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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**

2 Original research

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

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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  $\geq 7$  and all scores  $\geq 7$ ; no inclusion if median score  $\leq$   
12 3 and all scores  $\leq 3$ ; 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 NGCG 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.

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- 4 All remaining authors have declared no conflicts of interest.



## 1 References

- 2 [1] Birgisson H, Wallin U, Holmberg L, Glimelius B. Survival endpoints in colorectal cancer and the  
3 effect of second primary other cancer on disease free survival. *BMC Cancer* 2011;11:438.  
4 <https://doi.org/10.1186/1471-2407-11-438>.
- 5 [2] Van Cutsem E, Labianca R, Bodoky G, Barone C, Aranda E, Nordlinger B, et al. Randomized phase III  
6 trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant  
7 treatment of stage III colon cancer: PETACC-3. *J Clin Oncol* 2009;27:3117–25.  
8 <https://doi.org/10.1200/JCO.2008.21.6663>.
- 9 [3] International conference on harmonisation; guidance on statistical principles for clinical trials;  
10 availability--FDA. Notice. *Fed Regist* 1998;63:49583–98.
- 11 [4] Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines  
12 for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726–32.  
13 <https://doi.org/10.7326/0003-4819-152-11-201006010-00232>.
- 14 [5] Punt CJA, Buyse M, Köhne C-H, Hohenberger P, Labianca R, Schmoll HJ, et al. Endpoints in Adjuvant  
15 Treatment Trials: A Systematic Review of the Literature in Colon Cancer and Proposed Definitions  
16 for Future Trials. *J Natl Cancer Inst* 2007;99:998–1003. <https://doi.org/10.1093/jnci/djm024>.
- 17 [6] Bellera CA, Pulido M, Gourgou S, Collette L, Doussau A, Kramar A, et al. Protocol of the Definition  
18 for the Assessment of Time-to-event Endpoints in CANcer trials (DATECAN) project: Formal  
19 consensus method for the development of guidelines for standardised time-to-event endpoints'  
20 definitions in cancer clinical trials. *European Journal of Cancer* 2013;49:769–81.  
21 <https://doi.org/10.1016/j.ejca.2012.09.035>.
- 22 [7] Kramar A, Negrier S, Sylvester R, Joniau S, Mulders P, Powles T, et al. Guidelines for the definition  
23 of time-to-event end points in renal cell cancer clinical trials: results of the DATECAN project†. *Ann*  
24 *Oncol* 2015;26:2392–8. <https://doi.org/10.1093/annonc/mdv380>.
- 25 [8] Gourgou-Bourgade S, Cameron D, Poortmans P, Asselain B, Azria D, Cardoso F, et al. Guidelines for  
26 time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative  
27 (Definition for the Assessment of Time-to-event Endpoints in CANcer trials). *Ann Oncol*  
28 2015;26:873–9. <https://doi.org/10.1093/annonc/mdv106>.
- 29 [9] Bellera CA, Penel N, Ouali M, Bonvalot S, Casali PG, Nielsen OS, et al. Guidelines for time-to-event  
30 end point definitions in sarcomas and gastrointestinal stromal tumors (GIST) trials: results of the  
31 DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials).  
32 *Ann Oncol* 2015;26:865–72. <https://doi.org/10.1093/annonc/mdu360>.
- 33 [10] Bonnetain F, Bonsing B, Conroy T, Dousseau A, Glimelius B, Haustermans K, et al. Guidelines for  
34 time-to-event end-point definitions in trials for pancreatic cancer. Results of the DATECAN  
35 initiative (Definition for the Assessment of Time-to-event End-points in CANcer trials). *Eur J Cancer*  
36 2014;50:2983–93. <https://doi.org/10.1016/j.ejca.2014.07.011>.
- 37 [11] Leung K-M, Elashoff RM, Afifi AA. Censoring Issues in Survival Analysis. *Annual Review of Public*  
38 *Health* 1997;18:83–104. <https://doi.org/10.1146/annurev.publhealth.18.1.83>.
- 39 [12] Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, et al. Effect of oxaliplatin,  
40 fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected  
41 stage III colon cancer: a randomized trial. *JAMA* 2012;307:1383–93.  
42 <https://doi.org/10.1001/jama.2012.385>.
- 43 [13] Saltz LB, Niedzwiecki D, Hollis D, Goldberg RM, Hantel A, Thomas JP, et al. Irinotecan fluorouracil  
44 plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage  
45 III colon cancer: results of CALGB 89803. *J Clin Oncol* 2007;25:3456–61.  
46 <https://doi.org/10.1200/JCO.2007.11.2144>.

- 1 [14] Niedzwiecki D, Bertagnolli MM, Warren RS, Compton CC, Kemeny NE, Benson AB, et al.  
2 Documenting the Natural History of Patients With Resected Stage II Adenocarcinoma of the Colon  
3 After Random Assignment to Adjuvant Treatment With Edrecolomab or Observation: Results From  
4 CALGB 9581. *J Clin Oncol* 2011;29:3146–52. <https://doi.org/10.1200/JCO.2010.32.5357>.
- 5 [15] Dahl O, Fluge Ø, Carlsen E, Wiig JN, Myrvold HE, Vonnen B, et al. Final results of a randomised phase  
6 III study on adjuvant chemotherapy with 5 FU and levamisol in colon and rectum cancer stage II  
7 and III by the Norwegian Gastrointestinal Cancer Group. *Acta Oncol* 2009;48:368–76.  
8 <https://doi.org/10.1080/02841860902755244>.
- 9 [16] André T, Quinaux E, Louvet C, Colin P, Gamelin E, Bouche O, et al. Phase III Study Comparing a  
10 Semimonthly With a Monthly Regimen of Fluorouracil and Leucovorin As Adjuvant Treatment for  
11 Stage II and III Colon Cancer Patients: Final Results of GERCOR C96.1. *Journal of Clinical Oncology*  
12 2007;25:3732–8. <https://doi.org/10.1200/JCO.2007.12.2234>.
- 13 [17] Allegra CJ, Yothers G, O’Connell MJ, Sharif S, Petrelli NJ, Lopa SH, et al. Bevacizumab in Stage II-III  
14 Colon Cancer: 5-Year Update of the National Surgical Adjuvant Breast and Bowel Project C-08 Trial.  
15 *J Clin Oncol* 2013;31:359–64. <https://doi.org/10.1200/JCO.2012.44.4711>.
- 16 [18] André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved Overall Survival  
17 With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer  
18 in the MOSAIC Trial. *Journal of Clinical Oncology* 2009;27:3109–16.  
19 <https://doi.org/10.1200/JCO.2008.20.6771>.
- 20 [19] Aparicio T, Francois E, Cristol-Dalstein L, Carola E, Maillard E, Paillaud E, et al. PRODIGE 34-FFCD  
21 1402-ADAGE: Adjuvant chemotherapy in elderly patients with resected stage III colon cancer: A  
22 randomized phase 3 trial. *Dig Liver Dis* 2016;48:206–7. <https://doi.org/10.1016/j.dld.2015.11.023>.
- 23 [20] Chang W, Wei Y, Ren L, Zhong Y, Yu Y, Chen J, et al. Randomized Controlled Trial of Intraportal  
24 Chemotherapy Combined With Adjuvant Chemotherapy (mFOLFOX6) for Stage II and III Colon  
25 Cancer. *Ann Surg* 2016;263:434–9. <https://doi.org/10.1097/SLA.0000000000001374>.
- 26 [21] de Gramont A, Van Cutsem E, Schmoll H-J, Tabernero J, Clarke S, Moore MJ, et al. Bevacizumab  
27 plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3  
28 randomised controlled trial. *Lancet Oncol* 2012;13:1225–33. [https://doi.org/10.1016/S1470-2045\(12\)70509-0](https://doi.org/10.1016/S1470-2045(12)70509-0).
- 29 [22] Grothey A, Sobrero AF, Shields AF, Yoshino T, Paul J, Taieb J, et al. Duration of Adjuvant  
30 Chemotherapy for Stage III Colon Cancer. *N Engl J Med* 2018;378:1177–88.  
31 <https://doi.org/10.1056/NEJMoa1713709>.
- 32 [23] Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus  
33 oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon  
34 cancer. *J Clin Oncol* 2011;29:1465–71. <https://doi.org/10.1200/JCO.2010.33.6297>.
- 35 [24] Hamaguchi T, Shimada Y, Mizusawa J, Kinugasa Y, Kanemitsu Y, Ohue M, et al. Capecitabine versus  
36 S-1 as adjuvant chemotherapy for patients with stage III colorectal cancer (JCOG0910): an open-  
37 label, non-inferiority, randomised, phase 3, multicentre trial. *The Lancet Gastroenterology &*  
38 *Hepatology* 2018;3:47–56. [https://doi.org/10.1016/S2468-1253\(17\)30297-2](https://doi.org/10.1016/S2468-1253(17)30297-2).
- 39 [25] Hamaguchi T, Shirao K, Moriya Y, Yoshida S, Kodaira S, Ohashi Y, et al. Final results of randomized  
40 trials by the National Surgical Adjuvant Study of Colorectal Cancer (NSAS-CC). *Cancer Chemother*  
41 *Pharmacol* 2011;67:587–96. <https://doi.org/10.1007/s00280-010-1358-1>.
- 42 [26] Herrmann R, Lorenz M, Zuber M, Rufibach K, Laffer U. Perioperative and adjuvant chemotherapy in  
43 colon cancer: results of SAKK trial 40/93. *Int J Colorectal Dis* 2009;24:351–2.  
44 <https://doi.org/10.1007/s00384-008-0577-y>.
- 45 [27] Iveson TJ, Kerr RS, Saunders MP, Cassidy J, Hollander NH, Tabernero J, et al. 3 versus 6 months of  
46 adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): an  
47

- 1 international, randomised, phase 3, non-inferiority trial. *The Lancet Oncology* 2018;19:562–78.  
2 [https://doi.org/10.1016/S1470-2045\(18\)30093-7](https://doi.org/10.1016/S1470-2045(18)30093-7).
- 3 [28] Karoui M, Rullier A, Luciani A, Bonnetain F, Auriault M-L, Sarran A, et al. Neoadjuvant FOLFOX 4  
4 versus FOLFOX 4 with Cetuximab versus immediate surgery for high-risk stage II and III colon  
5 cancers: a multicentre randomised controlled phase II trial – the PRODIGE 22 - ECKINOXE trial.  
6 *BMC Cancer* 2015;15. <https://doi.org/10.1186/s12885-015-1507-3>.
- 7 [29] Köhne C-H, Bedenne L, Carrato A, Bouché O, Popov I, Gaspà L, et al. A randomised phase III  
8 intergroup trial comparing high-dose infusional 5-fluorouracil with or without folinic acid with  
9 standard bolus 5-fluorouracil/folinic acid in the adjuvant treatment of stage III colon cancer: the  
10 Pan-European Trial in Adjuvant Colon Cancer 2 study. *Eur J Cancer* 2013;49:1868–75.  
11 <https://doi.org/10.1016/j.ejca.2013.01.030>.
- 12 [30] Kuebler JP, Wieand HS, O’Connell MJ, Smith RE, Colangelo LH, Yothers G, et al. Oxaliplatin  
13 Combined With Weekly Bolus Fluorouracil and Leucovorin As Surgical Adjuvant Chemotherapy for  
14 Stage II and III Colon Cancer: Results From NSABP C-07. *JCO* 2007;25:2198–204.  
15 <https://doi.org/10.1200/JCO.2006.08.2974>.
- 16 [31] Matsuda C, Ishiguro M, Teramukai S, Kajiwara Y, Fujii S, Kinugasa Y, et al. A randomised-controlled  
17 trial of 1-year adjuvant chemotherapy with oral tegafur–uracil versus surgery alone in stage II  
18 colon cancer: SACURA trial. *European Journal of Cancer* 2018;96:54–63.  
19 <https://doi.org/10.1016/j.ejca.2018.03.009>.
- 20 [32] Papadimitriou CA, Papakostas P, Karina M, Malettou L, Dimopoulos MA, Pentheroudakis G, et al. A  
21 randomized phase III trial of adjuvant chemotherapy with irinotecan, leucovorin and fluorouracil  
22 versus leucovorin and fluorouracil for stage II and III colon cancer: A Hellenic Cooperative Oncology  
23 Group study. *BMC Med* 2011;9:10. <https://doi.org/10.1186/1741-7015-9-10>.
- 24 [33] Popov I, Carrato A, Sobrero A, Vincent M, Kerr D, Labianca R, et al. Raltitrexed (Tomudex) versus  
25 standard leucovorin-modulated bolus 5-fluorouracil: Results from the randomised phase III Pan-  
26 European Trial in Adjuvant Colon Cancer 01 (PETACC-1). *Eur J Cancer* 2008;44:2204–11.  
27 <https://doi.org/10.1016/j.ejca.2008.07.002>.
- 28 [34] Sadahiro S, Tsuchiya T, Sasaki K, Kondo K, Katsumata K, Nishimura G, et al. Randomized phase III  
29 trial of treatment duration for oral uracil and tegafur plus leucovorin as adjuvant chemotherapy  
30 for patients with stage IIB/III colon cancer: final results of JFMC33-0502. *Ann Oncol* 2015;26:2274–  
31 80. <https://doi.org/10.1093/annonc/mdv358>.
- 32 [35] Shimada Y, Hamaguchi T, Mizusawa J, Saito N, Kanemitsu Y, Takiguchi N, et al. Randomised phase  
33 III trial of adjuvant chemotherapy with oral uracil and tegafur plus leucovorin versus intravenous  
34 fluorouracil and levofolinate in patients with stage III colorectal cancer who have undergone  
35 Japanese D2/D3 lymph node dissection: Final results of JCOG0205. *European Journal of Cancer*  
36 2014;50:2231–40. <https://doi.org/10.1016/j.ejca.2014.05.025>.
- 37 [36] Schippinger W, Samonigg H, Schaberl-Moser R, Greil R, Thödtmann R, Tschmelitsch J, et al. A  
38 prospective randomised phase III trial of adjuvant chemotherapy with 5-fluorouracil and  
39 leucovorin in patients with stage II colon cancer. *Br J Cancer* 2007;97:1021–7.  
40 <https://doi.org/10.1038/sj.bjc.6604011>.
- 41 [37] Taieb J, Tabernero J, Mini E, Subtil F, Folprecht G, Van Laethem J-L, et al. Oxaliplatin, fluorouracil,  
42 and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-  
43 8): an open-label, randomised phase 3 trial. *The Lancet Oncology* 2014;15:862–73.  
44 [https://doi.org/10.1016/S1470-2045\(14\)70227-X](https://doi.org/10.1016/S1470-2045(14)70227-X).
- 45 [38] Twelves C, Scheithauer W, McKendrick J, Seitz J-F, Van Hazel G, Wong A, et al. Capecitabine versus  
46 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-  
47 ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy.  
48 *Annals of Oncology* 2012;23:1190–7. <https://doi.org/10.1093/annonc/mdr366>.

- 1 [39] Ychou M, Raoul J-L, Douillard J-Y, Gourgou-Bourgade S, Bugat R, Mineur L, et al. A phase III  
2 randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer  
3 (FNCLCC Accord02/FFCD9802). *Ann Oncol* 2009;20:674–80.  
4 <https://doi.org/10.1093/annonc/mdn680>.
- 5 [40] Yoshida M, Ishiguro M, Ikejiri K, Mochizuki I, Nakamoto Y, Kinugasa Y, et al. S-1 as adjuvant  
6 chemotherapy for stage III colon cancer: a randomized phase III study (ACTS-CC trial). *Ann Oncol*  
7 2014;25:1743–9. <https://doi.org/10.1093/annonc/mdu232>.
- 8 [41] Yothers G, O’Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. Oxaliplatin As  
9 Adjuvant Therapy for Colon Cancer: Updated Results of NSABP C-07 Trial, Including Survival and  
10 Subset Analyses. *Journal of Clinical Oncology* 2011;29:3768–74.  
11 <https://doi.org/10.1200/JCO.2011.36.4539>.  
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**

<b>Events</b>	<b>Time-to-event endpoints</b>
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 <sup>nd</sup> primary CRC	Red	Light Green	Light Red	Light Red	Light Red	Light Green
2 <sup>nd</sup> 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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