Patients' Preferences for 3 Months vs 6 Months of Adjuvant Chemotherapy for Colon Cancer

Prunella Blinman (iD), PhD,[1,2,3,*] Andrew Martin (iD), PhD,[2,3,4] Michael Jefford (iD), PhD,[2,5,6] David Goldstein, MD,[2,7] David Boadle (iD), MBBS,[2,8] Michelle Morris, MBBS,[2,9] Niall Tebbutt, PhD,[2,10] Christine Aiken, MHlthSc,[2,4] Andrea Harkin (iD), BA,[11] Eva Segelov (iD), PhD,[2,12] Andrew Haydon, PhD[2,13] Tim Iveson (iD), MD,[14] Martin R. Stockler (iD), MSc[2,3,4]

[1]Concord Cancer Centre, Sydney, Australia, [2]Australasian Gastro-Intestinal Trials Group, Australia, [3]University of Sydney, Australia, [4]NHMRC Clinical Trials Centre, University of Sydney, Australia, [5]Peter MacCallum Cancer Centre, Melbourne, Australia, [6]Sir Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Victoria, Australia, [7]Nelune Comprehensive Cancer Centre, Prince of Wales Hospital, Sydney, Australia, [8]Department of Medical Oncology, Royal Hobart Hospital, Hobart, Australia, [9]Sunshine Coast University Private Hospital, Birtinya, Australia, [10]Olivia Newton-John Cancer Wellness & Research Centre, Austin Health, Melbourne, Australia, [11]Clinical Trials Unit Glasgow, Glasgow, United Kingdom, [12]Department of Oncology, Monash Health and Monash University, Melbourne, Australia, [13]Department of Medical Oncology, Alfred Health, Melbourne, Australia and [14]Medical Oncology, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom

*Correspondence to: Prunella Blinman, PhD, Concord Cancer Centre, Concord Repatriation General Hospital, Hospital Rd, Concord NSW 2139, Australia (e-mail: prunella.blinman@health.nsw.gov.au).

Abstract

Background: SCOT was an international, randomized phase 3 trial of 3 months vs 6 months of adjuvant chemotherapy with oxaliplatin and a fluoropyrimidine in patients with colorectal cancer. We sought patients' preferences for 3 months vs 6 months of adjuvant chemotherapy in the SCOT trial. **Methods:** SCOT participants from Australia and New Zealand completed a validated questionnaire (at 3 and 18 months) to elicit the minimum survival benefits judged necessary to make an extra 3 months of adjuvant chemotherapy worthwhile, based on their experience. Standardized hypothetical scenarios used the following baseline survivals (with 3 months of chemotherapy): life expectancies (LE) of 5 years and 15 years and 5-year survival rates (5YS) of 65% and 85%. **Results:** Of the 160 participants, 82 were assigned 3 months adjuvant chemotherapy, and 78 were assigned 6 months. Adjuvant chemotherapy was FOLFOX in 121 (75.6%) and XELOX in 39 (24.4%). Preferences varied substantially and did not differ according to treatment group. The median survival benefits judged necessary to make the extra 3 months of chemotherapy worthwhile were an extra 3 years beyond a LE of 5 years; 3 years beyond a LE of 15 years; 15% beyond a 5YS of 65%; and 5% beyond a 5YS of 85%. Preferences were similar at 3 months and 18 months. Preferences were not predicted by participants' baseline characteristics. **Conclusion:** Preferences varied substantially, and the benefits many required to warrant an extra 3 months of adjuvant chemotherapy were larger than the benefits of an extra 3 months of chemotherapy calculated in the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) meta-analysis.

The optimal management of patients with stage III colon cancer includes surgical resection and adjuvant chemotherapy. Prior to the SCOT trial, the standard duration of adjuvant chemotherapy was 6 months. Recommended regimens for adjuvant chemotherapy included FOLFOX [5-fluorouracil and leucovorin (5FU/LV) and oxaliplatin] and CAPOX (capecitabine and oxaliplatin) (1).

The addition of oxaliplatin to 5FU/LV or capecitabine improves overall survival but at the cost of additional toxicity. In the MOSAIC trial, for example, the addition of oxaliplatin to 5FU/LV as FOLFOX statistically significantly improved 10-year overall survival in people with stage III colon cancer by 8% (from 59% to 67%; hazard ratio [HR] = 0.80; P = .016) (2,3). Chemotherapy-induced peripheral neuropathy (CIPN) is the major additional toxicity of oxaliplatin. In MOSAIC, rates of all-grade paresthesia were substantially higher with FOLFOX than 5FU/LV (92% vs 16%; P < .001) as were the rates of grade 3 paresthesia (12% vs 0.2%; P = .001), with 15% of those assigned FOLFOX reporting paresthesia of any grade at 48 months. CIPN and other toxicities attributable to oxaliplatin result in dose

reductions, delays, and discontinuations of adjuvant chemotherapy that reduce its potential efficacy. In MOSAIC, the planned 12 cycles of chemotherapy were received by 75% of participants assigned FOLFOX and 87% assigned 5FU/LV; the median dose of oxaliplatin administered was 80% (810 mg/m^2) of the total prescribed by the protocol (1020 mg/m^2).

The SCOT trial (ISRCTN59757862) was designed to determine if prescribing adjuvant chemotherapy for 3 months rather than 6 months would maintain efficacy but reduce toxicity (4). SCOT randomly assigned 6088 participants with resected high-risk stage II or stage III colorectal cancer from 6 countries between March 27, 2008, and November 29, 2013. The chemotherapy regimen was the physician's choice of either FOLFOX or CAPOX. The final efficacy analysis of 3-year disease-free-survival (DFS) after 1482 DFS events observed during a median follow-up of 37 months indicated that 3 months of adjuvant chemotherapy was noninferior to 6 months (3-year DFS was 76.7% vs 77·1%, respectively; HR = 1.006, 95% confidence interval [CI] = 0.909 to 1.114). CIPN of grade 2 or worse was less than half as frequent with 3 months vs 6 months adjuvant chemotherapy (25% vs 58%, respectively).

The choice of a shorter vs longer duration of adjuvant chemotherapy involves a trade-off between possible effects on survival vs side effects and inconveniences. This trade-off is a personal value judgment that can be studied by eliciting an individual's preferences for competing options (5). Some patients will prefer shorter, less toxic adjuvant chemotherapy and risk shorter survival, whereas others will prefer longer adjuvant chemotherapy with a higher risk of side effects aiming to maximize survival time. We previously studied the preferences of patients with stage III colon cancer who had experienced adjuvant chemotherapy, including some treated with oxaliplatin (6). The median benefits judged sufficient (by ≥50% of those participants) to make 6 months of adjuvant chemotherapy worthwhile (vs no chemotherapy) were remarkably small: an extra 1 day to 1 month beyond baseline survival times of 5 or 15 years or an extra 1% chance of surviving 5 years beyond baseline survival rates of 65% or 85%.

In this study, we sought to determine the survival benefits that participants in the SCOT trial judged necessary to warrant the longer vs shorter durations of adjuvant chemotherapy compared in the trial and the survival benefits needed to warrant the symptoms of CIPN.

Methods

Study Design and Participants

The preferences substudy was a prospective, observational, cohort study nested within the SCOT trial at all 41 Australian and New Zealand (ANZ) sites. SCOT was conducted in ANZ by the Australasian Gastrointestinal Trials Group in collaboration with the NHMRC Clinical Trials Centre, University of Sydney. ANZ sites only recruited patients with stage III colon cancer, as per local restrictions on the prescription of oxaliplatin during conduct of the trial. All ANZ patients with sufficient literacy in English to complete the questionnaires were invited to participate in the preferences substudy. All participants provided signed, written informed consent, and all participating sites had ethics approval for both the preferences substudy and the main trial.

Preferences Questionnaire

For the preferences substudy, participants were asked to complete a short, written, validated questionnaire. The questionnaire used the time trade-off method to evaluate 2 hypothetical trade-off scenarios: 1 trade-off between 3 months vs 6 months of adjuvant chemotherapy and 1 trade-off between participants' current symptoms of CIPN vs no symptoms of CIPN. Participants completed the questionnaires at 3 months (when participants in both treatment groups had experienced the same duration of chemotherapy) and again at 18 months (when chronic symptoms of CIPN would be present).

For the 3 months vs 6 months trade-off scenario, there were 4 questions, each using a different baseline for comparison: a survival time of 5 years, a survival time of 15 years, a 5-year survival rate (5YS) of 65%, and a 5YS of 85%. For each of the scenarios, participants were asked to indicate the smallest improvement in survival time (or rate) that was needed to warrant an extra 3 months of adjuvant chemotherapy given the baseline survival provided in the scenario for 3 months of adjuvant chemotherapy exactly as they experienced it. For example, for the baseline survival time of 5 years, participants were asked to choose between a survival of 5 years given 3 months of adjuvant chemotherapy or survival times longer than 5 years given 6 months of chemotherapy. The incremental benefits in survival times ranged from an extra 1 month to an extra 20 years; the incremental benefits in survival rates ranged from an extra 1% to a maximum survival rate of 100%. The endpoint we report here is the minimum benefit (extra survival time or rate) judged sufficient to make it worthwhile having 6 months of adjuvant chemotherapy rather than 3 months. (See Supplementary Methods, available online, for an example of a preferences question.)

For the CIPN trade-off scenario, participants were first asked to rate how troublesome were their symptoms of CIPN on a numerical rating scale from 0 (none at all) to 10 (worst I can imagine). Those who rated their symptoms of CIPN as 1 or more were asked to complete the CIPN trade-off question that asked participants to choose between a 5YS of 65% with adjuvant chemotherapy "just like theirs" (same length, side effects, and inconveniences) but with no symptoms of CIPN vs the higher survival rate with adjuvant chemotherapy just like theirs but with their current symptoms of CIPN. The survival benefits were in increments that ranged from 1% (ie, 5YS of 66%) to 35% (ie, 5YS of 100%).

Additional data included participants' demographics, cancer stage, chemotherapy regimen, and randomly assigned duration of adjuvant chemotherapy. We assessed participants' recollections of aspects of health-related quality of life during adjuvant chemotherapy and at 3 months and 18 months using the Patient Disease and Treatment Assessment Form (7).

Statistical Analysis

Medians were used to summarize the central tendency of the highly skewed preference data, and a normal score transformation was applied to responses prior to analysis with a mixed model for repeated measures (MMRM). The full MMRM included covariates for treatment group, time point (3 and 18 months), and an interaction term for treatment group by time point.

We defined patients' general preference disposition as the overall average response to the time trade-off questions asked

Table 1. Patient demographics

Demographic	3 months, No. (%) (n = 82)	6 months, No. (%) (n = 78)
Mean age (SD), y	63.5 (8.3)	63.6 (8.8)
Sex		
Female	32 (39.0)	37 (47.4)
Male	50 (61.0)	41 (52.6)
Performance status		
0	65 (79.3)	63 (80.8)
1	17 (20.7)	15 (19.2)
Education		
Primary school	5 (6.1)	6 (7.7)
High school	41 (50.0)	42 (51.2)
Trade/technical qualification	21 (25.6)	14 (17.9)
University/college degree	11 (13.4)	14 (17.9)
Employment		
Employed full-time	30 (36.6)	30 (38.5)
Employed part-time/casual	10 (12.2)	11 (14.1)
Retired or on pension	39 (47.6)	32 (41.0)
Unemployed	3 (3.7)	2 (2.4)
Marital status		
Married/de facto	49 (59.8)	58 (74.3)
Separated/divorced	12 (14.6)	9 (11.5)
Single	11 (13.4)	5 (6.4)
Widowed	10 (12.2)	6 (7.7)
Dependent children		
Yes	60 (73.2)	56 (71.8)
No	22 (26.8)	21 (26.9)
T stage		
1	4 (4.9)	3 (3.8)
2	9 (11.0)	9 (11.5)
3	55 (67.1)	49 (62.8)
4	14 (17.1)	17 (21.8)
N stage		
0	1 (1.2)	1 (1.3)
1	57 (69.5)	62 (79.5)
2	24 (29.3)	15 (19.2)
Chemotherapy		
XELOX	62 (75.6)	59 (75.6)
FOLFOX	20 (24.4)	19 (24.4)

at 3 and 18 months. We explored predictors of normal score transformed preference disposition using linear regression.

We compared randomly assigned groups on their (normal score transformed) responses to the CIPN trade-off scenario asked at 3 months among patients who reported troublesome symptoms of neuropathy using a t test.

A sample size of 160 provided more than 85% power to detect a difference of 0.5 standard deviations between randomly assigned groups at a 2-sided statistical significance level of 5%.
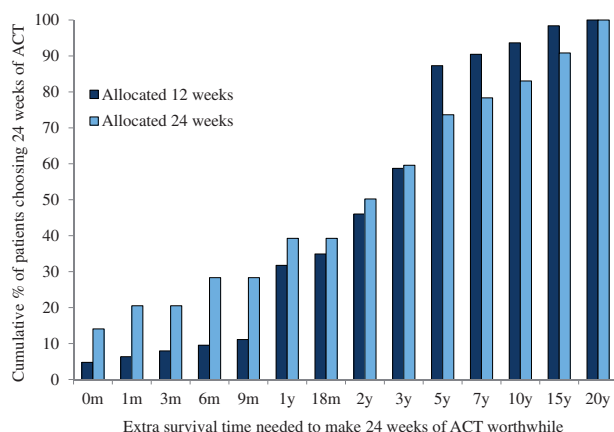
Results

Characteristics of the 160 participants are reported in Table 1. The mean age was 64 years. Of the participants, 82 (51.3%) participants were assigned 3 months of adjuvant chemotherapy and 78 (48.8%) were assigned 6 months of adjuvant chemotherapy. Approximately 2 times as many participants were treated with FOLFOX (n = 121, 75.6%) as CAPOX (n = 39, 24.4%).

Patients' preferences varied over a wide range, as expected (Figures 1-4): some judged the smallest possible benefits sufficient to make the extra 3 months of chemotherapy worthwhile, whereas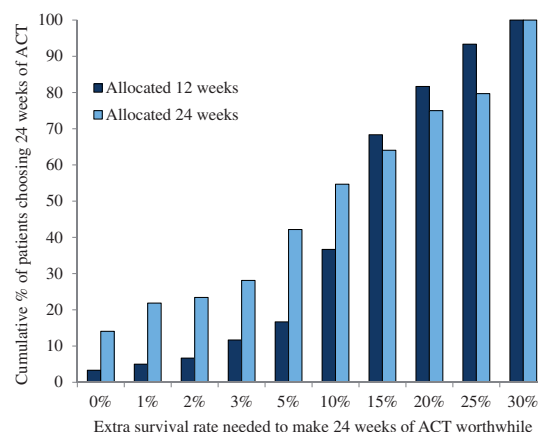 others required the largest possible benefits necessary, or even no benefit sufficient, to make the extra 3 months of chemotherapy worthwhile.

Preferences were unaffected by the randomly assigned treatment group, with MMRM analyses demonstrating no compelling statistical evidence of a time point by treatment group interaction or of a treatment group main effect. (See Supplementary Table 1, available online, for MMRM results.) There was some evidence that responses to the 15-year time trade-off question changed between the 3 month and 18 month time points ($P = .02$), but this observation was not corroborated by results for the other 3 preference questions (where no P value fell below .05; data not shown). We therefore averaged patients' responses at months 3 and 18 (to yield a more precise estimate) and present the distribution of these averaged responses for both treatment groups combined (see Figures 1-4). The median survival benefits judged sufficient (ie, by 50% of participants) to make worthwhile the extra 3 months of adjuvant chemotherapy were an extra 3 years beyond a life expectancy of 5 years, an extra 3 years beyond a life expectancy of 15 years, an extra 15% beyond a 5YS of 65%, and an extra 5% beyond a 5YS of 85% (Table 2).
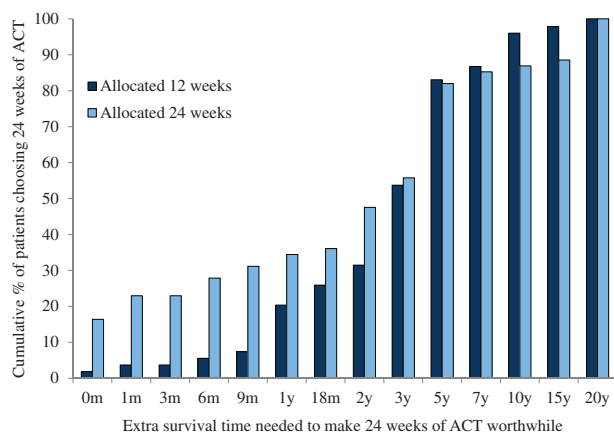
Participants' preferences were not associated with their characteristics at baseline. In particular, there was no evidence of an association between preferences and age, sex, education,
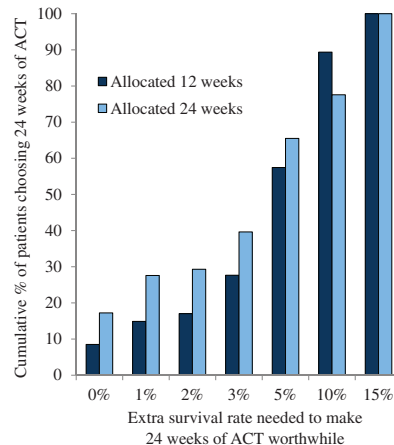
Figure 1. Cumulative proportions of patients considering whether 6 months of adjuvant chemotherapy (vs 3 months) is worthwhile for various improvements in 5-year survival times. ACT = adjuvant chemotherapy.

Figure 3. Cumulative proportions of patients considering whether 6 months of adjuvant chemotherapy (vs 3 months) is worthwhile for various improvements in 65% 5-year survival rate. ACT = adjuvant chemotherapy.

Figure 2. Cumulative proportions of patients considering whether 6 months of adjuvant chemotherapy (vs 3 months) is worthwhile for various improvements in 15-year survival times. ACT = adjuvant chemotherapy.

Figure 4. Cumulative proportions of patients considering whether 6 months of adjuvant chemotherapy (vs 3 months) is worthwhile for various improvements in 85% 5-year survival rate. ACT = adjuvant chemotherapy.

employment, marital status, or number of dependents. Of the 47 self-rated aspects of health-related quality of life during adjuvant chemotherapy that were tested for an association with general preference disposition, nausea ($P = .002$), reduced physical well-being ($P = .04$), and swollen face ($P = .008$) were associated with a need for larger benefits to justify the extra 3 months of chemotherapy (data not shown).

Any troublesome symptoms of CIPN were reported by 132 of 156 (85%) participants 3 months after randomization. The median survival benefit judged necessary to warrant their current symptoms of CIPN was an extra 5% over a baseline 5YS of 65%, with no statistically significant difference between the randomly assigned treatment groups (data not shown).

Discussion

The preferences of ANZ participants in the SCOT trial of adjuvant chemotherapy for 3 months vs 6 months varied widely, but the median survival benefits judged necessary to make the extra 3 months of adjuvant chemotherapy worthwhile were

substantial (an extra 2-3 years beyond life expectancies of 5 years or 15 years or an extra 5%-15% beyond baseline 5YS rates of 65% or 85%) and similar to those needed to justify troublesome symptoms of CIPN (an extra 5%-10% in 5YS). Participants' preferences were not associated with their baseline characteristics and were therefore unpredictable at baseline. Preferences were not affected by the randomly assigned treatment duration, and there was no consistent tendency to vary over the interval from 3 months to 18 months.

SCOT was part of the prospective International Duration Evaluation of Adjuvant Chemotherapy (IDEA) meta-analysis including 12 834 participants in 6 randomized trials comparing adjuvant chemotherapy durations of 3 months vs 6 months for localized colorectal cancer (8). Unlike the SCOT trial, the IDEA meta-analysis did not establish the noninferiority of 3 months vs 6 months of adjuvant chemotherapy for the primary endpoint of 3-year DFS (75% for 3 months vs 76% for 6 months; HR = 1.07; 95% CI = 1.00 to 1.15 crossing the prespecified upper 95% CI limit of 1.12 for noninferiority). In other words, the overall results of the IDEA meta-analysis did not establish that

Table 2. Median survival benefits judged necessary to justify an extra 3 months of adjuvant chemotherapy

| | | Median benefit | | | |
| | | Baseline prognosis in trade-off scenario | | | |
Time of preferences assessment	Allocated treatment	5 y	15 y	65%	85%
3 months	3 months	3	3	15%	5%
	6 months	2.5	3	10%	5%
18 months	3 months	5	2	15%	5%
	6 months	2	2	10%	3%
Average of 3 and 18 months	Both treatment groups combined	3	3	15%	5%

3 months of adjuvant chemotherapy was noninferior to 6 months of adjuvant chemotherapy. However, the results of the IDEA meta-analysis differed according to the chemotherapy regimen and stage of disease: 3 months of CAPOX was noninferior to 6 months of CAPOX, but 3 months of FOLFOX was inferior to 6 months of FOLFOX across low-risk (T1-3/N1) and high-risk (T4/N2-3) stage subgroups. The difference in the overall noninferiority conclusion between SCOT and IDEA may be because most participants in SCOT (67%) were treated with CAPOX, whereas the majority of participants in IDEA (60%) were treated with FOLFOX. The IDEA meta-analysis confirmed that toxicity was substantially lower with an adjuvant chemotherapy duration of 3 months rather than 6 months: rates of neurotoxicity grades 2-4 were 17% with FOLFOX and 14% with CAPOX in the 3-month arm vs 48% with FOLFOX and 45% with CAPOX in the 6-month arm. There was also less diarrhea, neutropenia, thrombocytopenia, nausea, mucositis, fatigue, and hand–foot syndrome with shorter duration chemotherapy.

The median benefits ANZ participants judged necessary to warrant an extra 3 months of adjuvant chemotherapy in SCOT were substantially larger than the benefits judged necessary by participants in our previous study assessing preferences for 6 months of oxaliplatin-based adjuvant chemotherapy vs observation without adjuvant chemotherapy (an extra 1 month of survival time or 1% improvement in 5YS) ([6]). We were unable to find other studies reporting preferences for different durations of adjuvant chemotherapy in colon cancer. We recently reported patients' preferences for different durations of adjuvant sorafenib after resection of localized renal cell cancer in the placebo-controlled SORCE trial ([9]). More than half of the participants surveyed in SORCE judged an extra 1 year of overall survival time necessary to warrant adjuvant sorafenib for a duration of 3 years rather than 1 year, a survival benefit similar to that required to warrant adjuvant sorafenib for 1 year vs observation without adjuvant sorafenib. These findings suggest that the duration of adjuvant systemic therapy matters to patients and is an important component of the trade-off between the benefits, harms, and inconveniences of adjuvant therapy.

The CIPN trade-off question was designed to determine the specific effects of CIPN on participants' preferences. CIPN is the toxicity of oxaliplatin that is most often responsible for dose modifications and early discontinuation. To our knowledge, there are no comparable studies that trade off CIPN with survival in adjuvant chemotherapy for bowel cancer or other types of cancer. A study of preferences for adjuvant chemotherapy in early breast cancer using different methods (conjoint analysis) reported that of 17 selected grade 1/2 and 3/4 chemotherapy side effects, a 5% reduction in the risk of grade 1-2 sensory

neuropathy and 3-4 motor neuropathy had the largest effects on the proportions of patients preferring chemotherapy to no chemotherapy ([10]). In our study, the survival benefits participants required to warrant the symptoms of CIPN were similar to those required to warrant an additional 3 months of adjuvant chemotherapy. This suggests that CIPN is of similar importance to the duration of adjuvant chemotherapy and should be discussed carefully when doctors and patients are considering the optimal duration of adjuvant chemotherapy including oxaliplatin.

The IDEA meta-analysis led ASCO to release a clinical practice guideline regarding the duration of oxaliplatin-containing adjuvant chemotherapy for patients with stage III colon cancer ([11]). These guidelines recommend a shared decision-making approach when determining the duration of adjuvant chemotherapy considering, among other factors, "patient characteristics, values, and preferences" and a discussion of the relative benefits and harms of the different treatment durations. The results of our study are an example of what these preferences are in the context of a clinical trial, and their variability shows the importance of eliciting the preferences of individual patients as per the recommendations of the guidelines. Clinicians could use the results of our study as a starting point for eliciting patients' preferences in clinical practice by informing their patients, for example, that most patients in a clinical trial required substantial survival benefit to justify an additional 3 months of chemotherapy.

The main strengths of our study were its prospective design, nesting within an ongoing randomized trial, and the use of a validated questionnaire to elicit preferences. This ensured that the eligibility criteria, chemotherapy regimens, and information provided to participants were standardized and relatively uniform.

The main limitations of our study are those inherent to the collection of data within an open-label, randomized trial. Participants in clinical trials are known to be younger and fitter and have fewer comorbidities than patients in real-world clinical practice ([12]), limiting the generalizability of our results to patients who would not have met the eligibility criteria. It was also difficult to design scenarios and a questionnaire to elicit preferences for a trial addressing a noninferiority question. We framed our preferences questions in terms of increases in survival associated with a longer duration of chemotherapy rather than reductions in survival associated with a shorter duration of chemotherapy. This might introduce a framing bias favoring a preference for a shorter duration of chemotherapy. The absence of baseline factors associated with preferences might partly be because of the limited power of our sample size, but

this finding mirrors many previous studies indicating that preferences are inherently unpredictable (6, 9, 13, 14). We did not assess participants' comprehension of the survey and therefore do not know whether their responses are accurate reflections of their preferences; ideally, this was done using qualitative methods.

The clinical implications of our findings are that discussions and decisions about the duration of adjuvant chemotherapy for colon cancer require careful consideration of both the pertinent results from clinical trials and the preferences of individual patients. Most patients prefer some adjuvant chemotherapy rather than none (6) but prefer a shorter duration of adjuvant chemotherapy rather than a longer duration. Relatively small differences in efficacy vs relatively large differences in duration and toxicity seemed important to participants in our study. These differences should be given prominence and priority by patients and doctors considering the optimal duration of adjuvant chemotherapy in routine clinical practice. Clinicians should ask patients about their circumstances, priorities, views, and attitudes to provide a personal context within which to interpret and apply data about shorter vs longer durations chemotherapy.

In conclusion, ANZ participants in SCOT varied widely in their preferences regarding 3 months vs 6 months of adjuvant chemotherapy, and these preferences were not associated with their baseline characteristics. Many of the participants judged that the overall survival benefits required to warrant adjuvant chemotherapy for 6 months rather than 3 months were substantially larger than the benefits observed in meta-analyses of randomized trials comparing these alternatives. Discussions and decision-making about the duration of adjuvant chemotherapy for patients with colon cancer should include careful consideration of both the pertinent data from clinical trials and of each patient's unique characteristics, circumstances, attitudes, and preferences.

Funding

Notes

Data availability

Data can be made available with approval of the study management committee following favorable review of a written proposal.

References

1. Labianca R, Nordlinger B, Beretta GD, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013; 24(suppl_6):vi64–vi72.
2. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27(19):3109–3116.
3. André T, Gramont A, Vernerey D, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC Study. *J Clin Oncol*. 2015;33(35):4176–4187.
4. Iveson TJ, Kerr RS, Saunders MP, et al. 3 versus 6 months of adjuvant oxaliplatin-fluoropyrimidine combination therapy for colorectal cancer (SCOT): an international, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2018;19(4):562–578.
5. Blinman P, King M, Norman R, et al. Preferences for cancer treatments: an overview of methods and applications in oncology. *Ann Oncol*. 2012;23(5): 1104–1110.
6. Blinman P, Duric V, Nowak AK, et al. Adjuvant chemotherapy for early colon cancer: what survival benefits make it worthwhile? *Eur J Cancer*. 2010;46(10): 1800–1807.
7. Stockler MR, O'Connell R, Nowak AK, et al. Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: a placebo-controlled double-blind randomised trial. *Lancet Oncol*. 2007; 8(7):603–612.
8. Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med*. 2018;378(13):1177–1188.
9. Blinman PL, Davis ID, Martin A, et al. Patients' preferences for adjuvant sorafenib after resection of renal cell carcinoma in the SORCE trial: what makes it worthwhile? *Ann Oncol*. 2018;29(2):370–376.
10. Beusterien K, Grinspan J, Kuchuk I, et al. Use of conjoint analysis to assess breast cancer patient preferences for chemotherapy side effects. *Oncologist*. 2014;19(2):127–134.
11. Lieu C, Kennedy EB, Bergsland E, et al. Duration of oxaliplatin-containing adjuvant therapy for stage III colon cancer: ASCO clinical practice guideline. *J Clin Oncol*. 2019;37(16):1436–1447.
12. Hurria A, Levit LA, Dale W, et al. Improving the evidence base for treating older adults with cancer: American Society of Clinical Oncology Statement. *J Clin Oncol*. 2015;33(32):3826–3833.
13. Blinman P, Mileshkin L, Khaw P, et al.; on behalf of the ANZGOG and PORTEC Group. Patients' and clinicians' preferences for adjuvant chemotherapy in endometrial cancer: an ANZGOG substudy of the PORTEC-3 intergroup randomised trial. *Br J Cancer*. 2016;115(10):1179–1185.
14. Blinman P, Hughes B, Crombie C, et al. Patients' and doctors' preferences for adjuvant chemotherapy in resected non-small-cell lung cancer: what makes it worthwhile? *Eur J Cancer*. 2015;51(12):1529–1537.