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Protocol of the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) project: Formal consensus method for the development of guidelines for standardised time-to-event endpoints' definitions in cancer clinical trials

Carine A. Bellera [a,b,*], Marina Pulido [a,b], Sophie Gourgou [c], Laurence Collette [d], Adélaïde Doussau [b,e,f], Andrew Kramar [g], Tienhan Sandrine Dabakuyo [h], Monia Ouali [d], Anne Auperin [i], Thomas Filleron [j], Catherine Fortpied [d], Christophe Le Tourneau [k], Xavier Paoletti [l], Murielle Mauer [d], Simone Mathoulin-Pélissier [a,b,f,o], Franck Bonnetain [m,n,o]

[a] *Clinical and Epidemiological Research Unit, Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, France and Data Center for Cancer Clinical Trials, CTD-INCa, Bordeaux, France*
[b] *INSERM, Centre d'Investigation Clinique – Épidémiologie Clinique CIC-EC 7, F-33000 Bordeaux, France*
[c] *Biostatistical Unit, Centre Val d'Aurelle, Comprehensive Cancer Centre, Montpellier, France and Data Center for Cancer Clinical Trials, CTD-INCa, Montpellier, France*
[d] *Statistics Department, EORTC (European Organization for Research and Treatment of Cancer), Bruxelles, Belgium*
[e] *CHU de Bordeaux, Pôle de santé publique, Service d'information médicale, F-33000 Bordeaux, France*
[f] *Univ. Bordeaux, ISPED, Centre INSERM U897 – Epidemiologie-Biostatistique, F-33000 Bordeaux, France*
[g] *Unité de Méthodologie et Biostatistique, Centre Oscar Lambret, Comprehensive Cancer Centre, Lille, France*
[h] *Biostatistics and Quality of Life Unit, EA4184, Centre Georges François Leclerc, Comprehensive Cancer Centre, Dijon, France*
[i] *Unit of Biostatistics and Epidemiology, Institut Gustave Roussy, Villejuif, France*
[j] *Biostatistical Unit, Institut Claudius Régaud, Comprehensive Cancer Centre, Toulouse, France*
[k] *Department of Medical Oncology, Clinical Trial Unit, INSERM U900, Institut Curie, Paris, France*
[l] *Department of Biostatistics, INSERM U900, Institut Curie, Paris, France*
[m] *Data Center for Cancer Clinical Trials, CTD-INCa, GERCOR, France*
[n] *Methodological and Quality of Life Unit in Oncology (EA3181), CHU Besançon, France*

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Abstract ***Introduction:*** In randomised phase III cancer clinical trials, the most objectively defined and only validated time-to-event endpoint is overall survival (OS). The appearance of new types of treatments and the multiplication of lines of treatment have resulted in the

* *Corresponding author*: Address: Clinical and Epidemiological Research Unit, Institut Bergonié, Comprehensive Cancer Centre, 229 Cours de l'Argonne, 33076 Bordeaux Cedex, France.
° These authors equally contributed to this work.

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use of surrogate endpoints for overall survival such as progression-free survival (PFS), or time-to-treatment failure. Their development is strongly influenced by the necessity of reducing clinical trial duration, cost and number of patients. However, while these endpoints are frequently used, they are often poorly defined and definitions can differ between trials which may limit their use as primary endpoints. Moreover, this variability of definitions can impact on the trial's results by affecting estimation of treatments' effects. The aim of the Definition for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) project is to provide recommendations for standardised definitions of time-to-event endpoints in randomised cancer clinical trials.

Methods: We will use a formal consensus methodology based on experts' opinions which will be obtained in a systematic manner.

Results: Definitions will be independently developed for several cancer sites, including pancreatic, breast, head and neck and colon cancer, as well as sarcomas and gastrointestinal stromal tumours (GISTs).

Discussion: The DATECAN project should lead to the elaboration of recommendations that can then be used as guidelines by researchers participating in clinical trials. This process should lead to a standardisation of the definitions of commonly used time-to-event endpoints, enabling appropriate comparisons of future trials' results.

1. Introduction

In randomised phase III cancer clinical trials, the most objectively defined and only validated time-to-event endpoint is overall survival (OS).[1] The combined effects of new therapies and the development of molecularly targeted agents (sometimes cytostatic rather than cytotoxic), the current context of strategic trials and the multiplication of lines of treatment have led to the use of surrogate endpoints of OS to measure treatment efficacy. In essence, these criteria are composite endpoints combining different events such as local and distant progressions, local and distant recurrences and occurrence of a second cancer, death or severe toxicity (Tox). Depending on the disease setting, commonly used criteria include disease-free survival (DFS), recurrence-free survival, progression-free survival (PFS), time to progression or cancer-specific survival.[2–4] The development of these endpoints has largely been motivated by the necessity of reducing clinical trial duration, cost and number of patients, as well as the difficulty to observe an OS benefit when patients receive multiple lines of treatment at progression. Currently, these types of potential surrogate endpoints are increasingly being used as replacements for OS in clinical trials.[5]

As recommended by the International Conference on Harmonisation (ICH) guidelines[6] and the CONSORT statement[7], each time-to-event endpoint should be precisely defined. This implies specifying the date of origin (time zero), the list of events to be considered as failures and the censoring process. However, most of these time-to-event endpoints currently lack standardised definition enabling a cross comparison of results from different clinical trials.[4]

In addition, the variability of definitions for a particular time-to-event endpoint can strongly impact the trial's conclusions by affecting both statistical power and estimation. This issue was recently highlighted by Birgisson et al.[8] in the context of colorectal cancer. The authors demonstrated that the inclusion of a second primary other than colorectal cancer as an event in the definition of DFS significantly impacted the results. The estimated DFS rate for patients with stage I–III disease was 62% after 5 years if this event was not counted as an event, compared with 58% if it was. The difference was larger for stage II (68 versus 60%) than for stage III (49 versus 47%). Again, for colon cancer, results of the PETACC 03 randomised study[9] were either significant or not significant depending on whether second primary tumours were accounted for in the DFS definition or not. Similarly, Nout et al. highlighted the significant impact of including or not including non-breast cancer-related deaths and contralateral breast cancer on the estimated outcome probability in early breast cancer.[10] Finally, this heterogeneity in time-to-event endpoint definitions also complicates trial design since the survival rates expected in the control group are usually estimated based on results of previous trials, which may have used potentially different definitions.

The variety of time-to-event endpoints and the variability of their definitions are recognised by the international community. This has been demonstrated by different publications recommending the definition of specific criteria and/or the preferred use of certain criteria in specific cancer sites such as colorectal cancer in the adjuvant setting,[11] hepatocellular carcinoma (HCC)[12] and in breast cancer.[13] To the best of our knowledge, these recommendations, however, were developed based on experts' opinions only, without formal consensus.

The formal consensus is a method initially aimed at developing practice guidelines, and more generally recommendations.[14,15] Since the consensus process could