Lessons learnt from scoring adjuvant colon cancer trials and meta-analyses using the ESMO-Magnitude of Clinical Benefit Scale V.1.1

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ABSTRACT

Background Form 1 of the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) serves to grade therapies with curative intent. Hitherto only few trials with curative intent have been field tested using form 1. We aimed to evaluate the applicability of the scale and to assess the reasonableness of the generated scores in early colon cancer, in order to identify shortcomings that may be rectified in future amendments.

Methods Adjuvant studies were identified in PubMed, Food and Drug Administration and European Medicines Agency registration sites, as well as ESMO and National Comprehensive Cancer Network guidelines. Studies meeting inclusion criteria were graded using form 1 of the ESMO-MCBS V.1.1 and field tested by ESMO Colorectal Cancer Faculty. Shortcomings of the scale were identified and evaluated.

Results Eighteen of 57 trials and 7 out of 14 meta-analyses identified met criteria for ESMO-MCBS V.1.1 grading. In stage III colon cancer, randomised clinical trials and meta-analyses of modulated 5-fluorouracil (5-FU) based chemotherapy versus surgery scored ESMO-MCBS grade A and randomised controlled trials (RCTs) and meta-analyses comprising oxaliplatin added to this 5-FU backbone showed a more modest additional overall survival benefit (grade A and B). For stage II colon cancer, the findings are less consistent. The fluoropyrimidine trials in stage II were graded ‘no evaluable benefit’ but the most recent meta-analysis demonstrated a 5.4% survival advantage after 8 years follow-up (grade A). RCTs and a meta-analysis adding oxaliplatin demonstrated no added benefit. Exploratory toxicity evaluation and annotation was problematic given inconsistent toxicity reporting and limited results of late toxicity. Field testers (n=37) reviewed the scores, 25 confirmed their reasonableness, 12 found them mostly reasonable. Moreover, they identified the inability of crediting improved convenience in non-inferiority trials as a shortcoming.

Conclusion Form 1 of the ESMO-MCBS V.1.1 provided very reasonable grading for adjuvant colon cancer studies.

Key questions

What is already known about this subject?

► Form 1 of the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) serves to grade therapies with curative intent. Hitherto only few trials with curative intent have been field tested using form 1.

What does this study add?

► We evaluated the applicability of the scale and assessed the reasonableness of the generated scores in early colon cancer. Form 1 of the ESMO-MCBS V.1.1 provided very reasonable grading for adjuvant colon cancer studies. Our exploratory analysis indicated that toxicity annotation is feasible but that the prevailing convention of physician reported toxicity may underestimate the true level of patient burden from both acute and late toxicity. The inability of crediting improved convenience in non-inferiority trials was identified as a shortcoming.

How might this impact on clinical practice?

► Future revisions of form 1 of the ESMO-MCBS will be cogniscente of these findings.

INTRODUCTION

Colorectal cancer is the third most common tumour in men, the second in women and second place in cancer-related cause of death in the world.1 Mortality has declined over the years for several reasons, including colorectal cancer screening and more effective systemic therapies in both the adjuvant setting and metastatic disease.

Adjuvant therapies for colon cancer have evolved over the past 40 years. Early studies failed to show overall survival (OS) benefit of single agent therapy including 5-fluorouracil (5-FU) monotherapy compared with surgery.
Adjuvant leucovorin modulated 5-FU (5-FU/LV) did, however, improve relative OS, but not absolute OS due to the increased incidence, and has been the standard of care since the mid-nineties. As of 2004, standard adjuvant therapy consists of a 5-FU/LV-based backbone to which oxaliplatin was added. Oxaliplatin did improve disease-free survival (DFS) and OS in stage III patients but it commonly caused substantial late toxicity (LT) with peripheral sensory neurotoxicity (PSN). Other agents including irinotecan, cetuximab and bevacizumab tested in the adjuvant setting, have been field tested using form 1. The main purpose was to evaluate the applicability of the scale in adjuvant colon cancer trials and further assess the reasonableness of the generated scores, in order to identify shortcomings that may be rectified in future amendments.

The ESMO-MCBS working group have suggested that adverse outcomes should be introduced for treatments with a high prevalence of strong acute toxicity (AT) or LT and this is currently under consideration.

The validity of the ESMO-MCBS is predicated on adherence to the public policy ethical standard of ‘accountability for reasonableness’. Whereas the grading of treatments of advanced and incurable cancer using forms 2a, b, c and 3 of the ESMO-MCBS has been extensively field tested and reviewed for reasonableness, hitherto only 13 trials with curative intent, including adjuvant therapies, have been field tested using form 1. The main purpose was to evaluate the applicability of the scale in adjuvant colon cancer trials and further assess the reasonableness of the generated scores, in order to identify shortcomings that may be rectified in future amendments.

**METHODS**

Randomised controlled trials (RCTs) and meta-analyses in the adjuvant treatment of stage II/III colon cancer, published since the review of negative studies by Buyse et al up to September 2019 were identified. Data were collected by electronic searches of PubMed (medical headings “colonic neoplasms” OR “colorectal neoplasms”, and the text words “adjuvant therapy” OR “adjuvant chemotherapy” OR “early colon cancer”) and by a manual review of Food and Drug Administration and European Medicines Agency registration sites and ESMO and National Comprehensive Cancer Network guidelines. Reference lists of included studies were also analysed.

We included also trials that investigated regimens, which are currently seen as obsolete, to ensure the most comprehensive overview of the treatment of early colon cancer over three decades. These obsolete regimens often serve as the control arm in newer trials. Furthermore, scoring these older trials might give valuable information regarding the applicability of the scale and identify possible shortcomings. Trials investigating adjuvant treatment regimens that resulted in only negative results were excluded from the analysis. However, a trial with negative results per se, if the regimen investigated had positive outcome in other trials, was not an exclusion criterion. In addition, trials including rectal cancer without a predefined colon cancer subgroup, were excluded from the analysis since radiotherapy is instrumental in (neo) adjuvant rectal cancer treatment which would make it difficult to assess the impact of chemotherapy. Meta-analyses that were not scoreable by the ESMO-MCBS scale were excluded for analysis as well (Consolidated Standards of Reporting Trials (CONSORT) diagram figure 1).

All studies meeting the inclusion and exclusion criteria were graded using form 1 of the ESMO-MCBS, based on OS or DFS results. Additionally, for non-inferiority trials, the grading was influenced by toxicity, quality of...
life (QoL) and costs. If there were up to three predefined subgroups included in the trial and there was an appropriate adjustment for multiplicity, these subgroups were graded individually. Trials that did not meet the criteria for scoring due to insufficient benefit (negative studies) have been designated as trials with ‘no evaluable benefit’ (NEB). Negative non-inferiority (NNI) studies were labelled as NNI. Extracted data and grading were reviewed by the ESMO-MCBS Working Group for accuracy.

An exploratory analysis of reported toxicity data was undertaken to determine the feasibility of toxicity annotations. Side effects during treatment or within 3 months after treatment completion were defined as AT. LT was defined as all events that occurred 3 months after treatment completion in accordance with Common Toxicity Criteria.18 AT as well as LT was annotated as overall less (-), equal (=) or more (+) toxicity for the intervention versus the control group. When there is insufficient data reported to draw conclusions, not reported (NR) is annotated.

The scores generated in this field testing were reviewed by the ESMO Gastro-Intestinal Tumours Faculty for reasonableness.

RESULTS
The literature search yielded 57 RCTs and 14 meta-analyses, with 18 RCTs and 7 meta-analyses finally found eligible and were included in the analysis. Reasons for exclusion for final analyses are summarised in the CONSORT diagram figure 1 and excluded studies and meta-analyses can be found in the supplementary references.

ESMO-MCBS grading
Information for the selected trials is summarised in table 1 for fluoropyrimidine regimens and in table 2 for oxaliplatin added to fluoropyrimidine regimens. Results in the tables are categorised to combined stage II and III, stage II and stage III.

Fluoropyrimidine regimens
Four trials and a meta-analysis compared 5-FU/LV chemotherapy with MOF combination chemotherapy (lomustine (MeCCNU), vincristine and non-modulated 5-FU)19 or surgery only for combined stage II and III colon cancers.20–23 They showed OS gain ranging from 5% to 14% at 3.0–5.0 years, resulting in the highest-grade ESMO-MCBS garde (A). These results were confirmed in three successive meta-analyses by the Adjuvant Colon Cancer End-points (ACCENT) Group showing a 7.0%–7.2% OS advantage at 5–8 years follow-up (grade A).24–26 Since 5-FU/levamisole (LEV) was included in these meta-analyses, the OS benefit of 5-FU/LV was probably underestimated since LEV was subsequently found to be inferior to LV as a 5-FU modulator.27–30 Table 1.

The two trials with 318 and 500 patients31,32 and a meta-analysis33 with 1016 patients evaluated adjuvant 5-FU/LV versus no adjuvant therapy in stage II colon cancer. None of these three studies demonstrated OS benefit and all were annotated as NEB. A 2004 meta-analysis involving 1440 patients34 demonstrated a non-significant 5-year survival gain of 1% (ESMO-MCBS grade NEB), however, a subsequent 2009 evaluation by the same group35 with more mature data reported a 5.4% OS benefit at 8 years (grade A). This discrepancy is addressed in the discussion below.

In grade III colon cancer, the observed OS benefit was 13.5% and 10.3% at 5 and 8 years, respectively, resulting in a grade A on the ESMO-MCBS.26,34

Uracil and tegafur (UFT)/LV in combined stage II and III colon cancer,35–37 capecitabine38 and S-139,40 in stage III colon cancer all did not provide an OS or DFS benefit compared with 5-FU/LV. Three of the four trials were non-inferiority trials. Although non-inferiority was proven, since neither QoL nor toxicity was improved; all studies were graded NBE.

Fluoropyrimidines with oxaliplatin combinations
Oxaliplatin added to 5-FU based regimens was evaluated in the MOSAIc41 and NSABP C-0742 trials including stage II and III patients and the NO16968 trial confined to stage III patients.43 Greater clinical benefit (grade A) was observed in the trial confined to stage III compared with the other two trials which were graded B and NEB, respectively. The ACCENT group published a meta-analysis of these studies in 2016.44 Based on 5-year OS data their analysis demonstrated an insignificant 0.8% OS gain for stage II (NEB) and a 4.2% OS advantage for stage III colon cancer (grade B). Table 2.

In 2018 the International Duration Evaluation of Adjuvant (IDEA) consortium reported the planned combined analysis of 6 individual RCTs, with a non-inferiority design, comparing folinic acid/5-FU/oxaliplatin (FOLFOX) and capecitabine/oxaliplatin (CAPOX) for 3 vs 6 months.45 The 3-year DFS rate was very similar but non-inferiority was not proven for the intention to treat population resulting in a NNI. A preplanned subgroup analysis showed that 3 months CAPOX was non-inferior compared with 6 months. The 3 months treatment arm received a grade B based on non-inferiority in combination with less toxicity.46–48 T4 versus T1-3 and N2 versus N1 subgroups were prespecified however their combinations in subgroups and its interaction test was not significant, thus these subgroup analyses were post hoc and could not be graded.

In one meta-analysis, in stage III patients, capecitabine with or without oxaliplatin versus 5-FU/LV with or without oxaliplatin was examined. As no OS and DFS benefit was seen, and neither QoL nor toxicity was improved, it was graded NEB.19

Toxicity, QoL and cost
AT and LT reported in the included trials are summarised in the online supplementary table 1. All trials reported AT using several different approaches to toxicity evaluation: one trial did not use any grading system,5 five did NR the grading system used,19,22,25,26 five used the WHO toxicity scoring system20,23,30,33,35 and seven the common terminology...
| Trial name, year first publication | Intervention versus control | N  | Primary outcome | Median follow-up | DFS control group | DFS gain | DFS HR | OS control group | OS gain | OS HR | Toxicity* | QoL | ESMO-MCBS V1.1 | Ref. |
|----------------------------------|-----------------------------|----|-----------------|------------------|------------------|----------|--------|------------------|---------|-------|-----------|-----|----------------|------|
| **Fluoropyrimidine treatment versus surgery or no active adjuvant therapy** | | | | | | | | | | | | | | | |
| **Combined stage II and III** | | | | | | | | | | | | | | | |
| NSABP C-03 1993 | 5-FU/LV versus MOF | 1041 | DFS | 3 years | 64% at 3 years | 9% | P=0.0004 | 77% at 3 years | 7% | P=0.003 | AT-LT NR | A | 19 | |
| Siena 1994 | 5-FU/LV versus surgery | 239 | DFS | 4.5 years | 59% at 5 years | 15% | 65% at 5 years | 14% | AT+LT NR | A | 20 | |
| Meta-analysis IMPACT1995 | 5-FU/LV versus placebo | 1493 | 5-FU/LV 3.3 yrsPlacebo 3.1 years | 62% at 3 years | 9% | 0.67 (0.56–0.80) | 78% at 3 years | 5% | 0.77 (0.62–0.96) | AT+LT NR | B | 21 | |
| NCCTG 8746511997 | 5-FU/LV versus placebo | 309 | DFS | 6 years | 0.58 at 5 years | 16% | 0.63 at 5 years | 11% | P=0.02 | AT+LT NR | A | 22 | |
| GIMO-SITAC 011998 | 5-FU/LV versus placebo | 869 | 5-FU/LV 5.4 yrsPlacebo 5.3 years | 0.54 at 5 years | 12% | 0.65 at 5 years | 7% | AT+LT NR | A | 23 | |
| Meta-analysis Sargent et al. 2001 | 5-FU/LV or 5-FU/LEV versus surgery alone | 3351 | OS | 5.17–8.54 years | 0.58 at 5 years | 11% | 0.68 (0.60–0.76) | 0.64 at 5 years | 7% | 0.76 (0.68–0.85) | A | 24 | |
| Meta-analysis Gill et al. 2004 | 5-FU/LV or 5-FU/LEV versus surgery | 3302 | DFS and OS | 5 years | 0.55 at 5 years | 12% | 0.7 (0.63–0.78) | 0.64 at 5 years | 7% | 0.74 (0.66–0.83) | A | 25 | |
| Meta-analysis Sargent et al. 2009 | 5-FU/LV or 5-FU/LEV versus surgery | 4922 | DFS | 8 years | NS (HR=0.61) | 0.543 at 8 years | 7.20% | HR=0.74 | P ≤0.001 | NEB | 26 | |
| **Stage II** | | | | | | | | | | | | | | | |
| Intergroup 00351990 | 5-FU/LV versus surgery | 318 | OS | 7 years | 71% at 7 years | 8% | 72% at 7 years | 0% | AT+LT NR | NEB | 31 | |
| Meta-analysis IMPACT B2 1999 | 5-FU/LV versus placebo | 1016 | DFS† | 5.8 years | 73% at 5 years | 3% | 0.83 (0.68–1.01) | 80% at 5 years | 2% | 0.86 (0.64–1.01) | AT+LT NR | NEB | 33 | |
| Meta-analysis Gill et al. 2004 | 5-FU/LV or 5-FU/LEV versus surgery | 1440 | DFS and OS | – | 72% at 5 years | 4% | p=0.049 | 80% at 5 years | 1% | NS p=0.11 | NEB | 25 | |
| ABCSG Schippinger et al. 2007 | 5-FU/LV versus surgery | 500 | OS | 95.6m (~8 years) | 69.4% at 7 years | 0.80 | 0.95 (0.69–1.31) | 76.6% at 7 years | 1.60% | 0.88 (0.61–1.27) | AT+LT NR | NEB | 32 | |
| Meta-analysis Sargent et al. 2009 | 5-FU/LV or 5-FU/LEV versus surgery | 8 years | 66.8% at 8 years | 5.40% | P=0.026 | A | | | | | | | | | |
| **Stage III** | | | | | | | | | | | | | | | |
| Intergroup 00351990 | 5-FU/LEV versus surgery alone | 619 | OS | 6.5 years | 43.8% at 5 years | 17.10% | 46.7% at 5 years | 13.50% | P=0.007 | AT+LT7 | A | 34 | |
### Table 1 Continued

| Trial name and year first publication | Intervention versus control | N | Primary outcome | Median follow-up | DFS control group | DFS gain | DFS HR | OS control group | OS gain | OS HR | Toxicity* | QoL | ESMO-MCBS V1.1 | Ref. |
|--------------------------------------|-----------------------------|---|----------------|-----------------|------------------|----------|--------|-----------------|---------|-------|-----------|-----|---------------|------|
| Meta-analysis Sargent et al 2009²⁶  | 5-FU/LV or 5-FU/LEV versus surgery alone | 8 years | 42.7% at 8 years | 10.30% | P≤0.001 | A | 26 |
| Duration of therapy and/or difference in fluoropyrimidine modulator | Combined stage II and III | 5-FU/LV/LV 12 m versus 5-FU/LEV 12 m | 446 | OS | 5.1 years | 63% at 5 years | –6% | 68% at 5 years | –5% | AT+LT NR | NEB | 27 |
| | | 5-FU/LV/LV 6 m versus 5-FU/LEV 12 m | 443 | OS | 5.1 years | 63% at 5 years | 0% | 68% at 5 years | 2% | AT- LT NR | NEB | 27 |
| | | 5-FU/LEV 6 m versus 5-FU/LEV 12 m | 442 | OS | 5.1 years | 63% at 5 years | –5% | 68% at 5 years | –8% | AT-LT NR | NEB | 27 |
| | NSABP C-041999 | 5-FU/LV/LEV versus 5-FU/LV | 1387 | DFS and OS | 5 years | 65% at 5 years | –1% | NS p=0.67 | 74% at 5 years | –1% | NS p=0.99 | AT=LT NR | NEB | 28 |
| | | 5-FU/LEV versus 5-FU/LV | 1382 | DFS and OS | 5 years | 65% at 5 years | –5% | P=0.04 | 74% at 5 years | –4% | P=0.07 | AT=LT NR | NEB | 28 |
| | Intergroup 0089 2004 | RPMI‡ versus 5-FU/LEV 12 m | 1568 | OS | 10 years | 45% at 10 years | 2% | 50% at 10 years | 2% | AT- LT NR | C | 29 |
| | | Mayo Clinic§ versus 5-FU/LEV 12 m | 1579 | OS | 10 years | 45% at 10 years | 4% | 50% at 10 years | 2% | AT- LT NR | C | 29 |
| | | Mayo Clinic+LEV versus 5-FU/LEV 12 m | 1658 | OS | 10 years | 45% at 10 years | 23% | 50% at 10 years | 9% | AT=LT NR | A | 29 |
| Stage III | adjCCA-012001 | 5-FU/LV versus 5-FU/LEV | 680 | OS | 82 m (~7 years) | 54% at 5 years | 8% | 60.8% at 5 years | 9.20% | P=0.01 | AT=LT NR | A | 30 |
| Convenience of therapy | Stage II and III | Kim et al 2003³⁵ | UFT/LV versus 5-FU/LV | 122 | DFS and OS | 28 m (~3 years) | 84.1% at 28 m | 3.40% | NS | 92.5% at 28 m | 2.40% | NS | AT+LT- = NEB | 35 |
| | | NSABP-C062006 non-inferiority trial | UFT/LV versus 5-FU/LV | 1551 | DFS and OS (margin not clear) | 62.3 m (~5 years) | 68.2% at 5 years | –1.20% | 1 (0.85–1.19) | 78.7% at 5 years | –0.20% | 1.01 (0.83–1.25) | AT=LT NR = NEB | 36 37 |
| | Stage III | X-ACT 2005 non-inferiority trial | cap versus 5-FU/LV | 1987 | DFS (margin DFS 1.20, OS 1.25) | 3.8 years | 60.6 at 3 years | 3.60% | 0.87 (0.75–1.00) | 77.6% at 3 years | 3.70% | 0.84 (0.69–1.01) | AT=LT NR = NEB | 38 |
| | | ACTS-CC 2014 non-inferiority trial | S-1 versus UFT/LV | 1518 | DFS (margin DFS 1.29) | 41.3 m (~3.5 years) | 72.5% at 3 years | 3% | 0.85 (0.70–1.03) | 92.7% at 3 years | 0.90% | AT=LT NR | NEB | 39 40 |

Continued
The most recent IDEA consortium trial was the most complete in adverse events reporting, summarised in online supplementary table 1. This non-inferiority trial was the only trial in which AT data influenced the grade, as one prespecified subgroup with non-inferior efficacy was rewarded for having less AT to a B grade.

Reporting of LT was very limited. Five trials (two were individual trials within the IDEA collaboration), reported late sensory neuropathy graded with the CTCAE V.1–3. In all trials, this was investigator reported data and the assessment times and follow-up period differed. Overall, the reported prevalence of late neuropathy was low. With regard to oxaliplatin treatment duration, in the IDEAFrance trial, at a median follow-up of 3.6 years, the prevalence of grade 3–4 neuropathy was 0.5% among patients exposed to 3 months of oxaliplatin versus 2% among those who received 6 months of oxaliplatin. In the ACHIEVE trial, at a median follow-up of 3 years, the prevalence all grade neuropathy was 23.3% vs 10%, while grade 3 was only 0.3 vs 0%. In the ACHIEVE trial, it was also observed that the incidence of any grade PSN was lower for patients treated with CAPOX compared with FOLFOX in both the 6 months and 3 months treatment groups. All other studies did NR any LT.

QoL data were only available for 5 of the 20 RCT (one was an individual trial within the IDEA collaboration). There was no consistency in the scales used. The only trial to report differences in QoL between the treatment arms was the SCOT trial of the IDEA consortium which compared 3–6 months of oxaliplatin based adjuvant therapy. After 3 months to 5 years of follow-up, there was major difference (p<0.001) in neuropathy-related QoL evaluated using the Functional Assessment of Cancer Therapy-Gynecologic Oncology Group Neurotoxicity questionnaire. Patients receiving 6 months oxaliplatin reported a worse QoL at 1, 3 and 5 years compared with those receiving 3 months oxaliplatin, and this disparity was associated with major differences in Global QoL between 3 and 6 months gradually attenuating over subsequent months and years.

None of the trials did a formal cost analysis and could therefore not be used for grading of non-inferiority trials. However, non-inferiority of a shorter treatment duration most likely leads to reduction in treatment cost.

### Expert peer review of the generated scores

Thirty-seven experts from the ESMO Gastro-Intestinal Tumours Faculty reviewed the generated scores. Twenty-five (67.6%) confirmed the reasonableness of the scores and 12 (34.4%) found the scores mostly reasonable. Experts pointed out that it was striking that the current recommended oxaliplatin-based treatment for stage III disease was only once graded with the highest A grade.

Two experts commented on non-inferiority trials that offer a similar efficacy despite evaluating a more convenient oral mode of administration. They expressed criteria for adverse events (CTCAE) V.1–3. Reporting was more complete in the latest reported studies.

| Trial name, year first publication | Intervention versus control | Primary outcome | Median follow-up | N | OS control group gain | OS gain | DFS control group gain | DFS gain | Toxicity* | QoL |
|---------------------------------|-----------------------------|----------------|-----------------|---|----------------------|---------|-----------------------|---------|-----------|-----|
| *All AT annotations are exploratory; not part of the latest ESMO-MCBS forms. Toxicity of experimental arm versus control arm. | *AT, acute toxicity; DFS, disease-free survival; EFS, event free survival; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; 5-FU, 5-fluorouracil; HDLV, high dose leucovorin; HR, hazard ratio; LDLV, low dose leucovorin; LEV, levamisole; LT, late toxicity; LV, leucovorin; MOF, lomustine (MeCCNU)/vincristine/5-fluorouracil; N, number of patients; NEB, no evaluable benefit; NR, not reported; NS, not significant; OS, overall survival; QoL, quality of life; RPMI, Roswell Park Memorial Institute; S-1, tegafur/gimeracil/oteracil; UFT, uracil and tegafur; vs, versus. |

The only trial to report differences in QoL between the treatment arms was the SCOT trial of the IDEA consortium which compared 3–6 months of oxaliplatin based adjuvant therapy. After 3 months to 5 years of follow-up, there was major difference (p<0.001) in neuropathy-related QoL evaluated using the Functional Assessment of Cancer Therapy-Gynecologic Oncology Group Neurotoxicity questionnaire. Patients receiving 6 months oxaliplatin reported a worse QoL at 1, 3 and 5 years compared with those receiving 3 months oxaliplatin, and this disparity was associated with major differences in Global QoL between 3 and 6 months gradually attenuating over subsequent months and years.

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The most recent IDEA consortium trial was the most complete in acute adverse events reporting, summarised in online supplementary table 1. This non-inferiority trial was the only trial in which AT data influenced the grade, as one prespecified subgroup with non-inferior efficacy was rewarded for having less AT to a B grade.

Reporting of LT was very limited. Five trials (two were individual trials within the IDEA collaboration), reported late sensory neuropathy graded with the CTCAE V.1–3. In all trials, this was investigator reported data and the assessment times and follow-up period differed. Overall, the reported prevalence of late neuropathy was low. With regard to oxaliplatin treatment duration, in the IDEAFrance trial, at a median follow-up of 3.6 years, the prevalence of grade 3–4 neuropathy was 0.5% among patients exposed to 3 months of oxaliplatin versus 2% among those who received 6 months of oxaliplatin. In the ACHIEVE trial, at a median follow-up of 3 years, the prevalence all grade neuropathy was 23.3% vs 10%, while grade 3 was only 0.3 vs 0%. In the ACHIEVE trial, it was also observed that the incidence of any grade PSN was lower for patients treated with CAPOX compared with FOLFOX in both the 6 months and 3 months treatment groups. All other studies did NR any LT.

QoL data were only available for 5 of the 20 RCT (one was an individual trial within the IDEA collaboration). There was no consistency in the scales used. The only trial to report differences in QoL between the treatment arms was the SCOT trial of the IDEA consortium which compared 3–6 months of oxaliplatin based adjuvant therapy. After 3 months to 5 years of follow-up, there was major difference (p<0.001) in neuropathy-related QoL evaluated using the Functional Assessment of Cancer Therapy-Gynecologic Oncology Group Neurotoxicity questionnaire. Patients receiving 6 months oxaliplatin reported a worse QoL at 1, 3 and 5 years compared with those receiving 3 months oxaliplatin, and this disparity was associated with major differences in Global QoL between 3 and 6 months gradually attenuating over subsequent months and years.

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### Table 2: ESMO-MCBS grades of oxaliplatin added to fluoropyrimidine treatment for combined stage II and III, stage III and stage II colon cancer

| Intervention versus control | Trial name, year first publication | N   | Median follow-up | DFS control group | DFS gain | DFS HR | OS control group | OS Gain | OS HR | Toxicity* | QoL       | ESMO-MCBS V1.1 | Ref. |
|----------------------------|------------------------------------|-----|------------------|-------------------|----------|--------|------------------|--------|-------|-----------|-----------|----------------|------|
| **Stage II and II**        |                                    |     |                  |                   |          |        |                  |        |       |           |           |                |      |
| MOSAIC 2004                | FOLFOX4 versus 5-FU/LV             | 2246| 9.5 yrs          | 61.7% at 10 yrs   | 5.80%    | 0.82 (0.71–0.95) | 67.1% at 10 yrs   | 4.60%  | 0.85 (0.73–0.99) | AT+ LT+   | B             | 41   |
| NSABP C-07 2007            | FLOX versus 5-FU/LV               | 2409| 8 yrs            | 64.2% at 5 yrs    | 5.20%    | 0.82 (0.72–0.93) | 78.4% at 5 yrs     | 1.80%  | 0.88 (0.75–1.02) | AT+ LT+   | NER          | 42   |
| Meta-analysis Shah et al 2016 | 5-FU/LV + OX versus 5-FU/LV     | 6468| 6 yrs            |                    |          |        | 77.7% at 5 yrs    | 2.30%  |       | Significant (HR not presented) | C           | 44   |
| **Stage II**               |                                    |     |                  |                   |          |        |                  |        |       |           |           |                |      |
| Meta-analysis Shah et al 2016 | 5-FU/LV + OX versus 5-FU/LV     | 1600| 6 yrs            |                    |          |        | 89.8% at 5 yrs    | 0.80%  |       | NS       |           | NER          | 44   |
| **Stage III**              |                                    |     |                  |                   |          |        |                  |        |       |           |           |                |      |
| NO16968 2011               | CAPOX versus 5-FU/LV              | 1886| 7 yrs            | 56% at 7 yrs      | 7%       | 0.8 (0.69–0.93)  | 67% at 7 yrs      | 6%     | 0.83 (0.70–0.99) | AT+ LT+   | A             | 43   |
| Meta-analysis Shah et al 2016 | 5-FU/LV + OX versus 5-FU/LV     | 4868| 6 yrs            |                    |          |        | 73.7% at 5 yrs    | 4.20%  |       | Significant (HR not provided) | B           | 44   |
| **Duration of therapy**    |                                    |     |                  |                   |          |        |                  |        |       |           |           |                |      |
| IDEA consortium            | NCT00958737 2018 non inferiority trial | 12834| 41.8 m (-3.5 yrs) | 75.5% at 3 yrs | -0.90% | 1.07 (1.00–1.15) | AT- LT† Overall =‡ PSN -‡ NNI | 45–48 |
|                          | CAPOX ± FOLFOX 3 versus 6 m       | 1236| 41.8 m (-3.5 yrs) | 74.8% at 3 yrs | 1.10%  | 0.95 (0.85–1.06) | AT- LT† B           |       |       |            |           |                |      |
|                          | CAPOX 3 versus 6 m                | 5071|                  | 76% at 3 yrs     | -2.40%  | 1.16 (1.06–1.26) | AT- LT- NNI         |       |       |            |           |                |      |
|                          | FOLFOX 3 versus 6 m               | 7763|                  |                   |         |        |                  |        |       |            |           |                |      |
| **Convenience of therapy** |                                    |     |                  |                   |          |        |                  |        |       |           |           |                |      |
| Meta-analysis Schmoll et al 2014 | CAP ± OX versus 5-FU/LV + OX | 5819| DFS              | 62.8% at 5 yrs   | 0%      | 1.01 (0.92–1.10) | 73.9% at 5 yrs    | -1.3%  | 1.02 (0.92–1.14) | AT = LT   | NER          | 49   |

*All toxicity annotations are exploratory; not part of the latest ESMO-MCBS forms. Toxicity of experimental arm versus control arm, more or less acute toxicity (duration of treatment and thus exposure time to drug and toxicity accounted for as well) of the experimental arm versus the control arm is shown as AT+ or AT-, more or less late toxicity is shown as LT+ or LT-. All toxicity data are summarised in Supplementary Table 4. Late toxicity data were not reported in the IDEA consortium pooled analyses. However, subsequently two of the six individual trials reported late toxicity data. Toxicity of experimental arm versus control arm is shown as AT+ or AT-, more or less late toxicity is shown as LT+ or LT-.

†QoL data were not reported in the IDEA consortium pooled analyses. However, subsequently one of six individual trials reported QoL data which is reported here.

‡QoL, quality of life; yrs, years.

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on September 16, 2020 at University of Groningen. http://esmoopen.bmj.com/ ESMO Open: first published as 10.1136/esmoopen-2020-000681 on 6 September 2020. Downloaded from https://esmoopen.bmj.com/ on September 16, 2020 at University of Groningen.
concern that the failure to reward this difference in convenience may fail to credit a true benefit. The ESMO-MCBS V.1.1 of form I does not offer the means to credit convenience.

DISCUSSION

This paper has evaluated the applicability of form I of the ESMO-MCBS V.1.1 to the adjuvant therapies for early colon cancer. Overall, the experience has been positive insofar as the scoring of adjuvant approaches in early colon cancer are considered reasonable (67.6%) or mostly reasonable (32.4%) by all experts.

For patients with stage III colon cancer, RCTs and meta-analyses of modulated 5-FU-based chemotherapy versus surgery only, consistently scored A in the ESMO-MCBS and the RCTs and meta-analysis comprising oxaliplatin added to this 5-FU backbone showed a modest additional OS benefit (grade B).

For stage II, the findings were less consistent. Whereas fluoropyrimidine trials in patients with stage II colon cancer consistently were graded NEB, the most recent meta-analysis demonstrated a 5.4% survival advantage after 8 years follow-up (grade A). The ACCENT investigators have subsequently cautioned that conclusions derived from older trials of FU-based adjuvant therapy in stage II colon cancer may be biased by stage migration over time. To date, there are no subgroup analyses restricted to stage II in trials with patients that were adequately staged by contemporary standards. RCTs and meta-analysis adding oxaliplatin demonstrated no added benefit for patients with stage II colon cancer.

Several meta-analyses analysed efficacy in stage II/III,41–46 as well as separately in II25 26 44 49 or stage III.44 49 Four of these were performed by the ACCENT Collaborative Group which, as of 2016, included detailed information collected from over 40,000 patients from 27 adjuvant colon cancer trials including patient demographics and disease characteristics, treatment data, biomarkers for selected studies, adverse events, as well as log term recurrence and survival follow-up for all patients. This has facilitated the capacity to undertake robust analysis of pooled individual patient data in meta-analyses and in the evaluation of the validity of surrogate outcomes.52 53

Regarding the surrogacy of DFS as a predictor of OS, analysis by the ACCENT Collaborative Group demonstrated a robust relationship for 2, 3, 5 and 6 years DFS and OS for stage III colon cancer.52 53 but this was not the case for stage II disease and indeed even 6 years DFS was only weakly associated with OS.53 Consequently, they concluded that unless DFS is considered a clinically relevant endpoint, OS should be regarded as the most appropriate endpoint for trials in unselected stage II disease.53

The ESMO-MCBS V.1.1 has no defined rules regarding the minimum quality perquisites for a meta-analysis to be evaluated. In future amendments of the scale, formal definitions of quality and improved clarity regarding the issue of multiplicity when there are several subgroup analysis will be important. In general, an impactful and valid meta-analysis should include at least the following ingredients: investigation of a plausible question based on randomised evidence using an exhaustive review of relevant studies; evaluation of consistency across studies regarding population of interest, relevant patient characteristics and control arm, coupled with lack of bias (publication, selective reporting); exploration of heterogeneity and clear description of limitations.54

Reporting of toxicity and QoL effects of new adjuvant systemic treatment modalities, especially if long-lasting, is important to optimally inform patients. A penalty system for toxicities, such as used in the non-curative setting in the ESMO-MCBS V.1.1 (forms 2 and 3), is not appropriate for the curative setting since patients may accept higher toxicity trade-off when treatment is with curative intent. Representatives of patient advocacy groups, in consultation with the ESMO-MCBS Working Group, have indicated preference for annotation of high likelihood of AT or LT versus penalties which may mask the magnitude of curative potential. We strongly believe toxicity annotations should indeed be introduced for treatments with a high prevalence of AT and especially LT.

Our exploratory evaluation of toxicity highlighted that toxicity evaluation and annotation is challenging in the setting of inconsistent methods of toxicity reporting, a high prevalence of apparent under reporting and minimum reporting of LT. The chronic neurotoxicity induced by oxaliplatin is a cumulative, dose-dependent, sensory, symmetric distal axonal neuropathy.55 56 Tingling is the most prominent symptom, but numbness and pain can also occur.54 In our review of the toxicity data, late grade 3/4 PSN was reported in only 0.5%–2% of patients, substantially lower than the prevalence data derived from patient reported outcome data.54 This highlights the risk of under-reporting of toxicities by physicians.57 In addition, even several years after adjuvant oxaliplatin-based chemotherapy, in some situations distal neurotoxicity symptoms are reported as re-induced by cold temperature or repeated use of fingers like key-board typing, piano playing or exercising precise finger movements. This is general not mentioned in the toxicity report of clinical trial but has a potential negative impact on QoL or professional career.

In our analyses, only 5 out of 18 trials evaluated QoL.55–58 The low rate of inclusion of QoL evaluation has been examined in a study comprised by phase III RCTs in cancer performed between 2012 and 2016 published in 11 major journals. In 210 of the 446 trials (47.1%), QoL was not included as an endpoint. The non-inclusion was even higher for RCTs in (neo)adjuvant disease as 81 of the 124 trials (65.3%) did not include QoL as an endpoint.58 Most of the adjuvant trials reporting QoL showed no difference between the investigational and control arm: 5-FU/LV or placebo,53 UFT/LV or 5-FU/ LV55–57 and capecitabine or 5-FU/LV.58 The findings of the SCOT trial58 which demonstrated worse QoL for PSN
at 1, 3 and 5 years for patients treated 6 vs 3 months were salient (p<0.001).

UFT/LV did not show OS benefit and a non-inferior OS for stage II/III colon cancer compared with 5-FU/LV in two trials and neither QoL nor toxicity was improved. Both trials were graded NEB as was the trial of capecitabine versus 5-FU/LV. While it is plausible that oral medication may be more convenient than intravenous treatment, there are no data that it actually improves QoL compared with conventional parenteral administration. Convenience is not credited in the current version of form 1 of the ESMO-MCBS.

Our findings confirm that form 1 was highly applicable to the studies of adjuvant systemic therapies of early-stage colon cancer and it provided very reasonable grading for adjuvant colon cancer studies. The exploratory analysis indicated that toxicity annotation is feasible but the prevailing convention of physician reported toxicity may underestimate the true level of patient burden from both AT and LT. Since patients in the curative setting potentially live decades after treatment, late and prolonged adverse effects that may undermine QoL should be annotated to optimally inform patients of recognised risks. Future revisions of form 1 of the ESMO-MCBS will be cogniscente of these findings.

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REFERENCES
1 GLOBOCAN website. Available: gabcancer.iarc.fr [Accessed 5 Nov 2018].
2 Buyse M, Zeleniuch-Jacquotte A, Chalmers TC. Adjuvant therapy of colorectal cancer. Why we still don’t know. JAMA 1988;259:3571–8.
3 Labianca R, Nordininger B, Beretta GD, et al. Early colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:v64–72.
4 Saltz LB, Niedzwiecki D, Hollis D, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803. J Clin Oncol 2007;25:3456–61.
5 Van Cutsem E, Labianca R, Bodoky G, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. J Clin Oncol 2009;27:3117–25.
6 Ychou M, Raoul J-L, Douillard J-Y, et al. A phase III randomised trial of FU/LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02/FFCD9802). Ann Oncol 2009;20:674–80.
7 Alberts SR, Sargent DJ, Nair S, et al. Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial. JAMA 2012;307:1383–93.
8 Taieb J, Balogou R, Le Malicot K, et al. Adjuvant FOLFOX +/- cetuximab in full Ras and BRAF wildtype stage III colon cancer patients. Ann Oncol 2017;28:824–30.
9 Allegri CJ, Ythers G, O’Connell MJ, et al. Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. J Clin Oncol 2011;29:11–16.
10 de Gramont A, Van Cutsem E, Schmoll H-J, et al. Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. Lancet Oncol 2012;13:1225–33.
11 Kerr RS, Love S, Segelov E, et al. Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial. Lancet Oncol 2016;17:1540–51.
12 Cherry NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for medical oncology monograph on clinical benefit scale [ESMO-MCBS]. Ann Oncol 2015;26:1547–73.
13 Cherry NI, Dafni U, Bogarts J, et al. ESMO-Magnitude of clinical benefit scale version 1.1. Ann Oncol 2017;28:2340–66.
14 Daniels N. Decisions about access to health care and accountability for Reasonableness. J Urban Health 1990;67:77–91.
15 Daniels N. Accountability for Reasonableness. BMJ 2000;321:1300–1.
16 ESMO website. Available: https://www.esmo.org/guidelines/esmo-mcbs/esmo-magnitude-of-clinical-benefit-scale [Accessed 5 Nov 2018].
17 Benson AB, Venook AP, Al-Hwary MM, et al. NCCN guidelines colon cancer, version 4, 2018. Available: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
18 Trotti A, Colevas AD, Setser A, et al. CTC-AE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176–81.
19 Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from national surgical adjuvant breast and bowel project protocol C-03. J Clin Oncol 1993;11:1879–87.
20 Francini G, Petrioli R, Lorenzini L, et al. Folinic acid and 5-fluorouracil as adjuvant chemotherapy in colon cancer. Gastroenterology 1994;106:899–906.
21 Labianca R, Marsoni S, Pancera G, et al. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International multicentre pooled analysis of colon cancer trials (impact) Investigators. Lancet 1995;345:939–44.
22 O’Connell MJ, Mailliard JA, Kahn MJ, et al. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. J Clin Oncol 1997;15:246–50.
23 Zaniboni A, Labianca R, Marsoni S, et al. GIVIO-SITAC 01: A randomized trial of adjuvant 5-fluorouracil and folinic acid administered to patients with colon carcinoma—long term results and evaluation of the indicators of health-related quality of life. Gruppo
Italiano Valutazione Interventi in Oncologia. Studio Italiano Terapia Adiuvante Colon. Cancer 1998;82:2135–44.
24 Sargent DJ, Goldberg RM, Jacobson SD, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med 2001;345:1091–7.
25 Gill S, Clavel F, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22:1797–806.
26 Sargent D, Sobrero A, Grothey A, et al. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,888 patients on 18 randomized trials. J Clin Oncol 2009;27:872–7.
27 O’Connell MJ, Laurie JA, Kahn M, et al. Prospectively randomized trial of postoperative adjuvant chemotherapy in patients with high-risk colon cancer: final report of intergroup 0089. J Clin Oncol 2005;23:867–1–9.
28 Arkenau HT, Bermann A, Rettig K, et al. 5-Fluorouracil plus leucovorin is an effective adjuvant chemotherapy in curatively resected stage III colon cancer: long-term follow-up results of the adCCGA-01 trial. Ann Oncol 2003;14:395–9.
29 Moertel CG, Fleming TR, Macdonald JS, et al. Intergroup study of fluorouracil plus leuvamisole as adjuvant therapy for stage II/Dukes’ B2 colon cancer. J Clin Oncol 1995;13:2396–43.
30 Schipper W, Samonigg H, Schaber-Moser R, et al. A prospective randomised phase III trial of adjuvant chemotherapy with S-fluorouracil and leucovorin in patients with stage II colon cancer. Br J Cancer 2007;97:1021–7.
31 Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and leuvamisole in high-risk stage II and III colon cancer: final report of intergroup 0089. J Clin Oncol 2005;23:867–1–9.
32 Moertel CG, Fleming TR, Macdonald JS, et al. Fluorouracil plus leuvamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Intern Med 1995;122:321–6.
33 Kim DJ, Kim TI, Suh JH, et al. Oral uracil and folinic acid in stage II colon cancer: a final report. Ann Intern Med 1995;13:2936–43.
34 Moertel CG, Fleming TR, Macdonald JS, et al. Fluorouracil plus leuvamisole as adjuvant chemotherapy for colorectal cancer: disease-free survival results from a randomized, open-label, International randomized evaluation of adjuvant (idea) France, phase III trial. J Clin Oncol 2018;36:1469–77.
35 Ivenson TJ, Kerr RS, Saunders MP, et al. Versus 6 months of oral oxaliplatin-based adjuvant chemotherapy for patients with stage III colon cancer: disease-free survival results from a randomized, open-label, International randomized evaluation of adjuvant (idea) France, phase III trial. J Clin Oncol 2018;36:1469–77.
36 Yonsei T, Yamanaka T, Oki E, et al. Efficacy and long-term peripheral sensory neuropathy of 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: the achieve phase 3 randomized clinical trial. JAMA Oncol 2019. doi:10.1001/jamaoncol.2019.2572. [Epub ahead of print: 12 Sep 2019].
37 Moertel CG, Fleming TR, Macdonald JS, et al. Fluorouracil and leucovorin for adjuvant therapy of resected colon carcinoma. N Engl J Med 1995;332:852–8.
38 Kim DJ, Kim TI, Suh JH, et al. Comparison of outcomes after 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial. Lancet Oncol 2018;19:562–78.
39 Sargent DJ, Wieand HS, Haller DG, et al. Disease-Free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from four randomised controlled trials. Lancet Oncol 2014;15:1481–92.
40 Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 2005;352:899–907.
41 Shi Q, Andre T, Grothey A, et al. Comparison of outcomes after fluorouracil-based adjuvant chemotherapy for stages II and III colon cancer between 1978 to 1996 and 1996 to 2007: evidence of stage migration from the accent database. J Clin Oncol 2013;31:3656–63.
42 Yohrthes G, O’Connell MJ, Allegrea CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. J Clin Oncol 2011;29:3786–74.
43 Schmoll H-J, Tabernero J, Marou J, et al. Capecitabine plus oxaliplatin is noninferior to fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial. J Clin Oncol 2015;33:3733–40.
44 Shah MA, Renfro LA, Allegrea CJ, et al. Impact of patient factors on recurrence risk and time dependency of oxaliplatin benefit in patients with colon cancer: analysis from modern-era adjuvant studies in the adjuvant colon cancer end points (accent) database. J Clin Oncol 2016;34:843–53.
45 Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. N Engl J Med Overseas Ed 2018;37:1177–88.
46 Andre T, Vernerey D, Mineur L, et al. Three versus 6 months of oxaliplatin-based adjuvant chemotherapy for patients with stage III colon cancer: disease-free survival results from a randomized, open-label, International randomized evaluation of adjuvant (idea) France, phase III trial. J Clin Oncol 2018;36:1469–77.
47 Yoshino T, Yamanaka T, Oki E, et al. Efficacy and long-term peripheral sensory neuropathy of 3 vs 6 months of oxaliplatin-based adjuvant chemotherapy for colon cancer: the achieve phase 3 randomized clinical trial. JAMA Oncol 2019. doi:10.1001/jamaoncol.2019.2572. [Epub ahead of print: 12 Sep 2019].
48 Ivenson TJ, Kerr RS, Saunders MP, et al. Versus 6 months of oral oxaliplatin-based fluopyrimidine combination therapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial. Lancet Oncol 2018;19:562–78.
49 Schmoll H-J, Twelves C, Sun W, et al. Effect of adjuvant capecitabine on survival in stage III colon cancer: an analysis of individual patient data from a randomized controlled trial. JAMA Oncol 2014;1:1481–92.
50 Sargent D, Shi Q, Yohrthes G, et al. Two or three year disease-free survival (DFS) as a primary end-point in stage III adjuvant colon cancer trials with fluoropyrimidines with or without oxaliplatin or irinotecan: data from 12,676 patients from mosaic, X-ACT, PETACC-3, C-06, C-07 and C89803. Eur J Cancer 2011;47:990–6.
51 Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
52 Pachman DR, Qin R, Seisler DK, et al. Clinical course of oxaliplatin-induced neuropathy: results from the randomized phase III trial N08CB (Alliance). J Clin Oncol 2015;33:3416–22.
53 Park SB, Lin CSY, Krishnan AV, et al. Long-Term neuropathy after oxaliplatin treatment: challenging the dictum of reversibility. Oncologist 2011;16:708–16.
54 Di Maio M, Basch E, Bryce J, et al. Patient-Reported outcomes in the evaluation of toxicity of anticancer treatments. Nat Rev Clin Oncol 2016;13:319–25.
55 Marandino L, La Salvia A, Sonetto C, et al. Deficiencies in health-related quality-of-life assessment and reporting: a systematic review of oncology randomized phase III trials published between 2012 and 2016. Ann Oncol 2018;29:2288–95.