IMMUNE-CHECKPOINT INHIBITORS AND SURROGATE ENDPOINTS IN CANCER TRIALS

SURROGATE-ICI

05/01/2017
NCT03963518

SYNOPSIS

Title of the study	Immune-checkpoint Inhibitors and Surrogate Endpoints in Cancer Trials (SURROGATE-ICI)
Abbreviation of the trial	**SURROGATE-ICI**
Number of patients	**631**
Medical conditions	**Cancer patients treated with**
Rationale of the study	Advanced cancer treatment has been recently revolutionized by the development of the immune-checkpoint inhibitors (ICI). These immunomodulatory monoclonal antibodies are designed to either elicit a novel anti-tumoral immune response or revitalize an existing one to fight against cancer. Patients with cancer are living longer due to these improved therapies. Powering a study for overall survival (OS), the gold standard primary endpoint in randomized controlled trial (RCT) of anticancer drugs is becoming increasingly challenging. Therefore, it is of importance to identify and validate novel surrogate endpoints (SE) for OS in ICI-treated patients for expediting patients' access to innovative and potentially life extending medicines.
Objectives	1/ We will first systematically review published studies reporting on an association between alternative endpoints and OS in ICI-treated patients. 2/ Then, based on the learnings from this systematic literature review and from the specificity of the mechanism of action of ICIs, we will evaluatd the surrogacy properties of an emerging intermediate endpoint in solid tumors, namely *time to next treatment* (TNT), in ICI-treated patients with advanced melanoma and renal cell carcinoma (aRCC), through recent innovative statistical models for the validation of SE.
Study design	Statistical analyses based on the re-utilization of already published data
Inclusion criteria	For objective 2 : advanced melanoma patients treated with immune checkpoint inhibitors
Treatment	For objective 2 : nivolumab monotherapy ; nivolumab plus ipilimumab
Endpoints	OS : time from the date of randomization to the date of death (any cause). TNT-D : the time between the date of randomisation and the date of subsequent systemic treatment initiation, or the date of death (any cause), whichever occurred first.
Statistical methods	OS and TNT-D distributions will be generated using the Kaplan-Meier estimator. Median follow-up will be estimated by the reverse KaplaneMeier method. To describe these efficacy outcomes, hazard ratios (HRs) will be estimated using a Cox proportional-hazards model stratified according to the factors used in the randomisation process. For the surrogate endpoint (SE) analysis, HRs will be estimated with a joint frailty-copula model. Robust assessment and validation of an SE require evaluation at both the individual and trial levels (meta-analytic approach). For two time-to-event endpoints, several metaanalytic surrogacy validation approaches are available, including 1-step and 2-step validation approaches. We Will consider the SE 1-step validation statistical method based on a joint frailty-copula model (Gumbel copula) as it has been demonstrated to reduce substantially numerical problems encountered with the 2-step method.

	In this approach, Kendall's s is used to estimate the strength of association between the candidate SE and the final endpoint at the individual level. The Kendall's s will be estimated as a function of the copula parameter, where values above an informal threshold of 0.6 are regarded as sufficient for the validity of the SE at the individual level, while it is uncommon to observe a value higher than 0.7.