarily in ALK-negative IMFTs, but local recurrence occurs regardless of ALK expression.

The role of chemotherapy in advanced IMFT is poorly defined. Several ALK fusion proteins are found in IMFT and induce transformation in cell lines and animal models, a finding that suggests that ALK rearrangement may define a subgroup of IMFTs that is sensitive to targeted kinase inhibition. Two patients with IMFT were enrolled in the dose-escalation Phase 1 trial of crizotinib. In 2010 Butrynski et al. reported a first sustained partial response (PR) to crizotinib in a patient with ALK-translocated IMFT, as compared with no observed activity in another patient without ALK translocation (Ref. 3).

1.1.3 Papillary renal cell carcinoma type 1 (PRCC)

PRCC occurs in sporadic and hereditary forms, accounting for 10 to 15% of carcinomas of the renal tubular epithelium. Current classification of a renal tumor as PRCC requires a minimum of 75% papillary or tubulopapillary architecture. Delahunt and Eble proposed a subclassification of PRCCs into type 1 and type 2 tumors, based on histological features.

Type 1 tumors consist of papillae and tubular structures covered by small cells with scant pale cytoplasm and small nuclei, whereas type 2 tumors are characterized by papillae covered by large cells with abundant eosinophilic cytoplasm and large spherical nuclei with prominent nucleoli. These categories correspond to the chromophil basophilic and chromophil eosinophilic carcinoma subtypes, respectively, described by previous classifications. Type 1 tumors have been shown to express cytokeratin 7 more frequently than type 2 tumors. Preliminary data suggests there are clinical differences as well as prognostic utility to the division of PRCC into type 1 and type 2 categories.

Recent molecular analysis identified missense mutations in the tyrosine kinase domain of the MET proto-oncogene (7q31.1-34) in hereditary and 5 to 13% of sporadic PRCCs. These mutant MET genes cause ligand-independent constitutive phosphorylation of the MET protein and induce transformation in the NIH 3T3 cell assay. The commonly observed tri- or polysomy 7 results in non random duplication of the mutant MET. Lubensky and colleagues have shown MET mutations occur exclusively in type 1 tumors (Ref. 4). Selective duplications of chromosome 7 regions, distinct from the MET locus, have also been described in some sporadic PRCCs.

In contrast with the more common clear cell renal cell carcinomas, PRCC is not sensitive to classic immunotherapy. PRCC patients have not been included in the more recent renal cell carcinoma registration trials with drugs such as sunitinib, sorafenib, pazopanib, everolimus or bevacizumab/interferon. The role of targeted agents in advanced or metastatic PRCC is at present unknown. A standard treatment for such tumors is not established (Ref. 5).

1.1.4 Alveolar soft part sarcoma (ASPS)

ASPS is a clinically and morphologically distinct soft tissue sarcoma first defined and named by Christopherson et al. in 1952. It is an uncommon tumor and uniformly malignant. Its frequency is estimated at 0.5 to 1% of all soft tissue sarcomas and it occurs principally in adolescents and young adults. There are two main locations of the tumor. When it occurs in adults, it is predominantly in the lower extremities, although it has been described in a variety of unusual locations, including the female genital tract, mediastinum, breast, urinary bladder, gastrointestinal tract, and bone. When the tumor affects infants and children, it is often located in the head and neck region, especially the orbit and tongue. ASPS usually presents as a slowly growing, painless mass.

Because of the relative lack of symptoms, in a number of cases, metastases to the lung or brain are the first clinical manifestation of the disease. Local relapse after complete resection is unusual, but metastases can occur even decades after resection of the primary tumor, despite the absence of local recurrence. As a rule, ASPS is a highly vascular tumor.

ASPS is characterized by the presence of a specific chromosomal translocation encoding the chimeric transcription factor (ASPL-TFE3) that activates expression of MET. A recent series of 8 patients revealed that all cases showed reactivity on immunohistochemistry for TFE3 and 75% MET positivity with a strong association between TFE3 expression and MET positivity. The high expression of MET in ASPL-TFE3 (+) ASPs supports the potential role of targeted agents against MET in this rare and very chemoresistant tumor. (Ref. 6, Ref. 7)

1.1.5 Clear cell sarcoma (CCSA)

CCSA is an aggressive soft tissue sarcoma that typically develops in the tendons and aponeuroses of children and young adults. A high rate of local and distant recurrence results in a 5 year overall survival of only 50%. Five year survival decreases to 20% for metastatic disease, consistent with the tumor's profound resistance to conventional chemotherapy and radiation therapy.

Molecularly, CCSA is characterized by the t(12;22)(q13;12) translocation which results in fusion of the Ewing sarcoma gene EWS with the cAMP-regulated transcription factor ATF1, a member of the CREB family. Gene fusion replaces the kinase dependent regulatory region of ATF1 with the amino terminal domain of EWS. By preserving the DNA binding and heterodimerization domains of ATF1, this chimera yields an oncoprotein capable of deregulating transcription of CRE regulated genes. The melanocyte master transcription factor (MITF) is a direct transcriptional target of EWS-ATF1. EWS-ATF1 mimics the Melanocyte Stimulating Hormone/CREB signaling pathway to directly and aberrantly activate MITF expression. MITF directly activates the MET gene. MET is also a transcriptional target of the ASPSCR1-TFE3 fusion, as predicted by the strong homology between TFE3 and MITF. MET normally mediates signaling from hepatocyte growth factor/scatter factor (HGF/SF) typically expressed by stromal and mesenchymal cells. MET signaling has been implicated in a wide range of biological activities including proliferation, survival and motility all of which are frequently dysregulated in cancer, including this rare entity. Davis et al. demonstrated that CCSA and tumor derived cell lines express MET that is activated in an autocrine fashion by HGF expression in some CCSA cell lines. MET expression is critical for CCSA invasion, chemotaxis and survival. The use of specific MET inhibitors or neutralizing antibodies against HGF significantly reduces CCSA growth in culture and in an autocrine xenograft model of CCSA (Ref. 8).

1.1.6 Alveolar rhabdomyosarcoma (ARMS)

Rhabdomyosarcoma is the most common soft tissue sarcoma in childhood and does also occur in adults. Although the precise cell type from which the tumor originates is still a matter of debate, the evidence points towards the myogenic lineage. Rhabdomyosarcoma expresses a variety of markers typical of both embryonic and mature skeletal muscle. A widely employed histologic classification of rhabdomyosarcomas defines three subtypes, differing from each other for body location, occurrence, mean patient age, and prognosis. The alveolar subtype (ARMS) typically consists of small round densely packed cells, resembling pulmonary alveoli, and it occurs more often in the trunk and extremities. Expression profiling of different subtypes of rhabdomyosarcomas has revealed that their two signatures differ widely.

Alveolar histology is an independent predictor of poor clinical outcome: a 5-year survival rate of <30% has been reported in children with metastatic ARMS. The most relevant feature of this subtype is the presence of one of two possible chromosomal translocations, t(2;13)(q35;q14) and t(1;13)(p36;q14), which result in expression of the chimeric PAX3-FKHR and PAX7-FKHR transcription factors, respectively. The PAX3/PAX7-FKHR translocations yield fusion proteins which are thought to have enhanced transcriptional activity. They consist of the DNA binding domain of PAX3 or PAX7 linked to the transactivation domain of the FKHR transcription factor. Both PAX3 and PAX7 are involved in skeletal muscle development. PAX3 is a key regulator of myogenesis, whereas PAX7 is the master gene of satellite cell specification. In myogenic precursors, PAX3 activates transcription of several target genes, among which myoD, lady-bird, and MET.

MET is highly expressed in ARMS cell lines established from human tumors and HGF/SF promotes their motility and resistance to chemotherapy. Consistently, MET is up-regulated in murine models of ARMS. Under experimental conditions, MET down-regulation affects the proliferation, survival, invasiveness, and anchorage-independent growth in ARMS cells. Induction of MET-directed shRNA promotes a dramatic reduction of tumor mass in ARMS xenograft models. ARMS-derived cell lines are known to be "addicted" to the MET oncogene, suggesting that MET may represent a target of choice to develop novel therapeutic strategies for this tumor type (Ref. 9).

In addition to the role of MET, ALK seems to have importance in ARMS as well. Immunohistochemical staining for ALK has been observed in ARMS. Previous studies have yielded conflicting results regarding the pattern of staining (nuclear versus cytoplasmic), and there has been no correlation with PAX3–7/FKHR fusion status. In a series of 30 cases of ARMS, ALK staining was positive in 53% of patients. Of 21 ARMS cases with PAX3-FKHR fusion, 10 of 21 (48%) were positive for ALK staining; of 6 ARMS cases with PAX7-FKHR fusion, 3 of 6 (50%) were positive. Among 6 ALK-positive ARMS studied by break-apart FISH for the ALK locus, there was no evidence of a translocation; one case had ALK amplification and two had low-level gains of the ALK gene. ALK is thus overexpressed in ARMS, most likely independent of fusion status. Amplification or upregulation of ALK may underlie ALK protein overexpression (Ref. 10).

1.2 Crizotinib (PF-02341066): mode of action

Crizotinib is a competitive small-molecule inhibitor of the ALK and MET/HGF receptor tyrosine kinases. The rationale for use of this mechanism to treat cancer is supported by an emerging paradigm in oncology that robust clinical efficacy can be obtained with well-tolerated inhibitors directed towards oncogenic tyrosine kinases that are altered through activating mutations, gene translocations, gene amplification, or other mechanisms of pathway activation. Prominent examples include imatinib mesylate in gastrointestinal stromal tumors with mutant c-Kit or chronic myelogenous leukemia with BCR-Abl gene translocations, erlotinib in non-small cell lung cancer (NSCLC) with mutant EGFR, trastuzumab in breast cancers with amplified HER-2/neu, and sunitinib targeting the VHL-dependent VEGF pathway in renal cell carcinoma.

Crizotinib demonstrated potent activity against NPM-ALK, an oncogenic fusion protein variant of the ALK, which results from a chromosomal translocation which is implicated in the pathogenesis of ALCL. Consistent with its predicted mechanism of action, crizotinib inhibited target-dependent tumor cell proliferation or invasion, induced tumor cell apoptosis, and inhibited angiogenesis in nonclinical tumor models. Oral administration of crizotinib had marked cytoreductive antitumor activity in several tumor models that expressed activated MET/HGFR or NPM-ALK. The collective rationale for investigation of crizotinib in clinical studies is built on alteration of its molecular targets, its predicted ability to target multiple processes that are common to cancer progression, and preclinical efficacy data.

1.3 Crizotinib: preclinical and clinical pharmacokinetic data

Extensive PK/toxicokinetic, distribution, metabolism, and excretion studies with crizotinib were completed in the rat and dog, with additional studies in the mouse, rabbit, and monkey. The results showed that the PK of crizotinib was similar across species and sufficient oral exposure was achieved for pharmacology and toxicology evaluation. Tissue distribution studies in rats indicated that crizotinib radioequivalents were widely distributed, did not cross the blood brain barrier, and had a prominent, but reversible, affinity for pigmented tissues containing melanin. Mass balance studies conducted in rats, dogs, and humans showed that drug-related material was excreted mainly in the feces and to a lesser extent in urine. Negligible amounts of unchanged crizotinib were found in the urine of all species, indicating that hepatic elimination is the primary clearance pathway for crizotinib.

The long-lived radioactivity in rat tissues and human plasma, and the incomplete extraction recovery of total radioactivity from human plasma, suggest the potential for some degree of binding of crizotinib-derived radioactivity to plasma proteins and/or tissue macromolecules. In mass balance studies, recovery of total radioactivity was on average >85% across species, indicating that any apparent binding to macromolecules would comprise only a small fraction of the total crizotinib dose.

The major metabolic pathways in humans were oxidation of the piperidine ring to crizotinib lactam and O-dealkylation, with subsequent Phase 2 conjugation of O-desalkyl metabolites. Qualitatively, the metabolism of crizotinib in rats was representative of that observed in humans. No disproportionate human metabolites were observed in circulation where the exposure markedly exceeded that determined in at least one nonclinical species.

In vitro studies demonstrated that cytochrome P450 (CYP) 3A4/5 were major enzymes involved in the metabolism of crizotinib and results from clinical drug-drug interaction studies with ketoconazole and rifampin confirmed this role *in vivo*. Crizotinib was shown *in vitro* to be a time-dependent inhibitor of CYP2B6 and CYP3A. Results from a clinical drug-drug interaction assessment in patients with cancer orally administered midazolam confirmed that crizotinib inhibits CYP3A *in vivo*. Crizotinib may increase plasma concentrations of drugs predominantly cleared by CYP2B6 based on these *in vitro* findings. It was also shown that crizotinib was a substrate for the efflux transporter P-glycoprotein (P-gp); however, P-gp was not expected to interfere with oral absorption to a significant extent at therapeutic doses. Crizotinib is an inhibitor of P-gp *in vitro* and may have the potential to increase plasma concentrations of co-administered drugs that are substrates of P-gp. Interactions resulting from crizotinib-mediated induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4 or inhibition of the hepatic uptake transporters, organic anion transporting polypeptides (OATP) 1B1 or 1B3 are unlikely based on *in vitro* findings.

In vitro studies showed the potential for crizotinib to inhibit CYP3A and P-gp. A clinical drug interaction assessment in cancer patients who orally received midazolam confirmed that crizotinib was a moderate CYP3A inhibitor. Repeat-dose toxicology studies up to 3 months in duration have been completed. In rats, the principal toxicities of crizotinib involved the bone marrow, testes, and bone. These toxicities were observed as bone marrow hypocellularity that affected both the myeloid and erythroid lineages, degeneration of pachytene spermatocytes in the testes, and a decrease in bone at the primary spongiosa. The primary effects observed in dogs were emesis and diarrhea, eosinophilia, and decreased cellularity of the thymus. An elevation of liver enzymes without a histologic correlate was observed in both the rat and dog. The no-observed-adverse-effect levels (NOAELs) in the 3-month studies were 30 mg/kg/day (males)/50 mg/kg/day (females) in the rat and 25 mg/kg/day in the dog, with associated AUC(0-24) values of 14.3/10.1 $\mu\text{g}\cdot\text{h}/\text{mL}$ and 34.6 $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively. Additionally, crizotinib was shown to affect retinal function in a rat electroretinography study, and an effect on embryofetal development was demonstrated in the rat and rabbit. In an assessment of secondary pharmacodynamics, crizotinib demonstrated functional antagonism for 5-HT_{4e} and 5-HT₇ serotonin and α_{1a} adrenergic receptors, and inhibition of dopamine and serotonin transporters with Kb or IC₅₀ values ≥ 40.7 nM. *In vitro* safety pharmacology studies identified crizotinib as a mixed-channel blocker (calcium channel antagonist) with human ether-a-go-go-related gene (hERG) potassium channel IC₅₀ and IC₂₀ values of 1.1 μM and 0.3 μM , respectively.

The cardiovascular evaluation in anesthetized dogs indicated that crizotinib also has the potential to cause hemodynamic changes, observed as decreases in heart rate and diastolic blood pressure, and decreased myocardial contractility. Crizotinib was aneugenic in genetic toxicology testing, and was identified with probable phototoxicity potential *in vitro*.

After oral administration of a single 250 mg dose in patients, crizotinib peak concentration was achieved at a median T_{max} of 4 hours, then declined in a multi-exponential manner with a mean terminal half-life of 42 hours. A radiolabeled mass balance study indicated that 63% and 22% of the administered dose was

recovered in feces and urine, respectively. Crizotinib was moderately bioavailable after oral administration (F_{oral} = 43%).

Following oral administration of crizotinib 250 mg BID, steady state was reached within 15 days and remained stable. The geometric mean values of steady-state trough concentrations (C_{trough, ss, mean}) ranged from 263 to 316 ng/mL for crizotinib, exceeding the target efficacious concentrations for ALK, c-Met/HGFR or ROS1 inhibition. Crizotinib may be taken with or without food, as a standard high-fat meal reduced crizotinib systemic exposure by only 14%.

Starting dose adjustment is not required when crizotinib is co-administered with agents that increase gastric pH (such as PPIs, H₂ antagonists, or antacids). Crizotinib is a substrate and inhibitor of CYP3A that appeared to exhibit non-linear PK as reflected by a 40% decrease in apparent clearance (CL/F) observed with multiple dosing. Co-administration of 200 mg ketoconazole BID, a strong CYP3A inhibitor, with a single 150 mg crizotinib dose increased the mean AUC by approximately 3.2-fold compared to crizotinib alone. At a dose of 250 mg BID administered to patients for 28 days, co-administration of rifampin (600 mg QD), a strong CYP3A inducer, decreased steady-state AUC_{tau} and maximum plasma concentration (C_{max}) of crizotinib by 84% and 79%, respectively, compared to crizotinib treatment alone. Crizotinib has been identified as a moderate inhibitor of CYP3A both in vitro and in vivo. Administration of 250 mg crizotinib BID for 28 days resulted in a mean oral midazolam AUC that was 3.7-fold that observed when crizotinib was administered alone.

An exploratory population PK analysis in 250 patients indicated that body weight (50-110 kg), gender, age, and race did not have noteworthy effects on steady state crizotinib exposure. However, the observed steady-state drug exposure in Asian patients was significantly higher than that seen in non-Asian patients.

Starting dose adjustment is not required for patients with mild ($60 \leq$ creatinine clearance <90 mL/min) and moderate ($30 \leq$ creatinine clearance <60 mL/min) renal impairment, since no clinically meaningful changes in steady-state crizotinib plasma through concentrations were observed in single arm studies.

After a single 250 mg dose in patients with severe renal impairment (creatinine clearance < 30 mL/min) not requiring peritoneal dialysis or hemodialysis, crizotinib significantly increased AUC and C_{max} compared to those with normal renal function. An adjustment of the dose of crizotinib to 250 mg taken orally once daily is recommended when administering crizotinib to patients with severe renal impairment not requiring peritoneal dialysis or hemodialysis.

1.4 Crizotinib: clinical safety data from ongoing or completed studies

Note for investigators: This summary reflects the information from the most recent investigator's brochure at the date of issue of this protocol. Investigator's brochures are updated yearly and the knowledge is evolving rapidly. The protocol will not be amended for that reason unless new information requires changes in the conduct of the study. Important safety information will be distributed in an ongoing fashion through safety alerts or other means by the pharmacovigilance unit of EORTC or Pfizer.

The primary Cycle 1 dose-limiting toxicity (DLT) observed in the Phase 1 study of single-agent crizotinib was fatigue, with a maximum tolerated dose (MTD) of crizotinib on a BID schedule determined to be 250 mg. The primary Cycle 1 DLTs observed on QD regimen were nausea and vomiting with an MTD of crizotinib determined to be 650 mg QD. The primary Cycle 1 DLTs observed in the Phase 1 studies of crizotinib in combination with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) were Dry eye syndrome and gastrointestinal disorders, with an MTD of crizotinib determined to be 150 mg BID in combination with erlotinib 100 mg QD. The DLTs observed in the Phase 1 study of crizotinib in combination with dacomitinib, an EGFR TKI, were diarrhoea, alanine aminotransferase (ALT) increased, and mucositis, with an MTD determined to be 200 mg BID in combination with dacomitinib 30 mg QD. In

combination with axitinib, a vascular endothelial growth factor receptor (VEGFR) TKI, on Cycle 2 Day 1, at the end of the DLT observation period, 1 DLT of LFT increase was reported in a patient on 250 mg crizotinib and 5 mg axitinib. The MTD was determined to be crizotinib at 250 mg BID in combination with axitinib at 5 mg BID.

Among 2071 patients with advanced non-small cell lung cancer (NSCLC) treated with single-agent crizotinib 250 mg BID, a total of 96 (5.2%) permanently discontinued crizotinib. The most commonly reported treatment-related adverse events (AEs) of any severity grade (experienced by at least 20% of patients) in decreasing frequency were VISION DISORDER*, diarrhea, nausea, vomiting, OEDEMA*, ELEVATED TRANSAMINASES*, constipation and NEUTROPENIA*.

The most common Grade 3 treatment-related AEs ($\geq 5\%$) were NEUTROPENIA* and ELEVATED TRANSAMINASES*. The most common treatment-related Grade 4 AEs ($\geq 1\%$) were NEUTROPENIA* and ELEVATED TRANSAMINASES*. Grade 5 treatment-related AEs were INTERSTITIAL LUNG DISEASE*, death, pneumonia, HEPATOTOXICITY* and lung infection.

Among the 172 patients with NSCLC treated with single-agent crizotinib 250 mg BID in a randomized Phase 3 study comparing crizotinib to standard of care chemotherapy (pemetrexed or docetaxel), 164 had treatment-related AEs during the study. The most common crizotinib-related AEs (reported in $\geq 20\%$ of patients) of any severity were VISION DISORDER*, diarrhea, nausea, vomiting, ELEVATED TRANSAMINASES*, constipation, EDEMA*, NEUTROPENIA*, dysgeusia, decreased appetite, and LEUKOPENIA*. Three (3) patients had Grade 5 treatment-related AEs (INTERSTITIAL LUNG DISEASE*, 2 patients; arrhythmia, 1 patient).

The safety profile observed for 159 patients with tumor types other than NSCLC treated with single-agent crizotinib 250 mg BID was similar to that of patients with advanced NSCLC. The most common treatment-related AEs (reported in $\geq 20\%$ of patients) of any severity grade were nausea, VISION DISORDER*, vomiting, diarrhea, and fatigue. There were 2 Grade 5 treatment-related AEs (INTERSTITIAL LUNG DISEASE* and cerebral infarction, 1 patient each).

Among the 93 patients with advanced NSCLC treated with crizotinib in combination with an EGFR TKI, (erlotinib or dacomitinib), the most commonly reported treatment-related AEs (reported in $\geq 30\%$ of patients) of any severity grade were diarrhea, nausea, fatigue, decreased appetite, vomiting and EDEMA. Diarrhea (7.5%) was the most commonly reported Grade 3 event. PULMONARY EMBOLISM*, INTERSTITIAL LUNG DISEASE, and hyperuricemia (1 patient, 1.1% each) were the only reported Grade 4 treatment-related AEs. There were no Grade 5 treatment-related AEs reported.

A total of 32 of the 34 patients treated in the combination study of crizotinib with VEGFR TKI (axitinib) had treatment-related AEs. The most commonly reported treatment-related AEs (reported in $\geq 20\%$ of patients) of any severity in decreasing frequency were diarrhoea, nausea, vomiting, fatigue, decreased appetite, and ELEVATED TRANSAMINASES. The most commonly reported Grade 3 treatment-related AEs were ELEVATED TRANSAMINASES, diarrhoea, fatigue and hypertension. Grade 4 treatment-related events were diarrhoea, sepsis and dehydration. No Grade 5 treatment-related events were reported.

The most commonly reported treatment-related SAEs (reported in ≥ 5 patients) in single-agent crizotinib studies were renal cyst (22 patients), pneumonitis (21 patients), ALT increased (16 patients), vomiting (14 patients), nausea (13 patients), death and interstitial lung disease (11 patients each), AST increased and dyspnoea (10 patients each), pneumonia (8 patients), diarrhoea and oedema peripheral (7 patients each), febrile neutropenia (6 patients), blood creatinine phosphokinase increased, bradycardia, decreased appetite, deep vein thrombosis and electrocardiogram QT prolonged (5 patients each). Of the 13 patients who received crizotinib in the combination studies who experienced treatment-related SAEs, 9 received crizotinib in combination with dacomitinib, 2 received crizotinib in combination with erlotinib, and 3 received crizotinib in combination with axitinib. The treatment-related SAEs reported in more than 1 patient were diarrhoea (6 patients), dehydration (4 patients), and hyperuricaemia, hypotension and nausea

(2 patients each). Of note, there were no treatment-related SAEs in the combination studies with immunotherapy agents, i.e., pembrolizumab or avelumab.

Most deaths while on crizotinib treatment were due to progression of the underlying disease. There were 40 treatment-related deaths reported during single-agent crizotinib treatment. Twelve (12) were cases of death (of unknown cause), sudden death, and death NOS, and were considered treatment-related because there were no data indicating a different cause of death. Other fatal events reported in more than 1 patient were pneumonitis (8 patients), pneumonia and interstitial lung disease (4 patients each), and hepatic failure, lung infection and dyspnoea (2 patients each). There have not been any treatment-related deaths on crizotinib in combination with an EGFR TKI, a VEGFR TKI or an immunotherapy.

Out of the 2071 patients with advanced NSCLC treated with single-agent crizotinib 250 mg BID, a total of 108 (5.2%) permanently discontinued crizotinib. The most common treatment-related AEs on single-agent crizotinib that were associated with permanent treatment discontinuation were INTERSTITIAL LUNG DISEASE* (1.4%), ELEVATED TRANSAMINASES* (0.8%) and HEPATOTOXICITY (0.6%). For patients with other tumor types treated with single-agent crizotinib 250 mg BID, the only AE associated with permanent treatment discontinuation that occurred in more than 1 patient was nausea (1.3%). For patients with advanced NSCLC who received crizotinib in combination with an EGFR TKI, the most common treatment-related AEs that were associated with permanent discontinuation were diarrhoea (3.2%) followed by esophagitis, vomiting, hypotension, INTERSTITIAL LUNG DISEASE*, and PULMONARY EMBOLISM* (2.2% each). For patients with solid tumors who received crizotinib in combination with a VEGFR TKI, the treatment-related AEs that were associated with permanent discontinuation were vomiting (5.9%) and ELEVATED TRANSAMINASES (2.9%).

Intra-patient dosing interruption and/or dose reduction of crizotinib to 200 mg BID, and then to 250 mg QD, may be required depending on the type and severity of toxicity encountered.

(*): Event terms written in ALL CAPITALS represent CLUSTERED TERMS which included multiple Preferred Terms.

Trial investigating the differences in testosterone levels in men with metastatic NSCLC receiving or not crizotinib (Ref. 13), has shown that crizotinib caused rapid suppression of T levels in men. Total T levels were low (<241 ng/dL) in 19 of 19 (100%) crizotinib-treated men and in 6 of 19 men (32%) with metastatic NSCLC who did not receive crizotinib (mean testosterone levels, 131 ng/dL and 311 ng/dL, respectively; $P = .0002$). Only 1 in 5 patients who had anaplastic lymphoma kinase (ALK) gene rearrangements and had not yet received crizotinib had low testosterone. The initiation of crizotinib in 2 patients who had previously normal testosterone levels was associated with a rapid decreases in testosterone and in luteinizing hormone and follicle stimulating hormone levels within 14 to 21 days. Discontinuation of crizotinib led to increases back to normal testosterone levels. The results indicated that the site of action included a central (hypothalamic or pituitary) effect, but additional direct testicular effects could not be excluded. Further work is required to assess the correlation between low testosterone levels and crizotinib side effects as well as the exact molecular mechanism and site of drug toxicity.

The Children's Oncology Group study ADVL0912 (Ref. 14) is an ongoing cooperative group study of single agent crizotinib in pediatric patients older than 12 months and younger than 22 years with measurable or evaluable solid or CNS tumors, or anaplastic large-cell lymphoma. The study was divided in 3 parts: the dose-finding phase (part A1), patients with confirmed ALK translocations, mutations, or amplification (part A2 of the study) or neuroblastoma (part A3) could enroll at one dose level lower than was currently given in part A1. Crizotinib was given twice daily without interruption. Six dose levels (100, 130, 165, 215, 280, 365 mg/m² per dose) were assessed in the phase part A1. A total of 79 patients were enrolled in the study with a median age of 10.1 years (range 1.1 - 21.4); 43 patients were included in the dose escalation phase, 25 patients in part A2, and 11 patients in part A3. Crizotinib was well tolerated with a recommended phase 2 dose of 280 mg/m² twice daily. Grade 4 adverse events in cycle 1 were neutropenia (two) and liver enzyme elevation (one). Grade 3 adverse events that occurred in more than one

patient in cycle 1 were lymphopenia (two), and neutropenia (eight). The mean steady state peak concentration of crizotinib was 630 ng/mL and the time to reach this peak was 4 h (range 1 - 6).

Increased blood creatinine levels have been reported in patients with advanced NSCLC treated with crizotinib, but there has not been any clear evidence of a clinically relevant effect of crizotinib on renal function. Data from the 4 clinical studies indicated that the use of crizotinib resulted in an increase in serum creatinine and a decline in estimated Glomerular Filtration rate which was first observed at 2 weeks and remained relatively constant from 12 weeks of treatment through the remainder of the time points examined. There did not appear to be any cumulative toxicity with continued crizotinib treatment. The frequency of blood creatinine increased was 8.0% in the 4 clinical studies. Renal function should continue to be monitored in patients treated with crizotinib.

Recently the development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic, and have developed from 2 and 6 months after starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended.

Moreover, a recent safety review of crizotinib based on data from clinical trials and reports from clinical practice showed that there is a risk of cardiac failure¹ following the use of crizotinib.

Across clinical studies in patients with ALK-positive NSCLC (n=1669), a total of 19 (1.1%) patients treated with crizotinib had any grade cardiac failure[#], 8 (0.5%) patients had Grade 3 or 4, and 3 (0.2%) patients had fatal outcome.

In the post marketing experience, as of 25 February 2015, it is estimated that more than 14700 patients have received crizotinib and cardiac failure was reported in 40 patients (reporting rate 0.27%). The majority occurred during the first month of treatment. A fatal outcome was reported for 15 of them. Seven cases have been identified where symptoms of cardiac failure resolved after discontinuation of crizotinib, and in three of these cases symptoms reoccurred when crizotinib was subsequently re-introduced. In 3 out of these 7 cases, no confounding cardiac disorders (past medical history, comorbid conditions, and concurrent medications) were identified.

Thus patients with or without pre-existing cardiac disorders, receiving crizotinib, should be monitored for signs and symptoms of heart failure (dyspnoea, oedema, rapid weight gain from fluid retention).

Cases of gastrointestinal perforation have been also reported, some of which were fatal. There were other possible contributing causes in many of the cases.

[#] Cardiac failure (Cardiac failure, Cardiac failure congestive, Ejection fraction decreased, Left ventricular failure, Pulmonary oedema)

1.5 Crizotinib: clinical efficacy data

An open-label, randomized, multicenter, multinational, phase 3 (Ref. 15) study of crizotinib versus standard of care chemotherapy (pemetrexed or docetaxel) was conducted in patients with ALK-positive advanced NSCLC. The median duration of study treatment was 31 weeks in the crizotinib arm and 12 weeks in the chemotherapy arm (18 weeks for pemetrexed and 9 weeks for docetaxel). This study met its primary objective by demonstrating that crizotinib significantly prolonged PFS compared to chemotherapy, as assessed by independent radiology review. In the primary PFS analysis, crizotinib more than doubled median PFS compared to chemotherapy, with a median PFS of 7.7 months for 173 patients randomized to crizotinib and 3.0 months for 174 patients randomized to chemotherapy. The hazard ratio comparing crizotinib with chemotherapy was 0.487 (95% CI: 0.371, 0.638) with a 1-sided p-value of <0.0001 (stratified log-rank test). Subgroup analyses of crizotinib vs pemetrexed and crizotinib vs

docetaxel also demonstrated superior PFS in the crizotinib arm. The median PFS was 7.7 months for 172 patients treated with crizotinib, 4.2 months for 99 patients treated with pemetrexed, and 2.6 months for 72 patients treated with docetaxel, and log-rank test 1-sided p-values was 0.0004 for the comparison of crizotinib vs pemetrexed and <0.0001 for the comparison of crizotinib vs docetaxel. The results of the primary PFS analysis were robust based on sensitivity analyses. The benefit from crizotinib treatment was generally comparable across subgroups of baseline patient characteristics, and the improvement in PFS was similar when using the investigators' assessments. Analyses of the secondary efficacy supported the primary PFS outcome (crizotinib vs chemotherapy): objective response rate (65% vs 20%), median time to tumor response (6 weeks vs 13 weeks), median duration of response (36 weeks vs 24 weeks), and disease control rate (81.5% vs 55.2% at 6 weeks; 64.2% vs 38.5% at 12 weeks).

Efficacy data from the United States Package Insert with 119 advanced ALK-positive NSCLC patients enrolled. The median duration of treatment was 32 weeks. Based on investigator assessments, there were 2 complete and 69 partial responses for an objective response rate (ORR) of 61% (95% CI: 52%, 70%). Fifty-five percent of objective responses were achieved during the first 8 weeks of treatment. The median duration of response was 48 weeks. In addition, preliminary results of treating an expansion cohort of 20 response-evaluable advanced ROS1-positive NSCLC patients with crizotinib 250 mg BID were recently reported, including an ORR of 50% and a DCR at 8 weeks of 70% (Ref. 16). The median duration of treatment was 22 weeks.

Efficacy data are provided from the United States Package Insert (Pfizer study A8081005). There were 136 patients with previously treated advanced ALK-positive NSCLC enrolled in this trial. The median duration of treatment was 22 weeks. Based on investigator assessments, there were 1 complete and 67 partial responses for an objective response rate (ORR) of 50% (95% CI: 42%, 59%). Seventy-nine percent of objective responses were achieved during the first 6 weeks of treatment. The median duration of response was 42 weeks.

In a Phase 3 study of first line use of crizotinib, 172 patients were randomized to crizotinib and 171 patients were randomized to chemotherapy. The median PFS was 10.9 months for crizotinib and 7.0 months for chemotherapy. Results of treating an expansion cohort of 50 advanced ROS1--positive NSCLC patients with crizotinib 250 mg BID were recently reported. The median PFS was 83 weeks (95% CI: 14.4, not reached) (Ref. 23).

In the Children's Oncology Group study ADVL0912 (Ref. 14), the objective tumor responses were documented in 14 of 79 patients (nine complete responses, five partial responses); and the anti-tumor activity was enriched in patients with known activating ALK aberrations (eight of nine with ALCL, one of 11 with neuroblastoma, three of seven with IMFT, and one of two with NSCLC). The results suggest that a targeted inhibitor of ALK has antitumor activity in childhood malignancies harbouring ALK translocations, particularly ALCL and IMFT, and that further investigation in the subset of neuroblastoma harboring known ALK oncogenic mutations is warranted.

Eight (8) of 9 (89%) adult patients with previously treated ALK-translocated anaplastic large cell lymphoma (ALCL) or diffuse large B-cell lymphoma who received compassionate-use crizotinib had objective responses, including 6 complete responses (Ref. 17). Similarly, 8 of 9 (89%) pediatric patients with previously treated ALK-translocated ALCL had objective responses to crizotinib treatment on Children's Oncology Group Study ADVL0912, including 7 complete responses (Ref. 14).

Three other patients with solid tumors other than ALK-positive or ROS1-positive NSCLC have also had objective responses on crizotinib treatment according to the published literature: 1 patient with glioblastoma multiforme harboring MET amplification (Ref. 18), 1 patient with gastro-esophageal carcinoma harboring MET amplification (Ref. 19), and 1 patient with IMFT harboring an ALK fusion with the RANBP2 gene (Ref. 21).

Currently, crizotinib is approved in more than 90 countries worldwide for the indication of ALK-positive advanced NSCLC. Approvals for a second indication of ROS1-positive advanced NSCLC were granted in the US and EU in March 2016 and August 2016, respectively, and marketing applications for this indication are planned or currently in review in several countries worldwide.

2 Objectives of the trial

2.1 General objectives

The study will primarily assess the efficacy of crizotinib in a variety of tumors with alterations in ALK and/or MET pathways. The targeted patient population will include patients with tumors harboring specific alterations leading to ALK and/or MET activation, where tyrosine kinase inhibitors against these targets have not yet been adequately explored.

2.1.1 Primary objective

- ◆ To study the antitumor activity and safety of crizotinib across predefined tumor types in patients whose tumors are harboring specific alterations in ALK and/or MET pathways.

2.1.2 Secondary objectives

- ◆ To study the specificity of the kinase inhibitor for tumors in all cohorts by explorative comparison of treatment results in patients with the same disease type with and without alterations in ALK and/or MET pathways (“ALK/MET+” and “ALK/MET-” sub-cohorts).
- ◆ To investigate sensitive and reliable methodologies for patient screening for such defects, to be potentially cross-validated and further developed by an accredited laboratory in later steps, based on prospectively collected biological material from this trial.
- ◆ To explore the potential value of selected biomarkers to study the pharmacological effects of crizotinib, to be used later in the context of future trials.
- ◆ To explore whether molecularly driven, high quality multi-tumor screening Phase 2 trials are feasible in a multi-institutional, multidisciplinary setting, when screening and treatment are performed by EORTC sites (+/- additional selected sites).

2.2 Endpoints

2.2.1 Primary endpoint

- ◆ Response rate documented by RECIST 1.1 (with response confirmation)

2.2.2 Secondary endpoints

- ◆ Safety (CTAE v 4.0)
- ◆ Progression free survival
- ◆ Disease control rate
- ◆ Overall survival
- ◆ Duration of response

- ◆ Correlative research endpoints

3 Patient selection criteria

3.1 General inclusion criteria for all patients

Patient enrollment will follow a three steps procedure as illustrated in section 4.3 (step 1 registration, step 2 central histopathology confirmation and step 3 enrollment). Subjects must meet all of the criteria described in sections 3.1 and 3.2 to be eligible for treatment with crizotinib.

The following criteria are a prerequisite for step 1 registration:

- ◆ Local diagnosis of locally advanced and/or metastatic malignant tumor (anaplastic large cell lymphoma, inflammatory myofibroblastic tumor, papillary renal cell carcinoma type 1, alveolar soft part sarcoma, clear cell sarcoma or alveolar rhabdomyosarcoma) deemed incurable by conventional surgery, radiotherapy, systemic therapy or any other means. Medical history and previous treatment need to meet the disease specific inclusion criteria (3.2). Proven presence of specific ALK and/or MET pathway alteration in tumor tissue is not mandatory for patient registration.
- ◆ Mandatory availability for shipment of formalin-fixed, paraffin-embedded, tumor-containing tissue blocks from primary tumor and/or metastatic site. Slides are not accepted. Information on previous histopathology reports and previous molecular analysis will be entered in an electronic CRF, to accompany the tissue samples.
- ◆ Before patient registration, written informed consent for central collection of tissue block and any other trial-specific procedures must be obtained from the patient according to ICH/GCP, and national/local regulations, allowing for collection, storage and analysis of tissue and screening procedures.

Histopathology central confirmation for step 2:

- ◆ Confirmation of receipt of tissue block and accompanying required local information, and confirmation that tissue block contains tumor tissue (quality assurance) by central biorepository through EORTC, as well as central pathology confirmation, are required before starting the patient screening according to chapter 6.4.

All the other inclusion criteria must be met for step 3 enrollment:

- ◆ Measurable disease according to RECIST 1.1 with target lesion of at least 20 mm (or 10 mm on spiral CT scans) and presence of at least one RECIST-measurable lesion outside of a previously radiated field or potential palliative irradiation fields.
- ◆ No malignant meningitis or leptomeningeal disease.
- ◆ Patients with brain metastases are eligible if treated and/or neurologically stable with no ongoing requirement for corticosteroids (off steroids for at least 2 weeks) and not taking contraindicated medications as specified in section 5.6. Absence of spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function.
- ◆ Any previous systemic anticancer therapy must have been completed at least 4 weeks prior to initiation of study medication.
- ◆ No treatment with any other investigational drug within the past 4 weeks or within less than 4 half-life times of the investigational drug before treatment with crizotinib (whatever is the longest period).
- ◆ No prior therapy directly targeting ALK and/or MET, no previous treatment with crizotinib.
- ◆ Major surgery must have been completed at least 4 weeks prior to initiation of study medication.

- ◆ Prior palliative radiotherapy must have been completed at least 24 hrs prior to initiation of study medication, and minor surgical procedures must have been completed at least two weeks prior to the initiation of study medication.
- ◆ Minimum age ≥ 1 year, no upper age limit.
- ◆ Eastern Cooperative Oncology Group (ECOG) performance status 0-2, or Lansky Play scale ≥ 50 for children aged 1 to 12 yo. (Appendix G).
- ◆ No other previous and active malignancy within the last three years with the exception of non-melanoma skin cancer, localized cervical cancer, localized and presumably cured prostate cancer or adequately treated basal or squamous cell skin carcinoma.
- ◆ Adequate hematological function: ANC $\geq 1 \times 10^9/L$, platelets $\geq 30 \times 10^9/L$ and hemoglobin ≥ 8 g/dL.
- ◆ Adequate renal function:
 - ◆ For patients up to 21 years old:

The Schwartz formula should be used for Clearance Creatinine [mL/min/1.73 m²= F x Height (cm) x 88.4/creatinine (blood) in $\mu\text{mol/L}$. CrCl of 80-140 mL/min/1.73 m² is considered as normal range

- ◆ F= 0.55 for boys 1-15 yo
- ◆ F= 0.70 for boys 16-21 yo
- ◆ F= 0.55 for girls 1-21 yo
- ◆ For patients 21 years or older: serum creatinine $\leq 2 \times$ ULN.
- ◆ Adequate liver function: Bilirubin $\leq 1.5 \times$ ULN unless due to Gilbert's syndrome (status of the disease documented by repeated laboratory values with slight increase in bilirubin without any other known causes). AST and ALT $\leq 2.5 \times$ ULN in the absence of liver metastases and $\leq 5 \times$ UNL if liver function abnormalities are due to the underlying malignancy.
- ◆ No laboratory abnormalities that would impart, in the judgment of the investigator and/or sponsor, excess risk associated with study participation or study drug administration, and which would, therefore, make the patient inappropriate for entry into this trial.
- ◆ All related adverse events from previous therapies must have recovered to \leq Grade 1 (except alopecia). No persistence of adverse events from prior anti-cancer therapy deemed clinically relevant.
- ◆ No acute or chronic severe gastrointestinal conditions such as diarrhea or ulcer.
- ◆ Clinically normal cardiac function based on the institutional lower limit of normal LVEF (assessed by MUGA or ECHO) and normal 12 lead ECG.
- ◆ Within the three months prior to starting study treatment, no myocardial infarction, no severe/unstable angina, no coronary/peripheral artery bypass graft, congestive heart failure or cerebrovascular accident including transient ischemic attack.
- ◆ No ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥ 2 .
- ◆ No uncontrolled atrial fibrillation of any grade.
- ◆ Machine-read ECG QTcF interval ≤ 470 msec.
- ◆ Note: Crizotinib should be avoided in patients with long congenital QT syndrome.
- ◆ No history of extensive disseminated/bilateral or known presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease, including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis, but not history of prior radiation pneumonitis.

- ◆ No concurrent use of drugs or foods that are known strong CYP3A4 inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice (see section 5.6). The topical use of these medications (if appropriate), such as 2% ketoconazole cream, may be allowed.
- ◆ No concurrent use of drugs that are known potent CYP3A4 inducers, within 12 days prior to first dose of crizotinib including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort (see section 5.6).
- ◆ No use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to pimozide, dihydroergotamine, ergotamine, astemizole, cisapride, and terfenadine (see section 5.6).
- ◆ No other severe acute or chronic medical (including severe gastrointestinal conditions such as diarrhea or ulcer) or psychiatric conditions or end stage renal disease on hemodialysis or laboratory abnormalities that would impact, in the judgment of the investigator and/or sponsor, excess risk associated with study participation or study drug administration, and which would, therefore, make the patient inappropriate for study entry.
- ◆ Women of child bearing potential (WOCBP) must have a negative serum pregnancy test prior to the first dose of study treatment.
- ◆ All patients (male and female) of childbearing/reproductive potential must use adequate birth control measures during the study treatment period and for at least three months after the last study treatment (effective contraception methods are implants, injectable, combined oral contraceptives, IUDs, sexual abstinence and vasectomized partners for female patients).
- ◆ Female subjects who are breast feeding should discontinue nursing prior to the first dose of study treatment and until three months after the last study treatment.
- ◆ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

3.2 Disease specific inclusion criteria (mandatory for step 1 registration)

3.2.1 Disease specific inclusion criteria for patients with anaplastic large cell lymphoma (ALCL)

- ◆ Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or metastatic disease.
- ◆ Patient must have received previous systemic chemotherapy (usually a CHOP-like multidrug combination, if not medically contraindicated, with or without monoclonal antibodies), and may not qualify for further conventional therapy with curative intent.
- ◆ No pretreatment limitations (including autologous or allogeneic stem cell- or bone marrow transplantation), provided all other patient selection criteria are met.

3.2.2 Disease-specific inclusion criteria for patients with inflammatory myofibroblastic tumor (IMFT)

- ◆ Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or metastatic disease.
- ◆ No mandatory pretreatment.
- ◆ No pretreatment limitations, provided all other patient selection criteria are met.

3.2.3 Disease-specific inclusion criteria for patients with papillary renal cell carcinoma type 1 (PRCC)

- ◆ Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or metastatic disease.
- ◆ No mandatory pretreatment.
- ◆ No pretreatment limitations, provided all other patient selection criteria are met.

3.2.4 Disease-specific inclusion criteria for patients with clear cell sarcoma (CCSA)

- ◆ Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or metastatic disease.
- ◆ No mandatory pretreatment.
- ◆ No pretreatment limitations, provided all other patient selection criteria are met.

3.2.5 Disease-specific inclusion criteria for patients with alveolar soft part sarcoma (ASPS)

- ◆ Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or metastatic disease.
- ◆ No mandatory pretreatment.
- ◆ No pretreatment limitations, provided all other patient selection criteria are met.

3.2.6 Disease-specific inclusion criteria for patients with alveolar rhabdomyosarcoma (ARMS)

- ◆ Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or metastatic disease.
- ◆ Patient must have received previous systemic chemotherapy (usually anthracyclin-based, if not medically contraindicated), and may not qualify for further conventional therapy with curative intent.
- ◆ No pretreatment limitations, provided all other patient selection criteria are met.

Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory.

4 Trial design

This is a biomarker-driven multi-tumor single agent Phase 2 trial, using Simon's optimal two stage design (Ref. 21). The study will assess the efficacy of crizotinib in a variety of tumors with specific alterations in either ALK and/or MET pathways. The patient population will include patients with tumors harboring specific alterations leading to ALK and/or MET activation (ALK/MET +). The trial will also include patients without those alterations (ALK/MET -). The study population will comprise the following diagnoses ("cohorts"):

1. Anaplastic large cell lymphoma (ALCL; can be associated with ALK alterations)
2. Inflammatory myofibroblastic tumor (IMFT; can be associated with ALK alterations)
3. Papillary renal cell carcinoma type 1 (PRCC; can be associated with MET alterations)
4. Alveolar soft part sarcoma (ASPS; can be associated with MET alterations)
5. Clear cell sarcoma (CCSA; can be associated with MET alterations)
6. Alveolar rhabdomyosarcoma (ARMS; can be associated with MET and ALK alterations)

4.1 Enrollment: three steps procedure

4.1.1 Step 1

All patients with one of these diagnoses as established by the local sites will be considered for trial participation at step 1, provided they meet the 3 first general inclusion criteria and the disease specific inclusion criteria, and they have signed informed consent (see 3.1 and 3.2). Availability of central molecular diagnostic results is not a pre-requisite for study participation, but if available such information should be provided to EORTC.

After informed consent, receipt of shipment to a central biorepository of formalin-fixed paraffin-embedded tumor-containing tissue blocks (slides not accepted) from either primary tumor or a metastatic site will be mandatory for trial participation. Histopathology report and previous molecular analysis information will be reported electronically in parallel with tissue shipment.

4.1.2 Step 2

Central review of histopathology and central molecular diagnostics will be performed on all samples according to a technical manual, and this will be done in academic laboratories.

The central confirmation of the actual diagnosis will be required before starting active screening. In case the quality of the original block is not satisfying, it will be allowed to ship another block or to take a new biopsy; however no biopsy should be taken after the treatment with crizotinib has started. EORTC will notify the investigational site if the diagnosis of ALCL, IMFT, PRCC, ASPS, CCSA or ARMS is confirmed by the central laboratory. Once the site has been notified, the patient can be screened for the other selection criteria.

The time from step 1 to diagnosis confirmation step 2 should be at the most 3 weeks.

4.1.3 Step 3

Patients with the central diagnosis of ALCL, IMFT, PRCC, ASPS, CCSA, ARMS (6 cohorts) will be entered into the trial, provided that they match patient selection criteria. The time for screening will be at the most 4 weeks.

Total time between step 1 registration and step 3 enrollment allowing treatment should not exceed 7 weeks, including the wash-out from previous treatments.

4.2 Sub-cohorts of patients

After central histopathology confirmation, each cohort will be split into two sub-cohorts: patients with tumors having ALK and/or MET pathway alterations (ALK/MET+) and those without ALK and/or MET pathway alterations (ALK/MET-). The primary objective of the trial is to study the efficacy of crizotinib in ALK/MET+ patients. The ALK/MET- sub-cohort mainly serves as an exploratory subset, but the same statistical rules will be applied. Each of the six cohorts treated in this trial (ALCL, IMFT, PRCC, ASPS, CCSA, ARMS), and also each of the ALK/MET + and - sub-cohorts are thus to be considered as separate Phase 2 trials (12 early Phase 2 studies combined in one protocol).

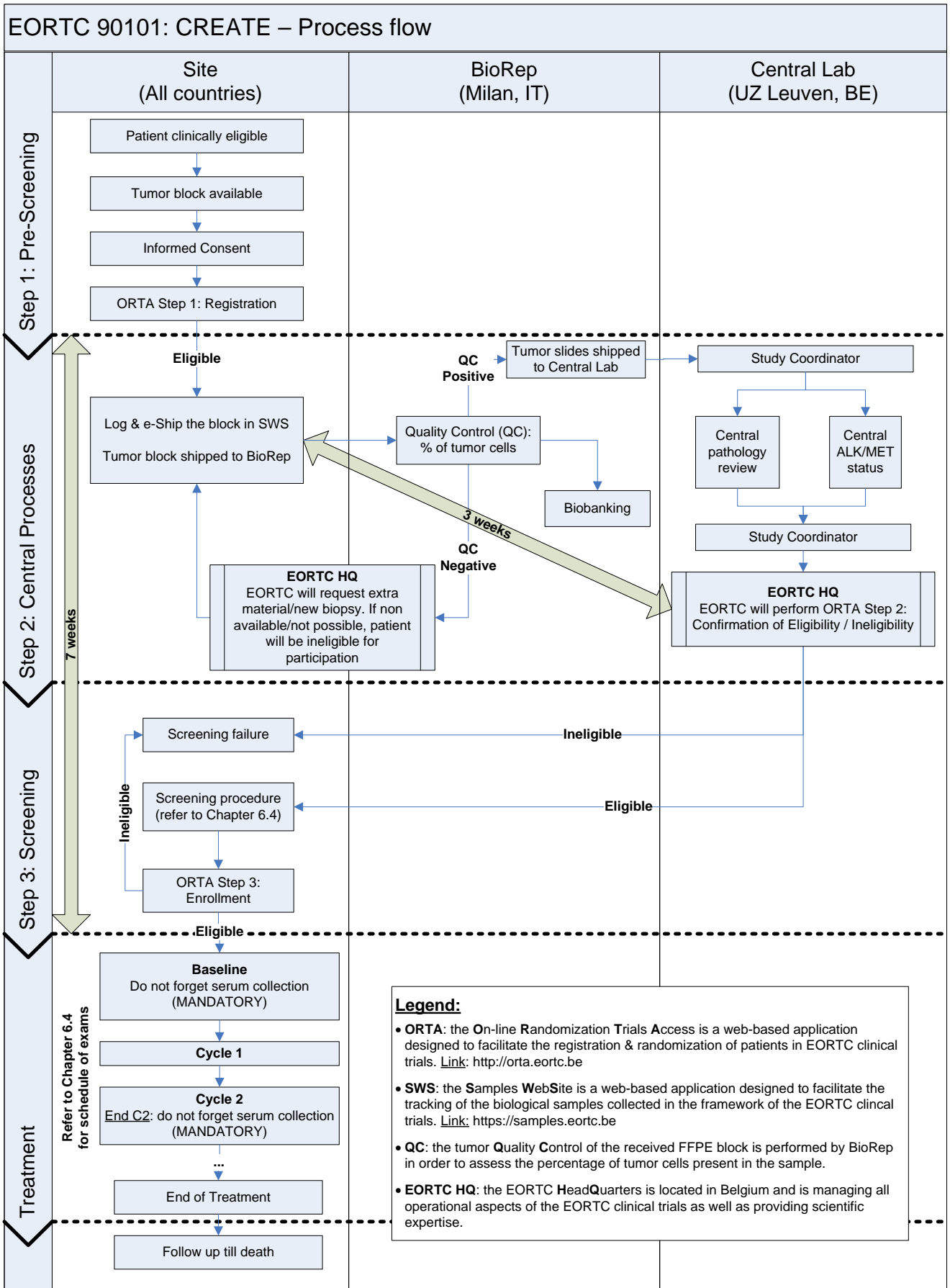
For each of the cohorts an Optimal Simon's Two Stage Design is used (see section 8.1). A maximum of 35 eligible and evaluable (see section 8.2.2) patients per sub-cohort are enrolled and treated. This number refers to all 12 sub-cohorts. However the ALK/MET- sub-cohorts mainly serve as exploratory groups in this trial.

Decision rules for stage I and stage II are described in section 8.1.2. Those decision rules are adapted according to the recruitment rate.

In addition, an early stopping rule is implemented if the true incidence of ALK/MET positivity turns out to be considerably lower than expected. Indeed, if the true percentage of ALK/MET+ tumors within a certain cohort is too low, the number of patients to be screened would become very high and that cohort would no longer be feasible, due to a long accrual period and high patient numbers.

4.3 Process flow

The following table represents an overview of the process. A detailed plan of the logistics of samples and information will be provided as part of detailed study guidelines, at time of site authorization.



5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Regimen and dosage

Cycles are defined in 21-day periods to facilitate scheduling of visits and assessments.

The use of capsules is recommended if the calculated dose with +/-10% can be given by the existing capsules, otherwise it is recommended to use oral solution.

Patients unable to swallow should receive the oral solution.

Patients should be instructed that if they vomit any time after taking a dose then they must not take an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed.

Crizotinib is dosed without regard to meals.

5.1.1 Patients of 15 years old or older

Crizotinib will be administered orally at a dose of 250 mg twice daily (BID) at approximately the same time each day on a continuous daily dosing schedule, i.e. no break in dosing, in the absence of drug related toxicity.

5.1.2 Patients younger than 15 years old

Crizotinib will be administered orally at a dose of 280 mg/m²/dose BID at approximately the same time each day on a continuous daily dosing schedule, i.e. no break in dosing, in the absence of drug related toxicity.

To calculate dosing volumes for each patient based on BSA, the following formula should be used:

$$\text{Dosing Volume (mL)} = [\text{Prescribed Dose (mg/m}^2\text{)} \times \text{BSA}^* \text{ (m}^2\text{)}] / 25 \text{ (mg/mL)}$$

Note:

Calculated dosing volumes should be rounded up to the nearest 0.1 mL for the actual deliverable dose.

For BSA >1.5 m², a flat fixed dose of 400 mg twice daily (1.6 x adult dose) will be used.

Example: Patient BSA 0.75 m²:

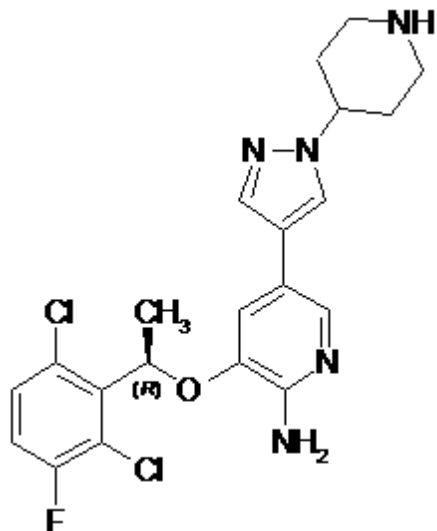
$$\text{Dosing Volume (mL)} = (280 \text{ mg/m}^2 \times 0.75 \text{ m}^2) / (25 \text{ mg/mL}) = 8.4 \text{ mL}$$

Dosing volume to be given to patient = 8.4 mL BID

*BSA will be calculated according to the Mosteller formula: $[\text{Height (cm)} \times \text{weight (Kg)} / 3600]^{1/2}$ (Ref. 22)

5.2 Drug information

5.2.1 General information



Molecular Formula

C₂₁H₂₂Cl₂FN₅O

Chemical Names

(R)-3-[1-(2,6-Dichloro-3-fluorophenyl)ethoxy]-5-[1-(piperidin-4-yl)-1H-pyrazol-4-yl]pyridin-2-amine

INN name: Crizotinib (PF-02341066)

Mode of action: small-molecule inhibitor of the ALK/MET receptor tyrosine kinases

5.2.2 Drug supply

After a patient has been allowed for active treatment the clinical site must follow the drug supply guidelines provided separately, which will describe in detail the drug handling and distribution procedures.

5.2.2.1 Crizotinib

Crizotinib will be provided as capsules containing 200 or 250 mg of study medication and will be packaged in HDPE bottles.

Capsules of 150 mg and oral solution (25mg/mL) will also be provided.

5.2.2.2 Preparation and dispensing

Only qualified personnel familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and disposal of agents. Crizotinib will be dispensed at the beginning of each treatment cycle (or as otherwise indicated). Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container.

Storage

Crizotinib capsules of 250, 200 and 150 mg should be stored at room temperature (15 to 30°C).

Crizotinib oral solution (25mg/mL) should be stored upright between +2 and +8°C.

5.2.3 Drug reconciliation procedures

Accountability of the investigational study drug(s) is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site. Accountability records should include receipt date, batch numbers, expiry dates, patient SeqID, use by subject, dispensing dates, quantities (lowest unit) and stock balance.

In addition to internal accountability documentation on site, EORTC study-specific accountability and drug destruction forms will be supplied for this purpose, if site-specific forms are deemed not sufficiently detailed or do not provide enough information, according to EORTC Quality Assurance criteria.

The drug accountability and destruction forms will be verified during monitoring visits.

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification by EORTC in order to allow drug destruction or return procedure.

Both the unused and expired study medication must be destroyed, upon authorization of the sponsor, according to local regulations and procedures, and a copy of the destruction form must be returned to the EORTC Headquarters.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients entered in this study.

5.3 Treatment duration

Treatment with crizotinib should be administered until documented disease progression, unacceptable toxicity or patient refusal.

5.4 Withdrawal criteria

Subjects or parents / legal representatives (for subjects younger than 18 years of age) may withdraw from the trial at any time at their own request. Subjects may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject or parents / legal representatives (for subjects younger than 18 years of age). In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject or parents / legal representatives (for subjects younger than 18 years of age) to return all unused investigational product, request the subject (for subject younger than 18 years of age to contact parents / legal representatives) to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

Patients having signs/symptoms of cardiac failure must permanently discontinue crizotinib.

If the subject or parents / legal representatives (for subjects younger than 18 years of age) withdraw(s) from the trial and also withdraw(s) consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Residual human biological material (HBM) left over from laboratory analysis will be stored in the central biobank. EORTC will be the coordinator of the chain of custodianship of the HBM remaining in the biobank. If the following situations arise (and in accordance with the respective patient consent), EORTC coordination of the chain of custodianship of HBM can be terminated: if there is no remaining HBM (i.e. the HBM is wholly used up or has been destroyed) or if the subject (18 years or older) or parents / legal representatives (for subjects younger than 18 years of age) withdraw(s) the consent for the use of HBM in research.

After progression, the treatment will be left to the discretion of the treating physician.

Any systemic anti-cancer therapy other than crizotinib given as single agent in the context of this trial will not be considered as part of the protocol treatment; patients would be taken off study.

Treatment beyond RECIST progression is not allowed in this protocol.

5.5 Dose and schedule modifications

Investigators are encouraged to employ best supportive care according to local institutional clinical practices and according to the guidance for selected adverse events provided below.

Patients will be monitored closely for toxicity and the dose of crizotinib may be adjusted as indicated below. Inpatient dose reduction by up to two dose levels will be allowed, depending on the type and severity of toxicity encountered.

In case of toxicity, dose reduction should be performed:

- ◆ Patients of 15 yo or older: to 200 mg BID as first reduction and to 250 mg QD (each day) as second reduction.
- ◆ Patients younger than 15 yo: to 80% as first reduction and to 60% as second reduction respectively of the initial dose.

Patients requiring more than two dose reductions should be discussed with the EORTC (study sponsor) and the study coordinator. In case treatment needs to be interrupted for more than 6 weeks, the patient should in principle be withdrawn, except if the benefit/risk assessment justifies continuation of the treatment.

5.5.1 Guidelines for treatment modifications for patients of 15 yo or older

5.5.1.1 Nausea and Emesis

See chapter 5.6.1.1.

5.5.1.2 Diarrhea

See chapter 5.6.1.1.

5.5.1.3 Liver toxicity

Refer to table below

For patients with Gilbert syndrome please contact the EORTC HQ and the study coordinator.

5.5.1.4 Dose Modifications for Treatment-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic General (except as noted below), eg, neuropathy, edema (including peripheral edema and localized edema), fatigue, and skin rash (including erythematous, macular, papular, and pruritic rash)	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤ 1 , or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator*.	Withhold dose until toxicity is Grade ≤ 1 , or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator*.
ALT or AST elevation with total bilirubin < 2 X ULN (in the absence of cholestasis or hemolysis) [§]	Continue at the same dose level.	Continue at the same dose level. Obtain repeat ALT or ALT and total bilirubin when symptomatic or within 7 days. For France only: Consult with EORTC HQ and the study coordinator to determine whether (1) to continue with same dose, level; (2) withhold dose until toxicity is Grade ≤ 1 or has returned to baseline, then resume treatment at the same dose level; or (3) withhold dose until toxicity is Grade ≤ 1 or has returned to baseline, then	Withhold dose until toxicity is grade ≤ 1 , or has returned to baseline, then resume treatment by reducing the dose by one dose level. If Grade 3 ALT or AST elevation recurs reduce further (at most by 2 dose levels from initial dose level). If recurrence at dose level -2, discontinue permanently. If Grade 3 ALT or AST elevation does not recur after at least 4 weeks, the dose may be escalated by single dose level increments up to the initial	See Grade 3. For France only: Discontinue treatment and do not retreat.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
		reduce the dose by 1 level.	dose level. For France only: Discontinue treatment and do not retreat.	
ALT or AST elevation concurrent with total bilirubin elevation ≥ 2 X ULN (in the absence of cholestasis or hemolysis)	Continue at the same dose level. Obtain repeat ALT or AST and total bilirubin within 48 hours, then repeat every 48-72 hours until ALT/AST < grade 1.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.
Left ventricular systolic dysfunction	Continue at the same dose level.	Continue at the same dose level.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.
Prolonged QTc	Continue at the same dose level.	Assess electrolytes and concomitant medications. Correct any electrolyte or magnesium abnormalities.	Withhold until recovery to Grade ≤ 1 , then resume at 200 mg twice daily. In case of recurrence, withhold until recovery to Grade ≤ 1 , then resume at 200 mg twice daily. Permanently discontinue in case of further Grade ≥ 3 recurrence.	Discontinue treatment and do not retreat.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis (in absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.	Discontinue treatment and do not retreat.
Bradycardia (heart rate less than 60 beats per minute)	Continue at the same dose level.	<p>Withhold until recovery to Grade ≤ 1 or to heart rate ≥ 60.</p> <p>Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications.</p> <p>If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to Grade ≤ 1 or to heart rate ≥ 60.</p> <p>If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose</p>	Same as for Grade 2 bradycardia.	<p>Permanently discontinue if no contributing concomitant medication is identified.</p> <p>If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at 250 mg once daily upon recovery to Grade ≤ 1 or to heart rate ≥ 60, with frequent monitoring.</p> <p>Permanently discontinue for recurrence.</p>

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
		upon recovery to Grade ≤ 1 or to heart rate ≥ 60 .		
Visual disturbance	Continue at the same dose level. Repeat ophthalmologic examination+.	Continue at the same dose level. Repeat ophthalmologic examination+.	Interrupt crizotinib until recovery. Repeat ophthalmologic examination+. Resume treatment by reducing by one dose level.	Discontinue treatment and do not retreat. Repeat ophthalmologic examination+.
Hematologic (excluding lymphopenia**)	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is Grade ≤ 2 , or has returned to baseline, then resume treatment at the same dose level or reduce by 1 level after discussion with EORTC HQ and the study coordinator **/**.	Withhold dose until toxicity is Grade ≤ 2 , or has returned to baseline, then reduce the dose by 1 level and resume treatment**.

* Patients who develop Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting, or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy, to require dose modification

** Patients who develop Grade 3 or 4 lymphopenia without other dose-limiting events (eg, opportunistic infection) may continue study treatment without interruption.

*** Patients entering with platelet counts $>30,000$ (to $<50,000/\mu\text{L}$) will be monitored for drug related decreases at which point dose modifications will be discussed with the EORTC HQ and the study coordinator.

§ Patients entering with ALT and/or AST $\geq 5 \times \text{ULN}$ (ie, Grade ≥ 3) due to underlying malignancy will be monitored for potential drug related increases at which point dose modifications will be discussed with the EORTC HQ and the study coordinator. (Note: this option does not apply for France).

+ Ophthalmologic examination includes visual acuity, slit lamp, and fundoscopy and should be performed by an ophthalmologist.

5.5.1.5 Renal impairment

Starting dose adjustment is not required for patients with mild ($60 \leq$ creatinine clearance < 90 mL/min) and moderate ($30 \leq$ creatinine clearance < 60 mL/min) renal impairment, since no clinically meaningful changes in steady-state crizotinib plasma through concentrations were observed in single arm studies.

After a single 250 mg dose in patients with severe renal impairment (creatinine clearance < 30 mL/min) not requiring peritoneal dialysis or hemodialysis, crizotinib significantly increased AUC and C_{max} compared to those with normal renal function. An adjustment of the dose of crizotinib to 250 mg taken orally once daily is recommended when administering crizotinib to patients with severe renal impairment not requiring peritoneal dialysis or hemodialysis.

5.5.1.6 Pneumonitis

Investigators must evaluate thoroughly patients who demonstrate potential signs/symptoms of pneumonitis/pneumonia. If a patient has a potential diagnosis of pneumonitis or drug related lung injury the following evaluations/procedures should be considered to assist or exclude the diagnosis of pneumonitis during this period:

- ◆ A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacteria.
- ◆ Blood culture should be performed in febrile patients.
- ◆ Thoracentesis if pleural fluid is present (examine for same pathogens as sputum).
- ◆ Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. The BAL fluid should be sent for culture and cytology (same pathogens as above).
- ◆ Lung biopsy (eg, open or thorascopic preferable, bronchoscopy with transbronchial biopsy) if appropriate.
- ◆ A plasma sample for BNP (B-type natriuretic peptide) to evaluate for evidence of congestive heart failure.
- ◆ For Asian patients, a blood sample for β -D-glucan to evaluate for the presence of fungal pneumonia (eg, *Pneumocystis jirovecii*);
- ◆ If clinically appropriate, high dose corticosteroid treatment should be initiated. Should the event be fatal an autopsy is highly recommended to confirm/exclude the diagnosis.
- ◆ For any case of suspected pneumonitis please contact both EORTC and the study coordinator. For appropriate dose modifications see section 5.5.

5.5.2 Guidelines for treatment modifications for patients younger than 15 yo

5.5.2.1 Hematologic adverse reactions

If a patient without known bone marrow involvement experiences Grade 4 neutropenia or thrombocytopenia, the treatment will be withheld. If a patient with known bone marrow involvement experiences an ANC $< 250/\text{mm}^3$, the treatment will be withheld. If it occurs during cycle 1, counts should be checked every other day during cycle 1 or twice weekly if during cycle 2 or subsequent cycles until Grade 3 or less.

If the toxicity resolves to meet the study parameters within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level (dose level-1 (80%)). Doses reduced for toxicity will not be re-escalated, even if there is a minimal or no toxicity with the reduced dose.

If hematologic toxicity recurs in a patient who has resumed treatment at the dose level-1, consider reduction to 60% of the initial dose

In absence of recovery within 6 weeks, the patient must be removed from the protocol treatment.

5.5.2.2 Non hematologic adverse reactions

If a patient experiences non-hematologic adverse reaction, the treatment will be withheld.

When the toxicity resolves to meet the study parameters within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level (dose level-1). Doses reduced for toxicity will not be re-escalated, even if there is a minimal or no toxicity with the reduced dose.

If non-hematologic toxicity recurs in a patient who has resumed treatment at the dose level-1, consider reduction to 60% of the initial dose.

In absence of recovery within 6 weeks, the patient must be removed from the protocol treatment.

5.5.3 Other recommendations

Please refer to chapter 7.3.2 for additional recommendations regarding:

- ◆ Drug Induced Liver Injury (DILI)
- ◆ ECG measurements
- ◆ Ophthalmology examinations
- ◆ Renal cysts
- ◆ Hypogonadism
- ◆ Cardiac failure

5.6 Concomitant medications and potential drug/drug-interaction

Crizotinib is a substrate of CYP3A4/5 and also a moderate inhibitor of CYP3A. In vitro studies in human liver microsomes demonstrated that crizotinib is a time-dependent inhibitor of CYP3A.

◆ Agents that may increase crizotinib plasma concentrations

Coadministration of crizotinib with strong CYP3A inhibitors may increase crizotinib plasma concentrations. The concomitant use of strong CYP3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole, should be avoided. Grapefruit or grapefruit juice may also increase plasma concentrations of crizotinib and should be avoided.

◆ Agents that may decrease crizotinib plasma concentrations

Coadministration of crizotinib with strong CYP3A inducers may decrease crizotinib plasma concentrations. The concurrent use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort, should be avoided.

◆ Agents whose plasma concentrations may be altered by crizotinib

Crizotinib has been identified as an inhibitor of CYP3A both in vitro and in vivo. Coadministration of crizotinib with CYP3A4 substrates with narrow therapeutic indices associated with life-threatening arrhythmias including, but not limited to, dihydroergotamine, ergotamine, pimozide, astemizole*, cisapride*, and terfenadine* (*drugs not marketed in all countries) must be avoided during crizotinib treatment. In addition, caution must be exercised in patients receiving crizotinib in combination with other CYP3A4 substrates, particularly those with narrow therapeutic indices, including but not limited to alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus.

In addition to drug interactions due to enzyme inhibition and induction, the possibility of an additive pharmacodynamic interaction of crizotinib and other negatively chronotropic medications (e.g., beta-blockers and non-dihydropyridine calcium-channel blockers) should be considered. Coadministration of crizotinib with these medications may lead to significant decreases in heart rate.

For further reference a list of potential drugs interacting with CYP3A can be found at:

<http://medicine.iupui.edu/clinpharm/DDIs/table.aspx>

Crizotinib is an inhibitor of CYP2B6 in vitro. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are predominantly metabolized by CYP2B6. Crizotinib is an inhibitor of P-gp, OCT1 and OCT2 in vitro. Therefore, crizotinib may have the potential to increase plasma concentrations of co-administered drugs that are substrates of P-gp, OCT1 or OCT2.

The concomitant use of known medicinal products which extend the interval of QTc is not advised and these medicinal products should be used with caution. For further reference a list of potential drugs interacting with QTc can be found in a new protocol Appendix F.

Additionally, the concurrent use of non-prescription drugs (excluding vitamins) or herbal supplements is not recommended. Acetaminophen/ paracetamol to a maximum total daily dose of 2 g is permitted.

Non-steroidal anti-inflammatory drugs (NSAID) with long half-lives, eg, >10 hours, should be discontinued at least 5 days before, the day of and 2 days following crizotinib dosing. Patients who take NSAIDs concomitantly with crizotinib should be monitored closely for toxicity, especially myelosuppression, renal and gastrointestinal toxicity.

5.6.1 Supportive care in case of toxicity

Medications intended solely for supportive care (i.e. antiemetics, analgesics, megestrol acetate for anorexia) are allowed.

5.6.1.1 Antiemetic and antidiarrheal therapy

Nausea and emesis: Standard anti-emetics (such as prochlorperazine or ondansetron) may be used for the treatment of vomiting. Taking the medication with food may reduce nausea. Prophylactic anti-emetics may be used.

Diarrhea: **CTCAE Grade 1**: Symptomatic care such as loperamide or no intervention at investigator judgment. **CTCAE Grade 2**: Loperamide (4 mg at first onset, then 2 mg every 2-4 hours until symptom free for 12 hours). No dose modification unless patient is intolerant or symptom is recurrent. **CTCAE Grade \geq 3** (despite use of loperamide): withhold treatment until recovery to Grade \leq 1.

5.6.1.2 Bradycardia

For a heart rate <40 beats per minute, evaluate patient fully including an assessment of concomitant medications. Adjust the dosage of any medication known to be associated with bradycardia eg, beta-blockers.

If the bradycardia is symptomatic at any time or does not improve within 7 days of adjusting the concomitant medications, hold crizotinib dosing until recovery. Patient may continue treatment only with the agreement with EORTC and the study coordinator.

WARNING: The concurrent use of crizotinib with other bradycardic agents (eg, beta-blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) should be avoided to the extent possible due to the increased risk of symptomatic bradycardia. Heart rate and blood pressure should be monitored regularly. Dose modification is not required in case of asymptomatic bradycardia.

5.6.1.3 Hematopoietic growth factors and transfusion of blood products

The use of hematopoietic growth factors is at the discretion of the treating physician and is in line with local regulatory guidelines. Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the treating physician. Patients with neutropenic fever or infection should be treated promptly and may receive therapeutic colony-stimulating factors if appropriate and available.

5.6.1.4 Other concomitant medications

Patients on this trial may be supported with appropriate hormone replacement therapy as clinically indicated in the absence of disease progression or unacceptable treatment-associated toxicity.

Anti-inflammatory (except as noted above) or narcotic analgesics may be offered as needed. Packed red blood cell and platelet transfusions should be administered as clinically indicated.

Bisphosphonate therapy for metastatic bone disease is permitted. Bisphosphonate therapy should be given as per local medical practice.

5.6.1.5 Concomitant radiotherapy or surgery

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. Palliative radiotherapy specifically refers to radiotherapy for symptom relief and excludes any radiotherapy for progression. All attempts should be made to rule out disease progression in the event of increased localized pain. Crizotinib treatment should be interrupted during palliative radiotherapy – stopping 1 day before and resuming treatment 1 day after. In case radiotherapy is administered to all evaluable lesions prior to achieving a confirmed RECIST PR or CR, the patient will become non-evaluable for primary endpoint of this trial. In case there are enough evaluable lesions outside the radiotherapy field, RECIST evaluation can proceed on those remaining lesions.

The effect of crizotinib on wound healing is not known and has not been investigated; therefore, caution is advised on theoretical grounds (potential antiangiogenic effect). In the event elective surgery is necessary during study participation, crizotinib dosing should be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery.

6 Clinical evaluation, laboratory tests and follow-up

6.1 Three-steps procedure

6.1.1 Step 1: Registration

Patients should be evaluated for potential eligibility for participation in this trial based on clinical data available to the investigator (tumor type, availability of paraffin embedded tumor tissue block, histopathology report, extent of disease, extent of previous treatment, organ function, comorbidity,...) and should then sign the informed consent. Availability of paraffin embedded tumor blocks, either from the primary tumor or from metastatic sites should be confirmed. The patient can then be registered.

6.1.2 Step 2: central confirmation of histopathology

The tumor block must then instantly be shipped to the central biobank (BioRep, Milan, Italy) together with the local histopathology report and, if available, the results of previous molecular analysis (instructions will be given through guidelines for biological material management and electronic capture of related information). As soon as the block has been received by the central biorepository and as soon as this institution confirmed presence of tumor tissue in the block, central pathology review will be performed in Leuven, Belgium and results will be submitted to EORTC.

6.1.3 Step 3: enrollment

Upon central confirmation of diagnosis by the central laboratory in Leuven, EORTC will instruct the investigational site that laboratory screening and baseline tumor assessment can be initiated on site. This includes documentation of extent of disease, ophthalmologic examination, ECG, LVEF (echo or MUGA scan), laboratory examinations, documentation of adverse events and concomitant medications. If applicable, a pregnancy test will also be performed. Upon confirmation of eligibility as per chapter 3, patient will be enrolled.

Cardiovascular evaluation:

Cardiac function will be assessed: LVEF (MUGA or ECHO) and standard 12-lead triplicate.

For open cohort the following information will be collected:

- ◆ Total dose of anthracyclines, date of last dose.
- ◆ Previous radiotherapy on mediastinum, total dose, date of last dose.
- ◆ Cardiac risk factors history of:
 - ◆ hypertension,
 - ◆ diabetes,
 - ◆ hyperlipidemia,
- ◆ coronary artery disease (cardiac angioplasty or stenting, myocardial infarction, unstable
- ◆ angina, coronary artery bypass graft surgery)
- ◆ Class III or IV Congestive Heart Failure (CHF), as defined by the New York Heart Association (NYHA) (see Appendix C)
- ◆ alcohol and tobacco use,

- ◆ stroke
- ◆ peripheral vascular disease
- ◆ Any additional risk factors for cardiomyopathy.

Imaging studies performed as standard of care within acceptable time windows, but prior to signature of informed consent, are acceptable if they match protocol-defined criteria. Acceptable time windows for performing each assessment are described in the column headings (section 6.4).

For patients aged ≤ 18 years old: a plain AP radiograph of a single proximal tibial growth plate must be obtained prior to the first dose of protocol therapy.

- ◆ If patients are found to have a closed tibial growth plate, no further radiographs will be required.
- ◆ If patients are found to have an open tibial growth plate, then repeat plain AP radiographs of the same tibial growth plate will be required during the treatment.

Repeated blood chemistry, hematology, coagulation, and physical examination will not be required at baseline if the according screening investigations have already been performed within 7 days prior to the start of study treatment.

As decreases in serum testosterone have been documented in male patients receiving crizotinib, the following hypogonadism laboratory tests will be performed in pubertal male patients: serum testosterone (LC-MS/MS), serum sex hormone binding globulin, serum luteinizing hormone, serum prolactin (met LC-MS/MS). Blood samples must be taken prior to 11:00 in the morning.

6.2 During treatment

Treatment can be started after central confirmation of diagnosis and successful local screening (chapter 4; enrollment step 3). Treatment should be started at the most 7 weeks after registration step 1.

All cycles are 21 days in duration.

Safety information (hematology, blood chemistry, adverse events and concomitant medications) will be collected at baseline, at day 15 of cycle 1 and at the end of every cycle.

Periodic monitoring of cardiac function will be performed by LVEF for all patients on treatment every 3 cycles and at the end of the treatment

If clinically indicated, more frequent monitoring will be performed. Consultation with a cardiologist is recommended. **IMPORTANT:** monitoring of hepatic laboratory test (transaminases and total bilirubin): the minimum frequency of monitoring must be every 2 weeks for the first 2 months and monthly thereafter.

Hypogonadism laboratory tests will be performed in male patients: serum testosterone (LC-MS/MS), serum sex hormone binding globulin, serum luteinizing hormone, serum prolactin (met LC-MS/MS), on day 15 cycle 1, day 1 of cycles 2 and 3 and depending on medical conditions the frequency of next assessments will be left to investigator's judgment thereafter. Blood samples must be taken prior to 11:00 am in the morning.

Tumor assessment will be performed every other cycle. RECIST 1.1 will be used to determine the tumor response. CT or MRI will include chest, abdomen and pelvis at all time-points at baseline, during treatment and at the end of the trial. Appropriate imaging for exclusion of renal cyst should be performed.

CT or MRI scan should also be performed whenever disease progression is suspected (e.g. symptomatic deterioration) or to confirm a PR or CR at least 4 weeks after the initial documentation of the response according to RECIST 1.1. All scans will be sent electronically to EORTC for documentation and response review (instructions will be provided as "imaging guidelines").

In case of long duration of response to crizotinib (CR/PR): Tumor assessments may be extended to every 4 cycles (q12 weeks) or according to standard practice for the indication beyond 16 cycles (+/- 10 months of treatment).

In case of long stabilization of the disease with crizotinib (SD): Tumor assessments may be extended to every 4 cycles (q12 weeks) for the indication beyond 20 cycles (+/- 12 months).

For patients aged ≤ 18 years old that have been found to have an open tibial growth plate at the baseline assessment, plain AP radiographs of the same tibial growth plate will be repeated at the end of cycle 3 and then approximately every 6 months thereafter (timed with the nearest disease evaluation).

Patients with evidence of growth plate thickening or other changes during treatment with crizotinib should have a knee MRI performed to further assess the degree of physal pathology and undergo more frequent x-ray follow up. MRI should be performed without contrast.

Patients with knee MRI changes should be managed in an individualized manner. Consultation with an orthopedic surgeon may also be indicated. Plans for follow-up imaging will also be made on an individualized basis, taking into account the presence of symptoms at the knee or other joints as well as the decision to continue crizotinib or not.

Decisions regarding continuation of crizotinib are left to the investigator, taking into account the presence of any symptoms referable to the knee as well as the patient's response to crizotinib.

The monitoring of patients will be adapted in case of occurrence of

- ◆ Drug Induced Liver Injury (DILI) refer section 7.3.2.1
- ◆ Prolonged QTc (>500 msec) refer section 7.3.2.2
- ◆ Cardiac failure refer section 7.3.2.3
- ◆ Ophthalmology examinations refer section 7.3.2.4
- ◆ Renal cyst refer section 7.3.2.5
- ◆ Hypogonadism section 7.3.2.6

6.3 After the end of treatment (Follow-up)

If the treatment with crizotinib is terminated for reasons other than RECIST progression or death, patients will be followed until they initiate another treatment. Tumor assessment will continue until documented disease progression or initiation of another anticancer treatment.

If the treatment is stopped for progression, the patient comes off treatment. Crizotinib treatment beyond progression is not allowed in this trial.

Upon end of treatment for any reason, physical examination, performance status, blood chemistry and hematology, pregnancy test and tumor assessment must be obtained.

Hypogonadism laboratory tests will be performed in male patients: serum testosterone (LC-MS/MS), serum sex hormone binding globulin, serum luteinizing hormone, serum prolactin (met LC-MS/MS), Blood sample must be taken prior to 11:00 am in the morning.

Assessments performed in the previous 4 weeks (6 weeks for disease assessment) should not be repeated. Adverse events and concomitant medications must be assessed. Subjects must be followed for adverse events until at least 30 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable", whichever is later. From day 31 after last protocol treatment, only SAEs related to the study drug must be reported.

After the end of treatment, post-study survival status will be collected every 3 months.

6.4 Summary table

Protocol activities	Step1 registration	Screening Upon pathology confirmation	Study treatment (after step3)[1]						End of treatment	
			Cycle 1		Cycle 2 (imaging + 7)		Cycle 3	Cycles > 3	End txt/ Withdrawal [3]	Post-txt follow up
	Day 1 (+2) [2]		Day 15 (+2)	Day 1 (+ 2)	Day 15 (+2)	Day 1 (+ 2) (imaging + 7)				
Baseline Documentation										
Informed Consent [4]	X									
Medical/Oncology history [5]		X								
Baseline signs/Symptoms		X	X							
Mandatory shipment of tumor block, accompanying pathology report and local molecular results for central for molecular profiling [6]	X									
Physical examination [7]		X	(X)		X		X	X	X	
ECOG/ Lansky performance status		X	X		X		X	X	X	
Ophthalmologic examination [8]		X						After baseline, Q 4 cycles		
Laboratory Studies										
Hematology [9]		X	(X)	X	X		X	X	X	
Blood chemistry [9] *Transaminases and total bilirubin:		X	(X)	X	X	X*	X	X	X	
Coagulation [9]		X	(X)	X	X		X	X	X	
12-lead ECG [10]		X	X		X		X	> Cycle 3 every 4 cycles		
LVEF [10]		X					X	> Cycle 3 every 3 cycles		
Hypogonadism laboratory tests[17]		X		X	X		X	X	X	
Pregnancy test (as appropriate) [11]		X							X	
10ml blood sample for serum biomarkers [16]			X		X					
Disease Assessments										
Tumor assessments (including scans) [12]		X			End of cycle 2			X	X	

Protocol activities	Step1 registration	Screening Upon pathology confirmation	Study treatment (after step3)[1]						End of treatment	
			Cycle 1		Cycle 2 (imaging + 7)		Cycle 3	Cycles > 3	End txt/ Withdrawal [3]	Post-txt follow up
	Day 1 (+2) [2]		Day 15 (+2)	Day 1 (+ 2)	Day 15 (+2)	Day 1 (+ 2) (imaging + 7)				
For patients aged ≤ 18 years old AP radiograph of a single proximal tibial growth plate		X					X	X ^[18]		
Other Clinical Assessments										
Adverse events [13]	(X)	X	X	X	X		X	X	X	X
Concomitant medications/treatments [14]		X	X	X	X		X	X	X	
Survival, follow-up and further anticancer treatments[15]										X
Study Treatment										
Oral administration of crizotinib			Twice daily, continuously						Stop	
Footnotes for Schedule of Activities										
(1)Study Treatment: All assessments should be performed prior to dosing with study medications unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headings. All cycles are 21 days in duration. Once the primary endpoint for a given cohort of the study has been summarized and reported, ongoing patients on crizotinib will only need to visit the clinic every other cycle for study assessments. Enough study medication for two cycles of treatment will be dispensed at each of such clinic visits. During the non-visit cycle, the clinical site must phone patients to obtain an update of adverse events and concomitant medications.										
(2)Cycle 1/Day 1: Blood chemistry, hematology, coagulation, and physical examination not required (X between brackets) if the same screening assessment have been performed within 7 days prior to the start of study treatment.										
(3)End of Treatment/Withdrawal: Obtain these assessments if not completed during the previous 4 weeks on study (during the last 6 weeks for disease assessments).										
(4)Informed Consent: Must be obtained prior to undergoing any trial-specific procedure.										
(5)Medical/Oncological History: To include information on prior regimens.										
(6)Mandatory tumor tissue: Paraffin block(s) of adequate size to allow for at least 15 slides with cuts that are 5 micron thick. Archived or new tumor samples are acceptable. Primary tumor or metastatic site acceptable. These samples will be used for pathology confirmation, ALK/MET assessment and exploratory TR by the central laboratory. Slides are not accepted. Samples must be accompanied by electronic submission of local histopathology and existing molecular profile of the tumor										
(7)Physical Examination: includes an examination of major body systems, height (at screening only); weight, blood pressure and pulse rate (at baseline and on Day 1 of each cycle, not to be repeated if baseline <7days).										
(8)Ophthalmologic examination: includes visual acuity and slit lamp and should be performed by an ophthalmologist or licensed practitioner. The ophthalmologic examination should be repeated during the study when clinically indicated and at least every 4 cycles of the treatment.										

Footnotes for Schedule of Activities
<p>(9) Hematology (hemoglobin, platelet count, white blood cell count and differential (neutrophils and lymphocytes), blood chemistry (total and indirect bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, albumin, sodium, potassium, chloride, CO₂, calcium, phosphorus, BUN, creatinine, uric acid, glucose) and coagulation (PT and PTT).</p> <p>Hepatic laboratory test (transaminases and total bilirubin): the minimum frequency of monitoring must be on day 1 and day 15 of cycle 1 and 2 and on day 1 of each cycle thereafter.</p> <p>There should be more frequent testing for Grade 2-4 elevations or in case of signs or symptoms consistent with hepatotoxicity or hepatic failure (e.g., fatigue, weakness, anorexia, nausea, vomiting, right upper quadrant abdominal pain, jaundice, dark urine, and in rare cases, fever and rash).</p>
<p>(10) 12 lead ECG then triplicate set on Day 1 of Cycles 1, 2 & 3 and thereafter every 4 cycles as described in section 7.3.2.2.</p> <p>LVEF: will be performed at baseline and every 3 cycles in absence of signs/symptoms during the treatment period and at the end of the treatment. If clinically indicated, more frequent monitoring will be performed. Consultation with a cardiologist is recommended.</p>
<p>(11) Pregnancy test: All female patients of child-bearing potential are required to have a negative serum test at screening. The test should be repeated whenever one menstrual cycle is missed during treatment or a potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations</p>
<p>(12) Tumor assessments: RECIST 1.1 will be used to determine the tumor response. CT or MRI will include chest, abdomen and pelvis at all time points. The baseline scan may not be older than 4 weeks (=28 days +/- 2). Assessment every 2 cycles. Appropriate imaging for the detection of renal cyst should be performed. CT or MRI scan should also be performed whenever disease progression is suspected (e.g. symptomatic deterioration) or to confirm a PR or CR at least 4 weeks after the initial documentation of the response (RECIST 1.1). All scans will be sent electronically to EORTC.</p> <p>In case of long duration of response to crizotinib (RECIST 1.1 CR/PR): tumor assessment may be extended to every 4 cycles (q12 weeks) or according to standard practice for the indication beyond 16 cycles (+/- 10 months of treatment).</p> <p>In case of long stabilization of the disease with crizotinib (RECIST 1.1 SD): tumor assessment may be extended to every 4 cycles (q12 weeks) for the indication beyond 20 cycles (+/- 12 months of treatment).</p>
<p>(13) Adverse events: Subjects must be followed for adverse events from the time the patient is registered in step 2 until at least 30 days after the last dose of study treatment, or until all serious or study drug-related toxicities have resolved or are determined to be “chronic” or “stable”, whichever is later. Serious adverse events (SAEs) should be monitored and reported from the time that the subject is enrolled for step 2 as described in the protocol. Adverse events will be graded using CTCAE version 4.0.</p> <p>(x) From step 1 adverse events and SAEs related to study procedures (such as biopsy) must be reported</p>
<p>(14) Concomitant medications/treatments: Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days post the last dose of study treatment.</p>
<p>(15) Survival follow-up: After discontinuation of study treatment, post-study survival status will be collected every 3 months until death or 18 months after the first dosing of the last patient. Includes collection of information on subsequent anticancer therapies. Telephone contact is acceptable.</p>
<p>(16) One 10 ml blood sample for serum biomarkers.</p>
<p>(17) Hypogonadism laboratory tests will be performed in male patients: serum testosterone (LC-MS/MS), serum sex hormone binding globulin, serum luteinizing hormone, serum prolactin (met LC-MS/MS). Blood samples must be taken prior to 11:00 am in the morning. At baseline, day 15 C1, D1 of cycles 2 and 3 and depending on medical conditions the frequency of next assessments will be left to investigator's judgment thereafter. At the end of treatment laboratory tests will also be performed.</p>
<p>(18) For patients aged ≤ 18 years old a plain AP radiograph of a single proximal tibial growth plate must be obtained prior to the first dose of protocol therapy. For patients that have been found to have an open tibial growth plate at the baseline assessment, plain AP radiographs of the same tibial growth plate will be repeated at the end of cycle 3 and then approximately every 6 months thereafter (timed with the nearest disease evaluation). Patients with evidence of growth plate thickening or other changes should have a knee MRI (without contrast) performed to further assess the degree of physal pathology and undergo more frequent x-ray follow up.</p>

7 Criteria of evaluation

7.1 Criteria of evaluation for integrated translational research

A central part of this protocol is the analysis of patient tumor tissue. This includes central review of histopathology based on a paraffin embedded tumor block, central molecular analysis of tissue for confirmation of diagnosis (required for some entities in this study), central analysis of tissue for confirmation and characterization of the presence of ALK and/or MET pathways alteration ("integrated translational research"), as well as correlative biomarker studies in serum ("exploratory translational research"). The molecular tissue analysis consists of two parts. The "integrated TR" defines the tumor of an individual patient as being ALK / MET positive or negative, to facilitate the statistical analysis of the trial, which is primarily focused on the ALK/MET + sub-cohort. It will be done in real time. The "exploratory TR" further characterizes the nature of the ALK and/or MET pathway alteration, to improve our understanding of the biology of the disease and the therapeutic effects of crizotinib. A number of correlative analyses will be performed. This will not be done in real time. Results of the genetic tests will not routinely be shared with the treating physicians or patients.

7.1.1 ALK/MET test specifications ("integrated TR")

Disease	Pathway	Biomarker for integrated TR	Assay	Cut-point	Decision rule	Percentage of patients expected to be enrolled classified as biomarker positive.
ALCL	ALK	Detection of the rearrangement of ALK (if translocated). FISH based on "break-apart" approach.	IHC (ALK MAb Clone CD246, DAKO) FISH (Vysis LSI ALK Dual Color, Break Apart Rearrangement Probe, Abbott Molecular).	IHC (0 vs greater than or equal to 1) FISH: at least 15% cells with re-arrangement.	Both IHC and FISH for ALK is used – the concordance between the two tests is very good. One positive result from either test.	ALK alteration in 50-60% (either IHC or FISH).
IMFT	ALK	Detection of the rearrangement of ALK (if translocated). FISH based on "break-apart" approach.	IHC (ALK MAb Clone CD246, DAKO) FISH (Vysis LSI ALK Dual Color, Break Apart Rearrangement Probe, Abbott Molecular).	IHC (0 vs greater than or equal to 1) FISH: at least 15% cells with re-arrangement.	One positive result from either test.	ALK alteration in 50%.

Disease	Pathway	Biomarker for integrated TR	Assay	Cut-point	Decision rule	Percentage of patients expected to be enrolled classified as biomarker positive.
PRCC	MET	MET mutational analysis AND TFE3 rearrangement (break-apart approach)	Direct, bi-directional sequencing of exon 16-19 of MET OR FISH home-made break-apart TFE3 probe set: RP11-344N17 and RP11-552J9.	Presence of somatic mutation FISH: at least 15% cells with re-arrangement.	Either test result positive.	Mutations in ~10% of cases, rearrangement in single case reports.
ASPS	MET	TFE3 rearrangement (break-apart approach).	FISH home-made break-apart TFE3 probe set: RP11-344N17 and RP11-552J9.	FISH: at least 15% cells with re-arrangement.	Positive test result.	80% of cases.
CCSA	MET	EWS rearrangement.	Vysis® LSI® EWSR1 (22q12) Dual Color, Break Apart Rearrangement Probe (Abbott Molecular).	FISH: at least 15% cells with re-arrangement.	Positive test result.	Unknown.
ARMS	MET or ALK	FKHR rearrangement (break apart approach) OR ALK rearrangement (break apart approach).	Vysis® LSI® FKHR (13q14) Dual Color, Break Apart Rearrangement Probe (Abbott) AND FISH (Vysis LSI ALK Dual Color, Break Apart Rearrangement Probe, Abbott Molecular).	FISH: at least 15% cells with re-arrangement FISH: at least 15% cells with re-arrangement.	Either test result positive.	Single report with 3/5 positive by IHC.

7.2 Criteria of evaluation for study endpoints

7.2.1 Overall response rate

The primary endpoint overall response is defined as confirmed complete and partial response (RECIST 1.1) observed during the whole treatment period. This endpoint will be used to define a success in the two stage Simon design as defined in chapter 8.

If a success or a failure cannot be determined in a patient, this case will be reviewed by the Trial Steering Committee.

7.2.2 Evaluation of efficacy

Objective tumor response and time to progression will be assessed according to RECIST (version 1.1, Ref. 11).

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.

The following paragraphs are a quick reference to RECIST (version 1.1). The complete criteria are included in the published RECIST document (Ref. 11) also available at <http://www.eortc.be/RECIST>.

7.2.2.1 Measurability of tumor lesions at baseline

7.2.2.1.1 Definitions

- ◆ **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- ◆ **Measurable lesions** - *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination [using calipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component > 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- ◆ **Non-measurable lesions** - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis < 10 mm at baseline are considered non-pathological and should not be recorded or followed.
- ◆ **Target Lesions.** When more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a *short axis* of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be calculated and recorded.
- ◆ **Non-target Lesions.** All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

7.2.2.1.2 **Methods of measurements**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion”.

- ◆ **Clinical Lesions.** Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- ◆ **Chest X-ray.** Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. **In this trial chest X-ray will not be used for response assessment.**
- ◆ **CT, MRI.** CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). **Ultrasound and endoscopy will not be considered appropriate documentation for this trial.**
- ◆ **Cytology, Histology.** These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

7.2.2.2 **Tumor response evaluation**

All patients will have their best response from the start of study treatment until the end of treatment classified as outlined below. The observation of objective responses anytime during crizotinib treatment will define how many patients have to be entered per sub-cohort in this trial.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later. Refer to the table below.

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Integration of Target, non-Target and New lesions into response assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
<i>Patients with Target lesions \pm non target lesions</i>				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 6 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
<i>Patients with Non target lesions ONLY</i>				
No Target	CR	No	CR	Normalization of tumor markers, all tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
<p><u>Note:</u> Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as “<i>symptomatic deterioration</i>”. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later. The best overall response can be interpreted as below:

Table on confirmation

Response: First time point	Subsequent time point	BEST overall response	Also requires
CR	CR	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	PR	SD, PD or PR (see comment*)	
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	

Response: First time point	Subsequent time point	BEST overall response	Also requires
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	
* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.			

7.2.2.2.1 Frequency of tumor re-evaluation

Evaluations will be performed at the end of cycle 2 and then every other cycle until end of treatment. PR and CR will have to be confirmed by repeated imaging at least 4 weeks after observation of response.

In case of long duration of response to crizotinib (RECIST 1.1 CR/PR): tumor assessment may be extended to every 4 cycles (q12 weeks) or according to standard practice for the indication beyond 16 cycles (+/- 10 months of treatment).

In case of long stabilization of the disease with crizotinib (RECIST 1.1 SD): tumor assessment may be extended to every 4 cycles (q12 weeks) for the indication beyond 20 cycles (+/- 12 months of treatment). However, the decision must be shared and agreed with the EORTC headquarters team and the study coordinator.

7.2.2.2.2 Date of progression

This is defined as the first day when RECIST (version 1.1) for PD are met. Refer to Ref. 11.

7.2.2.3 Reporting of tumor response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.

Early death is defined as any death occurring before the first per protocol time point of tumor re-evaluation (end of cycle 2).

Patients for whom response is not confirmed will be classified as "not evaluable", unless they meet the criteria for stable disease (or the criteria for partial response in case of an unconfirmed complete response). Patients' response will also be classified as "not evaluable" if insufficient data were collected to allow evaluation per these criteria (i.e. no treatment given, no baseline imaging assessment and no imaging assessment after 2 cycles).

7.2.2.4 Stable disease duration

Stable disease duration will be measured from the time of start of treatment (or randomization for randomized studies) until the criteria for progression are met.

7.2.2.5 Disease control rate

Disease Control Rate (DCR) will be the percentage of patients with a CR, PR or SD according to RECIST at the end of cycle 2 (e.g. 6 weeks) and at the end of cycle 4 (e.g. 12 weeks) in the group of patients evaluable for response.

7.2.2.6 Response duration

Response duration will be the time interval between the date that the criteria of CR/PR (whichever is first recorded) are met for the first time and the first date of documented re-appearance of the disease (recurrence, progression or death). If neither event has been observed, then the patient is censored at the date of the last follow up examination.

7.2.2.7 Progression free survival

Progression free survival (PFS) will be the time interval between the date of enrollment (step 3) and the date of disease progression or death (events), whichever comes first. If neither event has been observed, then the patient is censored at the date of the last follow up examination.

7.2.2.8 Overall survival

Overall survival (OS) will be the time interval between the date of enrollment (step 3) and the date of death. Patients who were still alive or lost to follow-up when last traced are censored at the date of last follow up.

7.3 Evaluation of toxicity

7.3.1 General evaluation of side effects

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for adverse event reporting. A copy of the CTCAE can be accessed on the CTEP home page (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm). A link to this page is provided on the EORTC web site <http://www.eortc.be/>; if the location is moved to another site, this link will be updated.

All adverse events will be recorded; the investigator will assess whether those events are drug related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events.

Only the worst grade per CTCAE category per patient will be recorded per cycle of 3 weeks.

Hematological or biochemical deviations for normal ranges will be recorded independent of causality to crizotinib treatment.

The collection period will start from step 1. Planned safety analysis and tabulations are described in the statistics section.

Note from step 1 any adverse event or SAEs related to study procedures (such as biopsy) must be reported.

7.3.2 Other Safety Assessments

7.3.2.1 Laboratory safety assessments

In case of suspected Drug Induced Liver Injury (DILI): report the event to EORTC as an SAE.

Drug-Induced Liver Injury is considered a medically important event, regardless of whether hospitalization is required or not:

- ◆ Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other

causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- ◆ Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥ 3 times the upper limit of normal (ULN) concurrent with a total bilirubin $\geq 2 \times$ ULN with no evidence of hemolysis and an alkaline phosphatase $\geq 2 \times$ ULN or not available.
- ◆ For patients with preexisting ALT, AST or total bilirubin values above the ULN, the following threshold values during treatment should be used in the definition mentioned above:
 - ◆ With pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥ 2 times the baseline values and $\geq 3 \times$ ULN, or $\geq 8 \times$ ULN (whichever is smaller)
 - ◆ With pre-existing values of total bilirubin above the normal range : total bilirubin increased by $1 \times$ ULN over baseline or $\geq 3 \times$ ULN (whichever is smaller)

7.3.2.2 ECG measurements

A 12-lead (with a 10-second rhythm strip) tracing will be used for all ECGs. Triplicate ECG measurements will be obtained at all time-points except a single ECG measurement at screening. For triplicate measurements, three consecutive 12-lead ECGs will be collected approximately 2 minutes apart. It is preferable that the machine used has a capacity to calculate the standard intervals automatically. ECG measurements will include PR interval, QT interval, RR interval and QRS complex. Additional ECGs will be performed as clinically indicated.

In case of prolonged QTc (>500 msec), the ECG should be reviewed by a cardiologist at the site to confirm the QTc prolongation. Crizotinib should be withheld until the drug relationship of the event is determined (rule out electrolyte imbalance or influence of concomitant medication). In case of a crizotinib treatment related QTc interval measurement higher than 500 msec (grade ≥ 3) dosing should be interrupted until recovery to Grade ≤ 1 then resume at 200 mg twice daily and permanently discontinued for a Grade 4 QTc prolongation event. In both circumstances (Grade 3 or 4) continuous electrocardiogram (ECG) monitoring will be done under physician supervision until the QTc value recovers to Grade ≤ 1 . Triplicate ECG surveillance will again be performed when crizotinib is restarted on a reduced dose due to Grade 3 prolongation of the QTc as described in section 5.5.

The timing of the triplicate assessment of ECGs should be prior to (0 hour) and 2-6 hours after morning dosing of crizotinib on Day 1 of Cycles 1, 2 & 3 and thereafter every 4 cycles.

7.3.2.3 Cardiac failure

In clinical studies with crizotinib and during post marketing surveillance, severe, life-threatening, or fatal adverse reactions of cardiac failure were reported.

Patients with or without pre-existing cardiac disorders, receiving crizotinib, should be monitored for signs and symptoms of heart failure (dyspnoea, oedema, rapid weight gain from fluid retention).

If signs/symptoms of cardiac failure are observed, patients must permanently stop crizotinib.

7.3.2.4 Ophthalmology examinations

At screening, each patient will have an ophthalmologic exam including visual acuity, fundoscopy and slit lamp performed by an ophthalmologist or licensed practitioner. Additional eye examinations will be performed as clinically indicated and at least every 4 cycles of the treatment.

7.3.2.5 Active surveillance for renal cysts

The development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic, and have developed from 2 and 6 months after starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended.

Active surveillance with appropriate imaging (contrast-enhanced CT scanning or magnetic resonance imaging) should be performed at the time of the renal cysts diagnosis and as scheduled per protocol (eg, every 6 weeks with contrast-enhanced CT scanning or magnetic resonance imaging assuring full visualization of the kidneys). Investigators should also review retrospectively all CT/MRIs for any prior occurrence of complex renal cysts.

In addition, dipstick urinalysis (should include test for protein and blood) should be performed at the time of the renal cysts diagnosis and on Day 1 of each cycle thereafter. Urine reflex microscopy is required whenever urine dipstick is positive for blood or protein.

7.3.2.6 Evaluation of hypogonadism

All male patients enrolled in the study after protocol amendment approval will undergo hypogonadism laboratory testing as described chapter 6 at screening/baseline, during treatment, and at the end of treatment.

7.3.3 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

**SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED
ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL**

(see chapter on Reporting Serious Adverse Events)

7.3.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events at least with reasonable possibility related to study treatment). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients could die from toxicity after a complete assessment of the response to therapy).

7.3.5 Phototoxicity

As crizotinib is identified with probable phototoxicity potential, patient should avoid sunbathing, prolonged unprotected sun exposure, or tanning for the duration of the study period.

7.3.6 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

For hematological events, the medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients.

Patients who have discontinued treatment because of toxicity will always be included in the toxicity analyses.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

The main endpoint of the trial will be the rate of confirmed response (CR or PR according to RECIST 1.1) achieved with crizotinib. It is aimed to achieve a response rate with crizotinib of at least 30% (P1) in ALK/MET+ sub-cohorts of patients. The treatment will be considered as ineffective if the response rate is 10% (P0).

As the treatment effect is essentially expected in the ALK/MET+ patients, the six cohorts have been divided in two sub-cohorts: ALK/MET+ and ALK/MET- patients.

For each of the 12 sub-cohorts, a Simon's optimal two stage design ($\alpha=\beta=0.10$) will be implemented (Ref. 21). The first stage will require 12 eligible and evaluable* patients in each sub-cohort. If at least 2 patients respond, the sub-cohort goes to the second stage and the accrual is continued until 35 eligible and evaluable* patients. At that time, if less than 6 patients respond, the sub-cohort is stopped and will be declared as ineffective. If at least 6 of the 35 patients respond (17%), the sub-cohort will be deemed successful.

Therefore the maximum sample size per cohort will be 70 eligible and evaluable* patients per cohort (or 35 eligible and evaluable* patients per each of the 12 sub-cohorts).

* A patient will be considered as "evaluable" if he/she started the study treatment (at least one dose) and he/she had an imaging assessment at baseline and at least the first imaging assessment after start of treatment (i.e. after 2 cycles of treatment).

8.1.2 Decision rules

8.1.2.1 ALK/MET+ sub-cohorts

As explained above a maximum of 35 eligible and evaluable patients will be recruited per sub-cohort. There is no intent to interrupt the recruitment up to 35 unless one of the below decision rules applies.

Once the first 12 eligible and evaluable patients from a same ALK/MET+ sub-cohort (as required for the stage I) are recruited, two scenarios are possible:

- ◆ If at least 2 (out of 12) patients have a confirmed response (CR or PR), then the recruitment will continue up to 35 in that sub-cohort.
- ◆ If at least 11 (out of 12) patients are non-responders (i.e. stopped their treatment without any confirmed response), then the recruitment is immediately stopped for that sub-cohort.

The response evaluation is based on the whole treatment duration. However, in the study patient population, response may require a very long observation time. Indeed, patients may remain in stable disease for a long period and then switch very late to either progression (best response being then SD) or response (best response being then CR or PR).

It thus may not be possible to apply the above decision rules before having reached the enrollment of 35 patients. In this case, the two stage procedures will not apply and the whole ALK/MET+ sub-cohort will be analyzed as one-stage procedure (see statistical methods 8.2.3).

The trial will have one result for each of the six ALK/MET + sub-cohorts. Reports can be released and published for one given sub-cohort as soon as the primary endpoint is met in the ALK/MET+ sub-cohort and complete data base lock and analysis have been performed.

8.1.2.2 ALK/MET- sub-cohorts

Since the study focuses on the ALK/MET+ patients, accrual of ALK/MET- sub-cohorts will be driven by the recruitment and outcome of the according ALK/MET+ sub-cohorts:

- ◆ If the accrual in the ALK/MET- sub-cohort is faster than in the ALK/MET+ sub-cohort, the same decision rule as described in 8.1.2.1 will apply to the ALK/MET- sub-cohort. The treatment will be deemed successful or ineffective in that ALK/MET- sub-cohort according to the above mentioned Simon's optimal two stage design.
- ◆ However, if the accrual in the ALK/MET- sub-cohort is slower than in the ALK/MET+ sub-cohort and the ALK/MET+ sub-cohort finished its recruitment (early stop after stage I analysis or 35 eligible patients recruited for stage II analysis), the accrual of ALK/MET- sub-cohort will be suspended and analyzed at the same time as the ALK/MET+ sub-cohort. At that point, the Trial Steering Committee will take the decision to continue the recruitment of the ALK/MET- sub-cohort or stop accrual of such patients. Only in the case of clinically relevant activity in the ALK/MET- sub-cohort, recruitment will continue until 35 eligible and evaluable patients have been treated.

8.1.3 Early stopping rules for low prevalence of ALK/MET+

If, in a given cohort, the true prevalence of ALK/MET+ is less than 25%, the inclusion for this cohort should be stopped early due to insufficient feasibility. This decision will be taken by the Trial Steering Committee.

When 20 patients are screened in a cohort, the results of the central molecular testing for ALK/MET (= integrated TR) will be checked:

- ◆ If only one patient is ALK/MET+, we can reject H_0 that the true percentage of ALK/MET+ is 25% or more ($p < 0.05$, based on exact binomial probabilities). In this case, the accrual in this cohort will be stopped for low prevalence of ALK/MET+.

If only 2-4 patients are ALK/MET+, the true incidence of ALK/MET+ patients is likely to be below 40%, and the Trial Steering Committee (see section 9) will decide if the cohort will continue to accrue more patients.

8.1.4 Screening for ALK/MET

The results of the molecular testing for ALK/MET (= integrated TR) and the outcome of RECIST response assessment have to be known prior to proceeding to the final analysis of the trial or deciding to discontinue a certain cohort or sub-cohort in this study.

If the recruitment is stopped for any reason in a given tumor sub-cohort (ALK/MET+ or ALK/MET-), the screening result of any new patient will have to be known before the start of treatment (real time molecular analysis) in order to exclude entry of patients into the closed sub-cohort.

8.2 Statistical analysis plan

8.2.1 Primary and secondary endpoints

The primary endpoint is response rate (CR+PR, documented by RECIST 1.1) with response confirmation.

Secondary endpoints are safety (CTAE v 4.0), PFS, OS, clinical benefit rate, duration of response and duration of clinical benefit.

8.2.2 Analysis populations

- ◆ Per protocol population: All eligible patients who have started their treatment (at least one dose of the study drug) and have their imaging assessment at baseline and at least after cycle 2.
- ◆ Safety population: All patients who have started their treatment (at least one dose of the study drug)

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol.

A patient will be considered to be evaluable if he/she started the study treatment (at least one dose) and he/she had an imaging assessment at baseline and at least the first imaging assessment after start of treatment (i.e. after 2 cycles of treatment).

Potential eligibility and evaluability problems will be assessed by the Clinical Research Physician at time of medical review.

8.2.3 Statistical methods

The primary endpoint (response rate (CR+PR), documented by RECIST 1.1, with response confirmation) will be analyzed per sub-cohort in the per protocol population as follows: the primary endpoint is binomial, i.e., each patient either has a response or not. The number of responding patients in each sub-cohort will be counted.

For the stage I analysis, if the number of responding patients is reached (i.e. at least 2 patients with confirmed CR or PR), the sub-cohorts goes to the stage II. However, there is enough evidence that the sub-cohorts will never fill the stage I criteria (i.e. at least 11 patients who stopped their treatment without any confirmed CR or PR), then the recruitment is stopped and final report will be provided once all patients finish their treatment.

If the sub-cohort goes to stage II and that the minimum number of responding patients is reached (6 responders out of 35 eligible and evaluable patients), it will be concluded that the new treatment is effective enough to warrant further research. If the minimum number of responses is not reached, it will be concluded that the new treatment is not effective enough. Also, the point estimate and the 90% confidence interval (one-sided) for response will be calculated.

However, if the recruitment of the sub-cohort is fast enough to avoid the stage I decision rule or if additional eligible and evaluable patients are included in the sub-cohort (due to the enrollment procedure in 3 steps), final analysis of the primary endpoint will be done on the whole sub-cohorts of eligible and evaluable patients. Actual α and power will be recalculated according to the number of patients analyzed. In addition, the decision rule on the minimum number of responders will not apply. Instead, the point

estimate and the $(100-\alpha)\%$ confidence interval (one-sided) will be used to conclude. If the lower bound of confidence interval is above 10%, it will be concluded that the new treatment is effective enough to warrant further research. If lower bound of confidence interval includes 10%, it will be concluded that the new treatment is not effective enough.

The secondary endpoint (Safety (CTAE v 4.0)) is reported as number of adverse events per patient and number of adverse events per patient/cycle in the safety population. Further, worst adverse event per patient is analyzed. The main analysis is based on the safety population for all adverse events. Serious adverse events are reported separately. Safety data will be presented per cohort.

PFS, OS, duration of response, clinical benefit rate, duration of clinical benefit will be analyzed in the per protocol population and presented per sub-cohort.

Both survival times (PFS and OS) will be analyzed using the Kaplan Meier method. PFS and OS between ALK/MET+ and - patients will be compared, using log rank test (exploratory only).

The clinical benefit rate is the number of patients who achieve CR, PR, or SD. For this analysis the point estimate and the 95% confidence interval will be calculated.

8.2.4 Pre-planned sensitivity or exploratory analyses

All the analyses mentioned above (response rate, PFS, OS) will also be performed in the safety population as sensitivity analyses.

In addition, the results will be compared between ALK/MET+ and ALK/MET- patients, for all endpoints, including PFS and OS. The latter analyses will be purely descriptive and no formal hypothesis testing will be conducted.

8.2.5 Analysis of predictive factors

A descriptive analysis is foreseen to assess the ALK/MET status as a predictor for treatment response. The outcomes that are described as primary and secondary endpoints will be analyzed in this regard.

8.2.6 Data recoding and display

Frequency tables will be tabulated for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of enrollment step 3 – date of past event + 1) and presented using the median and range. For example, on the enrollment checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of enrollment step 3 – last administration/diagnosis +1).

Other delays (e.g. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example $> 2.5 \times \text{ULN}$, $> 5 \times \text{ULN}$, $> 10 \times \text{ULN}$). For laboratory

data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose ...) are presented using the median and range (minimum, maximum).

The dose intensity of the treatment will be calculated as described in section 12 in ST-006-WIN-02 Version: 1.00 (February 2011) (Ref. 11).

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

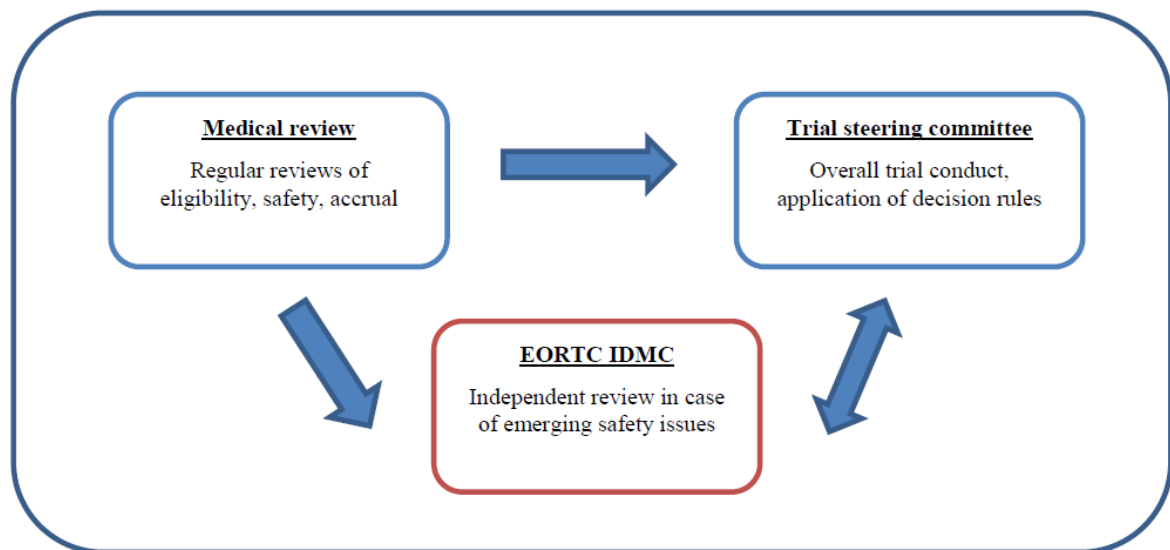
A descriptive table of the timelines for central histopathology analysis will be provided.

8.3 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Thirty days after all patients have stopped protocol treatment
2. The trial is mature for the analysis of the primary endpoint as defined in the protocol, if the trial reaches its primary endpoint
3. The database has been fully cleaned and frozen for this analysis

9 Data Monitoring



A Trial Steering Committee including the EORTC study coordinator, clinical research physician and statistician, equivalent functions from Pfizer, and trial independent experts will review safety and activity at each stage defined by the Optimal Simon's design and in case decision rules for low prevalence or for fast recruitment are met. The role of the Trial Steering Committee is further detailed by a charter.

The Medical Review Team will review accrual, eligibility and safety data within the EORTC Headquarters on a regular basis. Problems which are identified will be discussed with the Trial Steering Committee who will take appropriate measures. Safety information will also be included in trial status reports which serve

as a basis of discussion during EORTC Group meetings. These reports will be made available to investigators participating in the study.

The EORTC Independent Data Monitoring Committee (IDMC) will review all safety problems identified by the EORTC Headquarters (Medical Review Team) for which an advice is sought. The Trial Steering Committee can also ask to IDMC advices in case of issues with the application of the stopping rules. The Trial Steering Committee will be responsible also for Translational Research project (explained in section 10).

10 Translational research

10.1 Overview

A central part of this protocol is the analysis of patient biological material. The molecular tissue analysis consists of two components. The "integrated TR" component includes central review of histopathology based on paraffin embedded tumor blocks, central molecular analysis of tissue for confirmation of diagnosis (if required), central analysis of tissue for confirmation and characterization of the presence of ALK and/or MET pathway alterations, as well as correlative biomarker studies in serum.

The "exploratory (or correlative) TR" component further characterizes the nature of the genetic change in ALK and MET, to improve our understanding of the biology of the disease and the therapeutic effects of crizotinib. A number of correlative analyses will be performed. Results of the molecular tests will not routinely be shared with the treating physicians or patients.

This translational research program will be used to explore in further detail various molecular factors in tumor tissue and serum samples from the patients with ALCL, IMFT, PRCC, ASPS, CCSA or ARMS and their impact on response to crizotinib. This will allow a deeper understanding of the observed ALK and MET alterations and their implications for therapy with crizotinib.

Signal transduction downstream of the HGF receptor, MET, is involved in multiple cancer related pathways which induce invasiveness, motility and angiogenesis. Abnormal MET activation can be caused by either direct MET alteration (point mutations, amplification or chromosomal aberrations) or by MET phosphorylation via HGF overexpression. This can lead to engagement of key signaling pathways such as RAS, PI3K, STAT, NOTCH and beta-catenin/WNT that are known to be involved in initiation and progression of multiple cancer types. In addition, abnormal MET activation in cancer correlates with poor prognosis.

ALK is a membrane associated tyrosine kinase receptor. Alterations of ALK via chromosomal aberrations, amplifications and point mutations are known to play a role in several malignancies including ALCL and IMFT. Chromosomal rearrangements of ALK enhance cell proliferation and survival and hence it appears to play a key role in driving several cancer types.

The main challenge in translation of this molecular information into effective therapies is the accurate identification of patients who could benefit from the targeted therapy. Therefore it is crucial to conduct target validation such as for the molecular aberration in the ALK/MET pathways. As the level of activation of these pathways may be diverse, exploratory investigations and detailed characterization of targets in selected tumor subtypes will provide additional information and may help in improving patients' stratification.

10.2 Objectives

Key objectives of this translational research are:

- ◆ Identification and characterization of the ALK and/or MET status and pathway alteration in the different patient cohorts and sub-cohorts of this trial.
- ◆ Explorative correlation of specific molecular changes in tissue and serum that can potentially be used as predictive markers of response to crizotinib. This would potentially allow a better definition of the patient population most sensitive to crizotinib, in the future.
- ◆ Development and partial validation of reliable assays for future routine usage.

10.3 Methods

Fresh frozen or formalin fixed, paraffin embedded (FFPE) tissue samples collected either from the primary tumor or from metastatic sites will be analyzed. Chromosomal aberrations and gene fusions will be investigated including further characterization of key aberrations of ALK and MET pathways as used as part of the trial design (see Criteria for evaluation, ALK/MET test specifications, Section 7.1.1). Investigations will include characterization of ALK gene rearrangements or ALK protein expression in ALCL and IMFT, characterization of the chromosomal translocations associated with TFE3 gene rearrangements in PRCC, ASPS (e.g. ASPL-TFE3), EWS gene rearrangement in CCSA (e.g. EWS-ATF1), and FKHR gene rearrangements e.g. PAX3/7-FKHR translocation and ALK rearrangement in ARMS. Gene rearrangements will be identified by fluorescence in situ hybridisation (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) for detailed identification of fusion genes. ALK protein expression will be determined by IHC. In addition, the frequency of specific MET mutations will be investigated in PRCC by direct, bi-directional sequencing of exon 16-19 of MET.

The downstream effects of these molecular changes upon activation of the ALK and MET pathways will be investigated as well. Molecular markers relating to the ALK and MET pathways, e.g. downstream components of the signaling pathway such as GAB, will be investigated by looking at protein expression, protein phosphorylation status by immunohistochemistry (IHC) and expression analysis using reverse transcriptase polymerase chain reaction (RT-PCR).

Construction of tissue-micro arrays (TMA) from FFPE material is foreseen to allow a large-scale evaluation of molecular aberrations and their downstream effects on pathway activation.

Analysis of soluble factors relating to ALK and MET pathway activation, such as HGF in serum in the case of MET, will be done using immunoassay methods e.g. ELISA. This will be used to determine if serum factors can potentially serve as surrogate marker to predict response to crizotinib treatment.

All aspects and methodologies will be detailed in specific document that will be included in the technical appendix.

10.4 General principles for biological material collection and biobanking

Human biological material (HBM) collection involves the collection and storage of HBM, residual HBM or derivatives in compliance with ethical and technical requirements. Biobanking refers to the chain of procedures that encompass the life cycle of the HBM, e.g. from collection, and shipping to long term storage, use, and disposition, and may also be subject to local regulation and/or national/international legislation.

In this study, the collection of HBM will be centralized and stored at an independent service provider for biobanking in Milan,

BioRep s.r.l.
c/o Dibit 2, Via Olgettina, 60
20132 Milano
Italy

This facility will register, store, check and distribute the material. From here, the HBM will be distributed to the research laboratories involved in the histological confirmation of diagnoses translational research (TR) projects specified in this protocol and/or defined in the future (e.g. a new TR protocol for cross validation of TR results with other laboratories). Residual HBM left over from laboratory analysis will be stored in the central biobank. EORTC will be the coordinator of the chain of custodianship of the HBM remaining in the biobank. If the following situations arise (and in accordance with the respective patient consent), EORTC coordination of the chain of custodianship of HBM can be terminated: if there is no remaining HBM (i.e. the HBM is wholly used up or has been destroyed) or if the patient withdraws the consent for the use of HBM in research.

The following principles apply to storage of HBM:

- ◆ The biobank will have a designated manager who will act as a communication point with the EORTC.
- ◆ The collected HBM should be documented, e.g. the amount remaining and its location.
- ◆ The Study Coordinator in collaboration with the Trial Steering Committee (StC) will be responsible for TR project review and prioritization for access to residual HBM in the EORTC central repository, for the purpose of newly proposed TR projects not specified in the protocol. In the absence of the StC, responsibilities of the StC are transferred to the Study Coordinator and/or EORTC HQ, if applicable. Final decisions on the use of HBM will be determined by a majority vote of the StC. Additional expertise may be sought through advisory non-StC members.

Access to HBM (see EORTC Biobanking Policy POL020, Ref. 12): HBM may be used for another purpose than for which it was originally collected, subject to meeting ethical principles/and being covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

- ◆ A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with the StC.
- ◆ The StC will prioritize the TR projects. Access procedures defined by the StC will build on the following key points:
 - ◆ Project prioritization
 - ◆ should be strongly based on scientific merit,
 - ◆ should consider the contribution of the different investigators to the trial and TR project,
 - ◆ will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).
- ◆ Protection of confidentiality must be respected.
- ◆ An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are

responsible for collecting and providing information on availability of HBM for the feasibility assessment.

Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).

- ◆ Once StC prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.
- ◆ The EORTC Board will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the StC and the TR project leader(s), as needed.

10.5 Sampling & Biological material routing

If the patient has accepted to participate in the translational research program described in this chapter, the samples specified below will be used for this purpose. All samples will be shipped to and handled by the central biorepository (BioRep) in Milan.

10.5.1 Formalin fixed paraffin embedded blocks (mandatory)

Formalin fixed paraffin embedded (FFPE) tumor blocks will be collected for all patients (this is mandatory for study participation and biomarker assessment of ALK and MET needed for the trial design). Blocks must be accompanied by electronic information on histopathology reports and, if applicable, by written reports on previously performed molecular analysis of the tumor. Slides are not accepted. FFPE blocks may be from primary or metastatic sites. Residual FFPE material will be used for the correlative translational research program detailed here but also for future research projects as described via the access process in section 'General principles for biological material collection and biobanking'. All provided FFPE materials must be from tissue samples taken prior to any treatment with crizotinib.

10.5.2 Fresh frozen tissue samples (optional)

The collection of fresh frozen tissue samples (from primary or metastatic sites) is optional for this study. Handling and shipment of such material will be specified in a study-specific technical guidelines distributed to the sites at time of site authorization. All fresh frozen samples (including any samples from re-biopsy) must be taken prior to any treatment with crizotinib.

10.5.3 Serum samples (mandatory)

Serum will be collected from all patients. Serum will be prepared from whole blood (a guideline document providing details for preparation will be given in a separate study specific document for HBM collection). A 10 ml blood sample (used to prepare serum) will be collected at two time-points, at baseline and the end of second cycle of treatment. Serum samples will be sent frozen to the central biorepository in Milan. At the time of analysis of the serum samples, the collection of frozen samples and frozen serum samples will be shipped on dry-ice to the central laboratory (as needed for the TR program). All specific and logistical aspects of the HBM collection, shipment and usage will be detailed in specific guidelines that will be a part of a technical annex, distributed to the sites at time of site authorization.

10.6 Statistical analysis

Exploratory analyses will be performed to assess the ability of markers to predict treatment outcome:

- ◆ For the association analyses between ALK/MET status (+/-) or other binary markers and objective response, clinical benefit or other binary endpoints, markers predictive accuracy properties will be

analyzed by assessing sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV).

- ◆ For continuous markers where no cut-points has been previously identified, Receiver Operating Curves (ROC) technique will be used to find optimal cut points as well as for description of general operating characteristics. Youden index will be calculated to support ROC analysis.
- ◆ For the association analyses between ALK/MET status (+/-), other binary or continuous markers and PFS, OS or other time to event endpoints, both univariate and multivariate Cox regression models will be fit. Hazard ratios will be presented. In order to assess models predictive accuracy, Concordance indexes corrected for optimism by bootstrap technique (C-index) will be computed. Other (complementary) predictive accuracy parameters might also be calculated (eg.V-Schemper).

Due to the exploratory character of this project, no hypothesis-testing will be conducted. Estimates will be presented with their 95% confidence intervals.

A detailed Statistical Analysis Plan will be included in the technical appendices (see section 10.7).

10.7 Technical appendix

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. Separate technical documents (technical appendix) will be jointly developed for each project. These appendices will be written before starting any analysis and will specify the analytical and methodological details and will precise data transfer procedures.

Clinical and patient-reported outcome data will be stored in the EORTC clinical database and biological investigational data will be stored in respective collaborating institutions.

11 Investigator authorization procedure

Investigators will be authorized to register patients in this trial only once they have returned the following documents to the EORTC Headquarters:

- ◆ The updated signed and dated curriculum vitae of the Principal Investigator in English with a GCP training proof.
- ◆ The (updated) list of normal ranges for the investigator's institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator's institution.
- ◆ The Confirmation of interest by Principal Investigator Form (CIF), stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the CIF.

- ◆ The Study Agreement between EORTC and investigator's institution.
- ◆ A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- ◆ A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.

- ◆ The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Headquarters. Please keep in mind that all communication is done ONLY between the primary institution and the EORTC Headquarters.
- ◆ The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication.
- ◆ An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law.

The new investigator will be added to the “authorization list”, and will be allowed to register patients in the trial as soon as

- ◆ All the above mentioned documents are available at the EORTC Headquarters.
- ◆ All applicable national legal and regulatory requirements are fulfilled.

Patient registration from centers not (yet) included on the authorization list will not be accepted.

12 Patient registration & enrollment procedure

12.1 General procedure

This trial enrollment requires a three steps procedure: registration (step 1), central histopathology confirmation (step 2) and enrollment (step 3).

The EORTC investigators will register patients through the EORTC, following the standard EORTC procedure. Patient registration will only be accepted from authorized investigators (see chapter on “investigator authorization procedure”).

Patients should be registered directly on the EORTC online randomization system (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive registration/randomization program, the investigator needs a username and a password (which can be requested at <http://orta.eortc.be/>).

In case of problems investigators can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday in order to register patients via the EORTC call center. Registration via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (<http://orta.eortc.be/>) and it is updated annually.

Through Internet:	http://orta.eortc.be/
In case of problems by phone:	+32 2 774 16 00

Registration step 1, central histopathology confirmation step 2 and enrollment step 3 must be completed before the start of the protocol treatment. (See also chapter 4.1 for the detailed requirements)

12.2 Registration (step 1)

STANDARD INFORMATION REQUESTED:

- ◆ institution number
- ◆ protocol number 90101
- ◆ step number: 1
- ◆ name of the responsible investigator
- ◆ patient's code (*maximum 4 alphanumeric*s)
- ◆ patient's birth date (*day/month/year*) or year of birth (as allowed per applicable legislation)

PROTOCOL SPECIFIC QUESTIONS:

- ◆ tumor type will be checked
- ◆ tumor block availability will be confirmed
- ◆ date of written informed consent (*day/month/year*)

Once tumor type, tumor block availability and date of informed consent have been verified, a sequential patient identification number (“seqID”) will be allocated to the patient. This number will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

12.3 Central histopathology confirmation (step 2) done by EORTC central laboratory

Upon confirmation of reception of the tumor block(s) at the central biorepository, and verification of satisfactory quality of the sample(s), histopathology central review will be performed in Leuven, Belgium.

EORTC will notify the centers about the conclusion of the pathology review. The site will however not routinely be informed about results of central molecular testing.

12.4 Enrollment (step 3)

Upon confirmation of the pathology review and notification of the site about the correct diagnosis, the patient can be screened. After verification of all other eligibility criteria the patient can be registered for step 2, which completes the enrollment, and start the treatment protocol. Investigators will proceed with the enrollment of the patient through the same process described in section 12.1.

Previously indicated patient identifiers will be requested, step 3 has to be selected.

STANDARD INFORMATION REQUESTED:

- ◆ institution number
- ◆ protocol number 90101
- ◆ step number: 3
- ◆ name of the responsible investigator
- ◆ patient's code (*maximum 4 alphanumeric*s)
- ◆ patient's birth date (*day/month/year*) or year of birth (as allowed per applicable legislation)

PROTOCOL SPECIFIC QUESTIONS:

- ◆ all other eligibility criteria will be checked
- ◆ actual values for the eligibility parameters will be requested
- ◆ date foreseen for protocol treatment start

Please note that there should not be more than 7 weeks between registration step 1 and treatment start (enrollment step 3). A maximum of 2 days delay will be allowed for logistical issues. If the patient has to be enrolled for step 3 after this time frame, please contact the EORTC Clinical Research Physician and/or the Study Coordinator for approval.

If the patient is deemed to be ineligible or failed to be enrolled for any reason, the PIS/IC and the completed registration must be stored in the study master file. The form 0 for failure of patient enrollment should be completed identifying the reasons of non inclusion.

13 Forms and procedures for collecting data

13.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the SAE form and the Pregnancy notification form which are paper CRFs.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events).

A. Before the treatment starts

- ◆ The patient must be registered in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one day after the registration on <http://rdc.eortc.be/> or on <http://www.eortc.org> in the section for investigators.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members.

13.2 Data flow

The forms must be completed electronically, with the exception of the paper SAE form, according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The source data should be available for verification for each monitoring visit.

The EORTC Headquarters will perform extensive consistency checks on the received data and will issue queries in case of inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there directly.

The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

14 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

14.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information” (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A Serious Adverse Event is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- ◆ results in death
 - ◆ is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
 - ◆ requires inpatient's hospitalization or prolongation of existing inpatients' hospitalization
 - ◆ results in persistent or significant disability or incapacity
 - ◆ is a congenital anomaly or birth defect
 - ◆ results in any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above), e.g. secondary malignancy, AE as a result of an overdose.
 - ◆ The following events are considered as medical important conditions:
 - ◆ Renal cysts should be reported as SAEs.
 - ◆ Suspected Drug-Induced Liver Injury (DILI) events have to be reported as SAEs. Please refer to chapter 7.3.2.1 for laboratory assessments in case of DILI.
 - ◆ Any cardiac disorder should be reported as an SAE.
 - ◆ Gastrointestinal perforation should be reported as an SAE.
 - ◆ The following Adverse Events of Special Interest (AESI) are not necessarily SAEs but are also considered as medically important conditions in this protocol, and should be reported in the same timeframe as an SAE: Potential Sight-Threatening (PST) and Severe Vision Loss (SLV);
 - ◆ The following events would be considered indicative of a PST or SVL event: Amaurosis, Amaurosis fugax, Blindness, Blindness cortical, Blindness day, Blindness night, Blindness transient, Blindness unilateral, Hemianopia, Hemianopia heteronymous, Hemianopia homonymous, Optic atrophy, Optic ischaemic neuropathy, Optic nerve disorder, Optic neuropathy, Quadrantopia, Retinopathy, Sudden visual (or vision) loss, Toxic optic neuropathy, Tunnel vision, Visual cortex atrophy, Visual field defect, Visual pathway disorder, Retinal oedema, Retinal detachment, Maculopathy, Iritis, Uveitis, Visual field test abnormal.
- The occurrence of Grade ≥ 2 of any of these events should be treated as a SAE, except for Visual field defect, for which only Grade ≥ 3 should be treated as a SAE.

SAR: A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a **Serious Adverse Reaction**

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- ◆ Fatal or life-threatening SUSARs within 7 calendar days
- ◆ Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient or in-patient's hospitalization: A patient who is admitted to a hospital or clinic for at least one overnight stay.

14.2 Exceptions

The following situations are not considered to be SAEs and should not be reported on the SAE form:

- ◆ Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment
- ◆ A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated
- ◆ Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE
- ◆ Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, palliative care, rehabilitation, overdose without occurrence of an adverse event)
- ◆ Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, unless the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

14.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_v40

14.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following definitions in this table:

Relationship to the protocol treatment	Description
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event
No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the Serious Adverse Event form, if necessary with the reasoning of the principal investigator.

14.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following reference documents:

- ◆ For Crizotinib: Investigator's Brochure.

14.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from step 3 registration until 30 days after last protocol treatment. This procedure applies also for any SAE that occurs outside of the SAE detection period (as specified in table below), only if it is considered to have a reasonable possibility to be related to the investigational product or study participation (e.g. SAEs related to biopsy for tumor block, to screening procedure).

From step 1 registration until step 2 registration:	Only SAEs related to study procedure (e.g. related to biopsy for tumor block, to screening procedure)
From step 3 registration until 30 days after last protocol treatment:	All SAEs
From day 31 after last protocol treatment:	Only related SAEs

All reporting must be done by the principle investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE-related information must be faxed to:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027

To enable the EORTC to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principle investigator or any authorized staff member (i.e. on the signature list).

14.7 Reporting to investigators and competent authorities

The EORTC Pharmacovigilance Unit will forward all SAE reports within 24 hours of receipt to the appropriate persons within the EORTC Headquarters and to the pharmacovigilance contact at the pharmaceutical company, if applicable.

All SUSARs will additionally be forwarded to all participating investigators and Ethics committees

The EORTC Pharmacovigilance Unit will take in charge the expedited reporting to the Competent Authorities and EVCTM whenever applicable.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the group meeting report and which will be distributed to all participating investigators.

14.8 Pregnancy and exposure during lactation reporting

Pregnancy occurring during a patient's participation in this trial and exposure during lactation, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

- ◆ Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 30 days after last study treatment administration or exposure during lactation must be reported to the EORTC Pharmacovigilance Unit
- ◆ This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form/Fax
- ◆ If a Serious Adverse Event (SAE) occurs in conjunction with the pregnancy or with exposure during lactation, please also complete an SAE form as explained in the SAE chapter.

15 Quality assurance

15.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the VISTA/RDC (Remote Data Capture) system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

15.2 On-site quality control

The EORTC Headquarters will perform on-site quality control visits.

The first visit at a site will be performed within 3 months after the first patient's registration. Frequency of subsequent visits will depend on site's accrual and quality observed during the first / previous visit. Overall, the average frequency will be around one visit a year per site.

The aim of these site visits will be:

- ◆ to evaluate the local facilities available to the responsible investigators for performing the clinical trial, and the site's compliance with all protocol requirements

- ◆ to assess the consistency of the data reported on the case report forms with the source data
- ◆ to check that all Serious Adverse Events have been properly reported
- ◆ to assist the site in answering to any remaining queries
- ◆ to control the drug accountability process

15.3 Audits

The EORTC Quality Assurance and Control Unit (QA&C) regularly conducts audits of institutions participating in EORTC protocols. These audits are performed to provide assurance that the rights, safety and wellbeing of subjects are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives ...). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s) may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QA&C Unit immediately (contact at: QualityAssuranceandControlUnit@eortc.be).

In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

16 Ethical considerations

16.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (<http://www.wma.net>)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

16.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumeric) and date of birth or year of birth (as allowed per applicable legislation) will also be reported on the case report forms.

16.3 Informed consent

All patients or their legal representative will be informed about

- ◆ the aims of the study
- ◆ the possible adverse events
- ◆ the procedures and possible hazards to which the patient will be exposed
- ◆ the mechanism of treatment allocation
- ◆ strict confidentiality of any patient data
- ◆ medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The bold sections of the informed consent document must be reflected in any translation. The content of these bold sections can either be translated literally or translated in any way that best captures the information given.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

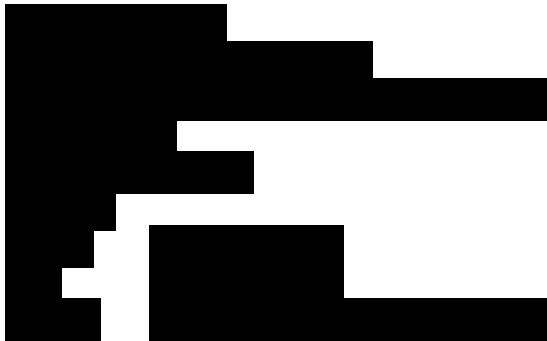
All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

17 Administrative responsibilities

17.1 The study coordinator

The Study Coordinator (in cooperation with the EORTC Headquarters) will be responsible for writing the protocol, contributing to the medical review, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and the medical review of the patients.

Study coordinator:



17.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: +32 2 7723545

Registration of patients:

<http://www.eortc.be/random>

Or

Phone (in case of problems): +32 2 774 16 00

18 Trial sponsorship and financing

EORTC is the legal Sponsor for all participants.

The contact details of the EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Phone: +32 2 7741611
Fax: +32 2 7723545
e-mail: eortc@eortc.be

19 Trial insurance

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

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

20 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy” version 4.1 dated 29 November 2011.

The final publications of the main trial results will be written by the EORTC Study Coordinator on the basis of the final analysis performed at the EORTC Headquarters and published in a major scientific journal.

The final publications of associated translational research studies will be written by the Coordinator of the corresponding translational research study.

The protocol allows separate publication of trial results obtained in individual (sub-)cohorts.

Authors of the manuscript(s) will include the Study Coordinators, investigators who have included eligible patients in the trial (by order of inclusion), and the statistician and clinical research physician in charge of the trial at the EORTC Headquarters. For publication of translational research results, co-authors will also include scientific collaborators who made substantial contribution to the research.

The title of all manuscripts will include “EORTC”, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, the EORTC Headquarters staff involved in the study, as well as supporting bodies.

Prior to submission, all publications (papers, abstracts, presentations...) including data pertaining to patients from the present trial will be submitted for review to the EORTC Headquarters, to all co-authors, and to the Company.

The above rules are applicable to publications involving any individual patient registered/randomized in the trial.

Appendix A: References

- Ref. 1 Kinney MC, Higgins RA, Medina EA. Anaplastic large cell lymphoma: twenty-five years of discovery. *Arch Pathol Lab Med* 2011;135(1):19-43.
- Ref. 2 Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. *N Engl J Med* 2011; 364:775-776.
- Ref. 3 Butrynski JE, D'Adamo DR, Hornick JL, Dal Cin P, Antonescu CR, Jhanwar SC, Ladanyi M, Capelletti M, Rodig SJ, Ramaiya N, Kwak EL, Clark JW, Wilner KD, Christensen JG, Jänne PA, Maki RG, Demetri GD, Shapiro GI. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. *N Engl J Med* 2010;363(18):1727-1733.
- Ref. 4 Sanders ME, Mick R, Tomaszewski JE, Barr FG. Unique patterns of allelic imbalance distinguish type 1 from type 2 sporadic papillary renal cell carcinoma. *Am J Pathol* 2002;161(3):997-1005.
- Ref. 5 Schmidt, L., Duh, F. M., Chen, F., Kishida, T., Glenn, G., Choyke, P., Scherer, S. W., Zhuang, Z., Lubensky, I., Dean, M., Allikmets, R., Chidambaram, A., Bergerheim, U. R., Feltis, J. T., Casadevall, C., Zamarron, A., Bernues, M., Richard, S., Lips, C. J., Walther, M. M., Tsui, L. C., Geil, L., Orcutt, M. L., Stackhouse, T., and Zbar, B.: Germline and somatic mutations in the tyrosine kinase domain of the MET protooncogene in papillary renal carcinomas. *Nat. Genet.*, 16: 68–73, 1997.
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- Ref. 9 Corao DA, Biegel JA, Coffin CM, Barr FG, Wainwright LM, Ernst LM, Choi JK, Zhang PJ, Pawel BR: ALK expression in rhabdomyosarcomas: correlation with histologic subtype and fusion status. *Pediatr Dev Pathol.* 2009 Jul-Aug;12(4):275-83
- Ref. 10 Taulli R, Scuoppo C, Bersani F, Accornero P, Forni PE, Miretti S, Grinza A, Allegra P, Schmitt-Ney M, Crepaldi T, Ponzetto C. Validation of met as a therapeutic target in alveolar and embryonal rhabdomyosarcoma. *Cancer Res.* 2006 66(9):4742-9.
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- Ref. 12 ST-006-WIN-02 Version: 1.00 (February 2011).
- Ref. 13 Weickhardt AJ, Rothman MS, Salian-Mehta S, Kiseljick-Vassiliades K, Oton AB, Doebele RC, Wierman ME, Camidge DR. *Cancer.* 2012 Nov 1;118(21):5302-9. doi: 10.1002/cncr.27450. Epub 2012 Apr 4. Rapid-onset hypogonadism secondary to crizotinib use in men with metastatic non small cell lung cancer.
- Ref. 14 Mossé YP, Lim MS, Voss SD, Wilner K, Ruffner K, Laliberte J, Rolland D, Balis FM, Maris JM, Weigel BJ, Ingle AM, Ahern C, Adamson PC, Blaney SM. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *Lancet Oncol.* 2013 May;14(6):472-80.

- Ref. 15 Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, De Pas T, Besse B, Solomon BJ, Blackhall F, Wu YL, Thomas M, O'Byrne KJ, Moro-Sibilot D, Camidge DR, Mok T, Hirsh V, Riely GJ, Iyer S, Tassell V, Polli A, Wilner KD, Jänne PA. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med*. 2013 Jun 20;368(25):2385-94.
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- Ref. 22 Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987 Oct 22;317(17):1098
- Ref. 23 Crizotinib (PF-02341066) Investigator's Brochure- October 2015

Appendix B: Abbreviations

NOTE: acronyms for antigens, molecular determinants or genes will not all be spelled out. For gene names, please consult <http://www.genenames.org/>

AE	Adverse Event
ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil count
AR	Adverse Reaction
ARMS	Alveolar rhabdomyosarcoma
ASPS	Alveolar Soft Part Sarcoma
AST	Aspartate Transaminase
AUC	Area Under Curve
BAL	Bronchoalveolar Lavage
BID	twice daily
BUN	Blood Urea Nitrogen
CA	Competent Authority
CCSA	Clear Cell Sarcoma
C _{max}	Maximum concentration
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed Tomography
cTR	correlative Translational Research
CV	Curriculum Vitae
CYP450	cytochrome P450
DILI	Drug Induced Liver Injury
DLT	Dose Limiting Toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked Immunosorbent Assay
EORTC	European Organisation for Research and Treatment of Cancer

EVCTM	Eudra Vigilance Clinical Trial Module
FFPE	Formalin-Fixed Paraffin-Embedded
FISH	Fluorescence In Situ Hybridisation
GI	Gastro-intestinal
HBM	Human Biological Material
HDPE	High Density Polyethylene
HGF	Hepatocyte Growth Factor
HQ	Headquarters
ICH GCP	International Conference on Harmonization Good Clinical Practice
IHC	Immunohistochemistry
IMFT	Inflammatory Myofibroblastic Tumor
IUD	Intra Uterine Device
INN	International Nonproprietary Name
iTR	integrated Translational Research
Ki	inhibition constant
Kinact	rate of enzyme inactivation
LDH	Lactate Dehydrogenase
MITF	Melanocyte Master Transcription Factor
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NOCI	Networks of Core Institutions
NPM	Nucleophosmin
NPV	Negative Predictive Value
NSCLC	Non-Small Cell Lung Cancer
ORTA	Online Randomization Trials Access
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PIS/IC	Patient Information Sheet/Informed Consent
PPV	Positive Predictive Value
PR	Partial Response
PRCC	Papillary renal cell carcinoma

PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QD	Once daily
RDC	Remote Data Capture
RECIST	Response Evaluation Criteria In Solid Tumors
ROC	Receiver Operating Curves
RP2D	Recommended Phase 2 Dose
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease
seqID	Sequential patient Identification number
StC	Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TKI	tyrosine kinase inhibitor
TRAC	Translational Research Advisory Committee
TR	Translational Research
TMA	Tissue-Micro Arrays
ULN	Upper Limit of Normal
UAR	Unexpected Adverse Reaction
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization
WOCBP	Women of child bearing potential

Appendix C: New York Heart Association (NYHA) classification of heart failure

- Class I Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
- Class II Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
- Class III Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
- Class IV Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

Appendix D: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the **Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.**

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: <http://ctep.cancer.gov/reporting/ctc.html>.

The EORTC Headquarters web site www.eortc.org/investigators-area/ctc provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix E: ECOG Performance Status*

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:

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

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix F: Agents possibly interfering with QTc interval

Antiarrhythmics

Class 1: ajmaline, cibenzoline, dihydroquinidine, disopyramide, encainide, flecainide, mexiletine, pirmenol, procainamide, propafenone quinidine

Class 3: almokalant, amiodarone, azimilide, bretylium, dofetilide, dronedarone, d-sotalol, ersentilide, ibutilide, nifekalant, sematilide, sotalol, terikalant

Anti-anginals/vasodilators

bepridil, lidoflazine, prenylamine, ranolazine, terodiline, vardenafil

Anti-hypertensives

indapamide, isradipine, moexipril/hydrochlorothiazide, nicardipine

Antihistamines

astemizole, azelastine, diphenhydramine, ebastine, hydroxyzine, terfenadine

Serotonin agonists and antagonists

cisapride, dolasetron, granisetron, ketanserin, ondansetron

Antimicrobials

Macrolide antibiotics: azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin, telithromycin

Quinolone antibiotics: ciprofloxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, ofloxacin, sparfloxacin

Antifungals: cotrimoxazole, fluconazole (caution with itraconazole), ketoconazole, voriconazole

Others: pentamidine, trimethoprim sulfa (bactrim)

Antiviral: foscarnet (HIV)

Antimalarials

amantidine, chloroquine, halofantrine, quinine

Psychiatric drugs

Tricyclic antidepressants: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine

Phenothiazines: chlorpromazine, fluphenazine, prochlorperazine, thioridazine, trifluoperazine

Others: atomoxetine, citalopram, clozapine, droperidol, fluoxetine, haloperidol, levomethadyl, lithium, maprotiline, mesoridazine, methadone, paroxetine, pericycline, pimozide, quetiapine, risperidone, sertindole, sertraline, trazodone, venlafaxine, zimeldine, ziprasidone

Anticonvulsant

felbamate, fosphenytoin (prodrug of phenytoin)

Anti-migraine

naratriptan, sumatriptan, zolmitriptan

Anti-cancer

arsenic trioxide, geldanamycin, sunitib, tacrolimus, tamoxifen

Others

alfuzosin, chloral hydrate, clobutinol, domperidone, galantamine, octreotide, organophosphates, perflutren lipid microspheres, probucol, solifenacin, tizanidine, tolterodine, vasopressin

Stimulant drugs

Some cold remedies contain these drugs so it is important always to check the label.

adrenaline (epinephrine), amphetamine, cocaine, dexmethylphenidate, dobutamine, dopamine, ephedrine, fenfluramine, isoprenaline (isoproterenol), levalbuterol, metaproterenol, methylphenidate, midodrine, norepinephrine (noradrenaline), phentermine, phenylephrine, phenylpropanolamine, pseudoephedrine, ritodrine, salbutamol (albuterol), salmeterol, sibutramine, terbutalin

Appendix G: Performance scale and Lansky-Play scale for children aged 1 to 12 yo

Lansky Play Performance Scale	Karnofsky Performance Status	WHO Performance Status
100 Fully active, normal.	100 Normal, no complaints; no evidence of disease.	0 Fully active, able to carry on all pre-disease performance without restriction.
90 Minor restrictions in physically strenuous activity.	90 Able to carry on normal activity; minor signs or symptoms of disease.	
80 Active, but tires more quickly.	80 Normal activity with effort, some signs or symptoms of disease.	1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.
70 Both greater restriction of, and less time spent in, active play.	70 Cares for self but unable to carry on normal activity or to do work.	
60 Up and around, but minimal active play; keeps busy with quieter activities.	60 Requires occasional assistance but is able to care for most of personal needs.	2 Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
50 Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.	50 Requires frequent assistance and medical care.	
40 Mostly in bed; participates in quiet activities.	40 Disabled; requires special care and assistance.	3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30 In bed; needs assistance even for quiet play.	30 Severely disabled; hospitalisation is indicated although death not imminent.	
20 Often sleeping; play entirely limited to very passive activities.	20 Very ill; hospitalisation and active supportive care necessary.	4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10 No play; does not get out of bed. Moribund.	10 Moribund, fatal processes progressing rapidly.	
0 Unresponsive. Dead.	0 Unresponsive. Dead.	5 Dead.

Table from the publication of Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. Cancer. 1987 Oct 1;60(7):1651-6.