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North Central Cancer Treatment Group (NCCTG) – Achievements and Perspectives

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Introduction

History

The North Central Cancer Treatment Group (NCCTG) was founded in 1977 as an outreach effort of the Mayo Clinic Cancer Center to provide access to promising therapeutic interventions to patients residing in the sparsely populated upper Midwest region of the United States. The basic premise of the group then, and now, is that the majority of adult cancer patients receive medical care in the community setting. Consequently, the most convenient and appropriate setting for assessing outcomes is likewise within the community oncology setting. These origins explain two distinguishing features of NCCTG: the emphasis upon clinical research within the community setting, and the strong ties to Mayo Clinic Cancer Center. In the previous five years, 78% of patients accrued to cancer treatment protocols were enrolled by community members. In contrast, both scientific and administrative leadership reside largely within the Mayo Clinic Cancer Center. While ideas are generated broadly by clinical and laboratory investigators located in many academic medical centers, the National Cancer Institute, the pharmaceutical industry, and community oncology practices, scientific leaders from the Mayo Clinic research base are responsible for selecting and prioritizing concepts to develop into specific clinical trials. Protocol development, conduct, biospecimen banking, data analysis, and publication are also centralized at Mayo Clinic. This partnership between community oncology practices and Mayo Clinic Cancer Center reflects the origins of the group and its principal organizational and administrative principle.

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Over the 30 years since its foundation, the NCCTG has expanded geographically beyond its origin as a regional cooperative group of the upper Midwest. As of 2007, the NCCTG has 41 members in 25 US states and Canada with more than 340 treating locations in 33 states, Canada, and Puerto Rico (Figure 1).

Scientific Aims and Approach

The primary aims of NCCTG are 1) to improve the duration and quality of life of cancer patients, 2) to improve our understanding of cancer biology and the biological consequences of treatment, 3) to improve methods of clinical trial conduct, and 4) to provide an infrastructure for cancer control research. These aims are accomplished through four disease-oriented scientific committees (Breast Cancer, Gastrointestinal Cancers, Lung Cancer, and Neuro-Oncology), three modality committees (Pathology, Radiation Oncology and Surgery), three discipline-oriented (Cancer Control, Novel Therapeutics and Quality of Life), and two advisory (Translational Research and Imaging) committees. The conduct of scientific committees is supported by five core function committees; Oncology Nursing, Clinical Research Associates Board, Patient Advocate, Gender and Ethnic Diversity, and Audit. All scientific efforts are supported by the Statistics and Data Center, the NCCTG Operations Office, and the NCCTG Biospecimen Resource located in Rochester, MN. Specific findings from research efforts are discussed within the individual disease-related sections within this article.

Breast Cancer (E.A. Perez)

The Breast Cancer Committee of NCCTG is committed to the development and conduct of clinically meaningful research addressing relevant clinical questions for patient management. The overarching goal is to improve the cure rate and reduce the burden of breast cancer. This is accomplished in the context of 3 thematic areas: 1) To improve cure rates and minimize morbidity in women with loco-regional breast cancer by developing biologically rational combinations of local and systemic therapies; 2) To evaluate markers of disease response and toxicity in order to optimize therapeutic approaches for individual patients; and 3) To improve survival and quality of life in women with metastatic breast cancer by developing improved regimens incorporating novel agents.

Adjuvant and locoregional management

NCCTG-led trials in early breast cancer initially focused on the value of adjuvant hormonal therapy such as tamoxifen alone or in conjunction with chemotherapy.¹ In addition, various studies helped to establish prognostic and predictive markers for the adjuvant therapy of breast cancer with early studies investigating DNA ploidy and S-phase index,²⁻⁴ and later distinct molecular signatures of breast cancers.^{5,6} These findings helped to establish the interest in molecular targeted agents in breast cancer which eventually led to the successful development of anti-HER2 directed therapy in adjuvant and metastatic breast cancer.

Results from the NCCTG N9831 study (including a joint analysis with the NSABP B-31 trial) demonstrated a dramatic 52% improvement in disease free survival at 4 years ($p < 0.00001$) by adding the anti-HER2 monoclonal antibody trastuzumab concurrent with

chemotherapy, along with acceptable cardiac and other safety profiles.^{7,8} Additionally, the interim analysis of the 3 arms of N9831 demonstrated a highly significant benefit in disease free survival comparing concurrent paclitaxel-trastuzumab after anthracycline/cyclophosphamide (AC) vs the control chemotherapy alone arm, but a non-statistically significant benefit of 13% improvement in DFS when comparing sequential trastuzumab after chemotherapy vs chemotherapy alone. This trial also demonstrated that approximately 2.5% of patients developed asymptomatic 15% drop of left ventricular ejection fraction (LVEF) after 4 cycles of AC, although most recovered in follow up.

In terms of cardiac effects of trastuzumab, the study showed a risk of clinical cardiac events of 2.5–3.3% at a median follow up of 4 years⁹, but no increased risk of cardiac events in patients who received radiation to the breast/chest wall.¹⁰ The importance of HER2 testing in central versus local laboratories to improve the reliability of HER2 analysis and optimizing patient selection for anti-HER2 targeted therapy was another important finding from this pivotal study.¹¹ A comprehensive analysis of potential predictive factors of benefit to trastuzumab is currently ongoing, evaluating membrane, cytoplasmic, and nuclear markers. Our group has now developed an adjuvant trial for patients with HER2-positive early breast cancer, as a logical follow to N9831, in collaboration with the Breast Intergroup (BIG). The rationale for this new worldwide adjuvant breast study (N063D, also known as BIG 2.06 or ALTO) includes the incorporation of a second agent that targets HER2 via tyrosine kinase inhibition (lapatinib) with the goals of improving efficacy, minimizing toxicity, and improving the understanding of molecular correlates of response.

The NCCTG conducted another pivotal adjuvant trial to address the controversy regarding the potential impact of menstrual cycle phase and timing of surgical treatment on patient outcome. Thus, we developed and completed a prospective clinical trial N0431, evaluating timing of menstrual cycle at time of definite breast surgery (luteal or follicular) and relationship to disease free and overall survival in patients with early breast cancer.¹² We determined that timing of menstrual cycle at the time of surgery phase (based on biochemical determination to distinguish follicular and luteal phase) did not correlate with patient outcome in terms of disease free or overall survival. The results of this prospective cohort study definitely demonstrate that menstrual cycle timing is irrelevant when considering breast cancer surgery, a finding important for clinical practice.

Correlative markers

Studies conducted by the NCCTG reported translational data evaluating the association between polymorphisms in the DNA repair enzymes XPD and XRCC1 and objective response to the chemotherapy regimen docetaxel and carboplatin in patients with metastatic breast cancer (N9932 substudy).¹³ The hypothesis tested was that genetic polymorphisms in XPD and XRCC1 influence the efficacy of carboplatin. Our data demonstrated that patients with the XPD 312 Asp/Asp genotype (wild type-WT) had lower response rate and clinical benefit vs. patients with the Asp312Asn SNP; $p=0.06$). Modest differences in response rate were observed for the XRCC1 polymorphism Arg399Gln, but the difference was not statistically significant, $p=0.33$). We plan to expand this type line of research, as our group

has recently completed study N0338 evaluating this same combination regimen of docetaxel plus carboplatin given every 2 weeks with growth factor support in the presurgical setting.

Data from evaluation of genetic polymorphisms of CYP2D6 and CYP43A in a subset of patients from NCCTG 89-30-52 demonstrated that postmenopausal patients with node negative resected breast cancer who had the CYP2D6 *4/*4 genotype had worse relapse free survival after adjuvant tamoxifen.^{14,15} This study was based on the hypothesis that genetic variation affects the activation of tamoxifen to the metabolite endoxifen, and is correlated with patient outcome to adjuvant tamoxifen. Another important correlative finding from this study was the impact of the HOXB13/IL-17 gene ratio on relapse free survival.¹⁶ Moreover, analysis of these 2 types of markers (involving host and tumor) demonstrated better predictive ability of outcome than either marker alone. We plan to expand the evaluation of pharmacogenetics of tamoxifen in premenopausal and postmenopausal women, by evaluating polymorphisms of CYP2D6, CYP19, SULT1A1, and others in both retrospective and prospectively conducted adjuvant breast trials.

Metastatic Disease

Trials conducted by the NCCTG were instrumental in defining the value of hormone therapy as palliative treatment for pre- and postmenopausal women with advanced breast cancer.
17-20

Our group conducted the first North American cooperative group study (NCCTG 95-32-52) establishing the activity of every 3 week paclitaxel and carboplatin in the setting of advanced breast cancer.²¹ We then developed a randomized phase II trial (98-32-52) exploring 2 different schedules of these chemotherapy agents with trastuzumab in patients with HER2-positive metastatic breast cancer. Specifically, we evaluated weekly vs. every 3-week combination of paclitaxel plus carboplatin plus trastuzumab. This study demonstrated the activity and tolerability of either schedule, but with much less toxicity and higher response rate (65% response rate for the 3 weekly and 81% for the weekly approach) for the weekly approach.²² Survival data were 2.3 years for the 3-weekly schedule and 3.2 years for the weekly approach.

Another important finding from our group was the elucidation of the response and tolerability of single agent topoisomerase I inhibitor irinotecan (using weekly or every 3 week schedules) in the setting of refractory metastatic breast cancer.²³ The response rate was approximately 20%, and in the same range of traditionally used agents for this disease, thus expanding therapeutic options for these patients. Analysis of the role of correlative markers of response is ongoing, and follow-up studies incorporating irinotecan (and other topoisomerase-1 inhibitors) have now been developed by NCCTG and other cooperative groups.

Our most recent studies incorporate novel HER2 and non-HER2 approaches including anti-angiogenesis (with agents such as bevacizumab, VEGF-trap alone or in combination with other agents or radiation), anti-tubulin agents including taxanes (nab-paclitaxel, polyglutamated paclitaxel, ixabepilone, vinflunine).

Gastrointestinal Cancers (S.R. Alberts, A. Grothey)

Colorectal Cancer

The advances made in the medical treatment of colorectal cancer in the last 30 years are closely linked to the achievements of the North Central Cancer Treatment Group.

The value of adjuvant chemotherapy in early stage colon cancer was first demonstrated almost 20 years ago when patients treated with 12 months of 5-FU/levamisole after curative surgery were found to have significantly improved outcome compared with surgery alone.²⁴ This trial established a worldwide standard of care and opened a new field of research in colon cancer with continued participation and leadership of NCCTG in various subsequent studies.²⁵ The ongoing, NCCTG-led Intergroup trial, N0147, attempts to further advance the standard adjuvant therapy in colon cancer by testing the addition of cetuximab to FOLFOX (5-FU/LV/oxaliplatin).

In early rectal cancer, NCCTG again helped to establish the adjuvant treatment standard by demonstrating that postoperative continuous infusion 5-FU parallel to radiation improved overall survival when compared with bolus 5-FU.²⁶

Of equal, if not greater importance for the understanding of tumor biology and the design of future clinical trials in early stage colorectal cancer was the participation of NCCTG in the characterization and development of prognostic and predictive biomarkers such as microsatellite instability (MSI).²⁷ These analyses formed the basis for the ongoing Intergroup trial in stage II colon cancer, E5202.

In advanced colorectal cancer, NCCTG conducted one of the first trials which established irinotecan as a active agent.²⁸ More recently, the landmark phase III trial N9741 defined the new standard first-line therapy in advanced CRC by demonstrating that FOLFOX4 is superior to the old standard regimen IFL in all efficacy parameters which eventually led to the FDA approval of oxaliplatin in this indication.²⁹ Beyond that, N9741 established port-a-cath devices for infusional 5-FU in the US oncologic community and introduced 60-day all-cause mortality as new toxicity parameter for the safety evaluation of clinical trials. N9741 carried forward extensive translational components with emphasis on pharmacogenomic analyses of pre-treatment quality-of-life, irinotecan-mediated toxicity, and oxaliplatin-mediated neurotoxicity which have greatly enhanced the understanding of parameters influencing efficacy and safety of palliative chemotherapy.^{30–34} Currently, NCCTG is co-chairing the ongoing second-line phase III Intergroup trial S0600 which evaluates the usefulness of continuing bevacizumab beyond tumor progression. The current programmatic approach in advanced colorectal cancer focuses on the development of rational combinations of biologic agents and their integration in treatment algorithms, as well as the initiation of biomarker-driven trials to individualize therapeutic choices based on molecular characteristics of tumor and host.

The NCCTG has conducted a series of trials focused on liver-only metastases from colorectal cancer. Clinical trials have focused on liver metastases that are both initially not optimally resectable and potentially resectable. The use of neoadjuvant chemotherapy has

allowed up to one-third of patients felt initially to be not optimally resectable to be able to undergo surgery with a resulting good long-term outcome.³⁵ For those undergoing surgery after receiving FOLFOX to downsize the metastases the median was 35 months. Similarly, postoperative therapy with hepatic artery infusion therapy alternating with systemic capecitabine and oxaliplatin resulted in over 80% of patients being alive at 2 years.³⁶ These trials continue to provide a strong rationale for a curative approach in select patients with metastatic colorectal cancer in clinical practice and future clinical studies.

To advance the surgical approach of colon cancer, the NCCTG-led Intergroup trial INT 0146 clearly demonstrated that laparoscopic-assisted surgery provides equal long-term outcome results compared with open colectomy, thereby providing a new surgical standard of care in addition to open laparotomy.^{37,38}

Upper Gastrointestinal Cancers

In upper gastrointestinal cancers the NCCTG helped to establish standards of care for both locally advanced and metastatic disease. In a randomized phase III trial in patients with metastatic pancreatic cancer 5-FU was compared to several multidrug regimens including the potentially promising regimen of 5-FU, cyclophosphamide, methotrexate and vincristine, followed by maintenance therapy with 5-FU and mitomycin C (Mallinson regimen).³⁹ The trial showed similar overall survival between single agent 5-FU and the Mallinson regimen, but significantly less toxicity with 5-FU alone. Subsequent trials have assessed multidrug regimens using either 5-FU or more recently gemcitabine. While none of these trials has shown a significant advantage over what is expected with single agent gemcitabine, they have helped guide clinical trial development in what has been a particularly challenging cancer to treat. More recent trials have provided more promising results with the addition of targeted therapy. The combination of gemcitabine, oxaliplatin and bevacizumab gave an overall survival approximately twice that seen with 5-FU.⁴⁰

Similar trials of chemotherapy or multimodality therapy with chemotherapy and radiation for gastroesophageal cancer have helped to define the standards of care. In a randomized trial involving over 250 patients with metastatic disease 5-FU was shown to be as active as three other multidrug regimens and better tolerated.⁴¹ Current trials are now focusing on the use of targeted or novel agents in combination with chemotherapy. In addition, recognizing the significant toxicity associated with many of the therapies used in gastroesophageal cancers, a variety of translational studies have assessed potential predictors of toxicity including pharmacogenomics.

Lung Cancer (A.A. Adjei)

Over the past three decades, the greatest contributions of the lung program of NCCTG has been in hypothesis-generating phase II studies and in pooled analyses of completed trials.

Predictive equation of patient outcome in phase II trials

Understanding that determinants of clinical efficacy and toxicity to anticancer agents are multi-factorial, a pooled analysis of nine first-line trials (with mostly conventional chemotherapy) in advanced NSCLC was performed to investigate the impact of potential

patient prognostic factors on clinical outcomes. Pretreatment hematologic parameters were found to be significant predictors of severe adverse events, as well as overall survival and time to progressive disease. Further, a predictive equation for overall survival of stage IV NSCLC patients was developed, and validated with an independent data set. This equation allows for a better evaluation of treatment benefit from single arm phase studies, by comparing the observed survival of a cohort to its expected survival using the patients' own prognostic factors in place of comparisons with historical data that may have substantially different baseline patient characteristics. This prediction equation is the first one of its kind in this advanced NSCLC population and is reasonably accurate in its prediction of the prognosis of newly diagnosed patients with stage IV NSCLC.^{42,43}

Studies of radiation therapy in the elderly with NSCLC

A phase III Trial, NCCTG 94–24-52 compared chemotherapy plus either once-daily thoracic radiotherapy (QDRT) or twice-daily radiotherapy (BIDRT). There was no difference in survival between the arms.⁴⁴ In a secondary analysis, the outcomes of patients aged >70 years (elderly patients) were compared with those of younger individuals. The 5-year survival rates were 18% in patients <70 years compared to 13% in elderly patients ($P=0.4$). Grade 4+ toxicity occurred in 62% of patients <70 years compared with 81% of elderly patients ($P=0.007$). Despite increased toxicity, elderly patients had similar survival rates as younger individuals.⁴⁵ This trial was combined with another trial; NCCTG 90–24-51 which included 3 arms: QDRT alone, BIDRT alone, and chemotherapy plus BIDRT. Patients aged >65 years (elderly) were included in this analysis. The median and 5-year survival rates were 10.5 months and 5.4% for the RT alone group vs. 13.7 months and 14.7% for the RT plus chemotherapy group ($P=0.05$). Patients who received RT plus chemotherapy experienced significantly greater severe toxicity (grade >3) compared with patients who received RT alone (89.9% vs. 32.4%; $P<0.01$). It was concluded that fit elderly patients appeared to gain a survival advantage from RT and chemotherapy compared with RT alone.⁴⁶

Studies with radiation therapy in the elderly with limited-stage small cell lung carcinoma (LSCLC)

A Phase III trial was performed (89–20-52) to determine whether chemotherapy plus either BIDRT or QDRT resulted in a better outcome in LSCLC.⁴⁵ There was no difference in survival between the two arms. NCCTG investigators then examined the relationship between age and outcome for these patients. The 5-year survival rates were 22% for younger patients vs. 17% for older (>70) patients ($P=0.14$). Despite having more weight loss, poorer performance status, increased pulmonary toxicity, and more deaths due to treatment, survival was not significantly worse in older individuals. Fit elderly patients with LSCLC can receive combined-modality therapy with the expectation of a relatively favorable survival.^{47,48}

Neuro-Oncology (K. A. Jaeckle)

Current efforts focus on improvement of outcome and quality of life of brain tumor patients, and the performance of novel translational correlative and database studies in association with our clinical trials.

Therapeutic trials

NCCTG demonstrated that 64 Gy RT is not better than 50 Gy radiation in the treatment of low-grade gliomas.⁴⁹ NCCTG also established proof of principle that patients with low-grade oligodendroglioma do respond to chemotherapy with procarbazine, CCNU and vincristine.⁵⁰ More recently, the NCCTG has investigated the potential of molecular targeted agents, alone and in combination with radiotherapy, chemotherapy or other targeted agents. In N0074, although gefitinib, administered following radiotherapy (RT) to newly diagnosed glioblastoma (GBM) patients, did not increase overall survival (OS) in the whole group as compared to database controls, those developing physiologic effects of treatment (rash, diarrhea) had significantly longer survival. In N997B, 36% of GBM patients treated with the mTOR inhibitor temsirolimus had imaging responses defined by a decrease in size of T2 hyperintensity on MRI, which correlated positively with high pre-treatment tumor p70s6kinase levels.⁵¹ The histone deacetylase-inhibitor vorinostat increased progression-free survival of recurrent GBM patients at 6 months (PFS6) to 15 % versus <10 % in NCCTG database controls; post-treatment tumor tissues showed evidence of inhibition of the target pathway as determined by tissue H4 acetylation and upregulation of E-cadherin ($p < 0.02$).⁵² Studies are currently being extended in newly diagnosed GBM, including separate Phase II trials which explore the potential additive effects of erlotinib (N0177)⁵³; temsirolimus (N047D); everolimus (N057K); and PARP-inhibitors, when added to standard RT plus temozolomide. In N0572, NCCTG is evaluating the combination of the VEGF-inhibitor sorafenib and temsirolimus in treatment of recurrent GBM. Additional combinations with sorafenib, vorinostat, and bevacizumab are in development. The NCCTG has active Intergroup collaborations with RTOG, ECOG, NCIC, and EORTC in ongoing and upcoming Phase III trials for newly diagnosed GBM (R0525), anaplastic grade 3 glioma with 1p/19q (EORTC), or without 1p/19q deletions (N0577), and low grade glioma (E3F05). Finally, the NCCTG is currently leading a Phase III intergroup trial (N0574) which compares stereotactic radiosurgery (SRS) versus SRS plus whole-brain radiotherapy for patients with 1–3 newly diagnosed cerebral metastases.

Neurocognitive and quality of life studies

In a prospective study of high grade gliomas, a greater extent of surgical tumor resection was not found to produce more cognitive disability than subtotal resection or biopsy.⁵⁴ In patients with low grade gliomas receiving RT, neurocognitive function remained stable unless there was tumor progression⁵⁵, and baseline Folstein mini-mental status score correlated significantly with survival.⁵⁶ In high grade glioma patients, deterioration in MMSE preceded MRI evidence of progression and was also a strong predictor of early progression and death.⁵⁷

Translational and database studies

In a study of low grade oligodendroglioma, the translocation t(1;19)(q10;p10) was found to mediate the well-known combined 1p/19q deletions in low grade oligodendroglioma (LGO) and predicted a better prognosis; median OS without fusion was 9.1 years, and 13 years with fusion ($p = 0.001$).⁵⁸ In a database of 208 patients treated on NCCTG studies with tissue at initial diagnosis and recurrence, the frequency of transformation from low to high grade

tumors was 70%, 68% and 43% for those initially with low grade astrocytoma, mixed glioma, and oligodendroglioma, respectively. OS from recurrence was significantly shorter for those transforming from low grade to GBM as compared with those with GBM initially and at recurrence.⁵⁹ In a database study compiled from 28 NCCTG trials, there was agreement of the surrogate endpoint (PFS6) with OS at 12 months in recurrent glioma 90% of the time, but only 75% of the time in newly diagnosed patients, suggesting that PFS6 is a reasonable endpoint for recurrent disease studies, but should not replace OS for newly diagnosed patient studies⁶⁰. NCCTG also demonstrated that RECIST criteria for tumor response are as accurate as traditional MacDonald criteria.⁶¹

Cancer Control (C. L. Loprinzi)

The Cancer Control Program of the NCCTG started a little over two decades ago, with the mandate that CCOPs participate in cancer control research, in addition to cancer treatment research. Cancer control research in the cooperative groups oftentimes includes studies related to cancer screening, cancer prevention, and the control of symptoms related to cancer and/or cancer therapy. The NCCTG has conducted trials in each of these areas, but most prominently has participated in the symptom control research arena.

A recent review of the NCCTG symptom control experience was published.⁶² This work included over 62 randomized, phase III NCCTG clinical protocols, affecting 13 symptom complexes (Table 1). A number of these NCCTG symptom control trials have influenced clinical practice.

This section of this manuscript will focus on NCCTG symptom control trials that have affected what oncologists do in clinical practice.

Mucositis

The NCCTG Cancer Control Program has conducted 14 randomized trials attempting to alleviate GI mucosal toxicity from cancer therapy (chemotherapy and/or radiation therapy). Many of these clinical trials have influenced clinical practice by detecting agents that did not work, therefore helping to help extinguish them from being used in clinical practice.^{63–75}

One of the NCCTG mucositis prevention trials has affected clinical practice in a positive manner.⁶⁸ This is a trial which was designed to look at oral cryotherapy as a means of preventing 5-FU induced mucositis. This idea was generated by NCCTG. Noting that bolus dose 5-FU has a relatively short half-life (10–15 minutes), it was hypothesized that the use of ice chips in the mouth for 30 minutes, given around the time of the 5-FU bolus treatment, would cause oral cooling, would result in vascular constriction, and would decrease the delivery of 5-FU to the oral mucosa. This was hoped to be able to result in less 5-FU-induced mucositis. The trial looking at this issue was a randomized controlled trial but, for fairly obvious reasons, did not have a blinded placebo arm. It included patients scheduled to receive their first ever chemotherapy with intravenous push 5-FU, 425 mg/m² plus leucovorin, 20 mg/m² each given daily for 5 doses. The trial, involving about 40 patients per arm, demonstrated that the patients receiving the oral cryotherapy had a substantial,

approximately 50%, reduction in mucositis ($p=0.0001$). This clinical trial was replicated by different groups, virtually all demonstrating similarly positive results.^{76–79}

As a results of this work, four small non-randomized phase I and II trials were subsequently conducted whereby cryotherapy was utilized with patients receiving the methotrexate analog edatrexate.^{80–82} The bulk of information from these trials has suggested that oral cryotherapy decreases mucositis from this drug. Current guidelines, from a multinational organization, recommend oral cryotherapy to decrease mucositis in patients treated with bolus edatrexate.⁸³ In addition, oral cryotherapy has been studied in patients with high dose melphalan therapy, when utilized as a preparative treatment regimen for stem cell rescue, also suggesting that oral cryotherapy is helpful for alleviating mucositis from high dose melphalan.^{84–89}

Anorexia/cachexia

The NCCTG has conducted 14 randomized clinical trials looking at various ways to alleviate cancer anorexia/cachexia.^{90–100} One of the earliest of these trials was a placebo-controlled trial looking at megestrol acetate, 800 mg per day in patients with cancer anorexia/cachexia.⁹⁵ This was the first ever reported placebo-controlled, double-blinded trial demonstrating that a drug could increase appetite and increase non-fluid weight gain in patients with cancer anorexia/cachexia. Subsequent to this publication, there have been over 15 placebo-controlled trials demonstrating that progestational agents such as megestrol acetate do improve appetite in patients with cancer anorexia/cachexia.⁹¹ Noting that this drug is not a panacea for this severe clinical problem, megestrol acetate appears to be the most commonly utilized drug used to try to stimulate appetite in patients with advanced cancer. NCCTG trials have also demonstrated that this drug can alleviate nausea and vomiting in patients with advanced cancer.^{95,100}

Other notable results from the NCCTG cancer anorexia/cachexia program have illustrated that there is a dose-response effect with megestrol acetate, revealing that doses up to 800 mg per day stimulate appetite more than do lower doses; but that a 1280 mg/d dose did not stimulate appetite more.⁹⁹ Another trial has demonstrated that megestrol acetate does not improve quality or life or survival in patients with lung cancer, when such therapy, vs. placebo, was started at the time of disease diagnosis.¹⁰⁰ Another clinical trial demonstrated that megestrol acetate and dexamethasone were relatively similar in their ability to stimulate appetite but that megestrol acetate was more tolerable than the dexamethasone.⁹⁷ The same trial demonstrated that both drugs appear to be better than the androgenic agent fluoxymestron. Other results from these trials have demonstrated that hydrazine sulfate is not helpful^{96,98}, eicosapentaenoic acid is no better than megestrol acetate⁹², dronabinol does not add to benefit to megestrol acetate⁹³, and that the tumor necrosis factor (TNF) inhibitors, infliximab and etanercept, do not appear to be helpful in patients with cancer anorexia/cachexia.

Non-estrogenic management of hot flashes—The NCCTG has conducted 10 phase III randomized trials looking at non-estrogenic means of trying to alleviate hot flashes in

women with breast cancer and/or men with prostate cancer.^{101–109} This work initiated the study of hot flashes in cooperative group settings.

A summary of the results of these trials have illustrated the following points:

- A placebo decreases hot flashes by 20–30% over a 4 week period of study.¹¹⁰
- Megestrol acetate or medroxyprogesterone acetate each decrease hot flashes by about 80–85%, similar to what would be expected with estrogenic therapy.^{105,106}
- The antidepressant venlafaxine decreases hot flashes by about 60% from baseline.¹⁰⁴
- Clonidine reduces hot flashes by approximately 40% from baseline, but has bothersome toxicities which limit its use.¹¹¹
- Vitamin E may decrease hot flashes a little bit better than does a placebo and is well tolerated.¹⁰¹
- Neither a tested soy product nor black cohosh appears to decrease hot flashes any more than does a placebo.^{108,109}

These hot flash studies have also provided information with regards to the treatment of hot flashes in men with prostate cancer receiving androgen ablation therapy. The following points summarize this work:

- A placebo decreases hot flashes by about 20–30% over a 4 week study period, similar to what is seen in women.¹⁰²
- Clonidine did not appear to decrease hot flashes any more than did a placebo.¹¹²
- Small doses of megestrol acetate decreases hot flashes by about 85%.¹⁰⁶
- Gabapentin, a non-hormonal anti-seizure agent, decreases hot flashes by about 50%.¹⁰²

Thus, the NCCTG Cancer Control Program has been quite productive over the past two decades. In addition to continuing to focus on the symptoms noted above, newer efforts are focusing on chemotherapy-induced neuropathy and also on skin toxicities induced by chemotherapy and biologic agents.

Patient-Reported Outcome/Quality of Life (J. A. Sloan)

The PROQOL Committee (PC) enables researchers to answer research hypotheses related to patient-reported and quality of life related outcomes. An 18-chapter monograph entitled ‘Applying QOL Assessments: Solutions for Clinical Practice and Research’ details the research advances achieved. Topics include defining QOL endpoints, choosing assessments, and analyzing results.¹¹³

The PC defined a new field of research linking the genetic makeup of cancer patients with their QOL throughout the disease process (QOLenomics). This idea arose from work on methods to identify prognostic QOL endpoints analogous to approaches used to find prognostic surrogate endpoint biomarkers (SEBs) in treatment trials.^{114–116} Data derived

from the practice-changing colorectal cancer trial N9741 to test this hypothesis was presented in a plenary session at ASCO in 2004.^{117,118} Results provided preliminary evidence of a genetic component within a patient's response to a cancer diagnosis, even before treatment is initiated. Genetic variants in DPYD*5 and TYMS TSER were associated with differences in QOL. The genes involved affect neurotransmitter synthesis, serve as methyl donors, and play a role in DNA synthesis, damage repair, or detoxify the cell, all of which mediate the cell's response to stress. The results may ultimately allow for the development of QOL-related individualized patient treatment based on genetic makeup.

The PC has used NCCTG clinical trials to test various methodological techniques. Three inter-connected lines of research involved: 1) the development of and consensus on what is a clinically meaningful effect size for QOL assessments;¹¹⁹ 2) the relative value of single-item QOL assessments to longer, multi-item assessments (less is more);¹²⁰ and 3) the relative value of clinician-completed adverse event assessments via the NCI's Common Toxicity Criteria (CTC) compared to that of patient-reported outcomes.¹²¹

The PROQOL Committee led an effort involving 30 of the world's experts on clinical significance to produce a series of six manuscripts published in the Mayo Clinic Proceedings and as a separate monograph.^{122–127} Two summary papers of this work were produced, one for psychometricians¹²⁸ and the other for clinicians.¹²⁹ The PC developed the Empirical Rule Effect Size (ERES) method to define a clinically meaningful effect size for any QOL assessment as being equal to ½ times the standard deviation of the measure involved (10 points on a 0–100 point scale).^{130,131}

The NCCTG published one of the first studies in oncology to do a head-to-head comparison of the psychometrics for competing QOL assessments.¹³² Results indicated that brief QOL assessments could impart comparable information relative to longer assessments and substantiated the claim that QOL was prognostic for survival, even via the use of a single-item measure of overall QOL. Subsequent NCCTG clinical trials used this minimalist approach where patient burden and “need to know” became key issues for study design.¹³³ The PC developed and tested a series of simple, single-item linear analogue self assessments (LASAs) for capturing data on the major QOL domains in numerous NCCTG clinical trials. The PC subsequently carried out analyses of cancer control, lung cancer, neuro-oncology, and colorectal cancer clinical trials, verifying that single-item assessments could provide comparable prognostic information relative to multi-item assessments. While detail is lost with the single-item assessments, improved ability to detect a clinically meaningful effect between treatment groups and within patients over time was demonstrated. These single-item assessments have become the most-used assessment in all NCI-sponsored cancer control studies.¹³⁴

The NCCTG addressed the question of the value that QOL assessments add over and above existing toxicity endpoints by exploring research studies embedded in treatment trials. For example, NCCTG studies have demonstrated that peripheral neuropathy can be detected two to three months earlier using simple single-item assessments rather than CTC assessments.¹³⁵ Clinician-assessed toxicity and patient-reported QOL outcomes provide different information regarding the well-being of the patient. Physicians tend to underestimate

oncology patient QOL and, using the CTC criteria, tend to under-report toxicity incidence and severity.

The PC led an effort to facilitate the dissemination and operationalization of the recent Food and Drug Administration (FDA) guidance for PROs in clinical trials. The three-day interactive process involved international experts and over 200 participants, delineated challenges, and recommended solutions addressing the logistical issues related to the design, analysis, and interpretation of PRO-related science. A compendium of this material will be published in *Value in Health* in the fall of 2007.

Incorporating targeted research hypotheses into NCCTG clinical trials has led to the discovery that: women experience toxicity related to 5-FU-based chemotherapy in greater frequency and with greater severity than men³³; phase II trials can be used as a testing platform to decide which QOL endpoints to include in subsequent phase III trials¹³⁶; plasma insulin-like growth factor proteins and C-peptide are related to metastatic colorectal cancer patient's QOL¹³⁷; and that after three months of 5-FU-based chemotherapy regimens (FOLFOX, FOLFIRI), patient QOL is comparable.²⁹ In summary, the PC has contributed a broad spectrum of advances in the state of the science of assessing PROQOL endpoints and identified numerous ways in which patient care involving both routine and novel treatments can be improved.

Biostatistics (D.J. Sargent)

The NCCTG Statistics and Data Center (SDC) is responsible for all statistical, data management, and information technology needs of the NCCTG. In the last 5–10 years, the NCCTG has completed the design and implementation of the NCCTG remote data capture systems including remote, web-based patient registration and data collection. A sophisticated electronic editing system has been implemented to assure the timeliness and quality control of patient data collected on NCCTG clinical trials. The SDC has completed a comprehensive set of NCCTG Standard Operating Procedures (SOPs). The SDC has successfully recruited and developed expertise within the NCCTG SDC in the rapidly developing fields of genomics and proteomics, including gene-chip microarray and proteomics data.

In addition to these 'traditional' roles of a cooperative group statistical center, the SDC, working in collaboration with the scientific committees of the Group, have contributed substantially to our understanding of clinical trials processes and study endpoints. The SDC has conducted research into 'clinical trials methodology' – making use of the NCCTG data and expertise to explore real-world issues in clinical trials to improve efficiency, reduce data collection, improve patient safety, and define novel endpoints for the conduct of NCCTG and other clinical trials. Here we report on selected highlights of 'clinical trials methodologic' research that has impacted NCCTG and other cancer clinical trials.

Toxicity monitoring

Implementation of the NCCTG real-time toxicity monitoring program. In this system, all AdEERs reported adverse events, as well as serious adverse events not reportable via

AdEERs (these events are submitted electronically to the NCCTG SDC via a simple one page form), are entered into the NCCTG database on a daily basis. Nightly, this information is used to generate an automatic email to the study chair, study statistician, and study QCS, providing detail on any new events as well as a summary of events to date on that trial, and providing the study team with a real-time assessment of the rate of severe adverse events on every trial. Details of this mechanism have been published twice.^{138, 139}

The NCCTG conducted a detailed analysis of adverse event data submitted on its clinical trials from 1999–2001, and determined that a great deal of time and expense were being used to collect data that was of limited value. As the result of this analysis, the NCCTG SDC proposed and the NCCTG adopted a new policy for adverse event reporting, where for standard trials all grade 1 events and unrelated or unlikely related grade 2 events need not be reported. A manuscript reporting these findings was recently published in the *Journal of Clinical Oncology*.¹⁴⁰

Assessing tumor response

The implementation of the RECIST guidelines for assessing tumor response elicited a strong response from the NCCTG membership, particularly the requirement that all lesions up to a maximum of 10 be measured and recorded at every evaluation. The NCCTG SDC undertook a detailed assessment of tumor measurement data from NCCTG clinical trials, and based on a variety of analyses, concluded that measuring 2 lesions as opposed to 10 would not substantially impact trial results.¹⁴¹ A manuscript reporting these results is being prepared and the findings have been communicated to the international RECIST committee for consideration in the revised RECIST guidelines which are under development.

Endpoints in clinical trials

The NCCTG SDC has also led several large pooled analyses exploring endpoints in cancer clinical trials. As a first example, in a large pooled analysis in adjuvant colon cancer, the NCCTG SDC assembled a dataset of individual patient data from 18 clinical trials including 20,898 patients.^{142,143} This dataset was again assembled to address a specific hypothesis that disease free survival, assessed after a median of 3 years of follow-up, could replace overall survival after 5 years of follow-up as a primary endpoint for colon adjuvant clinical trials. Based on multiple analysis techniques, ranging from simple (plots of survival estimates) to very complex (bivariate copula survival models), every analysis was consistent in supporting 3 year disease free survival as a valid surrogate. These data were published,¹⁴³ and presented to the Oncologic Drugs Advisory Committee of the FDA, which, based on this data, voted unanimously to accept disease free survival as an endpoint to permit full regulatory approval in adjuvant colon cancer.

Similarly, in Neuro-oncology, commonly used endpoints for Phase II glioblastoma multiforme (GBM) trials are the percentage of patients who are progression free at six months (PFS6) and the percentage of patients who are alive at 12 months (OS12). In an effort to identify the best endpoints for these trials, the NCCTG SDC Neuro-oncology statisticians, analyzed the relationship in past NCCTG trials between these endpoints separately for newly diagnosed GBM trials and recurrent GBM trials. The correlation of

these endpoints was moderate on a per study basis, but the agreement of study conclusions based on these endpoints was quite good (88%–90% based on simulations), particularly for recurrent disease trials. Based on these findings, the NCCTG Neuro-oncology Committee will use PFS6 for future recurrent trials but continue to use OS12 for future newly diagnosed GBM trials.⁶⁰

Statistical methodological research

Finally, NCCTG SDC members have multiple active lines of statistical methodological research. Historically¹⁴⁴ the NCCTG SDC group has had considerable strength in methods research, including landmark papers in clinical trials monitoring¹⁴⁵, stratification factors¹⁴⁶, and residuals for survival analysis^{144,147}, and design of phase II/III clinical trials.^{130,148} The current NCCTG statistical group has upheld and expanded this strong tradition. NCCTG SDC members currently have active, ongoing, research in the areas of quality of life assessment, clinical trials design, genomics, surrogate endpoints, and clinical trials methodology. The NCCTG SDC is committed to continuing our strong tradition of collaboration, clinical trials research, and statistical methodologic research to meet the challenges of the ongoing rapid evolution of cancer research.

Conclusion

In summary, NCCTG investigators have contributed key observations that have changed the practice of oncology, especially in the adjuvant treatment and surgical approach to colon and rectal cancer, adjuvant therapy of breast cancer, treatment of metastatic colon and breast cancer, and treatment of low-grade gliomas. The observations that elderly patients with lung cancer experience clinical benefit at the risk of higher toxicity will direct the future goals to reduce toxicity while maintaining efficacy in this common malignancy. Results of cancer control studies have demonstrated the benefits of interventions that reduce the mortality from both disease- and treatment-related complications, especially hot flashes, anorexia/cachexia, and mucositis. Translational observations have influenced the design and conduct of ongoing clinical trials including the concerns of quality control in her-2 testing, the importance of inheritance in response to tamoxifen, the importance of microsatellite instability in colon cancer, and the prognostic role of t(1p;19q) in low grade gliomas. Methodologic analyses have demonstrated the validity of disease-free survival in colon cancer and progression-free survival in glioblastoma multiforme, and the clinical significance of quality of life measures in clinical oncology. As we move forward, NCCTG is well positioned to identify promising therapeutic interventions through its extensive phase II trial portfolio, and to verify the clinical benefits of these interventions in definitive phase III trials. Coupled with its robust tissue collection and translational capabilities and integration of quality of life assessments into treatment assessments, the group will be able to accomplish its mission to improve the duration and quality of life of cancer patients and enhance our understanding of the biological consequences of cancer and its treatment.

References

1. Ingle JN, Everson LK, Wieand HS, et al. Randomized trial of observation versus adjuvant therapy with cyclophosphamide, fluorouracil, prednisone with or without tamoxifen following mastectomy

in postmenopausal women with node-positive breast cancer. *J Clin Oncol* 1988;6(9):1388–1396 [PubMed: 3047333]

2. Witzig TE, Gonchoroff NJ, Therneau T, et al. DNA content flow cytometry as a prognostic factor for node-positive breast cancer. The role of multiparameter ploidy analysis and specimen sonication. *Cancer* 1991;68(8):1781–1788 [PubMed: 1913523]
3. Witzig TE, Ingle JN, Cha SS, et al. DNA ploidy and the percentage of cells in S-phase as prognostic factors for women with lymph node negative breast cancer. *Cancer* 1994;74(6):1752–1761 [PubMed: 8082078]
4. Witzig TE, Ingle JN, Schaid DJ, et al. DNA ploidy and percent S-phase as prognostic factors in node-positive breast cancer: results from patients enrolled in two prospective randomized trials. *J Clin Oncol* 1993;11(2):351–359 [PubMed: 8426213]
5. Cunningham JM, Ingle JN, Jung SH, et al. p53 gene expression in node-positive breast cancer: relationship to DNA ploidy and prognosis. *Journal of the National Cancer Institute* 1994;86(24):1871–1873 [PubMed: 7990162]
6. Hartmann LC, Ingle JN, Wold LE, et al. Prognostic value of c-erbB2 overexpression in axillary lymph node positive breast cancer. Results from a randomized adjuvant treatment protocol. *Cancer* 1994;74(11):2956–2963 [PubMed: 7954259]
7. Perez EA, Romond EH, Suman VJ, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer. *ASCO Meeting Abstracts* 2007;25(18_suppl):512–
8. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *The New England journal of medicine* 2005;353(16):1673–1684 [PubMed: 16236738]
9. Perez EA, Suman VJ, Davidson NE, et al. Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial. *J Clin Oncol* 2004;22(18):3700–3704 [PubMed: 15365066]
10. Halyard MY, Pisansky TM, Solin LJ, et al. Adjuvant radiotherapy (RT) and trastuzumab in stage I–IIA breast cancer: Toxicity data from North Central Cancer Treatment Group Phase III trial N9831. *ASCO Meeting Abstracts* 2006;24(18_suppl):523–
11. Perez EA, Suman VJ, Davidson NE, et al. HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 intergroup adjuvant trial. *J Clin Oncol* 2006;24(19):3032–3038 [PubMed: 16809727]
12. Grant C, Hartmann L, Suman V, et al. Menstrual cycle and surgical treatment of breast cancer: Findings from the NCCTG N9431 study. *Breast cancer research and treatment* 2004;88 (Suppl 1):S213
13. Goetz M, Perez E, Suman V, et al. Association between polymorphisms in the DNA repair genes XPD and XRCC1 and clinical outcome in women treated prospectively with docetaxel and carboplatin as first-line therapy for metastatic breast cancer. *Proc Am Soc Clin Oncol* 2003;22:127, abstr. 510
14. Goetz MP, Rae JM, Suman VJ, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol* 2005;23(36):9312–9318 [PubMed: 16361630]
15. Goetz MP, Knox SK, Suman VJ, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast cancer research and treatment* 2007;101(1):113–121 [PubMed: 17115111]
16. Goetz M, Suman VJ, Ingle JN, et al. A two-gene expression ratio of HOXB13 and IL-17BR for predication of recurrence and survival in women receiving adjuvant tamoxifen Breast cancer research and treatment 2005;100 (Suppl 1):S53, abstr. 312
17. Ingle JN, Green SJ, Ahmann DL, et al. Randomized trial of tamoxifen alone or combined with aminoglutethimide and hydrocortisone in women with metastatic breast cancer. *J Clin Oncol* 1986;4(6):958–964 [PubMed: 3519885]

18. Ingle JN, Krook JE, Green SJ, et al. Randomized trial of bilateral oophorectomy versus tamoxifen in premenopausal women with metastatic breast cancer. *J Clin Oncol* 1986;4(2):178–185 [PubMed: 3511184]
19. Buckner JC, Ingle JN, Everson LK, et al. Results of salvage hormonal therapy and salvage chemotherapy in women failing adjuvant chemotherapy after mastectomy for breast cancer. *Breast cancer research and treatment* 1989;13(2):135–142 [PubMed: 2659104]
20. Ingle JN, Foley JF, Mailliard JA, et al. Randomized trial of cyclophosphamide, methotrexate, and 5-fluorouracil with or without estrogenic recruitment in women with metastatic breast cancer. *Cancer* 1994;73(9):2337–2343 [PubMed: 8168039]
21. Perez EA, Hillman DW, Stella PJ, et al. A phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma. *Cancer* 2000;88(1):124–131 [PubMed: 10618614]
22. Perez EA, Suman VJ, Rowland KM, et al. Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252. *Clinical breast cancer* 2005;6(5):425–432 [PubMed: 16381626]
23. Perez EA, Hillman DW, Mailliard JA, et al. Randomized phase II study of two irinotecan schedules for patients with metastatic breast cancer refractory to an anthracycline, a taxane, or both. *J Clin Oncol* 2004;22(14):2849–2855 [PubMed: 15254052]
24. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *The New England journal of medicine* 1990;322(6):352–358 [PubMed: 2300087]
25. Haller DG, Catalano PJ, Macdonald JS, et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. *J Clin Oncol* 2005;23(34):8671–8678 [PubMed: 16314627]
26. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *The New England journal of medicine* 1994;331(8):502–507 [PubMed: 8041415]
27. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *The New England journal of medicine* 2003;349(3):247–257 [PubMed: 12867608]
28. Pitot HC, Wender DB, O'Connell MJ, et al. Phase II trial of irinotecan in patients with metastatic colorectal carcinoma. *J Clin Oncol* 1997;15(8):2910–2919 [PubMed: 9256135]
29. Goldberg RM, Sargent D, Morton RF, et al. N9741: FOLFOX (oxaliplatin(Oxal)/ 5-fluorouracil (5-FU)/ leucovorin (LV) or reduced dose R-IFL (CPT-11 + 5-FU/LV) in advanced colorectal cancer (CRC): Final efficacy data from an intergroup study. *Proc Am Soc Clin Oncol* 2004;23:275, abstr. 3621
30. Goldberg RM, McLeod HL, Sargent DJ, et al. Genetic polymorphisms, toxicity, and response rate in African Americans (AA) with metastatic colorectal cancer (MCRC) compared to Caucasians (C) when treated with IFL, FOLFOX or IROX in Intergroup N9741. *ASCO Meeting Abstracts* 2006;24(18_suppl):3503–
31. McLeod HL, Parodi L, Sargent DJ, et al. UGT1A1*28, toxicity and outcome in advanced colorectal cancer: Results from Trial N9741. *ASCO Meeting Abstracts* 2006;24(18_suppl):3520–
32. Grothey A, McLeod HL, Green EM, et al. Glutathione S-transferase P1 I105V (GSTP1 I105V) polymorphism is associated with early onset of oxaliplatin-induced neurotoxicity. *ASCO Meeting Abstracts* 2005;23(16_suppl):3509–
33. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004;22(7):1209–1214
34. Goldberg RM, Tabah-Fisch I, Bleiberg H, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol* 2006;24(25):4085–4091 [PubMed: 16943526]

35. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005;23(36):9243–9249 [PubMed: 16230673]
36. Alberts SR, Mahoney MR, Donohue J, et al. Systemic capecitabine and oxaliplatin administered with hepatic arterial infusion (HAI) of floxuridine (FUDR) following complete resection of colorectal metastases (M-CRC) confined to the liver: A North Central Cancer Treatment Group (NCCTG) phase II intergroup trial. *ASCO Meeting Abstracts* 2006;24(18_suppl):3525–
37. The Clinical Outcomes of Surgical Therapy Study Group (COST). A comparison of laparoscopically assisted and open colectomy for colon cancer. *The New England journal of medicine* 2004;350(20):2050–2059 [PubMed: 15141043]
38. Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. *Jama* 2002;287(3):321–328 [PubMed: 11790211]
39. Cullinan S, Moertel CG, Wieand HS, et al. A phase III trial on the therapy of advanced pancreatic carcinoma. Evaluations of the Mallinson regimen and combined 5-fluorouracil, doxorubicin, and cisplatin. *Cancer* 1990;65(10):2207–2212 [PubMed: 2189551]
40. Kim GP, Oberg AL, Foster NR, et al. Phase II trial of bevacizumab, gemcitabine, oxaliplatin in patients with metastatic pancreatic adenocarcinoma. *ASCO Meeting Abstracts* 2007;25(18_suppl):4553–
41. Cullinan SA, Moertel CG, Wieand HS, et al. Controlled evaluation of three drug combination regimens versus fluorouracil alone for the therapy of advanced gastric cancer. North Central Cancer Treatment Group. *J Clin Oncol* 1994;12(2):412–416 [PubMed: 8113849]
42. Mandrekar SJ, Northfelt DW, Schild SE, et al. Impact of pretreatment factors on adverse events: a pooled analysis of North Central Cancer Treatment Group advanced stage non-small cell lung cancer trials. *J Thorac Oncol* 2006;1(6):556–563 [PubMed: 17409917]
43. Mandrekar SJ, Schild SE, Hillman SL, et al. A prognostic model for advanced stage nonsmall cell lung cancer. Pooled analysis of North Central Cancer Treatment Group trials. *Cancer* 2006;107(4):781–792 [PubMed: 16847887]
44. Schild SE, Stella PJ, Geyer SM, et al. Phase III trial comparing chemotherapy plus once-daily or twice-daily radiotherapy in Stage III non-small-cell lung cancer. *International journal of radiation oncology, biology, physics* 2002;54(2):370–378
45. Schild SE, Stella PJ, Geyer SM, et al. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. *J Clin Oncol* 2003;21(17):3201–3206 [PubMed: 12874270]
46. Schild SE, Mandrekar SJ, Jatoi A, et al. The value of combined-modality therapy in elderly patients with stage III nonsmall cell lung cancer. *Cancer* 2007;110(2):363–368 [PubMed: 17542000]
47. Jatoi A, Hillman S, Stella P, et al. Should elderly non-small-cell lung cancer patients be offered elderly-specific trials? Results of a pooled analysis from the North Central Cancer Treatment Group. *J Clin Oncol* 2005;23(36):9113–9119 [PubMed: 16361618]
48. Schild SE, Bonner JA, Shanahan TG, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. *International journal of radiation oncology, biology, physics* 2004;59(4):943–951
49. Shaw E, Arusell R, Scheithauer B, et al. Prospective randomized trial of low-versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. *J Clin Oncol* 2002;20(9):2267–2276 [PubMed: 11980997]
50. Buckner JC, Gesme D, Jr., O'Fallon JR, et al. Phase II trial of procarbazine, lomustine, and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. *J Clin Oncol* 2003;21(2):251–255 [PubMed: 12525516]
51. Galanis E, Buckner JC, Maurer MJ, et al. Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group Study. *J Clin Oncol* 2005;23(23):5294–5304 [PubMed: 15998902]

52. Galanis E, Jaeckle KA, Maurer MJ, et al. N047B: NCCTG phase II trial of vorinostat (suberoylanilide hydroxamic acid) in recurrent glioblastoma multiforme (GBM). ASCO Meeting Abstracts 2007;25(18_suppl):2004–
53. Krishnan S, Brown PD, Ballman KV, et al. Phase I trial of erlotinib with radiation therapy in patients with glioblastoma multiforme: results of North Central Cancer Treatment Group protocol N0177. International journal of radiation oncology, biology, physics 2006;65(4):1192–1199
54. Brown PD, Maurer MJ, Rummans TA, et al. A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: the impact of the extent of resection on quality of life and survival. Neurosurgery 2005;57(3):495–504; discussion 495–504 [PubMed: 16145528]
55. Laack NN, Brown PD, Ivnik RJ, et al. Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study. International journal of radiation oncology, biology, physics 2005;63(4):1175–1183
56. Brown PD, Buckner JC, O’Fallon JR, et al. Importance of baseline mini-mental state examination as a prognostic factor for patients with low-grade glioma. International journal of radiation oncology, biology, physics 2004;59(1):117–125
57. Brown PD, Jensen AW, Felten SJ, et al. Detrimental effects of tumor progression on cognitive function of patients with high-grade glioma. J Clin Oncol 2006;24(34):5427–5433 [PubMed: 17135644]
58. Jenkins RB, Blair H, Ballman KV, et al. A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. Cancer research 2006;66(20):9852–9861 [PubMed: 17047046]
59. Jaeckle KA, Decker PA, Ballman KV, et al. Analysis of paired glioma tissues from initial diagnosis and recurrence in patients enrolled on NCCTG clinical trials: De-differentiation and association with survival. ASCO Meeting Abstracts 2006;24(18_suppl):1521–
60. Ballman KV, Buckner JC, Brown PD, et al. The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. Neuro-oncology 2007;9(1):29–38 [PubMed: 17108063]
61. Galanis E, Buckner JC, Maurer MJ, et al. Validation of neuroradiologic response assessment in gliomas: measurement by RECIST, two-dimensional, computer-assisted tumor area, and computer-assisted tumor volume methods. Neuro-oncology 2006;8(2):156–165 [PubMed: 16533757]
62. Loprinzi CL, Barton DL, Jatoi A, et al. Symptom control trials: a 20-year experience. J Support Oncol 2007;5(3):119–125, 128 [PubMed: 17410810]
63. Fidler P, Loprinzi CL, O’Fallon JR, et al. Prospective evaluation of a chamomile mouthwash for prevention of 5-FU-induced oral mucositis. Cancer 1996;77(3):522–525 [PubMed: 8630960]
64. Foote RL, Loprinzi CL, Frank AR, et al. Randomized trial of a chlorhexidine mouthwash for alleviation of radiation-induced mucositis. J Clin Oncol 1994;12(12):2630–2633 [PubMed: 7989938]
65. Kozelsky TF, Meyers GE, Sloan JA, et al. Phase III double-blind study of glutamine versus placebo for the prevention of acute diarrhea in patients receiving pelvic radiation therapy. J Clin Oncol 2003;21(9):1669–1674 [PubMed: 12721240]
66. Loprinzi CL, Cianflone SG, Dose AM, et al. A controlled evaluation of an allopurinol mouthwash as prophylaxis against 5-fluorouracil-induced stomatitis. Cancer 1990;65(8):1879–1882 [PubMed: 2180557]
67. Loprinzi CL, Ghosh C, Camoriano J, et al. Phase III controlled evaluation of sucralfate to alleviate stomatitis in patients receiving fluorouracil-based chemotherapy. J Clin Oncol 1997;15(3):1235–1238 [PubMed: 9060567]
68. Mahood DJ, Dose AM, Loprinzi CL, et al. Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. J Clin Oncol 1991;9(3):449–452 [PubMed: 1999715]
69. Martenson J, Hyland G, Moertel CG, et al. Olsalazine is contraindicated during pelvic radiation therapy: results of a double-blind, randomized clinical trial. Int J Rad Oncol Biol Phys 1996;35(2):299–303
70. Martenson JA, Bollinger JW, Sloan JA, et al. Sucralfate in the prevention of treatment-induced diarrhea in patients receiving pelvic radiation therapy: A North Central Cancer Treatment Group

phase III double-blind placebo-controlled trial. *J Clin Oncol* 2000;18(6):1239–1245 [PubMed: 10715293]

71. Martenson JA, Sloan J, Deming RL, et al. Phase III double-blind study of depot octreotide vs. placebo in the prevention of acute diarrhea during pelvic radiation therapy: results of North Central Cancer Treatment Group protocol N00CA. *Am Soc Clin Oncol* 2006(in press)
72. McGinnis WL, Loprinzi CL, Buskirk SJ, et al. Placebo-controlled trial of sucralfate for inhibiting radiation-induced esophagitis. *J Clin Oncol* 1999;4(2):328–332
73. Okuno SH, Foote RL, Loprinzi CL, et al. A randomized trial of a nonabsorbable antibiotic lozenge given to alleviate radiation-induced mucositis. *Cancer* 1997;79(11):2193–2199 [PubMed: 9179067]
74. Okuno SH, Foote RL, Olmscheid MA, et al. Evaluation of an oral capsaicin lozenge for preventing radiation-induced mucositis. *J Cancer Integrative Med* 2004;2(4):179–183
75. Okuno SH, Woodhouse CO, Loprinzi CL, et al. Phase III controlled evaluation of glutamine for decreasing stomatitis in patients receiving fluorouracil (5-FU)-based chemotherapy. *Am J Clin Oncol* 1999;22(3):258–261 [PubMed: 10362332]
76. Baydar M, Dikilitas M, Sevinc A, Aydogdu I. Prevention of oral mucositis due to 5-fluorouracil treatment with oral cryotherapy. *J Natl Med Assoc* 2005;97(8):1161–1164 [PubMed: 16173332]
77. Karagozoglu S, Filiz Ulusoy M. Chemotherapy: the effect of oral cryotherapy on the development of mucositis. *J Clin Nurs* 2005;14(6):754–765 [PubMed: 15946284]
78. Nikolett S, Hyde S, Shaw T, Myers H, Kristjanson LJ. Comparison of plain ice and flavoured ice for preventing oral mucositis associated with the use of 5 fluorouracil. *J Clin Nurs* 2005;14(6):750–753 [PubMed: 15946283]
79. Papadeas E, Naxakis S, Riga M, Kalofonos C. Prevention of 5-fluorouracil-related stomatitis by oral cryotherapy: a randomized controlled study. *Eur J Oncol Nurs* 2007;11(1):60–65 [PubMed: 16829196]
80. Dreicer R, Propert KJ, Kuzel T, et al. A phase II trial of edatrexate in patients with advanced renal cell carcinoma. An Eastern Cooperative Oncology Group study. *Am J Clin Oncol* 1997;20(3):251–253 [PubMed: 9167747]
81. Edelman MJ, Gandara DR, Perez EA, et al. Phase I trial of edatrexate plus carboplatin in advanced solid tumors: amelioration of dose-limiting mucositis by ice chip cryotherapy. *Invest New Drugs* 1998;16(1):69–75 [PubMed: 9740546]
82. Gandara DR, Edelman MJ, Crowley JJ, Lau DH, Livingston RB. Phase II trial of edatrexate plus carboplatin in metastatic non-small-cell lung cancer: a Southwest Oncology Group study. *Cancer Chemother Pharmacol* 1997;41(1):75–78 [PubMed: 9443617]
83. Rubenstein EB, Peterson DE, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. *Cancer* 2004;100(9 Suppl):2026–2046 [PubMed: 15108223]
84. Aisa Y, Mori T, Kudo M, et al. Oral cryotherapy for the prevention of high-dose melphalan-induced stomatitis in allogeneic hematopoietic stem cell transplant recipients. *Support Care Cancer* 2005;13(4):266–269 [PubMed: 15668755]
85. Dumontet C, Sonnet A, Bastion Y, et al. Prevention of high dose L-PAM-induced mucositis by cryotherapy. *Bone Marrow Transplant* 1994;14(3):492–494
86. Inagaki N, Ohue Y, Shigeta H, Tasaka T. Cryotherapy is useful and safe in the prevention of oral mucositis after high-dose melphalan (L-PAM). *Rinsho Ketsueki* 2006;47(11):1469–1471 [PubMed: 17176891]
87. Lilleby K, Garcia P, Gooley T, et al. A prospective, randomized study of cryotherapy during administration of high-dose melphalan to decrease the severity and duration of oral mucositis in patients with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 2006;37(11):1031–1035 [PubMed: 16633359]
88. Meloni G, Capria S, Proia A, Trisolini SM, Mandelli F. Ice pops to prevent melphalan-induced stomatitis. *Lancet* 1996;347(9016):1691–1692 [PubMed: 8642978]
89. Mori T, Yamazaki R, Aisa Y, et al. Brief oral cryotherapy for the prevention of high-dose melphalan-induced stomatitis in allogeneic hematopoietic stem cell transplant recipients. *Support Care Cancer* 2006;14(4):392–395 [PubMed: 16633843]

90. Goldberg RM, Loprinzi CL, Mailliard JA, et al. Pentoxifylline for treatment of cancer anorexia and cachexia? A randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 1995;13(11):2856–2859 [PubMed: 7595749]
91. Jatoi A, Kumar S, Sloan JA, Nguyen PL. On appetite and its loss. *J Clin Oncol* 2000;18(15):2930–2932 [PubMed: 10920143]
92. Jatoi A, Rowland K, Loprinzi CL, et al. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. *J Clin Oncol* 2004;22(12):2469–2476 [PubMed: 15197210]
93. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002;20(2):567–573 [PubMed: 11786587]
94. Kardinal CG, Loprinzi CL, Schaid DJ, et al. A controlled trial of cyproheptadine in cancer patients with anorexia and/or cachexia. *Cancer* 1990;65(12):2657–2662 [PubMed: 2187585]
95. Loprinzi CL, Ellison NM, Schaid DJ, et al. Controlled trial of megestrol acetate for the treatment of cancer anorexia and cachexia. *Journal of the National Cancer Institute* 1990;82(13):1127–1132 [PubMed: 2193166]
96. Loprinzi CL, Goldberg RM, Su JQ, et al. Placebo-controlled trial of hydrazine sulfate in patients with newly diagnosed non-small-cell lung cancer. *J Clin Oncol* 1994;12(6):1126–1129 [PubMed: 8201374]
97. Loprinzi CL, Kugler JW, Sloan JA, et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. *J Clin Oncol* 1999;17(10):3299–3306 [PubMed: 10506633]
98. Loprinzi CL, Kross SA, O'Fallon JR, et al. Randomized placebo-controlled evaluation of hydrazine sulfate in patients with advanced colorectal cancer. *J Clin Oncol* 1994;12(6):1121–1125 [PubMed: 8201373]
99. Loprinzi CL, Michalak JC, Schaid DJ, et al. Phase III evaluation of four doses of megestrol acetate as therapy for patients with cancer anorexia and/or cachexia. *J Clin Oncol* 1993;11(4):762–767 [PubMed: 8478668]
100. Rowland KM, Jr., Loprinzi CL, Shaw EG, et al. Randomized double-blind placebo-controlled trial of cisplatin and etoposide plus megestrol acetate/placebo in extensive-stage small-cell lung cancer: a North Central Cancer Treatment Group study. *J Clin Oncol* 1996;14(1):135–141 [PubMed: 8558188]
101. Barton DL, Loprinzi CL, Quella SK, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol* 1998;16(2):495–500 [PubMed: 9469333]
102. Loprinzi CL, Khoiratty BS, Dueck AC, et al. Gabapentin for hot flashes in men: NCCTG trial N00CB. *J Clin Oncol* 2007;25(18S):494S (Abstract 9005)
103. Loprinzi CL, Kugler JW, Barton DL, et al. Phase III trial of gabapentin alone or in conjunction with an antidepressant in the management of hot flashes in women who have inadequate control with an antidepressant alone: NCCTG N03C5. *J Clin Oncol* 2007;25(3):308–312 [PubMed: 17146104]
104. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000;356(9247):2059–2063 [PubMed: 11145492]
105. Loprinzi CL, Levitt R, Barton D, et al. Phase III comparison of depomedroxyprogesterone acetate to venlafaxine for managing hot flashes: North Central Cancer Treatment Group Trial N99C7. *J Clin Oncol* 2006;24(9):1409–1414 [PubMed: 16505409]
106. Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. *The New England journal of medicine* 1994;331(6):347–352 [PubMed: 8028614]
107. Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol* 2002;20(6):1578–1583 [PubMed: 11896107]
108. Pockaj BA, Gallagher J, Loprinzi CL, et al. A phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG trial N01CC. *J Clin Oncol* 2007(in pres)

109. Quella SK, Loprinzi CL, Barton DL, et al. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial. *J Clin Oncol* 2000;18(5):1068–1074 [PubMed: 10694559]
110. Sloan JA, Loprinzi CL, Novotny PJ, et al. Methodologic lessons learned from hot flash studies. *J Clin Oncol* 2001;19(23):4280–4290 [PubMed: 11731510]
111. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol* 1994;12(1):155–158 [PubMed: 8270972]
112. Loprinzi CL, Goldberg RM, O'Fallon JR, et al. Transdermal clonidine for ameliorating post-orchietomy hot flashes. *J Urol* 1994;151(3):634–636 [PubMed: 8308973]
113. Halyard MY, Frost MH, Dueck A. Integrating QOL assessments for clinical and research purposes. *Current problems in cancer* 2006;30(6):319–330 [PubMed: 17123883]
114. Lee JJ, Lieberman R, Sloan JA, Piantadosi S, Lippman SM. Design considerations for efficient prostate cancer chemoprevention trials. *Urology* 2001;57(4 Suppl 1):205–212 [PubMed: 11295629]
115. Sloan JA, Loprinzi CL, Laurine JA, et al. A simple stratification factor prognostic for survival in advanced cancer: the good/bad/uncertain index. *J Clin Oncol* 2001;19(15):3539–3546 [PubMed: 11481361]
116. Sloan JA, Varricchio C. Quality of Life endpoints in prostate chemoprevention trials. *Urology* 2001;57(4 Suppl 1):235–240 [PubMed: 11295635]
117. Hampton T Patients' genes may influence quality of life after cancer chemotherapy. *Jama* 2004;292(6):673–674 [PubMed: 15304448]
118. Sloan JA, Zhao CX. Genetics and quality of life. *Current problems in cancer* 2006;30(6):255–260 [PubMed: 17123877]
119. Sloan JA, Dueck A. Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. *Journal of biopharmaceutical statistics* 2004;14(1):73–96 [PubMed: 15027501]
120. Huschka MM, Mandrekar SJ, Schaefer PL, Jett JR, Sloan JA. A pooled analysis of quality of life measures and adverse events data in north central cancer treatment group lung cancer clinical trials. *Cancer* 2007;109(4):787–795 [PubMed: 17211864]
121. Mandrekar S, Dueck A. Future directions in QOL research. *Current problems in cancer* 2005;29(6):343–351 [PubMed: 16311136]
122. Cella D, Bullinger M, Scott C, Barofsky I. Group vs individual approaches to understanding the clinical significance of differences or changes in quality of life. *Mayo Clinic proceedings* 2002;77(4):384–392 [PubMed: 11936936]
123. Frost MH, Bonomi AE, Ferrans CE, Wong GY, Hays RD. Patient, clinician, and population perspectives on determining the clinical significance of quality-of-life scores. *Mayo Clinic proceedings* 2002;77(5):488–494 [PubMed: 12004999]
124. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clinic proceedings* 2002;77(4):371–383 [PubMed: 11936935]
125. Sloan JA, Aaronson N, Cappelleri JC, Fairclough DL, Varricchio C. Assessing the clinical significance of single items relative to summated scores. *Mayo Clinic proceedings* 2002;77(5):479–487 [PubMed: 12004998]
126. Sloan JA, Cella D, Frost M, et al. Assessing clinical significance in measuring oncology patient quality of life: introduction to the symposium, content overview, and definition of terms. *Mayo Clinic proceedings* 2002;77(4):367–370 [PubMed: 11936934]
127. Symonds T, Berzon R, Marquis P, Rummans TA. The clinical significance of quality-of-life results: practical considerations for specific audiences. *Mayo Clinic proceedings* 2002;77(6):572–583 [PubMed: 12059128]
128. Wyrwich KW, Bullinger M, Aaronson N, et al. Estimating clinically significant differences in quality of life outcomes. *Qual Life Res* 2005;14(2):285–295 [PubMed: 15892420]
129. Sloan JA, Frost MH, Berzon R, et al. The clinical significance of quality of life assessments in oncology: a summary for clinicians. *Support Care Cancer* 2006;14(10):988–998 [PubMed: 16794811]

130. Sloan JA. Assessing the minimally clinically significant difference: scientific considerations, challenges and solutions. *Copd* 2005;2(1):57–62 [PubMed: 17136963]
131. Sloan JA, Cella D, Hays RD. Clinical significance of patient-reported questionnaire data: another step toward consensus. *Journal of clinical epidemiology* 2005;58(12):1217–1219 [PubMed: 16291464]
132. Sloan JA, Loprinzi CL, Kuross SA, et al. Randomized comparison of four tools measuring overall quality of life in patients with advanced cancer. *J Clin Oncol* 1998;16(11):3662–3673 [PubMed: 9817289]
133. Varricchio CG, Sloan JA. The need for and characteristics of randomized, phase III trials to evaluate symptom management in patients with cancer. *Journal of the National Cancer Institute* 2002;94(16):1184–1185 [PubMed: 12189214]
134. Buchanan DR, White JD, O'Mara AM, et al. Research-design issues in cancer-symptom-management trials using complementary and alternative medicine: lessons from the National Cancer Institute Community Clinical Oncology Program experience. *J Clin Oncol* 2005;23(27):6682–6689 [PubMed: 16170176]
135. Morton RF, Sloan JA, Grothey A, et al. A comparison of simple single-item measures and the common toxicity criteria in detecting the onset of oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer. *ASCO Meeting Abstracts* 2005;23(16_suppl):8087–
136. Hobday TJ, Kugler JW, Mahoney MR, et al. Efficacy and quality-of-life data are related in a phase II trial of oral chemotherapy in previously untreated patients with metastatic colorectal carcinoma. *J Clin Oncol* 2002;20(23):4574–4580 [PubMed: 12454115]
137. Meyerhardt JA, Sloan JA, Sargent DJ, et al. Associations between plasma insulin-like growth factor proteins and C-peptide and quality of life in patients with metastatic colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14(6):1402–1410 [PubMed: 15941948]
138. Sargent DJ, Goldberg RM, Mahoney MR, et al. Rapid reporting and review of an increased incidence of a known adverse event. *Journal of the National Cancer Institute* 2000;92(12):1011–1013 [PubMed: 10861314]
139. Gunderson LL, Sargent DJ, Tepper JE, et al. Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer: a pooled analysis. *International journal of radiation oncology, biology, physics* 2002;54(2):386–396
140. Furth AF, Sargent DJ. Duffy-Santner confidence intervals for the two-stage three-outcome design. *Journal of biopharmaceutical statistics* 2006;16(6):875–880 [PubMed: 17146985]
141. Hillman S, Sargent DJ, An M, et al. Evaluation of RECIST criteria in determining the response to treatment in solid tumors: A North Central Cancer Treatment Group (NCCTG) investigation. *Proc Am Soc Clin Oncol* 2003;22:(abstr. 2095)
142. Sargent DJ, Patiyl S, Yothers G, et al. End points for colon cancer adjuvant trials: observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT Group. *J Clin Oncol* 2007;25(29):4569–4574 [PubMed: 17876008]
143. 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 20,898 patients on 18 randomized trials. *J Clin Oncol* 2005;23(34):8664–8670 [PubMed: 16260700]
144. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994;81:515–526
145. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35(3):549–556 [PubMed: 497341]
146. Therneau TM. How many stratification factors are “too many” to use in a randomization plan? *Controlled clinical trials* 1993;14(2):98–108 [PubMed: 8500309]
147. Grambsch PM, Therneau TM, Fleming TR. Diagnostic plots to reveal functional form for covariates in multiplicative intensity models. *Biometrics* 1995;51(4):1469–1482 [PubMed: 8589234]
148. Sargent DJ, Goldberg RM. A flexible design for multiple armed screening trials. *Statistics in medicine* 2001;20(7):1051–1060 [PubMed: 11276035]

Figure 1:
NCCTG members as of 2007

Table 1:

Symptoms related to cancer and/or cancer therapy for which NCCTG clinical trials have been conducted

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- Mucosal toxicity
 - Anorexia/cachexia
 - Pain
 - Hot flashes
 - Skin toxicities
 - Sexual symptoms
 - Neuropathy
 - Lymphedema
 - Anemia
 - Cognitive dysfunction
 - Osteoporosis
 - Insomnia
 - Fatigue
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