

## Adjuvant Therapy in Stage II Colon Cancer: Current Approaches

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**Key Words.** Colon cancer · Stage II · Adjuvant chemotherapy

### LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the data concerning adjuvant chemotherapy for stage II colon cancer patients.
2. Discuss the current recommendations of the ASCO regarding adjuvant therapy for stage II colon cancer patients.
3. Describe points of discussion for the patient and physician when considering adjuvant chemotherapy for stage II colon cancer.

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An estimated 106,370 new cases of colon cancer were forecast to be diagnosed in the U.S. in 2004 [1]. Of these cases, approximately a quarter were predicted to be stage II disease. The overall survival rate for stage II patients after surgery alone ranges from 70%–80% [2]. Adjuvant chemotherapy has been shown to improve survival in patients with node-positive or stage III colon cancer in many studies [3–5]. The benefit of adjuvant therapy for patients with stage II colon cancer has been an area of controversy. Recently, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) published guidelines based on a thorough analysis of the available data [6–8]. The purpose of this article is to review the trials that have contributed to the current recommendations regarding adjuvant therapy for stage II colon cancer patients and to summarize recommendations.

Staging in colorectal cancer has recently undergone revision to better reflect the differences in survival within stages

II and III [9]. Stage II has been subdivided into IIA (T3N0) and IIB (T4N0). The 5-year disease-free survival (DFS) rate with surgery alone for stage IIA patients is 65%–73% (high-grade versus low-grade lesions), and it is 51%–60% for stage IIB patients (high-grade versus low-grade lesions) [10]. Stage III has also been subdivided to reflect differences in 5-year survival rates depending on depth of invasion as well as the number of lymph nodes involved. In a secondary analysis of the data from the Intergroup 0089 trial (INT-0089) of high-risk, stage II and stage III colon cancer patients, the number of lymph nodes analyzed was found to be an independent prognostic variable [11]. Whether lymph nodes were found to be positive or negative, survival increased as the number of lymph nodes analyzed increased ( $p = .0001$  and  $p = .0005$ , respectively, for stage III and II disease). The American Joint Committee on Cancer and the College of American Pathologists have recommended that at least 12 lymph nodes be examined [9, 12]. If fewer than

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12 nodes are sampled and reported, the patient should be considered inadequately staged, and it is appropriate to request re-examination of the surgical specimen. Nodal involvement upstages the patient, conferring a worse prognosis and thereby potentially changing the treatment recommendation.

The historical basis of the controversy regarding adjuvant treatment of stage II colon cancer patients is reflected, in part, in the differences between the Gastrointestinal (GI) Intergroup and National Surgical Adjuvant Breast and Bowel Project (NSABP) trials. INT-0035 randomized stage II patients to receive either 5-fluorouracil (5-FU) and levamisole (Ergamisol®; Janssen Pharmaceutica Products, L.P., Titusville, NJ, <http://www.janssen.com>) or surgery alone [3, 5]. In a separate trial within INT-0035, stage III patients were randomized to 5-FU and levamisole, levamisole alone, or surgery alone. For stage III patients, the 7-year survival rate for the 5-FU and levamisole treatment group was 60.2% versus 47% for the surgery alone group ( $p = 0.0007$ ). In contrast, the 7-year survival rate for stage II patients was 72% for both groups ( $p = .83$ ). The study thus demonstrated that stage III patients benefited significantly from adjuvant therapy; however, the same was not true for the small number ( $n = 318$ ) of stage II patients. The next generation Intergroup trial INT-0089 randomized 3,759 patients with high-risk (defined as those stage II patients with evidence of bowel obstruction, perforation, or adherence to or invasion of adjacent organs or tumor perforation) stage II (20% of accrual) and III patients to receive one of four combinations of 5-FU with leucovorin and/or levamisole [13]. No statistically significant differences among the four combinations were reported for either the high-risk stage II or the stage III patients. The 5-year overall survival rate for the treated high-risk stage II patients ranged from 75%–77%, comparable with the survival rate of the general population of stage II patients treated with surgery alone. It is thus uncertain whether this conventionally described high-risk group would have had a similar survival rate if no adjuvant therapy had been given. INT-0089 demonstrated that 6–8 months of 5-FU and leucovorin was comparable with 1 year of 5-FU and levamisole; therefore, 5-FU and leucovorin became the standard adjuvant regimen for stage III patients.

The NSABP conducted four adjuvant therapy trials for stage II and III colon cancer patients between 1977 and 1990. The C-01 and C-02 trials compared surgery alone with combination chemotherapy using semustine (methyl CCNU), vincristine, and 5-FU (MOF) [13] and with perioperative 5-FU portal vein infusion, respectively [14]. C-03 and C-04 compared 5-FU and leucovorin [15] with the MOF combination and with 5-FU plus levamisole, respectively [16]. Stage II patients comprised 41% of the patients in those combined studies (1,565 patients). The data from these four trials were

then pooled such that the best arm of each study was compared with the inferior arm. A 30% reduction in overall mortality was observed for the stage II patients [17]. The mortality reduction was greater than that observed for stage III patients, which was 18%. The reduction in mortality for stage II patients was observed for patients regardless of the presence or absence of high-risk features, including the presence of obstruction, perforation, or extension to adjacent organs, and resulted in an absolute survival improvement of 5%. These data resulted in the NSABP recommendation in favor of adjuvant chemotherapy for all stage II patients.

Data considered to be against the routine use of adjuvant chemotherapy for stage II patients were presented by the International Multicentre Pooled Analysis of B2 Colon Cancer (IMPACT B2) investigators. That report included 1,016 patients who had been enrolled in five trials that had randomized stage II colon cancer patients to receive either adjuvant treatment with 5-FU and leucovorin or observation [18, 19]. The hazard ratio for overall survival at 5 years was 0.86 (90% confidence interval [CI] 0.68–1.07) and was 0.83 (90% CI 0.72–1.07) for event-free survival. The clinical significance of this difference was considered questionable given that the 5-year survival rate for stage II patients after surgery alone is 75%–80% and the mortality associated with adjuvant 5-FU and leucovorin is 0.5%–1% [4].

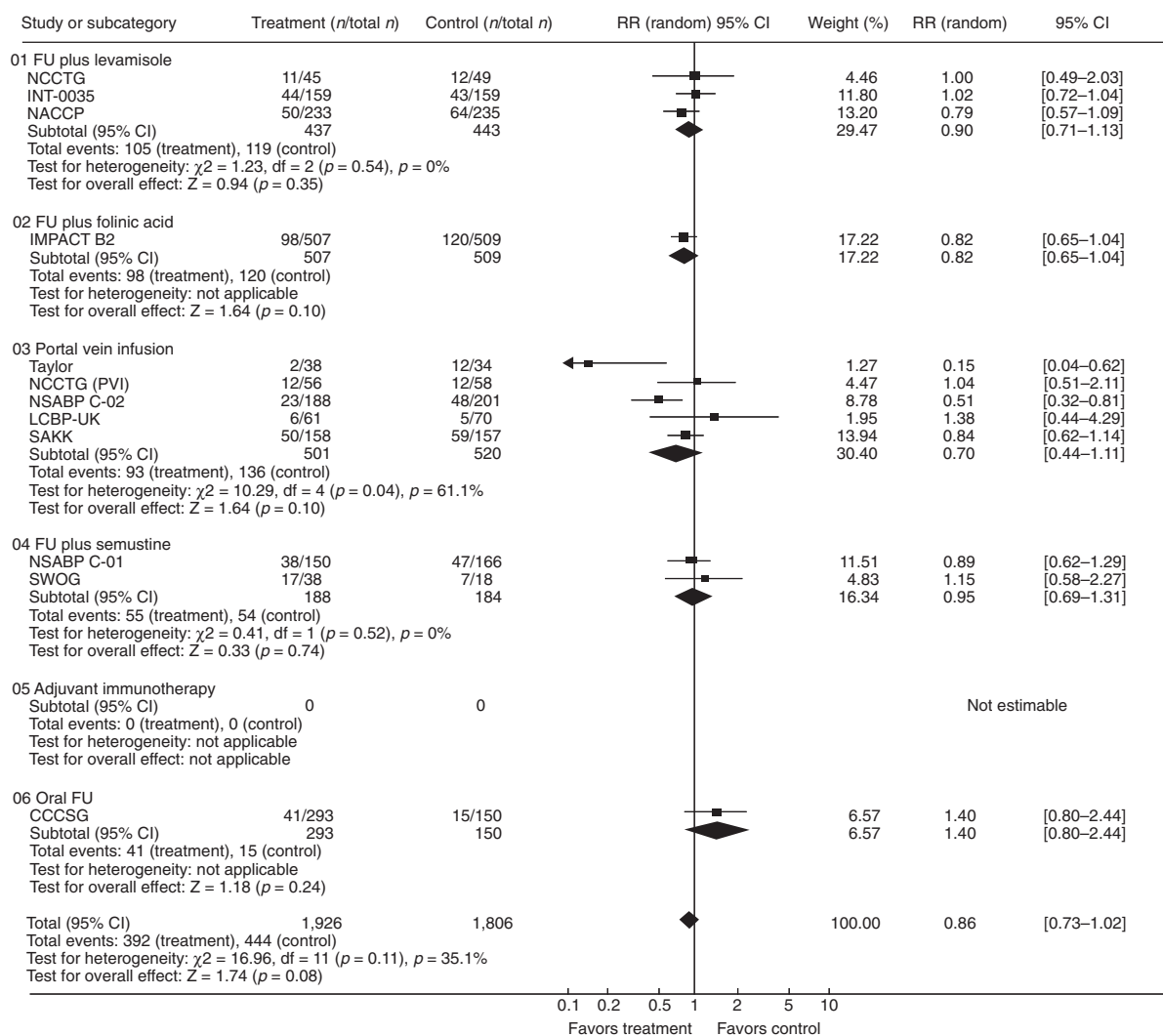
By the year 2000, data in favor of adjuvant therapy for stage II colorectal cancer patients were supported by the NSABP trial and data against adjuvant therapy were reinforced by the Intergroup trials and IMPACT analyses. A study of the treatment patterns of oncologists regarding stage II colon cancer patients was completed by analyzing the data from the Surveillance, Epidemiology, and End Results (SEER) Medicare database. The SEER evaluation included 3,151 stage II patients considered “usual” risk as defined by T3N0 tumor and the absence of obstruction and perforation. Twenty-seven percent of these stage II patients in the elderly Medicare population had received adjuvant chemotherapy. The overall survival rate of the group who received chemotherapy was 78% versus 75% for the group that did not receive chemotherapy [20]. The analysis confirmed that the findings in randomized studies of adjuvant therapy (e.g., IMPACT) were similar to those encountered in real-world practice. That analysis also confirmed that the improvement in overall survival with adjuvant therapy for stage II colon cancer patients is at best 2%–5%. The conclusion of that study was that, given the statistically insignificant improvement in overall survival with adjuvant therapy, the continuation of an observation arm in future trials is justified.

ASCO convened a panel to make recommendations based on available evidence regarding adjuvant therapy for stage II colon cancer patients. The recommendations were based on a

literature-based meta-analysis conducted by the Cancer Care Ontario Practice Guideline Initiative (CCOPGI) Gastrointestinal Cancer Disease Site Group. The most recent analysis by the CCOPGI staff included 37 trials and 11 meta-analyses [21]. Trials were included in the CCOPGI analysis if they were randomized, controlled, and compared adjuvant therapy with observation in patients with stage II colon cancer who had undergone a surgical resection with curative intent. The results of that review showed a mortality ratio of 0.87 ( $p = .07$ ), and the investigators concluded that although there was evidence of an improvement in the DFS rate (5%–10%)

with adjuvant treatment, there was no significant improvement in overall survival. The ASCO panel then requested that the CCOPGI complete a further analysis of 12 of the 37 trials that fulfilled the ASCO criteria of randomized controlled trials comparing a surgery control arm with adjuvant therapy, with a least one arm containing a 5-FU-based chemotherapy regimen. Analysis of that subset showed a mortality risk ratio for adjuvant therapy versus observation of 0.86 (Fig. 1) [6]. The ASCO panel did not recommend the routine administration of adjuvant chemotherapy for stage II colon cancer patients because of the lack of significant improvement in

Review: ASCO B2  
 Comparison: 01 adjuvant therapy versus observation  
 Outcome: 02 mortality risk ratio for adjuvant therapy versus observation: stage II patients



**Figure 1.** Meta-analysis of adjuvant therapy versus observation trials that include at least one FU-based chemotherapy arm. Reprinted with permission from Benson et al. [6]. Abbreviations: ASCO = American Society of Clinical Oncology; CCCSG = Colorectal Cancer Chemotherapy Study Group; CI = confidence interval; FU = fluorouracil; IMPACT = International Multicentre Pooled Analysis of Colon Cancer; INT = Intergroup; LCBP-UK = Large Bowel Cancer Project; NACCP = Netherlands Adjuvant Colorectal Cancer Project; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; RR = response rate; SAKK = Swiss Group for Clinical Cancer Research; SWOG = Southwest Oncology Group.

**Table 1.** Summary of ASCO recommendations [6]

Stage II medically fit patients	Routine adjuvant chemotherapy not recommended —absolute 5-year survival rate not improved by more than 5%.
Inadequately staged stage II patients (few nodes examined)	Offer of adjuvant therapy is reasonable
High-risk stage II patients (T4, perforation, poorly differentiated)	Direct evidence does not support adjuvant chemotherapy —absolute 5-year survival rate not improved by more than 5%. Indirect evidence of benefit extrapolated from stage III disease —a limited number of patients with high-risk disease have been evaluated. —the potential benefits have been inadequately tested.

overall survival (Table 1).

The ASCO panel also addressed the issue of adjuvant therapy for those stage II patients with high-risk features including a T4 lesion, perforation, or poorly differentiated histology. Randomized trials have not demonstrated an improvement in overall survival. However, an inadequate number of patients with high-risk stage II disease have been studied to demonstrate benefit. In this case, one may extrapolate from stage III data that adjuvant therapy may potentially be beneficial. Additionally, for those patients who have had suboptimal lymph node examinations, consideration of adjuvant therapy is reasonable. The ASCO panel provided a summary of the pertinent issues for discussion between the patient and physician concerning adjuvant therapy for stage II colon cancer (Table 2).

The Multi-center International Study of Oxaliplatin/5-fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial was a phase III randomized trial that investigated the benefit of the addition of oxaliplatin (Eloxatin<sup>®</sup>; Sanofi-Synthelabo Inc., New York, NY, <http://www.sanofi-synthelabo.us>) to 5-FU and leucovorin

as adjuvant therapy for resected stage II and III colon cancer patients [4]. Stage II patients comprised 40.2% of the patients in the oxaliplatin arm (451 patients) and 39.9% of patients in the control arm (448 patients). Among the stage II patients, only 12% (108 of 899) had high-risk features that included a T4 lesion, perforation, obstruction, or venous invasion [22]. After a median follow-up of 37.9 months, the stage II patients had disease-free survival rates of 87.0% in the treatment group and 84.3% in the control group; no *p* value was reported (risk recurrence reduction of 20%; *p* = .77). The addition of oxaliplatin resulted in a 12.4% incidence of grade 3 peripheral neuropathy, with 1.1% having persistent grade 3 neuropathy at 1 year. The value of a statistically insignificant 2.7% improvement in overall survival must be weighed against the inconvenience and potential side effects of 6 months of combination adjuvant therapy. The U.S. Food and Drug Administration approved the use of adjuvant 5-FU, leucovorin, and oxaliplatin (FOLFOX) for patients with stage III colon cancer only.

Results from the QUASAR trial were reported at the 2004 ASCO meeting. That trial was a randomized trial

**Table 2.** Points of discussion between the patient and physician: the value of adjuvant chemotherapy for stage II colon cancer

- Ask the patient how much prognostic information they wish to hear and whether they prefer numbers (e.g., 3%) or words (e.g., very small).
- Discuss the patient's perception of risks and benefits and tumor factors that may influence decision-making.
- Center discussion around whether the potential benefits of therapy outweigh the potential risks.
  - Surgically resected stage II colon cancer patients have a 5-year survival rate of 75%–80% with surgery alone, with IIa > IIb.
  - The improvement in cure rate with the addition of chemotherapy is limited. Clinical trials to date have been large enough to show that the improvement in 5-year survival is not more than 5% and may be in the range of 2%–4%; however, this has not been conclusively proven. The individual patient needs to consider whether the magnitude of survival benefit is worth the risk of toxicity and commitment to 6–8 months of therapy.
  - Potential risks of chemotherapy over 6–8 months and the potential late toxicities of newer chemotherapy drugs should be discussed in detail, including the risk of treatment-related death (<1%).
- Clarify that the definition of risk includes tumor characteristics: T and N stage, tumor differentiation, tumor perforation, vascular invasion, lymphatic invasion, neuroinvasion, and number of lymph nodes analyzed. It should be emphasized that, although these tumor characteristics may be prognostic markers, there are no data to suggest they serve as predictive markers (i.e., tumor characteristics that predict response to adjuvant chemotherapy).
- Discuss any comorbidities in detail and place them in perspective as to their effect on the potential benefit of therapy versus the potential risk.
- Consider the use of a numeracy program, which is a model estimate of survival and is stratified by age, tumor grade, nodal status, and T stage, which may assist the patient and physician in analyzing the individual patient's risk [28].

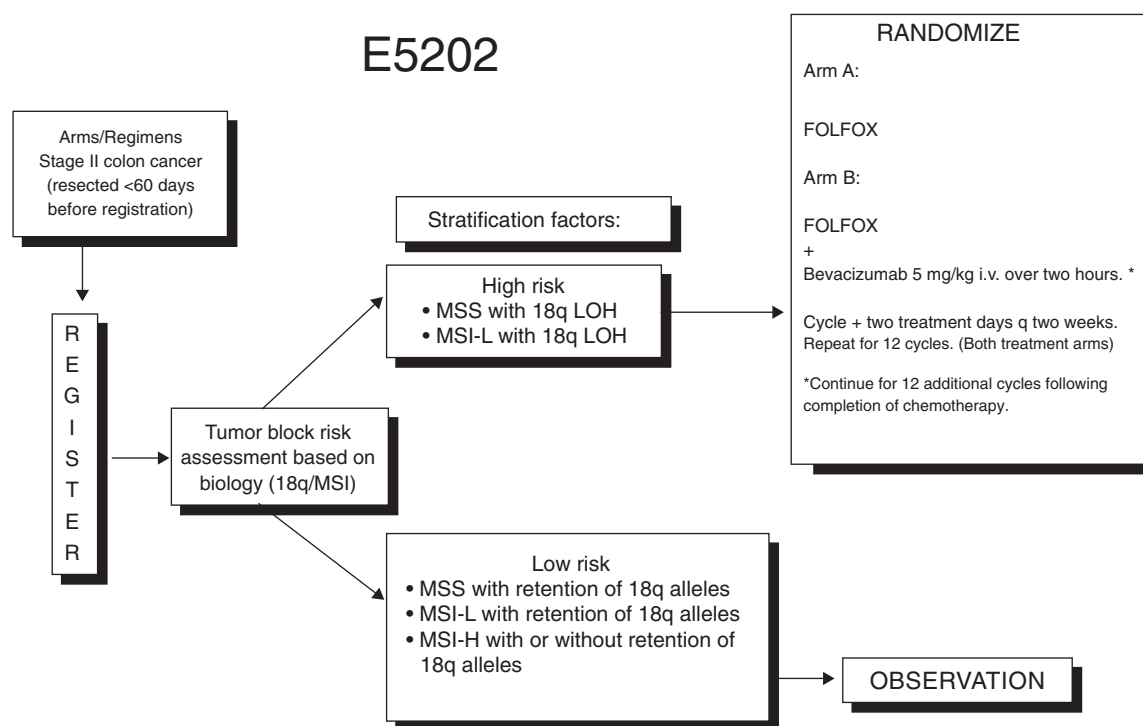
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comparing adjuvant chemotherapy with observation in 3,238 patients in whom physicians were uncertain about the level of benefit from adjuvant chemotherapy (91% were Duke's B and 71% were colon). After a median of 4.2 years of follow-up, the relative risk of death was 0.88 ( $p = 0.15$ ) and the relative risk of recurrence was 0.82 ( $p = 0.02$ ) with chemotherapy versus observation, translating to a 1%–5% survival benefit. These results are consistent with the findings of the meta-analysis providing the basis of the ASCO guideline [23].

Although these large analyses have shown that patients with stage II colon cancer do not have significantly better survival with adjuvant therapy, not all stage II patients are at equal risk. In addition to T stage and lymph node involvement, neural and vascular invasion have been reported to be associated with local and distant failure, respectively [12, 24, 25]. Allelic loss of chromosome 18q in colon tumors has been demonstrated to be a marker of poor prognosis [26]. In a study examining 145 tumor samples for 18q loss, investigators showed that the 5-year survival rate was lower in those with 18q loss than in those without 18q loss (54% versus 93%, respectively). The 52% 5-year survival rate for stage II patients with 18q loss was similar to that of patients with stage III disease without 18q loss. Microsatellite stability within colon tumors has also been reported to portend a poor prognosis [27]. In a retrospective study of 570 patients who

were enrolled in three trials of 5-FU–based adjuvant therapy, tumor samples were retrospectively analyzed for microsatellite instability. Among patients who did not receive adjuvant therapy, the 5-year survival rate was significantly better in patients with tumors that exhibited high-frequency microsatellite instability (88% versus 68.4%;  $p = .004$ ) than in those patients with tumors exhibiting microsatellite stability or low-frequency instability. Adjuvant chemotherapy improved the overall survival of patients with microsatellite-stable tumors or tumors exhibiting low-frequency microsatellite instability ( $p = 0.04$ ) but not those with high-frequency microsatellite instability.

Allelic loss of chromosome 18q and microsatellite instability in colon tumors are prognostic markers. However, the role of these as predictive markers of response to adjuvant therapy has yet to be defined. Currently, the GI Intergroup is conducting an Eastern Cooperative Oncology Group (ECOG)-coordinated study (E5202) of stage II patients to prospectively address the role of these markers as prognostic variables and as potential predictors of chemotherapy response. The markers will be used to risk stratify stage II patients and determine who will receive adjuvant chemotherapy (Fig. 2). Patients with retention of 18q alleles will be considered low risk and will be observed. Patients with 18q loss of heterozygosity will be designated as high risk and will be randomized to receive adjuvant therapy with FOLFOX,



**Figure 2.** Schema of Eastern Cooperative Oncology Group Trial 5202. Abbreviations: LOH = loss of heterozygosity; MSI = microsatellite instability; MSS = microsatellite stability; MSI-H = high-frequency microsatellite instability; MSI-L = low-frequency microsatellite instability.

with or without bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, <http://www.gene.com>) for 12 cycles plus an additional 12 cycles of bevacizumab after chemotherapy. The trial will accrue 3,000 patients. From ECOG's previous experience with an analysis of microsatellite instability/18q markers, it is expected that the high-risk control group will have a 3-year DFS rate of 80% and that the low-risk group undergoing observation may exhibit a 3-year DFS rate of about 90%, but that rate is not exactly known. With 3 years of follow-up, there will be at least an 88% power to detect a 37% difference in median DFS for the high-risk group (absolute difference of 5%, from 80% to 85%). There is an approximately 84% power to detect a 37% difference in median overall survival (absolute difference of 5% at 5 years, from 80% to 85%) with the analysis.

The NSABP recently opened an adjuvant trial for stage II and III colon cancer patients, C-08. That trial will also randomize patients to receive adjuvant therapy with FOL-FOX, with or without bevacizumab; however, in that trial, all stage II patients will receive therapy, and prognostic markers will be retrospectively analyzed.

In conclusion, the decision to give adjuvant chemotherapy to stage II colon cancer patients should take into account the minimal potential improvement in overall survival of

about 2%–5% and the real risk of mortality of 0.5%–1%. The morbidity related to chemotherapy side effects, such as the 12.4% incidence of grade 3 peripheral neuropathy reported with oxaliplatin in the MOSAIC trial, and the inconvenience of 6 months of therapy also need to be considered. Current NCCN and ASCO recommendations are against the routine use of adjuvant therapy for stage II colon cancer patients. High-risk stage II patients represent an appropriate group to consider for adjuvant therapy after thorough discussion (Table 2). Currently, factors that have been proven to be of prognostic value based on multiple trials include local tumor extent, lymph node metastasis, blood or lymphatic vessel invasion, presence of residual tumor, and elevated carcinoembryonic antigen preoperatively [12]. These and newer factors, including microsatellite instability and 18q loss of heterozygosity, require further assessment to determine which combination of these is the most important and correlates best with therapeutic benefit. The new generation of adjuvant trials will help to determine if recently developed therapies will further improve the survival of this particular population.

#### DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Dr. Benson has received research support and has served on the advisory boards of Genentech and Sanofi-Aventis.

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