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Guidelines for time-to-event end-point definitions in adjuvant randomised trials for patients with localised colon cancer: Results of the DATECAN initiative

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1 **Manuscript type**

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3 **Title**

4 Guidelines for time-to-event endpoint definitions in adjuvant randomized trials for localized colon
5 cancer patients: results of the DATECAN initiative

6 **Authors list**

7 Romain Cohen ^{1,2}, Dewi Vernerey ^{3,4}, Carine Bellera ^{5,6}, Aurélia Meurisse ^{3,4}, Julie Henriques ^{3,4}, Xavier
8 Paoletti ⁷, Benoît Rousseau ⁸, Steven Alberts ⁹, Thomas Aparicio ¹⁰, Ioannis Boukovinas ¹¹, Sharlene Gill ¹²,
9 Richard M. Goldberg ¹³, Axel Grothey ¹⁴, Tetsuya Hamaguchi ¹⁵, Timothy Iveson ¹⁶, Rachel Kerr ¹⁷, Roberto
10 Labianca ¹⁸, Sara Lonardi ¹⁹, Jeffrey Meyerhardt ²⁰, James Paul ²¹, Cornelis J.A. Punt ²², Leonard Saltz ⁸,
11 Marck P. Saunders ²³, Hans-Joachim Schmoll ²⁴, Manish Shah ²⁵, Alberto Sobrero ²⁶, Ioannis Souglakos ²⁷,
12 Julien Taieb ²⁸, Atsuo Takashima ²⁹, Anna Dorothea Wagner ³⁰, Marc Ychou ³¹, Franck Bonnetain ^{† 3,4},
13 Sophie Gourgou ³², Takayuki Yoshino ³³, Greg Yothers ³⁴, Aimery de Gramont ³⁵, Qian Shi ², Thierry André
14 ¹, on behalf of the ACCENT Group.

15 **Affiliation list**

1 Sorbonne Université, department of medical oncology, AP-HP, hôpital Saint-Antoine, F-7512 Paris,
France

2 Division of Biomedical Statistics and Informatics, Department of Health Science Research, Mayo
Clinic, Rochester, MN, USA

3 Methodology and Quality of Life Unit in Oncology, University Hospital of Besançon, F-25000,
Besançon, France

- 4 University Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, Interactions Hôte-Greffon-Tumeur/Ingénierie Cellulaire et Génique, F-25000, Besançon, France
- 5 Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Epicene team, UMR 1219, F-33000 Bordeaux, France
- 6 Inserm CIC1401, Clinical and Epidemiological Research Unit, Institut Bergonié, Comprehensive Cancer Center, F-33000 Bordeaux, France
- 7 Université de Versailles-St Quentin & Institut Curie, INSERM U900, équipe biostatistique France
- 8 Memorial Sloan Kettering Cancer Center, New York, NY USA
- 9 Department of Oncology, Mayo Clinic, Rochester, MN, USA
- 10 Service de Gastroentérologie et Cancérologie Digestive, Hôpital Saint Louis, APHP, Université de Paris, Paris, France
- 11 Bioclinic Oncology Unit of Thessaloniki, Thessaloniki, France
- 12 BC Cancer, Vancouver, Canada
- 13 West Virginia University Cancer Institute, Morgantown WV, USA
- 14 West Cancer Center and Research Institute, Germantown, TN, USA
- 15 Department of Gastroenterological Oncology, Saitama Medical University International Medical Center, Saitama, Japan
- 16 University Hospital Southampton NHS Foundation Trust, Southampton, UK
- 17 Adjuvant Colorectal Cancer Group, University of Oxford, UK
- 18 Ospedale Papa Giovanni XXIII, Bergamo, Italy
- 19 Istituto Oncologico Veneto-IRCCS, Padova, Italy
- 20 Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA
- 21 Cancer Research UK Clinical Trials Unit (CTU), Institute of Cancer Sciences, University of Glasgow, UK

- 22 Department of Medical Oncology, Amsterdam University Medical Centers, University of Amsterdam, Netherlands
- 23 Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK
- 24 EORTC GI study group, AIO colorectal cancer group, Martin Luther University, Halle, Germany
- 25 Department of Medicine, Division of Hematology and Medical Oncology, Center for Advanced Digestive Care, Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY, USA
- 26 Medical Oncology Unit at Ospedale San Martino, Genova, Italy
- 27 Medical School, University of Crete, Heraklion, Greece
- 28 Sorbonne Paris Cité, Paris Descartes University, Department of Digestive Oncology, Georges Pompidou European Hospital, Paris, France
- 29 National Cancer Center Hospital, Tokyo, Japan
- 30 Department of Oncology, Lausanne University Hospital and University of Lausanne, Switzerland
- 31 Department of Medical Oncology, Institut Régional du Cancer de Montpellier (ICM), France
- 32 Biometrics unit, Montpellier Cancer Institute, Univ Montpellier, Montpellier, France
- 33 National Cancer Center Hospital East, Kashiwa, Japan
- 34 NRG Oncology and University of Pittsburgh, USA
- 35 Department of Medical Oncology, Institut Hospitalier Franco Britannique, Levallois-Perret, France

1

2 **Full address for correspondence**

3 Romain Cohen, MD, PhD

4 Saint-Antoine hospital, department of medical oncology, 184 rue du faubourg Saint-Antoine,

5 75012, Paris France

6 Tel: +33 1 49 28 23 36, email address: romain.cohen@aphp.fr; ORCID ID 0000-0001-9602-5162

1 **Abstract**

2 Background: The variability of definitions for time-to-event (TTE) impacts the conclusions of randomized
3 clinical trials (RCTs). The DATECAN initiative aims to provide consensus definitions for TTE endpoints
4 used in RCTs. Here we formulate guidelines for adjuvant colon cancer (CC) RCTs.

5 Methods: We performed a literature review to identify TTE endpoints and events included in their
6 definition in RCT publications. Then, a consensus was reached among a panel of international experts,
7 using a formal modified Delphi method, with 2 rounds of questionnaires and an in-person meeting.

8 Results: Twenty-four experts scored 72 events involved in 6 TTE endpoints. Consensus was reached for
9 24%, 57%, and 100% events after the first, second round, and in-person meeting. For RCT not using
10 overall survival as their primary endpoint, the experts recommend using disease-free survival (DFS)
11 rather than recurrence-free survival (RFS) or time to recurrence (TTR) as the primary endpoint. The
12 consensus definition of DFS includes all causes of death, second primary colorectal cancers (CRCs),
13 anastomotic and metastatic relapse as an event, but not second primary non-CRCs. Events included in
14 the RFS definition are the same as for DFS with the exception of second primary CRCs. The consensus
15 definition of TTR includes anastomotic or metastatic relapse, death with evidence of recurrence and
16 death from CC cause.

17 Conclusion: Standardised definitions of TTE endpoints ensure the reproducibility of the endpoints
18 between RCTs and facilitate cross-trial comparisons. These definitions should be integrated in standard
19 practice for the design, reporting, and interpretation of adjuvant CC RCTs.

1 **Keywords**

- 2 Guidelines; colon cancer; adjuvant; chemotherapy; randomized controlled trials; time-to-event
3 endpoints.

1 **Main text**

2 **Introduction**

3 In randomised phase III cancer clinical trials, the most objectively defined time-to-event (TTE)
4 endpoint is overall survival (OS). The desire to reduce clinical trial duration and cost and meet endpoints
5 efficiently with the fewest possible number of patients has led to the use of surrogate endpoints of OS
6 to measure treatment efficacy, such as disease-free survival (DFS), recurrence-free survival (RFS),
7 progression-free survival (PFS) or time to recurrence (TTR). These criteria are composite endpoints
8 combining different events such as local and distant recurrences and occurrence of a second cancer,
9 death, or severe toxicity.

10 The variability of definitions for a particular TTE endpoint can strongly impact the trial by
11 affecting both statistical power and study conclusions. This issue was highlighted by Birgisson et al. in
12 the context of colorectal cancer [1]. The authors demonstrated that the inclusion of a second primary
13 cancer other than colorectal cancers as an event in the definition of DFS significantly impacted the
14 results. The estimated DFS rate for patients with stage I–III disease was 62% after 5 years if second
15 primary non-colorectal cancer was not counted as an event, compared with 58% if it was. Furthermore,
16 the results of the PETACC-03 study were either statistically significant or not significant depending on
17 whether second primary tumours were included in the DFS definition [2]. The recognition of the lack of
18 standardised definitions for TTE endpoints, as recommended by the International Conference on
19 Harmonisation (ICH) guidelines and the CONSORT statement [3,4], led to the publication of international
20 guidelines, including a template for colon cancer adjuvant trials [5]. However, the absence of a formal
21 consensus process and the fact that the process did not seek the input of international academic groups
22 in these studies may explain why existing guidelines are not consistently employed by researchers
23 designing trials.

1 The international DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints
2 in CANcer trials) has been set up to provide recommendations to standardise definitions of TTE
3 endpoints used in randomized cancer clinical trials, using a formal consensus process [6]. Here we report
4 guidelines for the definition of TTE endpoints used in adjuvant randomized controlled trials (RCTs) for
5 localized colon cancer patients. This research work is registered on the international clinical trials
6 registry (ClinicalTrials.gov Identifier: NCT03676010).

7

8 **Methods**

9 The DATECAN methodology has been published in an earlier communication [6]. As of today,
10 the DATECAN initiative has led to the publication of international guidelines in several cancer sites,
11 notably pancreatic, breast, kidney cancer and sarcoma/GIST [7–10].

12 Literature review

13 We conducted literature reviews to assess the development of guidelines for TTE endpoints and
14 listed TTE endpoints reported in RCTs, either as primary or secondary endpoints, as well as events
15 included in the definition of these TTE endpoints. We limited our search to papers published in English
16 from January 2007 to December 2018. The research algorithms are available in Appendix A1 (online
17 only).

18 The Consensus process

19 A formal consensus method was used to develop these guidelines (for a full description of the
20 methodology of the consensus process, see [6]). Four committees of experts were involved in this
21 process: the coordinating committee (CC), the steering committee (SC), the rating committee (RC: 20-30
22 experts representative of international academic groups chosen by the RC with the help of the SC) and

1 the peer-review committee (PRC). Two experts of the DATECAN methodology (DATECAN founders) were
2 included in the CC and the SC (C.B and S.G). All RC experts had to be a current or past principal
3 investigator of at least one phase III adjuvant colon cancer study or to be the first or last author of at
4 least one phase III trial publication reporting phase III trial results.

5 Briefly, we relied on a modified Delphi consensus method, with two rounds of online
6 questionnaires and a final in-person meeting to discuss items for which consensus has not been reached
7 after two rounds of rating. For the first round, all RC experts received the questionnaire elaborated by
8 the SC and were asked to score from 1 (totally disagree) to 9 (totally agree) whether each event should
9 be included or not in the definition of each TTE endpoint. For the second round, experts were asked to
10 rescore items for which no strong consensus had been reached during the first round (*i.e.* inclusion of an
11 event in the TTE endpoint definition if median score ≥ 7 and all scores ≥ 7 ; no inclusion if median score \leq
12 3 and all scores ≤ 3 ; up to 2 missing responses or outliers were tolerated for the second round; see
13 Appendix A2 (online only). By design the formal consensus process aims to guide experts to take a
14 position, while accurately determining their opinion. Items for which no strong consensus had been
15 reached during the 2 rounds of rating were discussed during a final in-person meeting.

16

17 **Results**

18 Selection of TTE endpoints to be defined and clinical events of interest

19 During the literature review process, 32 RCTs published from January 2007 to December 2018
20 were identified (Appendix A3, online only). A total of 5 distinct time-to-event endpoints which included
21 12 distinct events (*i.e.* 60 events to be scored; table 1) were reported. Variations were observed for the
22 definition of all TTE endpoints except time to recurrence that was used in only one trial. Discrepancies

1 were notably observed in the definition of DFS. Among 25 trials using DFS as their primary endpoint,
2 80% included second primary colorectal cancer as an event for DFS, and 40% included second primary
3 non-colorectal cancer (Appendix A3, online only). During the development of the questionnaires, the SC
4 proposed to discuss an additional time-to-event endpoint named colon cancer specific survival (C-CSS)
5 that, to our knowledge, had never been reported in published trials but might be more relevant than
6 cancer specific survival (CSS). This methodology led us to score 72 events. Due to some variability in the
7 choice of the reference date (“t0”) in the literature, a supplementary question was added to the
8 questionnaires to obtain the experts’ opinion.

9 Experts for the scoring process

10 The CC drafted a list of 45 international experts that were representative of academic research
11 groups. Of the 24 experts who completed the first questionnaire, 20 (83%) also answered the second
12 round (4 experts did not participate to the second round of rating despite several reminder emails were
13 sent during a 6-week period). They were mainly medical oncologists (19 out of 20), working at academic
14 institutions in multiple countries (Appendix A4, online only). Multiple cooperative groups were
15 represented: AIO colorectal cancer study group (Arbeitsgemeinschaft Internistische Onkologie), Alliance
16 for Clinical Trials in Oncology, CCTG (Canadian Cancer Trials Group), Dutch Colorectal Cancer Group,
17 EORTC GI (European Organisation for Research and Treatment of Cancer, Gastro-intestinal group), FFCD
18 (Fédération Francophone de Cancérologie Digestive), GERCOR (French Multidisciplinary Group in
19 Oncology), GISCAD (Italian Group for the Study of Gastrointestinal Cancer), Hellenic Oncology Research
20 Group (HORG), JCOG (Japan Clinical Oncology Group), NRG Oncology (NSABP/RTOG/GOG: National
21 Surgical Adjuvant Breast and Bowel Project / Radiation Therapy Oncology Group / Gynecologic Oncology
22 Group), UCGI (Unicancer Gastrointestinal Group).

23 Standardized definitions of the TTE endpoints

1 After the first round of rating, there was a strong consensus on 17 items out of 72 items (24%).
2 Thus, 55 items were submitted to the rating process for the second round. After the second step of the
3 rating process, the group reached a strong consensus on 41 additional items (57%; table 2 and Appendix
4 A5, online only). Therefore, the attendees (12 experts: 7 from the RC, 2 from the CC, 3 from the SC)
5 discussed the 31 items where consensus had not become apparent during the face-to-face meeting
6 (Appendix A6, online only).

7 Events to be included in the definition of each TTE endpoint following the consensus process are
8 summarized in table 3. After consensus, the definition of DFS included all causes of death as an event as
9 well as second primary colorectal cancers, and both anastomotic and metastatic relapses. Events
10 included in the RFS definition were: all types of death, as well as anastomotic and metastatic relapse.
11 TTR definition includes anastomotic and metastatic relapse as well as death with evidence of recurrence
12 and death from colon cancer.

13 The definitions of CSS and C-CSS (which had been added to the questionnaire by the SC) were
14 identical: death with evidence of recurrence, death related to protocol treatment and death from colon
15 cancer. In the experts' opinion, with respect to adjuvant colon cancer trials, the relevant endpoint
16 should be designated as 'colon cancer specific survival' rather than 'cancer specific survival'.

17 Considering the reference date (surgery or date of randomization), the experts agreed that date
18 of randomization should be used in RCTs for adjuvant treatment in localized colon cancer in order to
19 maintain the notion of intention to treat.

20 Validation of the guidelines and peer-review

21 The minutes of the face-to-face meeting, which included the final guidelines, were validated by
22 email by all the participating experts. Following this preliminary review, the first draft of the manuscript

1 of guideline recommendations was sent to the experts and then submitted to a peer-review group for
2 external comments. This group provided a formal, advisory opinion on the content and form of the
3 initial version of the guidelines, in particular their applicability, acceptability, and readability.

4

5 **Discussion and conclusion**

6 It is desirable to standardize the methodology of RCTs that enroll cancer patients in order to
7 harmonize the reporting of clinical research, especially for colon cancer studies, the second most
8 common cancer killer worldwide. The experts involved in this study were drawn from the leadership of
9 international cancer clinical trials cooperative groups and had coordinated clinical trials in the setting of
10 the adjuvant treatment of colon cancer. We also had experts in the use and application of the DATECAN
11 methodological framework. We believe that this approach will enhance the reproducibility of the
12 endpoints between studies and to facilitate the comparison of results across different RCTs.

13 We intentionally did not include recommendations about the censoring process. Indeed, events
14 that are not included in the TTE endpoint can be censored, ignored, or accounted for (using competing-
15 risk analysis) in the statistical analysis, and the selected method is study-specific depending on the the
16 trial's objectives [5,11].

17 Considering DFS, strong consensus was already obtained for 5 events after the 2 steps of the
18 rating process: anastomotic and metastatic relapse, death with evidence of recurrence, death related to
19 treatment protocol or death from colon cancer cause. The experts agreed that DFS should include all
20 causes of death as an event, to avoid bias in the interpretation of the cause of the death. A consensus
21 emerged to include second primary colorectal cancers in the definition of DFS. During the last decade,
22 second primary colorectal cancers were included in the definition of DFS, with the exception of NCCTG

1 N0147, CALGB 89803, CALGB 9581, and in a study of the NCGC Norwegian Gastrointestinal Cancer
2 Group [12–15]. The potential difficulty to distinguish second primary colorectal cancers from
3 anastomotic relapse was one of the reasons for this unanimous decision. Second primary non-colorectal
4 cancers were discussed at length. It has been included in the definition of DFS in 10 out of 27 trials
5 (PETACC3, FNCLCC Accord 02, NASBP C-07, NASBP C-08, NASBP-C09, JCOG0205, JMC33-0502,
6 JCOG0910, SACURA, ECKINOXE) using DFS as the primary or secondary objective since 2007 [2,12–
7 16,16–41]. Importantly, in the PETACC-3 trial, 45 patients (4.3%) in the LV5FU2 group and 55 patients
8 (5.3%) in the irinotecan plus LV5FU2 group had a second primary malignancy other than colon cancer
9 that was recorded as a disease-free survival event, with potential impact on the trial’s conclusions [2].
10 Considering the presumed absence of relationship between adjuvant therapy for colon cancer and the
11 occurrence of second primary non-colorectal cancer, the experts decided not to include this item in the
12 definition of DFS for adjuvant colon cancer trials.

13 For the definition of RFS, strong consensus had been reached during the rating process not to
14 include second primary non-colorectal cancers. This has not been defined as an RFS event in trials
15 reported in the last decade with the exception of PETACC-3, X-ACT, CALGB 89803, and XELOXA studies
16 [2,13,23,38]. In published trials, death of any cause was considered as an event for RFS in almost all
17 trials, except in X-ACT and XELOXA where it was limited to “treatment-related or cancer-related death if
18 relapse had not been reported”, and in CALGB 89803 in which only “death with documented cancer
19 relapse” was included in the definition of RFS [13,23,38]. Finally, as well as for DFS, the experts agreed
20 to include all causes of death in the definition of RFS: given the difficulty in defining the true cause of
21 death, all deaths, whatever the cause, should be considered events for “survival” TTE endpoints, except
22 for (colon) cancer-specific survival.

1 In the only trial (NCCTG N0147) that used TTR as an endpoint, the events included in the TTR
2 definition were recurrence or death with recurrence [12]. Strong consensus was obtained for these 2
3 items, as well as for death caused by colon cancer. All other causes of death, as well as second primary
4 cancers, were not considered as events to be considered in the definition of time to recurrence. TTR
5 might be useful for populations for which death from non-colon cancer cause and from unknown cause
6 might compete with cancer relapse events, such as the elderly, which may die before cancer relapse, or
7 stage II colon cancer patients, whose risk of recurrence is low. TTR may also be more informative than
8 DFS for biomarker association analyses.

9 Cancer specific survival was used in 2 trials only [15,36]. The included event was death caused
10 by colon cancer and also treatment-related death in one of these 2 trials. Importantly, a strong
11 consensus to include death with evidence of recurrence (whatever the cause of the death), was
12 obtained during the first round of rating by the experts. The 2 rounds of rating and the discussion during
13 the final meeting brought to light the fact that CSS and colon cancer specific survival (C-CSS) seemed
14 similar to the experts. Of note, the definition of CSS by the National Cancer Institute is as follows: “the
15 percentage of people in a study or treatment group who have not died from a specific disease in a
16 defined period of time; patients who died from causes other than the disease being studied are not
17 counted in this measurement”. Therefore, considering adjuvant colon cancer trials, the relevant
18 indicator might be named colon cancer specific survival rather than CSS. CSS can be confusing in the
19 context of trials of adjuvant therapy in colon cancer because of deaths due to non-colorectal cancers.
20 Importantly, strong consensus was obtained during the first round to include death with evidence of
21 recurrence in the definition of C-CSS. This determination was made given the poor prognosis of relapsed
22 colorectal cancer. The experts confirmed that death with evidence of recurrence should be considered
23 as event for C-CSS. Besides, considering the fact that patients do receive anti-tumor treatment because

1 of the disease and would have not received it if they have not been diagnosed with colon cancer, the
2 experts consensually decided to integrate death related to protocol treatment in the definition of C-CSS.

3 Consensus was obtained for all items after this formal consensus rating with 2 rounds of rating
4 and a final face-to-face meeting. Given its strong correlation with OS, the experts unanimously
5 recommend using DFS, a surrogate endpoint approved by the Food and Drug Administration, as primary
6 endpoint rather than RFS, TTR, and C-CSS in adjuvant RCTs for patients with localized colon cancer.

7

8

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11

12 **Conflict of interest statement**

13 LS has received research funds from Taiho Pharmaceutical.

14 MS has received honoraria for meetings/lectures from Roche, Merck, Sanofi, Servier and Amgen.

15 RC has received honoraria from Amgen, Sanofi and Servier, and travel fees from Sanofi.

16 TA has served in a consulting/advisory role and or received honoraria for, Amgen, Bristol-Myers Squibb,
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- 4 All remaining authors have declared no conflicts of interest.

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12

1 **Table 1: Events and time-to-event endpoints used as primary or secondary objectives in randomized**
 2 **trials published between 2007 and 2018**

Events	Time-to-event endpoints
Anastomotic relapse	Overall survival
Metastatic relapse	Disease-free survival
Second primary colorectal cancer	Relapse-free survival
Second primary non-colorectal cancer	Time to recurrence
Death with evidence of recurrence	Cancer specific survival
Death without evidence of recurrence	Colon cancer specific survival*
Death related to protocol treatment	
Death from colon cancer cause	
Death from non-colon cancer cause	
Death from unknown cause	
Death from any cause	
Loss to follow-up	

3 *: the steering committee suggested including colon cancer specific survival during the elaboration of
 4 questionnaires

1 **Table 2: Results of the 2 rounds of rating**

2 OS: overall survival; DFS: disease free survival; RFS: relapse free survival; TTR: time to recurrence; CSS:

3 cancer specific survival; C-CSS: colon cancer specific survival

4 Strong consensus to include (green) or not to include (red) the item; relative consensus to include (light

5 green) or no to include (light red) the item; no consensus or uncertainty: white

	OS	DFS	RFS	TTR	CSS	C-CSS
anastomotic relapse	Red	Green	Green	Green	White	Light Green
metastatic relapse	Red	Green	Green	Green	Light Green	Light Green
2 nd primary CRC	Red	Light Green	Light Red	Light Red	Light Red	Light Green
2 nd primary non-colorectal cancer	Red	White	Red	Red	Red	Red
death with evidence of recurrence	Green	Green	Green	Green	Green	Green
death without evidence of recurrence	Green	Light Green	Light Red	Red	Red	Red
death related to protocol treatment	Green	Green	White	Light Red	Light Green	White
death from colon cancer cause	Green	Green	Green	Green	Green	Green
death from non-colon cancer cause	Green	Light Green	Light Red	Red	Light Red	Red
death from unknown cause	Green	Light Green	White	Light Red	White	Light Red
death from any cause	Green	Light Green	Light Red	Red	Light Red	Light Red
lost of follow-up	Light Red	Light Red	Red	Red	Red	Light Red

6

1 **Table 3: DATECAN guidelines for events to be included in the definitions of time-to-event endpoints in**
 2 **randomized clinical trials for adjuvant treatment in localized colon cancer**

3 Green box: inclusion of the event; Red box: events that should not be considered in the definition of the
 4 time to event endpoint

5 OS: overall survival; DFS: disease free survival; RFS: relapse free survival; TTR: time to recurrence; C-CSS:
 6 colon cancer specific survival

	OS	DFS	RFS	TTR	C-CSS
Anastomotic relapse	Red	Green	Green	Green	Red
Metastatic relapse	Red	Green	Green	Green	Red
Second primary CRC	Red	Green	Red	Red	Red
Second primary non-colorectal cancer	Red	Red	Red	Red	Red
Death with evidence of recurrence	Green	Green	Green	Green	Green
Death without evidence of recurrence	Green	Green	Green	Red	Red
Death related to protocol treatment	Green	Green	Green	Red	Green
Death from colon cancer cause	Green	Green	Green	Green	Green
Death from non-colon cancer cause	Green	Green	Green	Red	Red
Death from unknown cause	Green	Green	Green	Red	Red
Death from any cause	Green	Green	Green	Red	Red
Loss to follow-up	Red	Red	Red	Red	Red

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