PREDICTING SEVERE TOXICITY OF TARGETED THERAPIES IN ELDERLY PATIENTS WITH CANCER

Pre-ToxE Summary

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SPONSOR **INSTITUT BERGONIÉ**

SUMMARY OF TRIAL

Study title	**Predicting severe toxicity of targeted therapies in elderly patients with cancer**
Abbreviation	**Pre-ToxE**
Sponsor	**Institut Bergonié, Comprehensive Cancer Center**
Coordinating investigator	**Professor Antoine ITALIANO**
Number of centres	Multi-centre
Number of patients	250 patients
State of the question Purpose of the research	The incidence of cancer in elderly subjects is constantly increasing and improving their management by taking into account their specific needs is one of the objectives of the 3rd cancer plan published in February 2014. New anti-cancer molecules are placed on the market after validation by clinical trials in which elderly subjects are under-represented. There is therefore little data available on the toxicity of these new molecules in elderly patients. Tyrosine kinase inhibitors (TKIs) are indicated in different types of metastatic cancer. Several elements suggest that their toxicity is higher in elderly subjects than in younger subjects: firstly, the pharmacokinetic modifications, drug interactions and more fragile ground, making these toxicities more severe. As the geriatric population is heterogeneous, identifying those subjects most at risk of complications is a crucial issue. It is also a major socio-economic issue, the occurrence of adverse events being the source of a significant additional cost. Our study will evaluate prospectively (cohort) among geriatric (G8 screening score, ADL, IADL, MNA, comorbidities, Performance Status, Get up and Go Test, visual or verbal fatigue scale), biological, pharmacokinetic and pharmacogenomic data, those prognostic factors of severe TKI toxicity in the elderly. The primary objective of this study is to predict severe toxicity (defined as the occurrence of treatment-related adverse events resulting in either discontinuation of more than 3 weeks of treatment, permanent discontinuation of treatment, hospitalisation, or death, i.e. disability or significant or lasting incapacity) of TKIs prescribed in the context of the Marketing Authorisation (MA) in subjects over 70 years of age. The secondary objectives are the rate of non-progression at 6 months (percentage of patients with complete response, partial response or stable disease according to RECIST v1.1 criteria), progression-free survival and the correlation between the pharmacogenomic data and the rate of non-progression at 6 months.
Target population	This study concerns patients aged 70 and over with cancer and treated with a TKI prescribed in the context of the Marketing Authorisation and having signed an informed consent.
Method of observation	This is a non-interventional, multi-centre, prospective research study with collection of biological samples, in which 250 elderly cancer patients should be included for 24 months at several centres. Once the patient has signed the informed consent, the investigator will collect clinical data before the start of treatment. The investigator or the geriatric nurse will carry out a geriatric evaluation and take an initial blood sample to perform pharmacogenomic analyses. During treatment, the investigator will collect data concerning the type of treatment, toxicities and tumour response. A second blood sample will be taken at the end of the first month of treatment in order to perform pharmacokinetic analyses. A geriatric evaluation will be carried out after 2 months of treatment, either during a telephone interview or in consultation, in order to assess any toxic effects on the patient's general condition. Once treatment has been stopped, patient follow-up data will be collected along with a final geriatric evaluation.

Information collected	The investigator sends to the Institut Bergonié coordinating clinical research assistant (CRA) the inclusion form including the number of the centre, the name of the principal investigator, the first letter of the patient's last name and the first letter of their first name, their age on inclusion, the eligibility criteria, identification of the treatment with TKI, the date of signature of the consent form, along with the date scheduled for the start of treatment. Each patient's personal data will be confidential (data protection act of 6 January 1978 amended by the act of 6 August 2004). On the case report form or any other study document, patients will be identified by their initials (first letter of last name and first letter of first name) and an inclusion number. The investigators should, however, keep a patient identification list in their binder.
Collection of blood samples	As part of this protocol, two blood samples (2 * 5 ml = 10 ml) will be taken for each patient. An initial sample will be taken before the start of treatment upon inclusion and a second sample will be taken at the end of the first month of treatment. Each sample will be anonymised and the following information will appear on the tubes: name of the study, number of the study centre, number of the patient in this centre, date of sample and type of analysis carried out (pharmacokinetics and pharmacogenomics). At the end of the study, blood samples intended for pharmacokinetic analyses will be sent to the pharmacology department of the Bordeaux University Hospital headed by Prof. Mathieu Molimard, while the samples intended for pharmacogenomic analyses will be sent quarterly (according to the rhythm of inclusions) to the biological resources centre of Institut Bergonié. These samples will be accompanied by the sample routing form on which the date of signing of the sample preservation consent will be indicated. These biological samples will never be linked to nominative data and will be used for research purposes only. Any samples not immediately used will remain stored for future use to help researchers advance their knowledge of oncology and pharmacology.
Study duration	Enrolment period: 24 months Follow-up: 12 months Total duration: 36 months
Information collection methods	After checking the eligibility criteria, and once the informed consent has been signed, eligible patients will be registered centrally at Institut Bergonié by the study coordinator CRA (request by fax from each participating centre). A confirmation of inclusion with an inclusion number will be returned to the investigator. The patient's enrolment in the study will not be effective until the inclusion number has been assigned.
Data analysis method	Primary endpoints: prediction of severe toxicity (defined as the occurrence of adverse events attributable to treatment resulting in either discontinuation of more than three weeks of treatment, permanent discontinuation of treatment, hospitalisation, death, disability or significant or lasting incapacity) of TKIs prescribed in the context of the Marketing Authorisation in patients aged 70 years or over with cancer. Secondary endpoints: description of toxicities, non-progression rate at 6 months and progression-free survival at one year. **Analysis of toxicity**: The severe toxicity rate, along with the incidence rates for toxicities grades 1-4 will be reported according to the eligible and evaluable population. These endpoints will be described using frequency, percentage and 95% confidence interval. The toxicity rate will also be reported by subgroup of patients according to the TKI. Prognostic factors of severe toxicity will be evaluated using logistic regression analyses. **Non-progression analysis**: The non-progression rate at 6 months will be reported according to the eligible and evaluable population, but also by subgroup of patients according to the TKI used. This endpoint will be described using frequency, percentage and 95% confidence interval. Prognostic factors (clinical and geriatric) of 6-month non-progression rates will be evaluated using logistic regression analyses. **Analysis of PFS**: PFS will be analysed using the Kaplan-Meier method. Median survival will be presented with a 95% confidence interval. Median follow-up will be calculated using the reverse Kaplan-Meier method. Multivariate analyses will be performed according to the Cox proportional hazards model after verifying the risk proportionality assumption. **Intermediate statistical analysis:** After the inclusion of the first 150 patients, an intermediate statistical analysis will be performed.

Number of subjects	In this study, we predict that approximately 30% of patients will experience severe toxicity. A population of 250 eligible and evaluable patients will allow us to estimate this proportion with an accuracy of ±5%, leading to a 95% confidence interval (24.3%; 35.7%). Subgroup analyses will also be carried out. Subgroups of patients will therefore be defined according to the TKI treatment received (pazopanib, regorafenib, sorafenib, etc.). Assuming that 50 patients are included in a subgroup with a toxicity rate of 30%, the resulting precision will be ±12%, for a 95% confidence interval (17.3% ; 42, 7%).

Institut Bergonié
Pre-ToxE Protocol

STUDY FLOWCHART

		TREATMENT					
	SCREENING	**Start of treatment** *D1*	**Month 1** *(D28, ±2 days)*	**Month 2** *(D56, ±2 days)*	**Month N**	**Discontinuation of treatment** *(within 28 days)*	**Follow-up** *(Beyond 28 days after TKI discontinuation and up to 12 months after TKI initiation)*
TKI	*Information*	..... **MA**					
Consultation	**X**	**X**	**X**				**X**
Eligibility criteria	**X**						
Informed consent	**X**						
Demographic data	**X**						
Height	**X**						
Weight	**X**		..... **X**				
History of the disease / Medical history / Previous treatments	**X**						
Performance status *(ECOG)*	**X**	**X**	**X**				
Biological assessment	**X**[1]						
Tumour evaluation	**X**[2]		..... **According to the centre's routine practice**				
Geriatric evaluation	**X**[3]			**X**[4]		**X**[4]	
Blood sample for pharmacogenomics		**X**					
Blood sample for pharmacokinetics			**X**				
Toxicities		..... **X**				**X**[5]	
Concomitant treatments	..... **X**					**X**[5]	
Vital status							**X**[6]

[1] **Within 7 days before D1 of treatment initiation** (same day possible)**:** Haematology (*CBC, platelets*), Biochemistry (*sodium, potassium, calcium, magnesium, phosphorus, glucose, LDH, urea, creatinine, ASAT, ALAT, Alkaline Ph. , total bilirubin, albumin, total protein*), Coagulation (*INR, PT, aPTT*), Thyroid function (*free T4, TSH*).

[2] **Within 4 weeks before D1 of treatment initiation** (same day possible).

[3] **Within 7 days before D1 of treatment initiation** (same day possible)**:** G8, Charlson, Cardiovascular diseases, ADL, IADL, ECOG, Get Up and Go Test, verbal or visual fatigue scale, MNA.

[4] **Evaluation method during a consultation or telephone interview:** % weight loss over the past few months, falls, verbal fatigue scale, ADL, IADL.

[5] To be collected for 28 days after discontinuation of treatment.

[6] **Follow-up** according to the centre's routine practice.