**ID: IB2015-NTRK** **A Retrospective Study to Determine the Incidence of NTRK Fusions. NTRK Study**

*The format of this form can be modified, but the criteria mentioned herein are considered minimum. Information to be obtained about an IIR prior to Second-tier Review.*

| Document history |
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| November 2, 2021 |

| General information | | |
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| Please provide information for all items marked "**M**" (mandatory).<br>Items marked "**O**" are optional. | | |
| M | **Investigator/institution and contact person:** Antoine ITALIANO<br>Institut Bergonié, Bordeaux, France | |
| M | **IIR Subtype** | Non-interventional/Observational |
| M | **Study Title (Full)**<br>A retrospective Study to Determine the Treatment Outcomes of Subjects with Locally advanced/unresectable or Metastatic Solid Tumors with NTRK Fusions | |
| M | **Indication: Solid Tumors** | |
| M | **Phase of Study** | Observational |
| M | **Country** | France |
| M | **Retrospective or prospective study** | Retrospective |
| M | **Planned number of sites/ subjects** | 3750 subjects (up to 10 sites) |
| M | **Blinding & Control** | n/a |

| Additional request details | | |
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| M | **Primary Endpoint/ objective is safety** | No |
| M | **Study exploring new combinations, alternative dosing/dosing schdules or new formulations** | No |

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| M | **Study with clinical pharmacology objectives, including biomarker, pharmacokinetic (PK) or pharmacodynamics (PD) evaluations** | | No |
| O | **Author** | Antoine Italiano, MD, PhD<br>Institut Bergonie<br>Early Phase Trials and Sarcoma Units<br>229 cours de l'Argonne<br>33000 Bordeaux<br>Phone: + 33 5 47 30 60 88<br>Fax: + 33 5 47 30 60 83<br>E-mail: a.italiano@bordeaux.unicancer.fr | |
| O | **Investigator**<br>**Operations Manager**<br>**email** | Antoine Italiano, MD, PhD<br><br>Head of Clinical Research Unit:<br>Simone MATHOULIN-PÉLISSIER<br>Institut Bergonié – Bordeaux<br>Phone :+ 33 5 56 33 33 98<br>E-mail : s.mathoulin@bordeaux.unicancer.fr | |
| M | **Study support** | Financial | |
| M | **Study is financially supported by other organizations** | | No |

| **Rationale and objectives** | |
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| O | **Please explain why this study is non-blinded (if applicable):** This is a retrospective study. |
| M | **Study Type and Design**<br>This multicenter, retrospective study has a primary objective to assess the impact of NTRK gene fusions on the PFS of first-line systemic therapy for the treatment of locally advanced/unresectable or metastatic solid tumors.<br>Control subjects will be matched based on the characteristics of the NTRK fusion study population to the greatest extent possible. |
| M | **Rationale**<br>The tropomyosin receptor kinase (Trk) receptor family comprises 3 transmembrane proteins referred to as Trk A, B and C (TrkA, TrkB and TrkC) receptors that are encoded by the NTRK1, NTRK2 and NTRK3 genes, respectively. These receptor tyrosine kinases are expressed in human neuronal tissue and play an essential role in the physiology of development and function of the nervous system through activation by neurotrophins. Gene fusions involving NTRK genes lead to transcription of chimeric Trk proteins with constitutively activated or overexpressed kinase function conferring oncogenic potential. These genetic abnormalities have recently emerged as targets for cancer therapy, because novel compounds have been developed that are selective inhibitors of the constitutively active rearranged proteins. Developments in this field are being aided by next generation sequencing methods as tools for unbiased gene fusions discovery. However, the incidence |

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| | of NTRK aberrations in solid tumors is unknown as well as the natural history of NTRK-rearranged tumors. |
| M | **Primary Study Objective**<br>To assess retrospectively the effect of NTRK gene fusions on the progression free survival (PFS) of first-line systemic therapy for the treatment of locally advanced/unresectable or metastatic solid tumors |
| O | **Secondary Study Objectives**<br>• To evaluate the frequency of NTRK gene fusions in subjects with locally advanced/unresectable or metastatic solid tumors.<br>• To assess the treatment outcome to first-line anti-cancer therapy in terms of objective response rate (ORR), duration of response (DOR), and overall survival (OS) in subjects with locally advanced/unresectable or metastatic solid tumors with NTRK gene fusions.<br>• To explore possible demographic characteristics prevalent in subjects with locally advanced/unresectable or metastatic solid tumors and NTRK gene fusions.<br>• To explore the frequency and treatment outcome interaction of concomitant genetic alterations.<br>• To look for trends in the data that may suggest relationships between covariates of interest and treatment outcome in subjects with locally advanced/unresectable or metastatic solid tumors harboring NTRK gene fusions. |
| M | **Study operational/organizational aspects**<br>This will be a multicenter, retrospective study. Institut Bergonié as the Sponsor of this study, will be responsible for getting regulatory approvals, selecting the investigational sites, capturing study data in an appropriate data base |

| **Population and methods** | |
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| M | **Study Population**<br>Adult and pediatric patients with locally advanced/unresectable or metastatic solid tumors |
| M | **Inclusion Criteria (detailed)**<br>For inclusion of a subject in the study population, all of the following criteria must be fulfilled:<br>1. Age ≥ 1 month. |

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| | 2. Subject has/had a histologically or cytologically confirmed diagnosis of solid tumor including but not exclusively: soft tissue sarcoma, BRAF wild type melanoma, KRAS wild-type colorectal cancer, central nervous system, EGFR-wild type non-small cell lung cancer.<br>3. Subject has locally advanced/unresectable or metastatic disease.<br>4. Subject has received at least one systemic anti-cancer therapy for locally advanced/unresectable or metastatic disease for which there is available outcome information in terms of PFS, or the latter can be estimated based on the subject's records.<br>5. Subject has tumor material available for immunoscreening (IHC for NTRK gene fusions).<br>6. Written and voluntary informed consent understood, signed and dated, or a waiver of consent is granted according to French regulations<br><br>Subjects who are tested positive by IHC (Pan-Trk IHC testing with mAb EPR17341) will *be the subject of molecular assays such as next-generation sequencing* (Archer Dx fusion assay) of tumor material [parrafin embedded material]), so that tumor harboring *NTRK1*, *NTRK2* or *NTRK3* gene fusions, is identified properly.<br><br>After identification of the NTRK fusion study population, control subjects with locally advanced/unresectable or metastatic solid tumors, who do not have NTRK fusions will be selected in an attempt to closely match NTRK fusion subjects. |
| M | **Exclusion Criteria**<br>The following exclusion criterion should be considered:<br>Subjects who have not yet received or completed at least one systemic anti-cancer therapy for locally advanced/unresectable or metastatic cancer. |
| M | **Test Treatment(s) (Description)**<br>n/a<br>. |
| O | **Test Treatment(s) or Investigated Treatment(s): Rationale for unusual or novel approaches**<br>n/a |
| M | **Request for Study Drug Supply**<br>No |
| M | **Reference Treatment or Modality/Treatment or Modality of Comparison (Description)** |

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| | n/a |

| Safety reporting | |
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| M | **Safety reporting (valid for clinical studies only)**<br>n/a |

| Statistical analysis | |
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| O/M | **Standard of Reference/Standard of Truth**<br>n/a |
| M | **Rationale for selection of a reference treatment**<br>n/a |
| M | **Assignment of subjects to study arms or groups (Randomization/Stratification)**<br>n/a (this will be a retrospective study) |
| M | **Blinding**<br>n/a |
| M | **Concomitant Treatment(s)**<br>n/a |
| M | **Primary Outcome**<br>Progression-free survival observed with first-line anti-cancer therapy |
| O | **Secondary Outcomes**<br>• Frequency of NTRK fusions in subjects with locally advanced/unresectable or metastatic solid tumors.<br>• Treatment outcome to first-line anti-cancer therapy in terms of objective response rate (ORR), duration of response (DOR), and overall survival (OS) in subjects with locally advanced/unresectable or metastatic HNSCC with NTRK gene fusions.<br>• Demographic characteristics in subjects with locally advanced/unresectable or metastatic solid tumors harboring NTRK gene fusions |
| M | **Safety Outcomes**<br>n/a |
| O | **Measurement of results (How assessed)** |

Data collection (see below)

M **Visit schedule**

| Activity | Screening | Data Collection for Enrolled Subjects |
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| ICF, Inclusion/exclusion criteria evaluation | X | |
| Collection of Demographic Information:<br>• Date of birth<br>• Vital status: dead/alive/unknown<br>• Gender<br>• Smoking status: Smoker/never smoker/prior smoker at the time of first line treatment<br>• Other relevant carcinogen exposure (e.g. consumption of betel nut) | | X |
| Collection of Medical Information:<br>• Date of initial diagnosis of cancer<br>• Stage of disease at diagnosis<br>• Anatomical disease site(s) at diagnosis<br>• Anatomical (organ) disease site(s) (e.g. lung metastases) at the time of first line treatment<br>• Locally advanced/unresectable or metastatic disease at the time of first line treatment<br>• Current stage of disease<br>• Other relevant medical history. Date of prior medical events | | X |
| Collection of Treatment Information:<br>• Prior/current surgical treatments for cancer.<br>  ◦ Dates of surgeries<br>• Prior/current radiological treatments for cancer.<br>  ◦ Anatomical sites.<br>  ◦ Dates of radiation treatments<br>• First line systemic treatment for locally advanced/unresectable or metastatic cancer:<br>  ◦ Dates of treatment (start, end).<br>  ◦ Performance status at the time of first line therapy for treatment of recurrent or metastatic disease.<br>  ◦ Treatment outcome (response and response criteria).<br>  ◦ Date of progression(s) (progression criteria).<br>• Other prior/current systemic treatments for cancer.<br>  ◦ Dates of treatment (start, end).<br>  ◦ Treatment outcome (response and response criteria).<br>• Date of progression(s) (progression | | X |

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| | criteria)<br>• Date of death (if any) and cause of death | | |
| | Collection of NTRK fusion Information:<br>• Anatomical biopsy sample site (including blood/urine sample). Date of sampling and setting (initial diagnosis, locally advanced/unresectable or metastatic disease)<br>• Matrix (tumor biopsy, blood, urine)<br>• Tumor histology (from biopsy sample or primary diagnosis)<br>• NTRK fusion in sample. Allele frequency (if available); this information is not applicable for control subjects.<br>• Other relevant mutations or genetic alterations, if available. Allele frequencies (if available)<br>• Test platform (e.g. NGS). Mutations tested (PCR methods) or exons sequenced (sequencing methods). | | X |

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**Follow-up period**

n/a

**Statistical & Analytical Plan and Methodology**

The primary objective of this descriptive study is to determine if there are statistically significant differences in PFS to first line systemic therapy between subjects with recurrent/metastatic disease and NTRK fusion versus those without a known NTRK fusion.

The two groups will be matched with respect to histological subtype, sex, age (+/-5 years), and pathological tumor-node-metastasis (TNM) stage.

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The Kaplan-Meier method will be employed for the analysis of PFS. A nonparametric test, such as the log-rank test, based on the Kaplan-Meier estimator for survival curves, will be employed to assess the association between PFS and the presence of NTRK fusion. In addition, predictive modeling, including Cox proportional hazards models with NTRK fusion as a predictor may also be used to estimate the relative risk of the exit-event of subjects with tumors with NTRK fusion versus subjects with tumors without known NTRK fusion. If the data allow it, other types of predictive modeling may also be explored. If the proportionality of hazard assumption fails, then parametric approaches will be used.

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| | Given the rarity of NTRK fusions among subjects with solid tumors, the sample size for this study will not be driven by powering the study. A post hoc power calculation will be provided. Clinically relevant changes will be defined as increases in median survival times that are greater than 30%, regardless of confidence interval width.<br><br>An assessment of the impact of certain covariates will be conducted by comparing their associated hazard ratios from the Cox proportional hazard (or parametric model) analysis.<br><br>Descriptive statistics will be employed to define demographic and treatment outcome, as well as overall frequency of NTRK fusions in the screened population. This will include exploration of potential effects on subject's treatment outcomes of different forms of NTRK fusions and of other genetic alterations. |

| **Timelines** | |
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| M | **Planned Study Timelines:**<br>1. Enrolment rate (patients per month): 300 patients/months<br>2. Planned estimate of treatment duration: not applicable<br>3. Submission date to health authority/ethics: not applicable<br>4. Start of subject enrolment: December 2018<br>5. End of Subject enrolment: December 2019<br>6. All patients completed: December 2019<br>7. End of Study: March 2020<br>8. Report (as described in the contract): Report every 3 months<br>9. Planned publication/presentation: June 2020 |

| **Limitations** | |
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| O | **Criteria for selection of evaluable cases:**<br>All patients:<br>who have received at least one systemic anti-cancer therapy for locally advanced/unresectable or metastatic disease for which there is available outcome information in terms of PFS,<br>who have tumor material tested by IHC for NTRK gene fusions,<br>will be included in the analysis. |
| M | **Interim Analyses (if applicable)** |

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| | Interim analyses will be the subject of periodic reports based upon collection of data on first 1,000, 2,000 patients and a final analysis will be conducted after completion of the whole data set analysis.<br>At each interim analyses, the proportion of NTRK-rearranged cases will be estimated in order to assess the feasibility of a comparative analysis with matched controls. |
| M | **Number of Evaluable Patients (estimate):** it is anticipated to collect data on 3,700 patients |
| M | **Sample Size Assumptions/Target Number of Valid Cases (incl. Power and Confidence)**<br>No sample size estimate has been calculated. It is assumed that a sample size of 3,700 patients should be sufficient to address the primary objective of this study. |
| 0 | **Statistical analyses**<br>• Quantitative variables will be described using mean and standard deviations if the normality assumption is satisfied, else other descriptive statistics (median, range, quartiles) will be reported.<br>• Qualitative variables will be described using frequency, percentage and 95% confidence interval (binomial law).<br>• Survival endpoints will be analysed using the Kaplan-Meier method. The median survival rates will be reported with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan-Meier method. |
| M | **Health Economic Variables (if applicable)**<br>n/a |