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Comparative clinical benefits of systemic adjuvant therapy for paradigm solid tumors

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Abstract

Adjuvant therapy employing cytotoxic chemotherapy, molecularly targeted agents, immunologic, and hormonal agents has shown a significant impact upon a variety of solid tumors. The principles that guide adjuvant therapy differ among various tumor types and specific modalities, but generally indicate a greater impact of therapy in the postsurgical setting of micrometastatic disease, for which adjuvant therapy is commonly pursued, vs. the setting of gross unresectable disease. This review of adjuvant therapies in current use for five major solid tumors highlights the rationale for current effective adjuvant therapy, and draws comparisons between the adjuvant regimens that have found application in solid tumors.

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Introduction

The aim of systemic adjuvant therapy following tumor resection is to reduce the risk of disease recurrence and distant metastasis, thereby improving survival. Recurrence risks after resection generally increase with the extent of invasion of primary tumor and degree of regional lymph node involvement. In solid tumors, adjuvant therapy ranges from chemotherapy that has shown benefit in advanced disease to more specific application of hormonal, immune, and molecularly targeted therapies. Adjuvant use of these agents is based upon increased understanding of tumor biology and progression pathways, as well as an understanding of the processes that accompany progression (e.g., immunomodulation). In colon cancer, recent trials suggest that we cannot always extrapolate outcomes in advanced disease to the adjuvant setting, particularly with targeted therapies, and that new paradigms are needed to identify agents that should be considered for use in the adjuvant setting. This overview of the current status of adjuvant therapy for a number of paradigmatic solid tumors compares and contrasts the progress that has been made in the different disease areas. Non-small-cell lung cancer (NSCLC), colorectal cancer, sarcoma, melanoma, and breast cancer were selected for this review as leading solid tumors that represent the major incident and rising tumors, as well as tumors for which the use of adjuvant therapy has been established in cooperative group studies. Information sources searched were online libraries (PubMed/Medline) and recognized national/international treatment guidelines.

Current status of adjuvant therapy in major solid tumors

The current adjuvant therapies applicable for the major solid tumors reviewed here are summarized in Table 1.

In non-small-cell lung cancer (NSCLC), adjuvant chemotherapy is currently considered following resection of stage II–III disease and in high-risk, margin-negative, stage IB disease (Table 1).[1] Cisplatin-based chemotherapy doublets are the mainstay of adjuvant therapy. Various doses and regimens are used but commonly 4 cycles of 21 or 28 days are given. There is no specific recommendation to treat based on histologic subtype. However, in the treatment of metastatic NSCLC, a subgroup analysis of squamous cell histology demonstrated inferior survival in the cisplatin and pemetrexed arm.[2] It is unclear if this can be extrapolated to the adjuvant setting.

Chemotherapy based on 5-fluorouracil (5FU) is the standard adjuvant therapy for resected stage III colorectal cancer; its relative contribution in stage II disease remains controversial. National Comprehensive Cancer Network (NCCN) guidelines[3] recommend 6 months of adjuvant chemotherapy with combinations of 5FU/leucovorin [LV]/oxaliplatin (FOLFOX; FLOX), capecitabine/oxaliplatin (XELOX; CapeOx), capecitabine alone, or 5FU/LV alone, in stage III disease and in high/intermediate-risk stage II patients, based on clinicopathologic

risk factors after discussion of the risks and benefits with the patient (Table 1). If oxaliplatin is not appropriate, 5FU/LV may be used. Observation, 5FU/LV, capecitabine, or a clinical trial is recommended for stage II disease without high-risk features.

Sarcomas are a biologically complex group of mesenchymal tumors. Chemotherapy using anthracyclines and alkylating agents is currently the standard adjuvant approach for osteosarcoma, Ewing's sarcoma, and soft tissue sarcomas (STS). Adjuvant chemotherapy is accepted for the treatment of localized, high-grade osteosarcoma and is recommended in low grade or periosteal sarcoma with high-grade pathology.[4] The currently recommended combination chemotherapy regimens are summarized in Table 1. In Ewing's sarcoma, the high rates of relapse after local therapy suggest that micrometastatic disease should be considered present at diagnosis.[5–7] Therefore, adjuvant therapy with cyclophosphamide, doxorubicin, vincristine, ifosfamide and etoposide combinations is recommended in all patients (Table 1).[4] In STS, adjuvant chemotherapy has resulted in small but consistent benefits. Adjuvant doxorubicin in combination with other chemotherapy agents is accepted (Table 1). NCCN guidelines suggest anthracycline-based adjuvant chemotherapy in high-risk patients with good performance status.[8] However, the use of adjuvant chemotherapy in STS remains controversial and is therefore subject to regional and individual practice patterns; patient selection is paramount. It should be restricted to patients with high-risk stage II and III disease at presentation, identified on the basis of clinicopathologic features, namely those with large (>5 cm), high-grade extremity tumors, excellent performance status, and no comorbidities that would increase their risk of cardiac and/or renal failure associated with doxorubicin and ifosfamide. For truncal or retroperitoneal sarcomas the evidence is less supportive, and treatment should be considered on a case-by-case basis.

There is substantial evidence that host immunity plays a key role in melanoma, and that induction of immune response is important for disease control both in the adjuvant and advanced disease settings.[9–14] As a result, immunotherapy has been widely examined and chemotherapy has played a smaller role. Adjuvant therapy is accepted following resection of melanoma at high risk of recurrence (stage IIB–III) (Table 1). Currently, only interferon-α2b (IFN-α2b) is approved worldwide for melanoma while inter-feron-α2a (IFN-α2a) is approved in Europe and pegylated IFN-α2b (PEG-IFN-α2b) was recently approved in the US. IFN-α dosing regimens vary but have had uniform, significant benefits upon relapse and smaller benefits upon survival.

Most patients with operable breast cancer are considered candidates for systemic adjuvant therapy. Compared with the other solid tumors discussed here, adjuvant therapy for breast cancer has been longer established and more broadly accepted, with recent progress in terms of personalized application of therapy according to individual characteristics of each patient's tumor. Options include cytotoxic, endocrine, and/or targeted anti-HER2 therapy. The criteria for treatment selection are summarized in Table 1.[15] The predictive factors that are useful for patient and physician decision-making are well defined: estrogen receptor (ER) and *HER2/neu* oncogene expression[16,17] are used to select candidates for endocrine or anti-HER2-directed therapy, respectively. Tamoxifen is the preferred endocrine therapy for ER and/or progesterone receptor-positive disease in pre- and perimenopausal women. For postmenopausal women, aromatase inhibitors (AIs) are recommended either as initial

endocrine therapy for 5 years, or sequentially following a 2–5 year course of tamoxifen. Adjuvant anti-HER2 therapy is indicated for any patient with *HER2/neu* overexpressing disease who has a sufficiently high risk of recurrence to justify the use of adjuvant chemotherapy (as described below). *HER2/neu* overexpression is commonly defined by criteria established by the American Society of Clinical Oncology/College of American Pathologists (ASCO-CAP) guidelines.[18]

Beyond the selection of hormonal and targeted therapeutic agents, the application of adjuvant chemotherapy is generally decided based upon the risk of recurrence, as in the majority of solid tumors.[17] Adjuvant chemotherapy is recommended for patients with stage I–III breast cancer, including those with axillary lymph nodes positive for tumor or for those with negative nodes and a primary tumor >1 cm. The choice of regimen is individualized based upon each patient's underlying estimated risk of recurrence, their comorbidities, and likely tolerance of toxicity. Anthracyclines, alkylating agents, and taxanes are commonly used components,[19] including sequential therapy (e.g., an anthracycline/cyclophosphamide doublet followed sequentially by a taxane) or concurrent therapy (e.g., docetaxel/doxorubicin/cyclophosphamide). In some circumstances, a non-anthracycline regimen may be considered (e.g., docetaxel/cyclophosphamide or cyclophosphamide/methotrexate/5FU).

Clinical trial data supporting adjuvant therapy

Non-small-cell lung cancer

The use of chemotherapy as adjuvant therapy in NSCLC is well supported by clinical trial data. The first meta-analysis of adjuvant chemotherapy was published in 1995 by the NSCLC Collaborative Group.[20] Subset analysis of eight trials demonstrated a 13% overall reduction in the risk of death and a trend towards improved survival at 5 years with cisplatin-based therapy; the absolute benefit of therapy was 5% (not statistically significant [NS]; $p = 0.08$). This work prompted an extensive evaluation of adjuvant cisplatin-based chemotherapy in NSCLC.

In the ALPI trial,[21] 1209 patients with completely resected stage I–IIIA NSCLC were randomized to surgery alone, or surgery then adjuvant mitomycin C, vindesine, and cisplatin. There was no statistically significant difference between the two groups in OS (hazard ratio [HR] = 0.96; 95% confidence interval [CI] 0.81–1.13; p = NS) but a trend towards improved disease-free survival (DFS) in the chemotherapy arm (HR = 0.89; 95% CI 0.76–1.03; p = NS) with an absolute benefit of 7.6 months (95% CI −1.5 to 16.6). The lack of statistical significance was attributed in part to poor compliance, as only 69% of patients received all three cycles of therapy. However, multiple trials following ALPI have reported statistically significant improvements in outcomes with adjuvant chemotherapy.[22–24] The IALT included 1867 patients with resected stage I–III NSCLC who were randomized to a cisplatin-based regimen or observation alone.[22] The trial was stopped early due to declining enrollment rates, attributed to emerging interest in neoadjuvant therapy. Despite early closure, 5-year OS was 40.4% with surgery alone and 44.5% with surgery and adjuvant therapy (HR = 0.86; 95% CI 0.76–0.98; $p < 0.03$); median OS was 44 and 50 months, respectively. An update of IALT based on median follow-up of 7.5 years

reported that the OS and DFS benefits were maintained up to 5 years, but suggested an increase in non-cancer-related deaths with chemotherapy compared with observation after this point.[25] The National Cancer Institute of Canada JBR.10 trial randomly assigned 482 patients with completely resected earlier stage IB or II (excluding T3N0) NSCLC to four cycles of cisplatin plus weekly vinorelbine or observation.[23] Five-year OS was 69% with chemotherapy vs. 54% with observation ($p = 0.03$). This translated to an absolute benefit of 15% in 5-year OS for cisplatin-based adjuvant therapy. Updated survival data from JBR.10 at 9 years' follow-up reported that the statistically significant survival benefits of 11% with adjuvant therapy vs. observation were maintained over time (5-year OS 67% vs. 56%, respectively; HR = 0.78; 95% CI 0.61–0.99; $p = 0.04$).[26] The ANITA trial compared adjuvant cisplatin and vinorelbine with observation in 799 patients with stage IB–IIIA NSCLC.[24] Median OS was 44 months with observation and 66 months with adjuvant therapy (HR = 1.26; 95% CI 1.05–1.52; $p = 0.013$). Five-year OS was 51% vs. 43% with chemotherapy and observation, respectively, and the benefit was sustained at 7 years.

Given the toxicity and poor tolerability of cisplatin, there has been interest in substituting it with carboplatin for adjuvant treatment. The Cancer and Leukemia Group B (CALGB) compared carboplatin and paclitaxel ($n = 173$) to observation alone ($n = 171$) in patients with stage IB NSCLC.[27] Preliminary analysis noted significantly improved OS at 4 years (71% with carboplatin vs. 59% observation) and the trial was closed early. However, at 74 months' follow-up the difference in OS was no longer statistically significant, although the HR remained the same (HR = 0.83; 95% CI 0.64–1.08; $p = 0.12$). Patients treated with carboplatin had a 5-year OS of 60% vs. 58% with observation ($p = 0.190$). Multiple factors, including small sample size ($n = 344$) and restriction to stage IB NSCLC could have contributed to these results. Prior trials have noted relatively small benefits for stage IB disease, so this study may have been underpowered. Based upon this trial, it is generally accepted that carboplatin cannot be used in lieu of cisplatin, although it is still to be considered with paclitaxel in patients at high risk for cisplatin toxicity. The role of taxanes requires further study.

The major toxicities associated with the cisplatin and vinorelbine combination in ANITA included grade 3 or 4 neutropenia (85%), febrile neutropenia (9%), nausea and vomiting (27%), constipation (5%), and neuropathy (3%). The incidence of chemotherapy-related death was 2%. In JBR.10 the major toxicities included grade 3 or 4 neutropenia (73%), febrile neutropenia (7%), fatigue (15%), vomiting (10%), and anorexia (10%). Assessment of a subset of patients from this trial demonstrated a slight decrease in the quality of life during and directly after adjuvant therapy. However the quality of life-adjusted survival was higher in the adjuvant therapy arm, despite toxicity.[28] The direct cost of adjuvant therapy, including supportive care, emergency room visits, surgery, and radiology, was assessed in a subset analysis of 172 patients from JBR.10. The average cost of adjuvant therapy was $31,319 vs. $23,878 in the observation arm, with a very favorable incremental cost effectiveness ratio of $7175 per life-year gained. However, this analysis only considered treatment in Canada, and health care costs and standard practices differ in other countries.[29]

Colon cancer

Relevant studies of adjuvant therapy in resected colon cancer are summarized in Table 2.[30–41] Adjuvant 5FU/LV for stage III disease was originally supported by an Intergroup study[42,43] and later by IMPACT,[30] a pooled analysis of three prospective studies including ~4000 patients with stage II–III colon cancer. This revealed a significant improvement in 3-year DFS. In addition, the X-ACT study[34] established the non-inferiority of 6 months of capecitabine compared with 5FU/LV, with trends towards improvement in 3-year DFS and OS in stage III patients. In MOSAIC[31,44] the addition of oxaliplatin to 5FU/LV (FOLFOX) provided significant DFS and OS advantages vs. 5FU/LV in stage II–III patients, particularly evident in stage III disease. NSABP C-07[45] enrolled a similar patient population, finding a 5% absolute DFS benefit at 5 years with the addition of oxaliplatin to 5FU/LV-based therapy, although 8-year OS data did not show a survival advantage with oxaliplatin.[32] The addition of oxaliplatin to capecitabine (XELOX) was successful in XELOXA,[35] a European phase III randomized study comparing XELOX to bolus regimens of 5FU/LV for resected stage III patients, finding superiority of XELOX in 3-year DFS.

The use of 5FU/LV in stage II disease is common in the oncology community but has not been validated in prospective randomized trials. The QUASAR[33] study revealed a small, statistically significant benefit of 5FU/LV over observation in stage II disease (absolute OS benefit 3.6%), but other studies,[46,47] and a systematic review,[48] as well as a further pooled analysis by IMPACT investigators[49] including 1600 stage II patients from five prospective trials did not find DFS or OS benefits. MOSAIC[44]revealed only a trend towards improved DFS with the addition of oxaliplatin to 5FU/LV in subset analyses of stage II (node negative) disease. An update of MOSAIC[31] revealed a trend toward 5-year DFS advantage with the addition of oxaliplatin in high-risk stage II disease (T4 lesions, poorly differentiated histology, venous invasion, perforation, obstruction, <10 lymph nodes examined) based on exploratory subset analyses, but no survival advantage. In NSABP C-07,[45] DFS favored the addition of oxaliplatin but this difference was not significant in node-negative patients using multivariate analysis. A recently published retrospective database review found no 5-year survival benefit with adjuvant chemotherapy in stage II patients with or without poor prognostic features.[50] Currently, there are no prospective, high quality studies specifically in high-risk stage II disease that demonstrate a DFS or OS advantage with adjuvant chemotherapy. Thus, routine use of oxaliplatin is not recommended in stage II patients and treatment with single agent 5FU/capecitabine needs to involve a detailed risk/benefit discussion.

Acute toxicity with FOLFOX includes myelosuppression, fatigue, nausea, diarrhea, mucositis, and hand-foot syndrome. The modest but statistically significant benefit of adding oxaliplatin in stage III disease should be considered in balance with the 40% risk of chronic neuropathy[51] and 10–50% risk of chronic hepatotoxicity with vascular sinusoidal injury[52] that may occur with this agent. In addition, NSABP C-07[32] and the ACCENT database[53] raised concerns that older patients may not derive a survival benefit from the addition of oxaliplatin to a 5FU based regimen, although contrary data exists.[35,54] Acute oxaliplatin neurotoxicity occurs in 65–98% of patients,[55] often beginning during infusion and peaking hours or days later.[56] It is characterized by symptoms including cold-induced

dysesthesias and paresthesias of the upper extremities and face, cold hypersensitivity, jaw tightness, pharyngolaryngeal dysesthesia (loss of sensation of breathing without any objective evidence of respiratory distress), muscle spasms, fasciculations, voice changes, and ocular pain.[57–63] Risk of chronic neuropathy, but not acute neurotoxicity, can be reduced by 50% with calcium and magnesium infusions given pre- and post-oxaliplatin.[51] In terms of adjuvant treatment costs in the US for stage III colon cancer, the lifetime expense of FOLFOX was higher than that of 5FU/LV ($56,320 versus $39,285). The ratio of cost per quality-adjusted life-year (QALY) gained was very acceptable at $22,804.[64]

Sarcoma

Osteosarcoma is the most common primary malignant bone cancer. Evidence for the therapeutic benefit of chemotherapy emerged in the 1970s, with improvements in RFS compared with amputation noted in non-controlled trials.[65–68] RCTs confirmed a significant reduction in recurrence risk and improved survival in patients with localized disease.[69,70] The T10 protocol (methotrexate, doxorubicin, cyclophosphamide, dactinomycin, and bleomycin) led to a 5-year DFS rate of 76% compared with historic survival rates of around 20% in patients having surgery alone.[71] A randomized trial conducted by the European Osteosarcoma Intergroup suggested that doxorubicin 75 mg/m^2 and cisplatin 100 mg/m^2 for six cycles had comparable DFS and OS benefits compared with the more complicated and protracted T10 chemotherapy regimen, with greater likelihood of being fully delivered.[72] Several subsequent studies examined the omission of doxorubicin and/or cisplatin, concluding that both agents are necessary.[73–75] The combination of ifosfamide and etoposide (IE) has emerged as an active, alternative regimen in advanced osteosarcoma.[76,77]

Ewing's sarcoma accounts for 10–15% of malignant bone sarcomas.[78] The first Intergroup Ewing's Sarcoma Study (IESS) showed a clear advantage for the addition of doxorubicin to cyclophosphamide, dactinomycin, and vincristine in patients with tumors localized in an extremity.[79] The second IESS showed a survival advantage for cyclophosphamide 1400 mg/m^2 administered every 3 weeks compared with cyclophosphamide 500 mg/m^2 given weekly.[80] The addition of IE to cyclophosphamide, doxorubicin, and vincristine significantly improved 5-year event-free survival (EFS) and OS for patients with localized disease.[7] This study confirmed previous findings that presence or absence of metastases and tumor size were important prognostic factors for EFS and OS. Specifically, a pelvic site had a 50% EFS compared with 68% and 61% among patients with tumors of the distal extremity and proximal extremity, respectively ($p = 0.003$). Age was also confirmed to be predictive of a worse outcome in older patients (patients ⩾18 years vs. <10 years, relative risk [RR] = 2.5; $p = 0.001$).[7] Ewing's tumors are sensitive to ionizing radiation, providing local control without surgery in up to 30% of patients, which is germane for pelvic tumors.[7,81]

STS comprise at least 50 different histologic subtypes with a heterogeneous clinical course largely determined by the tissue of origin and tumor grade. Several clinicopathologic factors predict poor outcome in STS, including tumor grade, size, and relationship to fascia; large, high-grade, deep tumors recur resulting in death in over 50% of patients despite local control.[82–85] Clinical evidence is limited but the findings suggest benefit with adjuvant doxorubicin and ifosfamide for patients with high-risk STS, particularly

involving an extremity. Early adjuvant trials were conducted with doxorubicin alone or combined with radiation therapy.[86,87] The addition of ifosfamide resulted in significantly higher response rates for advanced/metastatic sarcoma than doxorubicin alone.[88] Conflicting data are available from small, randomized trials accumulated over two decades.[89–92] These conflicting data, and the lack of feasibility of a large adjuvant trial to prove small but clinically significant benefits, led to the use of meta-analysis.[93,94] The Sarcoma Meta-Analysis Collaboration (SMAC) pooled individual patient data from 1568 patients enrolled on 14 trials. SMAC found benefit from doxorubicin-based adjuvant chemotherapy, with a 27% RR reduction for local relapse at 10 years (6% absolute benefit), and a 30% RR reduction for distant metastasis (10% absolute benefit), while there was an 11% RR reduction in death corresponding to an absolute survival benefit of 4% at 10 years, although the HR for OS did not reach significance (0.89 [95% CI 0.76–1.03]; $p = 0.12$).[95] Patients with high-grade extremity STS had a slightly higher absolute survival benefit of 7% at 10 years.[95] The most recent update included a total of 1953 patients from 18 trials, reflecting the results of modern ifosfamide-containing regimens, and confirmed small but statistically significant benefits from adjuvant chemotherapy on all measures of local and distant recurrence as well as OS.[96] Overall the data suggest only modest effects of adjuvant therapy on OS in STS and the risk/benefit ratio should therefore be considered on a case by case basis.

The survival benefit of chemotherapy is established in osteosarcoma and Ewing's sarcoma; however, the long-term sequelae of chemotherapy must be considered. Long term follow-up has revealed that survivors of childhood Ewing's sarcoma have increased mortality unrelated to recurrence, and are at substantially higher risk of infertility and other morbidity, including second malignancies, chronic health conditions, and functional impairment.[97,98] In STS, the addition of ifosfamide to doxorubicin-based chemotherapy imparted additional benefits but came at increased risk of toxicity;[96] doxorubicin and ifosfamide are associated with well-documented cardiac and renal toxicity.

Melanoma

Melanoma is highly curable by surgery when treated early, but may carry a lethal prognosis when inoperable.[99,100] The best opportunity for cure through systemic medical therapy lies in the postoperative adjuvant setting among patients at high risk for recurrence and death (Stage IIB–III). More than 20 trials of IFN-α worldwide have evaluated the optimal dose, schedule, and duration of therapy. There is overall agreement and consistent evidence for a significant improvement of RFS with IFN-α at high and intermediate doses in multiple clinical trials and meta-analyses; the OS effects have been less clear cut.[101–107] Meta-analysis of 12 randomized adjuvant trials was therefore pursued and confirmed highly significant reduction in recurrence with IFN-α over observation and a trend towards improved benefit with increasing dosage.[107] A larger individual patient data meta-analysis of 13 randomized trials showed a statistically significant benefit for event-free survival (EFS) (odds ratio [OR] = 0.87; 95% CI 0.81–0.93; $p = 0.00006$) and a significant, smaller overall impact upon OS (OR = 0.9; 95% CI 0.84–0.97; $p = 0.008$),[106] corresponding with an absolute survival benefit of ~3% (95% CI 1–5%) at 5 years.[106] The largest meta-analysis of 14 published adjuvant RCTs[105] showed statistically significant improvements

in both DFS and OS. Adjuvant IFN-α or PEG-IFN-α2b significantly improved DFS in 10 of 17 comparisons (disease recurrence HR = 0.82; 95% CI 0.77–0.87; $p < 0.001$) and improved OS in four of 14 comparisons (death HR = 0.89; 95% CI 0.83–0.96; $p = 0.002$) corresponding with an 18% improvement in DFS and 11% improvement in OS.[105] The European Organisation for Research and Treatment of Cancer (EORTC) trial 18991 compared observation with an intended 5 years of maximally tolerable doses of PEG-IFN-α2b for resected stage III melanoma (TxN1–2M0).[108] PEG-IFN-α2b was administered at 6 μg/kg/week for 8 weeks followed by 3 μg/kg/week maintenance for up to 5 years. There was early improvement in RFS (HR = 0.82; $p = 0.01$) at 3.8 years median follow-up but no significant improvement in OS or distant metastasis-free survival (DMFS) at 3.8 years median follow-up. The improvement in RFS was diminished at the 7.6 year follow-up reported in 2011 (HR = 0.87; 95% CI 0.76–1.00; $p = 0.05$).[109]

High-dose IFN-α2b is associated with substantial toxicity; this can lead to discontinuation of the recommended 1-year regimen among 10–26% of patients, although most toxicity is manageable with dose reductions and supportive care.[110] The toxicity profile has been shown to be manageable by experienced medical oncologists, with a toxicity attrition rate of only 10% in the largest Intergroup trial of high-dose IFN-α2b (E1694).[102] The most common side effects are flu-like syndrome (e.g., fatigue, fever, myalgia, and nausea), myelosuppression, hepatotoxicity, and depression. Intermediate doses have been pursued to reduce toxicity, often for longer than 1 year. Although the meta-analyses have not clarified an optimum dose or duration, DFS benefits appear to be greater and more durable with high-dose IFN-α2b than with intermediate or low doses at >5 years of follow up. PEG-IFN-α2b has a more convenient dosing schedule than IFN-α2b, requiring weekly administration. The toxicity profile is similar; however, the most common side effects are fatigue, hepatotoxicity, fever, headache, anorexia, myalgia, nausea, chills, injection site reactions, and depression.[108] The toxicity and financial cost of therapy has prompted the search for identifiers of patient groups that are most likely to benefit from adjuvant therapy and is the subject of ongoing research. There is evidence of higher levels of pro-inflammatory cytokines in the pretreatment serum of patients who remain relapse-free more than 5 years.[111] Because melanoma affects the younger members of society in their most productive years, the relative societal cost of this solid tumor eclipses that of many other solid tumors. A cost-benefit analysis following the initial regulatory approval of high-dose IFN-α2b showed costs that compare favorably with accepted standards of cost per year of life gained in non-malignant diseases.[112,113]

Breast cancer

Breast cancer mortality decreased in the United States for the first time in 2000,[114] which has been attributed in part to improvements in adjuvant therapy.[115] The specific benefits for each intervention for this solid tumor are summarized in Table 3.[116–120]

Adjuvant chemotherapy

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported that adjuvant polychemotherapy reduced the risk of recurrence and death substantially after 15 years of follow-up, with greater relative benefits among younger women (<50 years) compared

with older women (50–69 years), but similar benefits otherwise, irrespective of tamoxifen use, ER status, nodal status, or other tumor characteristics.[116] An update of the EBCTCG meta-analysis indicated that the standard chemotherapy regimens of 4 cycles of doxorubicin/cyclophosphamide (4AC) and 6 cycles of cyclophosphamide/methotrexate/5FU (CMF) were equivalent in terms of breast cancer mortality (RR = 0.98 [SE = 0.05]; two-sided significance [2p] = 0.67).[117] However, anthracycline-based regimens with a substantially higher cumulative dosage than standard 4AC (e.g., 6 cycles of cyclophosphamide/doxorubicin/5FU [CAF] or cyclophosphamide/epirubicin/5FU) were associated with lower breast cancer mortality than standard CMF (RR = 0.78 [SE = 0.06]; 2p = 0.0004). There were greater reductions in breast cancer mortality with CAF versus no chemotherapy (RR = 0.64 [SE = 0.09]; 2p < 0.0001) than with standard 4AC (RR = 0.78 [SE = 0.09]; 2p = 0.01) or standard CMF (RR = 0.76 [SE = 0.05]; 2p < 0.0001) versus no chemotherapy. Other analyses with shorter follow-up suggested less benefit for ER-positive disease, which may reflect an effect of chemotherapy in preventing early recurrence, which characterizes ER-negative disease.[121] There is little information about chemotherapy use in women ⩾70 years old.

Multiple individual studies have shown that taxanes administered every 3 weeks either concurrently (docetaxel)[122] or sequentially (paclitaxel)[123,124] after anthracycline-containing therapy further reduced the risk of recurrence and death. Interpretation of initial studies was confounded by longer duration of therapy for the taxane arms (eight treatment cycles over 24 weeks) compared with non-taxane arms (four cycles over 12 weeks);[123,124] subsequent studies confirmed a benefit for the sequential anthracycline–taxane strategy when the comparator arm included anthracyclines given alone for a comparable duration.[125,126] A single study involving 1016 patients with 0–3 positive axillary nodes demonstrated that four cycles of the TC regimen (docetaxel 75 mg/m^2 plus cyclophosphamide 600 mg/m^2 every 3 weeks) was associated with significantly improved DFS and OS compared with four cycles of standard anthracycline-based chemotherapy (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks).[127] A meta-analysis of phase III randomized trials including >15,500 patients confirmed that taxane-based adjuvant chemotherapy significantly improves both DFS and OS (Table 3), with absolute benefits of 3.3% and 2.0%, respectively.[118] In concordance with this, the updated EBCTCG meta-analysis found a reduction in breast cancer mortality with taxane plus anthracycline regimens versus anthracycline control regimens (RR = 0.87 [SE 0.03]; 2p < 0.00001) (Table 3).[117] The EBCTCG also found that extending treatment duration by adding four separate cycles of a taxane to a fixed anthracycline-based control regimen reduced breast cancer mortality (RR = 0.86 [SE = 0.04]; 2p = 0.0005), although similar benefits were not seen in this meta-analysis when the four additional taxane cycles were offset with extra cycles of non-taxane regimens to effectively double the non-taxane dose (RR = 0.94 [SE = 0.06]; 2p = 0.33). Proportional risk reductions with taxane-based regimens were not influenced by age, nodal status, tumor size, grade, estrogen receptor status, or tamoxifen use. Paclitaxel appears to be more effective when given weekly for 8–12 cycles compared with every 3 weeks for 4 cycles,[128] and when given twice weekly in a dose-dense schedule for four cycles as part of a sequential anthracycline–cyclophosphamide–taxane regimen compared with the same agents given every 3 weeks for four cycles.[129] In contrast, other studies have not

shown benefits for dose-dense schedules of other chemotherapy regimens (concurrent 5FU, epirubicin, cyclophosphamide).[130]

Common reversible toxicity of adjuvant chemotherapy includes alopecia, myelosuppression, and fatigue, although other adverse effects such as neuropathy associated with taxanes may persist. Delayed effects associated with anthracyclines include cardiomyopathy and acute leukemia, although these are uncommon.

Adjuvant endocrine therapy

A 5-year course of the selective estrogen receptor modulator tamoxifen was previously considered standard therapy for patients with ER-positive disease, including pre-, peri-, and postmenopausal women. Several trials failed to demonstrate greater benefit from a 10-year course.[131–134] Tamoxifen remains the preferred endocrine therapy in pre- and perimenopausal women. Aromatase inhibitors (AIs) are also an option for postmenopausal women in whom the ovaries no longer serve as a source of endogenous estrogen. Several large, randomized, phase III trials in postmenopausal women have evaluated AIs as initial adjuvant endocrine therapy compared with tamoxifen,[135,136] as sequential therapy after 2–3 years of tamoxifen (compared with continued tamoxifen),[137–139] or as extended adjuvant therapy after 5 years of tamoxifen.[140–143] Based upon these studies, an American Society of Clinical Oncology (ASCO) expert panel has recommended that a strategy incorporating an AI as initial endocrine therapy for 5 years, an AI sequentially following 2–3 years of tamoxifen (for a total of 5–7.5 years), or an AI after 5 years of tamoxifen (for a total of 10 years), because each of these strategies has been shown to reduce the risk of recurrence compared with 5 years of tamoxifen alone.[119,144] Tamoxifen and AIs differ in their adverse effect profiles, and these differences may inform treatment preferences. Tamoxifen is associated with more thromboembolic events, endometrial pathology, hot flushes, night sweats, and vaginal bleeding, whereas AIs are associated with more arthralgias and bone fractures. AIs may also reduce recurrence when initiated well after completion of a 5-year course of adjuvant tamoxifen.[142] AIs should be used only in postmenopausal women because they block the conversion of androgen into estrogen by aromatase in tumor and peripheral tissues[145] rather than preventing estrogen production by the ovaries. In women with chemotherapy-induced amenorrhea lasting <1–2 years, estradiol and follicle stimulating hormone levels should be obtained in order to confirm menopause prior to initiating an AI.[146]

Adjuvant anti-HER2 therapy

Trastuzumab is a humanized monoclonal antibody directed against the HER2/neu protein, and was approved for the treatment of HER2-positive metastatic disease when it was shown to prolong survival and improve response and time to disease progression.[147,148] Five randomized trials including patients with HER2-positive disease compared chemotherapy alone or in combination with trastuzumab for up to 1 year or longer as adjuvant therapy for early stage disease.[120,149–152] Pooled results from these trials demonstrated significant reductions in recurrence (HR = 0.53; $p < 0.00001$) and death (HR = 0.52; $p < 0.00001$) for trastuzumab, accompanied by more grade 3–4 cardiac toxicity (4.5% vs. 1.8%).[120]

Lessons learned from adjuvant therapy

A number of valuable lessons have been learned during the application of adjuvant therapy in the solid tumors described here. This section discusses the data supporting the following findings: (1) Benefit of an agent in the metastatic setting does not necessarily guarantee benefit in the adjuvant setting; (2) We should avoid the use of unplanned, underpowered subset analyses, and avoid the extrapolation of promising early data from studies that closed prematurely, to predict benefit; (3) In colon cancer, a statistically significant benefit in DFS after 3 years' follow-up generally translates into a statistically significant survival benefit after 5–6 years' follow-up.

In the absence of major differences among chemotherapy doublets used for advanced NSCLC, many clinicians have extrapolated advanced disease data to earlier stage disease, and use "third generation" cytotoxic drugs in combination with cisplatin (such as pemetrexed, docetaxel, and gemcitabine) – albeit without Level 1 data. In melanoma, the first survival-improving agents, including anti-CTLA-4 immunotherapy and molecularly targeted inhibitors of mutated BRAFV600E, have rapidly entered evaluation in the adjuvant setting following their success and regulatory approval in advanced disease. However, studies in other solid tumors such as colorectal cancer suggest that this paradigm may not translate from advanced to adjuvant arenas. In colon cancer, this approach was successful in some cases but a failure in others. The addition of oxaliplatin chemotherapy to 5FU-based therapy or capecitabine was successful, with benefits in advanced disease that translated to the adjuvant setting (Table 2);[35,44] however, three promising agents that were shown to be of use in advanced colon cancer (the cytotoxic agent irinotecan, and anti-angiogenic/molecularly targeted agents bevacizumab and cetuximab) did not improve outcomes when added to FOLFOX regimens in the adjuvant setting. Three large, randomized, phase III studies (ACCORD-02,[36] CALGB 89803,[37] and PETACC-3[38]) revealed neither DFS nor OS benefits in stage III disease with irinotecan/5FU/LV vs. 5FU/LV alone. Furthermore, NSABP C-08,[39] AVANT,[40] and Intergroup N0147[41] revealed no additional benefit of adding bevacizumab or cetuximab to standard chemotherapy in the adjuvant setting, although more mature follow-up may be needed to determine the long-term effects of the added biologics. These findings underscore the importance of conducting rigorous, adequately powered RCTs to directly determine the efficacy of new approaches in the adjuvant setting or treatments that have benefits in metastatic, inoperable disease. It is not safe to assume that agents active in advanced disease will have the same efficacy in early, curative disease.

Caution should also prevail when attempting to infer the success of adjuvant therapy based on unplanned, underpowered subset data from patients selected from overall patient populations evaluated in trials of adjuvant therapy (e.g., from Stage III to Stage II), and when extrapolating initial promising results from trials that have been stopped early. As discussed, 5FU/LV is used in stage II colon cancer based on its efficacy in stage III disease, but the benefit in stage II disease has not yet been confirmed. In NSCLC, data suggest that greater benefits are seen in Stage II and IIIA when compared with Stage Ib disease. There is also evidence that the benefit of adjuvant PEG-IFN-α2b in melanoma may be greater in patients with microscopic (lower) nodal disease burden arising from ulcerated primary melanoma compared with gross macroscopic nodal disease, as detailed in the

next section. These potential differences should be the focus of prospective future research trials. Similarly, although early prediction of OS rates in clinical trials is desirable to speed the transition of new, effective adjuvant therapies from trials into clinical use, long-term follow-up remains essential to validate the results of trials in the adjuvant setting more than any other setting. The IALT and CALGB NSCLC studies were stopped early and initial results were promising. However, in the CALGB trial the differences in OS lost statistical significance at longer follow up. In IALT, at a median follow-up of 7.5 years, cumulative lung cancer-related death rates still favored the use of chemotherapy but noted an excess of non-cancer-related deaths observed with chemotherapy compared with observation, raising the question of detrimental long-term effects of chemotherapy.[25] These losses of effect have not been reflected in long-term follow up of the JBR.10 and ANITA trials. Reasons for these differences in long-term outcomes are not clear, but may include differences in patient populations, differences in chemotherapy regimens used, use of postoperative radiation therapy, and differences in reporting causes of death.[153] The similar loss of significance for trials of high-dose IFNα2b in melanoma has been conjectured to be due to the potential occurrence of non-neoplastic causes of mortality, since RFS has been preserved for more than 12.6 years but OS benefits appear to erode after 10 years.[103] However, in adjuvant trials for all solid tumors, these findings suggest that longer term follow-up is needed to assess the true balance of benefit and risk from each of the diverse chemotherapy, hormonal, immunological and targeted therapies; consideration of the long-term risks are increasing in correlation with increasing survival times.[25,153]

For many solid tumors, the endpoint of new trials has been RFS improvement; in others the more rigorous goal of improving OS has been adopted, or RFS and OS have been evaluated as coprimary endpoints. As clinical trials of adjuvant therapy require long follow up to determine OS benefits, it would be desirable to use the endpoint of RFS as a surrogate for OS, if RFS reliably predicts OS benefit, to assess the impact of new agents upon disease outcome over shorter intervals. The ACCENT stage II–III colon cancer database, which includes data from 20,898 patients from 18 randomized trials treated with adjuvant 5FU/LV or observation alone has been critical for our understanding of the relationship between DFS and OS. Sargent et al.[154,155] found a strong correlation between 2- and 3-year DFS and 5-year OS, especially in stage III disease. In addition, the DFS benefit of adjuvant chemotherapy vs. observation was significant in the first 2 years (with trends in years 3 and 4), and the recurrence rate in the adjuvant treatment group never exceeded that of the observation group, supporting the hypothesis that cure and not just delay in recurrence had been achieved.[156] Using multiple hypothetical data sets from ACCENT[157] and actual data from six newer adjuvant studies[158] where median survival after recurrence has approximately doubled (from 12 to 20–24 months), it was clear that stronger correlations exist between 2- and 3-year DFS and OS at >6 years as compared with 5 years. However, the results of the NSABP C-07 trial of stage II and III colon cancer patients should also be considered in this context. Three-year DFS rates were improved with FLOX vs. 5FU/LV,[45] but at a median of 8-years' follow up, although the DFS benefit was maintained with FLOX, there was no difference in OS between the two groups.[32] Subgroup analysis suggested that patient age may impact on the effects of oxaliplatin, as the 8-year OS benefit was significant in patients <70 years old. Overall, 2- and 3-year DFS can probably be taken as

surrogate endpoints to predict OS in trials that continue to follow colon cancer patients for 6 or more years, with the caveat that factors such as patient age may affect outcomes; this warrants further research. These data are specific to colon cancer but the model may also apply to other tumors, although the impact of salvage treatments given after relapse must be considered.[159] The magnitude of impact upon DFS must also be sufficient to translate to an impact upon OS.

Predictive markers of adjuvant therapy success

Clinicopathologic features associated with response to specific therapeutic interventions are referred to as "predictive" factors (e.g., tumor characteristics, biomarkers, gene expression patterns). The success of individualizing adjuvant treatment rests on the availability of large tumor banks linked to high-quality, prospectively collected data in large clinical trials, which can be used to accelerate the validation of prognostic factors and novel biomarkers. Such markers are now being investigated in the various solid tumors to work towards individualized therapy; the key markers discussed in this section are summarized in Table 4.[16,24,26,108,109,160–165]

In NSCLC studies, benefit appeared to differ by disease stage. In the JBR.10 trial of cisplatin-based adjuvant therapy, subset analysis showed that the primary benefit appeared with stage II disease, with significant improvement in 5-year OS of 59% vs. 44% for observation. Paradoxically, patients with tumors <4 cm had clinically poorer outcomes compared with patients in the observation arm (5-year OS 73% vs. 79%, respectively) whereas patients with tumors >4 cm had a significant improvement in 5-year OS with adjuvant chemotherapy (79% vs. 59%). In the ANITA trial, subset analysis suggested that patients with stage II and IIIA disease derived the most benefit from adjuvant treatment, gaining absolute benefits in 5-year OS of 13% and 16%, respectively.[24] Other potential predictive markers are under investigation in NSCLC. The ongoing TASTE trial is directing therapy based upon DNA repair and cell proliferation pathways (baseline tumor ERCC1 levels and EGFR mutations), and an ongoing CALGB study is assigning treatment based upon a genetic signature called the lung Metagene model.[160]

In colon cancer, Ribic et al.[161] found a lack of OS benefit for adjuvant 5FU/LV vs. observation in microsatellite instability-high (MSIH) patients, with a trend towards higher mortality ($p = 0.10$), in data from 5 large randomized trials. Sargent et al. pooled data from 5 high-quality prospective RCTs and confirmed that in patients with stage II MSI-H tumors, there was a lack of benefit with adjuvant 5FU in terms of DFS (HR = 2.30; 95% CI 0.84–6.24; $p = 0.09$) and 5-year OS (HR = 2.95; 95% CI 1.02–8.54; $p = 0.04$) vs. observation.[162] ECOG 5202 has recently completed enrollment of stage II patients using MSI-H status as well as 18q loss of heterogeneity, which is considered a poor prognostic factor, to categorize patients into high vs. low risk and treat only high-risk patients with adjuvant oxaliplatin-based therapy. Other strategies for identifying high-risk colon cancer patients include multi-gene expression profiles to predict recurrence and response to adjuvant therapy. Kerr et al.[166] presented a large, prospectively designed validation study using patients enrolled in the QUASAR trial. Seven prognostic genes significantly and monotonically predicted recurrence risk as well as DFS and OS, and retained prognostic

significance independent of T stage, nodes examined, lymphovascular invasion, tumor grade, and MSI status. Unfortunately, six treatment–benefit genes were unable to predict a response to adjuvant chemotherapy.

The utility of adjuvant therapy in sarcoma was revealed when neoadjuvant chemotherapy was utilized to allow time for surgical planning and construction of osseous and joint prostheses, and also seemed to provide benefit related to treating micrometastatic disease. Use of neoadjuvant chemotherapy also allows the evaluation of histologic response to this initial treatment,[167] thereby informing the selection of adjuvant chemotherapy. Appropriate patient selection is at the heart of obtaining benefit from adjuvant chemotherapy of sarcomas. Current parameters involve risk classification on the basis of specific histologic subtypes (e.g., synovial sarcoma, rhabdomyosarcoma, osteosarcoma, Ewing's), tumor grade (low, intermediate, or high), location (extremity vs. non-extremity), and patient characteristics (performance status, comorbidities, personal values). The advent of therapies that are more effective for certain subtypes (trabectedin for liposarcoma and leiomyosarcoma, or gemcitabine-docetaxel for uterine sarcomas) will inform better treatment decisions on the basis of histology, but for the majority of sarcomas, other selection strategies are direly needed. Several molecular signatures have been developed in small studies that could allow a better patient selection algorithm and improve the risk/benefit ratio; however, those signatures still await prospective validation.[163,164,168] The EORTC is planning an adjuvant study with trabectedin (ET-743) in patients with high-grade STS with a molecular signature based on DNA repair proteins. Efforts guided by a biological understanding of the mechanisms underlying tumor recurrence and resistance to chemotherapy are likely to yield the most benefit.

In the analysis of outcomes across trials of high-dose IFNα2b in melanoma, there has been no consistent stage-related impact of therapy, and the benefits have been observed for patients with bulky nodal disease (AJCC IIIB) from the earliest pivotal trial E1684 onward. Subanalysis of data from the 18991 PEG-IFN-α2b study suggests that micrometastatic disease (N1 or AJCC IIIA) is a predictor of adjuvant therapy benefit in stage III melanoma. PEGIFN-α2b significantly improved RFS and DMFS vs. observation in the subset of patients with microscopic nodal involvement, but no benefit was found in the subset of patients with macroscopic nodal involvement (N2, AJCC IIIB). The significant difference in RFS in the N1 group persisted at the 7.6 year follow-up (HR = 0.82; 99% CI 0.61–1.10; $p = 0.08$).[109] These findings point to potential differences in tumor biology in early vs. advanced disease. In a post hoc meta-analysis of data from EORTC studies 18991 and 18952 (intermediate dosage IFNα−2b for 1 or 2 years vs. observation in stage IIB–III patients), RFS, DMFS and OS benefits were greater in the subgroup of patients with primary tumor ulceration ($n = 849$) vs. non-ulcerated ($n = 1336$) patients. In addition, the greatest reductions in risk were seen in patients with primary tumor ulceration and microscopic nodal N1 disease, with an HR = 0.69 ($p = 0.003$) for RFS, HR = 0.59 ($p < 0.0001$) for DMFS, and HR = 0.58 ($p < 0.0001$) for OS.[169] These data suggest that both tumor burden (stage) and biology (primary tumor ulceration) may predict the efficacy of therapy with intermediate doses of adjuvant IFN-α2b or PEG-IFN-α2b therapy. In melanoma, a clear path to the efficient evaluation of therapeutic efficacy, and the mechanism of action has been reported using neoadjuvant trial designs. Neoadjuvant studies of IFN-α2b[12] have demonstrated levels

of antitumor activity that are several-fold higher than observed in inoperable advanced melanoma and revealed the immunological rather than anti-angiogenic or antitumor basis of action for this agent. More recent neoadjuvant evaluation of ipilimumab has shown a role in modulating myeloid-derived suppressor cells in the blood of melanoma patients, and further neoadjuvant studies of new, molecularly targeted agents and combinations of targeted and immunological, as well as doublets of immunological therapy, are likely to provide a more facile and informative path to optimization of these therapeutic agents and combinations for adjuvant therapy.

In breast cancer, several multiparameter gene expression assays are now routinely used in clinical practice. Oncotype DX™ (Genomic Health Inc., Redwood City, CA) is a 21-gene assay that has been shown to predict response to tamoxifen and chemotherapy. An expert ASCO panel concluded that "…the Oncotype DX assay can be used to predict the risk of recurrence in patients treated with tamoxifen…(and) may be used to identify patients who are predicted to obtain the most therapeutic benefit from adjuvant tamoxifen and may not require adjuvant chemotherapy. In addition, patients with high recurrence scores appear to achieve relatively more benefit from adjuvant chemotherapy (specifically cyclophosphamide, methotrexate, and 5FU) than from tamoxifen."[16] Since that publication in 2007, other studies have shown that the assay provides prognostic information for AI-treated postmenopausal patients,[170] and also predicts benefit from anthracycline-based chemotherapy for postmenopausal women with axillary node-positive disease.[171] Other assays, such as the 70-gene Mammaprint assay, have also been shown to provide useful prognostic information.[172] Several randomized clinical trials are now in progress to further define the clinical utility of these assays in clinical practice. TAILORx[173] (NCT00310180) and RxPONDER (NCT01272037) are investigating Oncotype DX and MINDACT[174] (NCT00433589) is comparing genomic profiling using the Mammaprint assay, with clinical assessment to determine the need for chemotherapy in women with node-negative breast cancer. In addition, *CYP2D6* polymorphisms that result in diminished enzyme activity and biotransformation of tamoxifen to its active metabolite (endoxifen) have been associated with a higher risk of recurrence in tamoxifen-treated patients;[175–177] however, routine testing for *CYP2D6* polymorphisms remains controversial.[178]

Future directions for adjuvant therapy

As new, "targeted" agents with activity in advanced disease are identified, the next logical step will be to study them in the adjuvant setting. As our understanding of tumor biology and the relevant progression pathways for solid tumors increases, new treatment modalities or combinations may also be of benefit in the adjuvant setting. These new approaches, coupled with the use of the predictive markers discussed above to better select patients who are more likely to respond to such therapy, offer the prospect of more rapidly developing and more precisely understanding the mechanism of action for new adjuvant therapies, toward optimization and ultimate individualization of adjuvant therapy.

In NSCLC, ongoing randomized phase III adjuvant trials are investigating chemotherapy with and without the anti-angiogenic agent bevacizumab (ECOG E1505) and the role of erlotinib in patients with overexpression of the *EGFR* gene (RADIANT). As in other solid

tumors where cancer-germline antigens are strongly expressed, the potential relevance of immunotherapy is currently under evaluation. The cancer-germline vaccine MAGE-A3 is being tested in NSCLC tumors expressing the tumor-specific MAGE-A3-antigen (MAGRIT trial).[179] MAGE-A3 may be present in up to 50% of early NSCLCs.

In resected colon cancer, the focus of clinical investigation is currently on improving adjuvant therapy combinations, inclusion of biologic agents, and improved risk stratification to better predict the potential benefit of adjuvant therapy and aid the interpretation of clinical trial results, particularly in stage II disease. The newest AJCC staging manual[180] acknowledges a more refined prognostication for colon cancer including subdivision of T4 tumors as well as nodal status. These subcategories can vary in SEER-observed 5-year OS by as much as 10–15% and may help better risk-stratify patients for adjuvant chemotherapy. Currently, international efforts are focused on investigating the utility of 6 versus 12 cycles of FOLFOX in stage III colon cancer in an effort to balance the intent of cure with that of leaving patients with chronic, adverse cumulative effects from oxaliplatin (e.g., chronic neuropathy). In addition, CALGB 80702 will be randomizing patients to 3 years of celecoxib (COX-2 inhibitor) vs. placebo in order to explore the practical utility of these agents in improving DFS.

Management of sarcomas is multidisciplinary because of the multitude of potential sites of incidence requiring expertise in orthopedic, surgical, medical, and radiation oncology. Evidence suggests that patients treated at high-volume centers with specialized expertise in sarcoma management have improved outcomes.[181] The Children's Oncology Group is conducting a study (COG-AOST0331) in which patients with poor histologic response to standard therapy are randomized to receive alternating cycles of IE with the standard cisplatin/doxorubicin/methotrexate regimen. The expression of multiple cancer-germline antigens in sarcoma poses an opportunity for adjuvant immunotherapy, but to date this has not been fully embraced. In the COG-AOST0331trial, patients showing a favorable histologic response to chemotherapy are randomized to observation or maintenance immunotherapy with PEG-IFN-α2b for 1 year after surgery and chemotherapy, in follow-up to a Swedish study that suggested antitumor activity of IFN in osteosarcoma.[182]

CTLA-4-blocking antibodies (ipilimumab, tremelimumab) have shown promise as monotherapy of metastatic melanoma,[183,184] although as discussed above, this may not translate to the adjuvant setting. RCTs are currently testing the benefit of therapy with high-dose (10 mg/kg) ipilimumab vs. placebo (EORTC 18071) and vs. standard high-dose IFN-α2b (US Intergroup E1609) as adjuvant therapy for high-risk stage III or stage IIIB/IV resectable melanoma; no data are expected from either of these studies for several years. Anti-CTLA-4 therapy has novel immunologic mechanisms of action, disrupting the immune checkpoint molecule CTLA-4, a key regulator of T cell activity that plays an important role in maintaining tolerance.[185] Its toxicities, including skin, liver, endocrine and GI immune-related toxicity, have posed new, potentially life-threatening autoimmune challenges to investigators, and require rigorous follow-up and anticipatory management of patients. The identification of activating mutations in the *BRAF* gene in >50% of patients with cutaneous melanoma, and the recent dramatic successes of second-generation small molecule BRAF inhibitors in advanced melanoma,[186,187] has also prompted consideration of

their adjuvant application, alone or with MEK inhibitors that have been shown to mitigate some of the toxicities of the BRAF inhibitors.[188,189] Vaccines are under evaluation as adjuvant immunotherapy for melanoma following promising EORTC phase I–II studies testing the MAGE-A3 vaccine given with a potent new immuno-modulator (CpG), which has shown results superior to prior immunomodulators. As in NSCLC, application of vaccine immunotherapy with MAGE-A3 requires expression of the antigen in the tumor. Expression of MAGE-A3 was found in 66% of patients with melanoma, so appears not to be a limiting factor. In melanoma, the evaluation of a predictive gene signature that may be associated with greater MAGE-A3 vaccine antitumor efficacy is also being evaluated.[190,191] Combinations of new agents and established immuno-modulators are the likely future of adjuvant therapy for melanoma.

In breast cancer, several randomized clinical trials are now in progress that will further define the clinical utility of gene expression assays in clinical practice as discussed previously, including the TAILORx,[173] MINDACT,[174] and RxPONDER trials.

Discussion

Postoperative adjuvant therapy is now a standard consideration in many resectable solid tumors, and significantly reduces the risk of recurrence vs. observation. In an attempt to compare magnitude of efficacy across different tumor types we have compared studies assessing adjuvant therapy vs. observation alone (Table 5[21–26,30,33,49,95,96,105–109,116,117,156,192] and Table 6[21–25,30,49,95,101,104,108,116,117,156,192,193]). In tumors for which adjuvant therapy has now evolved, these rates are likely to be conservative estimates of benefit. HRs for DFS improvement range from 0.59 (SE 0.03) for 5-year tamoxifen in breast cancer to 0.89 (95% CI 0.76–1.03; not significant) for cisplatin-based chemotherapy in NSCLC, although the majority fall between 0.75–0.9 and are statistically significant, suggesting relatively consistent effects upon DFS (Table 5). The benefits upon OS are less pronounced and there have been fewer significant improvements at intervals of more than 1–2 years. Nonetheless, OS benefits are observed, with HRs of 0.56 (0.36–0.85; $p = 0.01$) for doxorubicin plus ifosfamide therapy in STS, 0.66 (SE 0.04) for breast cancer, and 0.77 (0.62–0.96; $p = 0.018$) for colorectal cancer, suggesting that a magnitude of RFS impact in the order of 0.70–0.80 may be required to achieve a meaningful impact upon OS. A modest impact upon RFS (HR = 0.87; 0.76–1.00; $p = 0.05$ for PEG-IFN-α2b in melanoma) has shown no corresponding impact upon OS (0.96; 0.82–1.11; $p = 0.57$), although analysis of patient subsets indicate that the effects may be confined to those with low tumor burden (micrometastatic N1 disease). Differences in efficacy outcomes according to disease stage have also been suggested by clinical trial data in NSCLC. More widespread use of the predictive markers that are now becoming available for each of the tumor types will allow better selection of the patients who will benefit from adjuvant therapy; it is therefore reasonable to expect to see greater improvements in both DFS and OS with adjuvant therapy in the future.

As expected for different tumor types, the 5-year and 10-year DFS and OS data are variable (Table 6). In some tumors the magnitude of improvement in DFS and OS is concordant (e.g., NSCLC), while for others the impact upon DFS exceeds that upon OS (e.g., melanoma).

Regardless of the relationship between DFS and OS, DFS is an important endpoint for the assessment of therapeutic benefit, given its earlier maturity, impact upon quality-of-life, and the debilitating consequences of recurrent disease.[154]

The adjuvant therapies employed in solid tumors reflect our current knowledge of the molecular pathogenesis of each disease, and the associated immunopathology of some solid tumors such as melanoma. Emerging targeted therapies demonstrate greater specificity than conventional chemotherapy but are believed to be unlikely to achieve durable benefits in the management of most solid tumors as single agents, given the multiple pathways identified in the progression of each solid tumor and the reactivation of the key driver pathways through multiple changes in the tumor, associated with targeted inhibitors (e.g., of BRAFV600E in melanoma) to date. Their use is likely to be in combination with existing adjuvant therapies. The role of immunity has been established in the progression of some solid tumors and not in others. The role of immunomodulation has been pursued perhaps most aggressively in melanoma, where the importance of immune response is recognized regarding disease prognosis and outcome, and where adjuvant chemotherapy was ineffective and molecular therapies did not exist until recently. In breast cancer, the complex algorithm used for determining the most appropriate adjuvant therapy reflects the broader understanding of its heterogeneity, and the efficacy of chemo-, hormonal-, and molecularly targeted therapy tailored according to tumor histopathology, hormone receptor status, and HER2 status.

The balance between the therapeutic outcome, acute toxicity, and long-term side effects is an important consideration for adjuvant therapy and should be determined on an individual patient basis. Patient age and their likely tolerance of treatment may also need to be factored in. The majority of adjuvant therapies are associated with toxicity that may limit or delay their administration; however, the benefits are generally agreed to outweigh the potential risks, given unequivocal improvements in DFS and/or OS. The tolerability of more intensive chemotherapy regimens may fall with increasing intensity of therapy. In breast cancer, the expected effects of hormone therapy (e.g., hot flushes, menstrual cycle changes, fatigue) are troublesome but rarely life-threatening, although they affect patient compliance, and potentially compromise efficacy. Adherence to tamoxifen after surgery for breast cancer is modest, with <50% of women continuing therapy for the prescribed 5 years in one UK study.[194] Long-term toxicity of adjuvant therapies are also an issue, such as musculoskeletal and cardiovascular problems associated with AIs in breast cancer and possible late, non-cancer-related mortality in NSCLC. In melanoma, the greater impact upon RFS than OS in multiple trials of IFN-α has raised the question of morbidity associated with treatment that does not improve survival.

In summary, adjuvant therapy given for operable disease earlier in the course of progression for multiple solid tumors has demonstrated clear benefits in terms of reduced risk of recurrence and improved OS. OS benefits have been smaller in general than the RFS benefits for a number of solid tumors. To optimize the benefits and refine the application of adjuvant therapy the focus is now shifting towards more precise staging and risk stratification for each disease, since the benefits and the risk–benefit ratio may differ according to patient subset (e.g., macro- vs. micrometastatic nodal disease). Further optimization of adjuvant therapy will also likely emerge from mechanistically tailoring therapy to target both tumor

cell drivers of progression, and the host immune deficits that permit tumor evasion of immunity. The disparity between the benefits observed in the differing stage groupings of disease may not only be related to the burden of disease and overall prognosis but also to different disease biology in localized and nodal disease, or between different biological processes such as angiogenesis associated with certain primary disease prognostic groups (e.g., ulcerated and non-ulcerated melanoma). The identification of more precise prognostic indicators and factors that will predict therapeutic benefit (e.g., hormone receptor and *HER2/neu* expression in breast cancer, antigen expression for vaccine therapies, and gene expression profiling for multiple solid tumors) may better guide the application of each therapy. These advances may allow individualization of therapy and further improvement of the risk–benefit ratio. As research advances with the expansion of our knowledge of the molecular and cellular basis of progression in these tumors, adjuvant therapy is likely to be refined further, with greater improvements in long-term survival and the potential for cure of solid tumors using multimodal therapies informed by the biology of the underlying disease.

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Table 1

Current adjuvant systemic therapy for five major solid tumors.

Tumor	Adjuvant therapy	Selection factor	Proportion of patients eligible
NSCLC[1]	Cisplatin-based chemotherapy doublets[a]	High-risk margin-negative stage IB	<37%[b]
		Stage II–III	
	Carboplatin and paclitaxel	Patients as above not able to tolerate cisplatin	–
Colon cancer[3]	FOLFOX or FLOX or XELOX (CapeOx)	High or intermediate risk stage II[c]	21%[d]
		Stage III	
	5FU/LV	As above if oxaliplatin not appropriate	–
	Capecitabine alone		
	Observation, 5FU/LV, capecitabine, or clinical trial	Stage II without high-risk features	-
Osteosarcoma[4]	Cisplatin and doxorubicin ± high dose methotrexate ± ifosfamide	High-grade disease	>90%
	Ifosfamide + etoposide (IE)	Low-grade disease with high-grade pathology	
	Ifosfamide + cisplatin + epirubicin		
Ewing's sarcoma[4]	Vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide combination	All patients	100%
Soft tissue sarcoma[8]	Doxorubicin-based CT[e] Epirubicin and ifosfamide	Stage II–III	50–60%
Melanoma	IFN-α (high and intermediate dose) or	Stage IIB–III	<92%[b]
	PEG-IFN-α2b	Stage IIIA/N1	
Breast cancer[15,18]	Endocrine therapy (tamoxifen, aromatase inhibitors)	Stage I–III disease	60–70%
		ER and/or PR-positive disease	
	Anti-HER2 therapy	Stage I–III disease	15–20%
		HER2/neu overexpressing disease	
	Chemotherapy (doublets or triplets)[f]	Stage I–III	60–70%
	Anthracycline/cyclophosphamide doublet with sequential taxane	Selection based upon recurrence risk, age, comorbidities, and other factors	

ER, estrogen receptor; FLOX/FOLFOX, 5FU/LV/oxaliplatin; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; XELOX (CapeOx), capecitabine/oxaliplatin.

[a]Cisplatin plus vinorelbine or etoposide or vinblastine or gemcitabine or docetaxel.

[b]Estimates based on SEER Cancer Statistics Review (1975–2008) data for localized and regional disease at diagnosis (includes patients with very early stage disease who would not be suitable for adjuvant therapy).

[c] T4 tumors (IIB or IIC), grade 3 or 4, lymphovascular or perineural invasion, bowel obstruction, localized perforation or close/indeterminate/positive margins, inadequately sampled nodes.

[d] Estimated from the American Joint Committee on Cancer 7th edition (page 154).

[e] Combination agents include ifosfamide, dacarbazine and mesna.

[f] Examples of commonly used doublets include TC (docataxel, cyclophosphamide) and AC (doxorubicin, cyclophosphamide), and triplets include CMF (cyclophosphamide, methotrexate, and 5FU), FEC (5FU, epirubin, cyclophosphamide), and TAC (docetaxel, doxorubicin, and cyclophosphamide).

Table 2

Summary table of recent adjuvant chemotherapy trials in stage II and III resected colon cancer.

Trial	Study patients	Treatment	Disease-free survival	Overall survival
IMPACT[30]	Duke B + C	5FU 370–400 mg/m^2 + folinic acid 200 mg/m^2 daily days 1–5	3 year	3 year
	n = 1493	q28 days × 6 months	71%	83%
			(*p* < 0.001)	(*p* = 0.029)
		vs. observation	62%	78%
MOSAIC[31]	Stage II + III	FOLFOX4 × 6 months	5 year	6 year[a]
	n = 2246		73.3%	78.5%
			(*p* = 0.003)	(*p* = 0.046)
		vs. FU5LV × 6 months	67.4%	76%
NSABP C-07[32]	Stage II + III	FULV + oxaliplatin 85 mg/m^2 weeks 1, 3, and 5 q8 weeks × 3 cycles	8 year	8 year
	n = 2409		69.4%	80.2%
			(*p* = 0.002)	(*p* = 0.08)
		vs. FULV × 3 cycles	64.2%	78.4%
QUASAR[33]	Surgically resected	5FU 370 mg/m^2 + LV 25 or 175 mg/m^2 days 1–5 q28 days or	NA	5.5 year
	(90% stage II)	weekly × 30 5FU treatments		HR = 0.82
	n = 3239	vs. observation		(*p* = 0.008)
X-ACT[34]	Stage III	Capecitabine 1250 mg/m^2 PO BID days 1–14 q21 days × 8 cycles	3 year	3 year
	n = 1987		64.2%	81.3%
			(*p* = 0.12)	(*p* = 0.05)
		vs. 5FU 425 mg/m^2 + LV 20 mg/m^2 bolus days 1–5 q28 days × 6 cycles[b]	60.6%	77.6%
XELOXA[35]	Stage III	XELOX × 8 cycles	3 year	5 year
	n = 1886		70.9%	77.6%
			(*p* = 0.0045)	(*p* = NS)
		vs. FULV or Mayo	66.5%	74.2%
ACCORD-02[36]	Stage III	FU5LV + irinotecan 180 mg/m^2 day 1 q14 days × 6 months	3 year	5 year
	n = 400		51%	61%
			(*p* = 0.22)	(*p* = 0.26)

Trial	Study patients	Treatment	Disease-free survival	Overall survival
		vs. FU5LV × 6 months	60%	67%
CALGB 89803[37]	Stage III	LV 20 mg/m^2 + 5FU 500 mg/m^2 + irinotecan 125 mg/m^2 weekly	5 year	5 year
	n = 1264	for 4 weeks q6 weeks × 5 cycles	59%	68%
			(*p* = 0.85)	(*p* = 0.74)
		vs. FULV × 4 cycles	61%	71%
PETACC 3[38]	Stage II + III	FU5LV + irinotecan 180 mg/m^2 day 1 q14 days × 6 months	5 year[c]	5 year[c]
	n = 3278	(or LV 500 mg/m^2 + 5FU 2000 mg/m^{2}over 24 h + irinotecan	56.7%	73.6%
		80 mg/m^2 weekly for 6 weeks q8 weeks × 4 cycles)	(*p* = 0.106)	(*p* = 0.094)
		vs. FU5LV or alternative	54.3%	71.3%
NSABP C-08[39]	Stage II + III	mFOLFOX6 × 6 months	3 year	NA
	n = 2672	vs. mFOLFOX6 × 6 months + bevacizumab 5 mg/kg q2 weeks × 1 year	HR = 0.89	
			(*p* = 0.15)	
AVANT[40]	Stage II + III	FOLFOX4 × 6 months	NS[d]	NA
		vs. FOLFOX4 + bevacizumab 5 mg/kg q2 weeks × 6 months followed		
		by bevacizumab 7.5 mg/kg q3 weeks alone × 6 months		
		vs. XELOX + bevacizumab 7.5 mg/kg q3 weeks × 6 months followed by		
		bevacizumab 7.5 mg/kg q3 weeks × 6 months		
Intergroup N0147[41]	Stage III	mFOLFOX6 + cetuximab 250 mg/m^2 (initial dose 400 mg/m^2)	NS	NA
		q2 weeks × 6 months		
		vs. mFOLFOX6 × 6 months		

5FU, 5-fluorouracil; LV, leucovorin; NS, not significant; NA, not applicable or not reported.

FULV = 5FU 500 mg/m^2 + LV 500 mg/m^2 bolus weekly for 6 weeks q8 weeks.

FU5LV = LV 200 mg/m^2 + 5FU 400 mg/m^2 bolus, followed by 5FU 600 mg/m^2 22 h infusion day 1 and day 2 q14 days. FOLFOX4 = FU5LV + oxaliplatin 85 mg/m^2 day 1 q14 days × 6 months.

mFOLFOX6 = LV 400 mg/m^2 + 5FU 400 mg/m^2 + oxaliplatin 85 mg/m^2 day 1 followed by 5FU 2400 mg/m^2 over 46 h q2 weeks. Mayo = 5FU 500 mg/m^2 + LV 20 mg/m^2 bolus weekly × 30 treatments.

XELOX = capecitabine and oxaliplatin.

[a]Includes stage II and III patients. Stage II patients: no overall survival advantage, stage III patients 72.9% vs. 68.7%; *p* = 0.023.

[b]Non-inferiority trial design.

[c]For stage III only. Stage II 5-year disease-free survival and overall survival are NS, but pooled stage II + III patients disease-free survival is significant (*p* = 0.045).

[d] No disease-free survival benefit for the addition of bevacizumab.

Table 3

Therapeutic benefit from adjuvant systemic therapies in breast cancer.

Intervention	Comparison	Follow-up	Hazard rate for disease-free survival	Hazard rate for overall survival	Reference
Chemotherapy	Polychemotherapy vs. none				EBCTCG[116]
	<50 years	At 15 years	0.63 (SE ± 0.02)	0.71 (SE ± 0.04)	
			$p < 0.00001$	$p < 0.00001$	
	⩾ 50 years	At 15 years	0.81 (SE ± 0.02)	0.88 (SE ± 0.03)	
			$p < 0.00001$	$p < 0.00001$	
	Anthracycline-based chemotherapy vs. none[a]	At 10 years	0.73 (SE ± 0.03)	0.84 (SE ± 0.03)	EBCTCG[117]
			$p < 0.00001$	$p < 0.00001$	
	CMF chemotherapy vs. none[a]	At 10 years	0.70 (SE ± 0.04)	0.84 (SE ± 0.05)	
			$p < 0.00001$	$p = 0.0004$	
	Taxane vs. non-taxane containing chemotherapy	Median of ~5 years	0.86 (95% CI 0.81–0.91)	0.87 (95% CI 0.81–0.93)	Bria et al.[118]
			$p < 0.00001$	$p < 0.0001$	
	Taxane + anthracycline-based regimen vs. anthracycline-based control[a]	Median of	0.86 (SE ± 0.02)	0.89 (SE ± 0.03)	EBCTCG[117]
		8 years	$p < 0.00001$	$p < 0.00001$	
Endocrine therapy	Tamoxifen vs. none	At 15 years	0.61 (SE ± 0.04)	0.69 (SE ± 0.05)	EBCTCG[116]
			$p < 0.0001$	$p < 0.0001$	
	AI vs. tamoxifen for 5 years	Median of 5.8 years	0.77 (SE ± 0.05)	0.94 (SE ± 0.06)	Dowsett etal.[119]
			$p < 0.0001$	p = NS	
	Tamoxifen for 2–3 years followed by an AI vs. tamoxifen for 5 years	Median of 3.6 years	0.71 (SE ± 0.060)	0.79 (SE ± 0.07)	Dowsett etal.[119]
			$p < 0.0001$	$p = 0.04$	
Trastuzumab	Chemotherapy plus trastuzumab vs. no trastuzumab	Median of ~2 years	0.53 (95% CI 0.46–0.60)	0.52 (95% CI 0.44–0.62)	Viani et al.[120]
			$p < 0.00001$	$p < 0.00001$	

CI, confidence intervals; CMF, cyclophosphamide/methotrexate/5FU; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; SE, standard error.

[a]Relative risk reported (not hazard rate).

Table 4

Predictive markers of response to therapy.

Tumor	Predictive marker	Status
NSCLC	Disease stage	JBR.10 trial: primary benefit in stage II disease with tumor >4 cm[26]
		ANITA: primary benefit in stage II and IIIA disease[24]
	Tumor ERCC1 levels	Under investigation
	EGFR mutations	Under investigation
	Genetic signature ‘lung Metagene model’	Under investigation[160]
Colon cancer	Microsatellite instability	Poor outcome in microsatellite instability-high tumors[161,162]
Osteosarcoma, Ewing’s sarcoma, soft tissue sarcoma	Risk classification based on specific histologic subtypes, tumor grade, location and patient characteristics	
	Molecular signatures	Under investigation[163,164]
Melanoma	Disease stage	Greater benefits in micrometastatic vs. macrometastatic nodal disease[108,109]
	Ulceration of primary tumor	Greater benefits in patients with ulcerated vs. non-ulcerated primary tumor[165]
Breast cancer	Oncotype DX™ 21-gene assay	Predicts risk of recurrence in patients treated with tamoxifen, identifies patients who will obtain most benefit from adjuvant tamoxifen and those who might derive greater benefit from chemotherapy vs. tamoxifen[16]
	Mammaprint 70-gene assay	Predicts which patients may benefit most from adjuvant chemotherapy

Table 5

Clinical benefit of adjuvant therapy vs. observation or placebo (control) across tumor types: data from meta-analyses, pooled studies and large, controlled trials.

Tumor type	Hazard ratio (95% confidence interval) vs. control	
	Disease-free survival	Overall survival
NSCLC		
Cisplatin-based CT (ALPI)		
Median follow-up 64.5 months[21]	0.89 (0.76–1.03); $p = 0.128$	0.96 (0.81–1.13); $p = 0.589$
Cisplatin-based CT (IALT; $n = 1867$)[22]		
Median follow-up 56 months[22]	0.83 (0.74–0.94); $p < 0.003$	0.86 (0.76–0.98); $p < 0.03$
Median follow-up 7.5 years[25]	0.88 (0.78–0.98); $p = 0.02$	0.91 (0.81–1.02); $p = 0.10$
Cisplatin + vinorelbine (JBR.10)[23]	0.60; $p < 0.001$	0.69; $p = 0.04$
Median follow-up 9.3 years[26]		0.78 (0.61–0.99); $p = 0.04$
Cisplatin + vinorelbine (ANITA)[24]		0.80 (0.66–0.96); $p = 0.017$
Cisplatin-based CT meta-analysis (LACE; n = 4584)[192]	0.84 (0.78–0.91); $p < 0.001$	0.89 (0.82–0.96); $p = 0.005$
Colon		
5FU/LV (IMPACT)[30]	0.67 (0.56–0.80); $p < 0.0001$	0.77 (0.62–0.96); $p = 0.018$
Stage II only[a]	0.84 (0.62–1.12)	0.91 (0.63–1.34)
Stage III only[a]	0.55 (0.44–0.70)	0.70 (0.53–0.92)
5FU/LV (IMPACT) stage B2 only[b,49]	0.88 (0.72–1.07)	0.86 (0.68–1.07)
5FU/LV (QUASAR) stage 2[33]	0.78 (0.67–0.91) $p = 0.001$	0.82 (0.70–0.95) $p = 0.008$
5FU/LV (ACCENT)[156]	0.61 (estimated years 1–2)	0.74 (estimated over 8 years)
Soft tissue sarcoma		
Meta-analysis of doxorubicin-based regimens (14 trials)[95]	0.75 (0.64–0.87); $p = 0.0001$	0.89 (0.76–1.03); $p = 0.12$
Meta-analysis of doxorubicin-based regimens (18 trials)[96]		
Doxorubicin alone		0.84 (0.68–1.03); $p = 0.09$
Doxorubicin + ifosfamide		0.56 (0.36–0.85); $p = 0.01$
Melanoma		
IFN-α meta-analysis (all doses)[107]	0.83 (0.77–0.90); $p = 0.000003$	0.93 (0.85–1.02); $p =$ NS
IFN-α individual patient data meta-analysis (all doses)[106]	0.87 (0.81–0.93); $p = 0.00006$	0.90 (0.84–0.97); $p = 0.008$

Tumor type	Hazard ratio (95% confidence interval) vs. control	
	Disease-free survival	**Overall survival**
High-dose IFN-α (pooled data 4 studies)[107]	0.74	0.86 (0.74–1.00); $p = 0.05$
IFN-α[105]	0.82 (0.77–0.87); $p < 0.001$	0.89 (0.83–0.96); $p = 0.002$
PEG-IFN-α2b (EORTC 18991; $n = 1256$)[108]	0.82 (0.71–0.96); $p = 0.01$	0.98 (0.82–1.16); $p = 0.78$
7.6 year follow up[109]	0.87 (0.76–1.00); $p = 0.05$	0.96 (0.82–1.11); $p = 0.57$
Breast		
Single-agent CT meta-analysis[116]	0.86[c] (0.04); $2p = 0.001$	0.96[c] (0.05); $2p > 0.1$
PolyCT meta-analysis[116]	0.77[c] (0.02); $2p < 0.00001$	0.83[c] (0.02); $2p < 0.00001$
Anthracycline-based CT 10-year meta-analysis[117]	0.73[d] (0.68–0.79); $2p < 0.00001$	0.84[d] (0.78–0.91); $2p < 0.00001$
CMF-based CT 10-year meta-analysis[117]	0.70[d] (0.63–0.77); $2p < 0.00001$	0.84[d] (0.76–0.93); $2p = 0.0004$
Tamoxifen 1–2 years meta-analysis (ER-positive patients)[116]	0.74[c] (0.02)	0.82[c] (0.03)
Tamoxifen ~5-years meta-analysis (ER-positive patients)[116]	0.59[c] (0.03)	0.66[c] (0.04)

CMF, cyclophosphamide/methotrexate/fluorouracil; CT, chemotherapy; ER, estrogen receptor; 5FU/LV, 5-fluorouracil + leucovorin; IFN-α, interferon-α; PEG-IFN-α2b, pegylated interferon-α2b.

[a] Unadjusted data.

[b] Adjusted for age and grade.

[c] Annual event ratio (treatment vs. control) and standard error.

[d] Event rate ratio and 95% confidence interval (treatment vs. control).

Table 6

Comparisons of 5- and 10-year disease-free survival and overall survival data across different tumor types vs. no adjuvant therapy.

Tumor type	Disease-free survival: difference with adjuvant therapy vs. no therapy, %		Overall survival: difference with adjuvant therapy vs. no therapy, %	
	5-year	10-year	5-year	10-year
Lung				
Cisplatin-based CT meta-analysis (LACE; $n = 4584$)[192]	5.8		5.4	
Median follow-up 7.5 years[25]	Absolute gain 4.3		Absolute gain 3.9	
Cisplatin-based CT (IALT, $n = 1867$)[22]	5 ($p < 0.003$)		5 ($p < 0.03$)	
Cisplatin + vinorelbine[23]	12 ($p = 0.08$)		15 ($p = 0.03$)	
Cisplatin + vinorelbine (ANITA)[24]			8.6	
Cisplatin-based CT (ALPI)[21]	Absolute increase 4 (95% CI −1, 10)		Absolute increase 1 (95% CI −4, 7)	
Colon				
5FU/LV (IMPACT)[30]	9[a]		5[a]	
5FU/LV (IMPACT) Stage B2 only[49]	3 (p = NS)		2 (p = NS)	
5FU-based CT (ACCENT)[156]				7.2[b] ($p < 0.0001$)
Stage II				5.4[b] ($p = 0.026$)
Stage III				10.3[b] ($p < 0.0001$)
5FU-based CT (elderly)[193]	11 ($p < 0.001$)		7 ($p < 0.001$)	
Soft tissue sarcoma				
Doxorubicin-based meta-analysis (14 trials)[95]		10 (95% CI 5, 15)		4 (95% CI 1, 9)
Melanoma				
IFN-α2b E1684 trial ($n = 287$)[104]	11 ($p = 0.0023$)		9 ($p = 0.0237$)	
IFN-α2b E1690 trial ($n = 642$)[101] HDI arm	9 ($p_2 = 0.03$)		−3 (p = NS)	
PEG-IFN-α2b (EORTC 18991; $n = 1256$)[108]				
All patients	7[c] ($p = 0.01$)		1[c] (p = NS)	
Stage N1 only	13[c] ($p = 0.016$)		4[c] (p = NS)	
Breast				
PolyCT meta-analysis[116]				

Tumor type	Disease-free survival: difference with adjuvant therapy vs. no therapy, %		Overall survival: difference with adjuvant therapy vs. no therapy, %	
	5-year	10-year	5-year	10-year
<50 years	12.5	12.4	4.7	7.9
50–69 years	6.0	4.7	2.6	2.9
Anthracycline-based CT meta-analysis[117]	8.5	8	5.1	5.0
Standard CMF-based CT meta-analysis[117]	9.9	10.2	2.7	4.7
Tamoxifen ~5 years meta-analysis (ER positive)[116]	11.4	13.6	3.6	7.9

CT, chemotherapy; ER, estrogen receptor; 5FU/LV, 5-fluorouracil + leucovorin; IFN-α2b, interferon-α2b; PEG-IFN-α2b, pegylated interferon-α2b.

[a] 3-year data. Significance testing not reported.

[b] 8-year data.

[c] 4-year data.