Since the publication of the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial in 2004, 6 months of FOLFOX (leucovorin calcium [folinic acid], fluorouracil, and oxaliplatin) has remained the standard of care for treating younger patients with resected lymph node–positive colon cancer. However, in 2018, the International Duration Evaluation of Adjuvant Therapy (IDEA) collaborators—who had aggregated the results of multiple simultaneous trials investigating the efficacy of 3 vs 6 months of adjuvant therapy in this setting—presented the findings of their joint work as a plenary paper at the annual American Society of Clinical Oncology conference. Those results were later published in the *New England Journal of Medicine*.2

That data set has become something of a Rorschach test for investigators and clinicians. Some physicians have pointed out that, strictly statistically speaking, the IDEA collaboration2 was negative. The 95% CI for the primary end point (3-year disease-free survival) crossed the preset hazard ratio (HR) boundary threshold; therefore, the trial failed to conclusively demonstrate that 3 months of adjuvant doublet therapy was noninferior to 6 months of therapy. In addition, the most appealing conclusions that can be gleaned from the trial—the results in the T3N1 subgroup and the apparently improved efficacy of XELOX (capecitabine and oxaliplatin, also called CAPOX) compared with FOLFOX if shorter therapy is to be given—are based on faulty statistical assumptions: the T3N1 subgroup was identified as part of a post hoc (exploratory) analysis, and the trials were not randomized between use of 5-fluorouracil and capecitabine, thus making any putative conclusions about their comparative efficacy suspect.

However, other clinicians believe the above criticisms of the data are overly parsimonious and ignore the real-world significance of the IDEA collaboration.2 After all, the 3-year disease-free survival curves are virtually identical. Furthermore, as supporters point out, while the choice between capecitabine and infusional 5-fluorouracil was not randomized, the combined IDEA data nonetheless represent the experience of more than 10,000 patients, and thus the conclusions ought not to be ignored. By the same token, while the T3N1 subgroup may have been identified post hoc, it nonetheless seems a clinically reasonable way to identify a group with very low risk that would be least likely to benefit from an additional 3 months of therapy. Finally, supporters observe that the statistical “failure” of the trial is based on the overlap of the HR 95% CI with a prespecified, but ultimately fairly arbitrarily chosen, HR boundary of 1.12. Had the group that decided the number chosen a value just a bit higher, the trial would then be rendered strictly positive, with even more far-reaching implications.

All of this debate is not academic because the choice between 3 and 6 months of therapy occurs in the setting of administering a highly neurotoxic agent (oxaliplatin), which leaves a significant proportion of patients with long-lasting (if not lifelong) impairments. These impairments can worsen even after discontinuation of therapy and are much less common with just 3 months of therapy.

Given the lingering debate spawned by these results, we welcome the systematic review and meta-analysis by Boyne et al.3 After careful screening and appropriate analysis, this team selected 22 studies involving 43,671 patients for inclusion in their meta-analysis. After considering possible
sources of heterogeneity within these data, they restricted their conclusions to patients with stage III colon cancer and then broke down their results into those who receive doublet and singlet therapy. Their most important findings were that (1) among patients who received doublet therapy, there was no statistically significant evidence indicating the superiority of 6 months over 3 months of therapy, but (2) among patients who received singlet therapy, there was statistically significant evidence of superiority of the longer regimen.

These conclusions deserve individual comment. With regard to the first finding, it is likely that the results presented strengthen (but do not significantly change) the findings of the IDEA collaboration.² Boyne et al³ are correct that using "real-world" data—with just 2 randomized trials and the other 20 being observational studies—may represent findings that more closely resemble daily oncology practice. However, of the 43,671 patients included in the meta-analysis, more than 10,000 patients came from the IDEA collaboration, and another almost 25,000 patients came from a single retrospective study by investigators in South Korea (which has been published in abstract form, but a full-text article was not available). The number of patients in those 2 studies dwarfs the combined remainder of the patients included. This consideration makes it difficult to extrapolate beyond the nuanced and controversial analysis drawn from the IDEA collaboration as described above. That said, perhaps the most important finding on this question is actually a lack of one: if the meta-analysis by Boyne et al³ did indicate inferiority in a real-world setting, that would be greater cause for concern and might spur further debate.

With regard to the second finding, the results by Boyne et al³ (among patients who received singlet therapy) give greater support to the National Comprehensive Cancer Network’s decision to propose 3 months of FOLFOX/XELOX as a viable option for adjuvant treatment of resected colon cancer in low-risk patients, while continuing to recommend 6 months if a single-agent fluoropyrimidine is used. One question raised is where, exactly, this recommendation will be of most use. Single-agent therapy is mostly used in elderly patients (a state that has been variably defined by both chronological and physiological means), among some patients with stage II disease, and with patients who have preexisting comorbidities that make use of oxaliplatin imprudent (eg, existing neuropathy). Patients with stage II colon cancer are excluded from the analysis by Boyne et al,³ so no conclusions can be drawn in that group. However, these findings serve as a strong reminder that elderly patients will likely benefit significantly from a full 6 months of therapy, and this corroboration of existing practice is clinically meaningful.

ARTICLE INFORMATION
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