The Evolving Role of Chemotherapy and Predictive Markers in Early-stage Non-small-cell Lung Cancer

Eric W Humke[1] and Heather Wakelee[2]

1. Instructor of Medicine; 2. Assistant Professor of Medicine, Department of Medicine, Division of Oncology, Stanford Cancer Center, Stanford University School of Medicine

Abstract

Lung cancer continues to be the leading cause of cancer mortality worldwide. The utility of traditional chemotherapy has reached a plateau in both the metastatic and adjuvant settings. However, we have entered an era of better targeting of both traditional cytotoxic agents and newer compounds for select subsets of patients based on genetic analysis of the tumour. Substantial evidence supports the use of adjuvant chemotherapy in both stage II and stage III non-small-cell lung cancer (NSCLC), but it remains unclear which combination of either traditional or targeted therapies will work best for an individual patient. The use of chemotherapy and targeted therapies in patients with resected stage I NSCLC remains controversial because we cannot predict who benefits from its usage. This article focuses on the evolving role of predictive biomarkers in early-stage NSCLC and summarises the trials that are prospectively evaluating the use of those biomarkers to individualise treatment of NSCLC.

Keywords

Early-stage non-small-cell lung cancer, chemotherapy, predictive markers

Disclosure: Eric W Humke has no conflicts of interest to declare. Heather Wakelee has received research funding from Genentech BioOncology, Bayer, AstraZeneca, Eli Lilly and Company, Novartis and Pfizer.

Received: 23 March 2010 **Accepted:** 17 February 2011 **Citation:** *European Oncology & Haematology*, 2011;7(2):109–15 *DOI: 10.17925/EOH.2011.07.02.109*

Correspondence: Heather Wakelee, Thoracic Oncology, 875 Blake Wilbur Drive, Room 2233, MC 5826 Stanford, CA 94305, US. E: hwakelee@stanford.edu

Lung cancer is the leading cause of cancer mortality worldwide. Surgery remains the optimal treatment for early-stage non-small-cell lung cancer (NSCLC); however, five-year survival rates for resected NSCLC without additional treatment range from 20 to 40% for stage IIIA disease to 70 to 80% for stage IA disease.[1] Mortality occurs most commonly from recurrences at sites outside the lung, suggesting that the cancer had spread before surgery.

The goal of systemic therapy in patients with resected NSCLC is to eradicate the prior seeded micrometastases to improve overall survival. Several clinical trials and meta-analyses have shown improved survival in resected NSCLC with different combinations of chemotherapy.[2–7] These analyses are still based on empiric treatment and do not address the question of who will benefit the most from therapy and who may be harmed. The ultimate goal of adjuvant NSCLC treatment is to predict which patients will benefit from the use of chemotherapy, targeted therapy and radiation therapy, and to individualise therapy based on the patient's tumour characteristics, including histology and genetic analysis. Recently, trials have begun to use novel biomarkers as a first step towards individualised adjuvant therapy.

In this article, we will give a brief historical background on the use of chemotherapy in the adjuvant setting, followed by previously investigated biomarkers to guide adjuvant therapy and end with a discussion of ongoing clinical trials to address the important question of how to personalise adjuvant therapy.

History of the Use of Chemotherapy in Resected Non-small-cell Lung Cancer

Initial use of chemotherapy in NSCLC was only for metastatic disease. In 1991, an international panel recommended against the routine use of adjuvant chemotherapy outside of clinical trials.[8] Four years later a meta-analysis was undertaken to investigate the role that chemotherapy after surgery had played in trials up to that point.[9] Fourteen trials were evaluated and the meta-analysis showed a 5% improvement in five-year survival but failed to reach statistical significance. Owing to this encouraging result and the established benefit of adjuvant chemotherapy in multiple other solid tumours, several follow-up studies were initiated.

The follow-up clinical trials validated the use of adjuvant chemotherapy in resected NSCLC.[10] The major adjuvant trials are beyond the scope of this article; however, they are highlighted in *Table 1*.

Although not all the trials were positive, a large meta-analysis of the data has reaffirmed the use of adjuvant chemotherapy. The Lung adjuvant cisplatin evaluation (LACE) meta-analysis was conducted to identify treatment options for post-operative chemotherapy.[5] Data from 4,584 patients were pooled from the five largest adjuvant trials (Adjuvant lung project Italy [ALPI],[11] Adjuvant International Trialist Association [ANITA],[3] Big lung trial [BLT],[12] International adjuvant lung cancer trial [IALT][2] and JBR.10[4]). The overall hazard ratio (HR) was 0.89, corresponding to a five-year overall survival benefit of 5.4% from

Table 1: Post-1995 Meta-analysis – Non-small-cell Lung Cancer Randomised Adjuvant Platinum Trials

Trial	Stage	n	Chemotherapy	Significant?	Survival Benefit	Long-term Follow-up
E3590	II–IIIA	488	Cis/VP16	No	NA	NA
ALPI	I–III	1,209	Cis/MVd	No	NA	NA
BLT	I–III	381	Cis/4 options	No	NA	NA
IALT	I–III	1,867	Cis/Vinca or VP16	Yes	4% at 5 years	Benefit lost at 7 years
JBR.10	IB–II	482	Cis/Vinca	Yes	11% at 5 years	Benefit retained >9 years
CALGB	IB	344	Carbo/Pac	Yes	20% at 4 years	Benefit lost at 57 and 74 months
ANITA	I–IIIA	840	Cis/Vinca	Yes	8.6% at 5 years	Benefit retained at 7 years

ANITA = Adjuvant Navelbine® international trialist association trial; ALPI = Adjuvant lung project Italy; BLT = Big lung trial; CALGB = Cancer and leukemia group B; Carbo = carboplatin; Cis = cisplatin; IALT = International adjuvant lung cancer trial; MVd = mitomycin C and vindesine; Pac = paclitaxel; Vinca = vinca alkaloid, Vin = vinorelbine; VP16 = etoposide.

Table 2: Early-stage Non-small-cell Lung Cancer Prognostic Biomarkers

Marker	Trial	n	HR Survival	Reference
MSH2	IALT	768	HR 0.66; p=0.01	Kamal et al., 2010[51]
ERCC1	IALT	761	HR 0.66; p=0.009	Olaussen et al., 2006[18]
MRP1	IALT	782	HR 1.37; p=0.007	Filipits et al., 2007[52]
p53 expression	JBR.10	253	HR 1.89; p=0.03	Tsao et al., 2007[31]
β-Tubulin III	JBR.10	256	HR 1.72; p=0.04	Seve et al., 2007[39]
Ras mutation	JBR.10	253	Not prognostic	Tsao et al., 2007[31]
MET	Retrospective	447	HR 0.66; p=0.04	Tsao et al., 2007[31]
BRCA1	Retrospective	126 58	HR 1.98; p=0.02 HR 2.4; p=0.04	Rosell et al., 2007[33]

BRCA1 = breast cancer 1; ERCC1 = excision repair cross-complementation group 1; HR = hazard ratio; IALT = International adjuvant lung cancer trial.

chemotherapy. The effect of the adjuvant therapy did not significantly differ between all the chemotherapy regimens, which incorporated cisplatin plus at least one additional drug.

The Evolving Role of Biomarkers for Choosing Chemotherapy in Resected Non-small-cell Lung Cancer

The limited benefit of using adjuvant chemotherapy seen so far in trials, and the lack of benefit in certain subsets, such as most stage IB tumours, highlight the fact that we do not yet understand who will be most helped by treatment and which agents to use. To make further improvements in survival, we will need to identify those patients most at risk for recurrence and determine which chemotherapy will work the best in each person. In addition, we will need to identify those at low risk to avoid the unnecessary toxicity of chemotherapy, a point highlighted by the long-term IALT data indicating potential harm in the form of increased non-cancer mortality.[2] In this large trial, initial analysis indicated an overall survival benefit, but with longer-term follow-up to 7.5 years, the significance of the benefit was lost and there was an indication of excess non-cancer mortality in the chemotherapy arm. This increased non-cancer death and loss of benefit over time has not been seen in other adjuvant trials, including JBR.10 and ANITA,[3,4] but the IALT long-term data are concerning. Although we still have a lot to learn about the basic biology of NSCLC, which is a very heterogeneous disease, there are some promising emerging prognostic and predictive markers that are beginning to be incorporated into our decisions for adjuvant therapy. A prognostic marker is one that indicates survival benefit (or detriment) regardless of therapy. Examples of this include tumour stage, tumour size and patient sex. A predictive maker is one that predicts for differential benefit from a particular therapy. Although we will not discuss prognostic markers here in much detail, there have been several early-stage prognostic biomarkers published (see *Table 2*). The predictive markers and how they fit into the ongoing clinical trials are discussed below. Although there is a great need for biomarkers in NSCLC, each biomarker must be rigorously tested and validated before it is implemented.[13–16]

Excision Repair Cross-complementation Group 1

The excision repair cross-complementation group 1 (ERCC1) protein functions in the nucleotide excision repair pathway and is required for the proper repair of DNA after damage from insults such as ultraviolet (UV) light or cisplatin. ERCC1 was one of the first proteins to be studied in a retrospective fashion using immunohistochemistry (IHC) on operative specimens taken from patients who had participated in the IALT trial. In the 'IALT-Bio' analysis, 761 tumour specimens were evaluated and ERCC1 expression was positive in 335 (44%) and negative in 426 (56%). A benefit of cisplatin-based adjuvant chemotherapy was associated with the absence of ERCC1 (test for interaction; p=0.009).[17] Adjuvant chemotherapy, as compared with observation, significantly prolonged survival among patients with ERCC1-negative tumours (HR 0.65; 95% confidence interval [CI], 0.50–0.86; p=0.002) but not among patients with ERCC1-positive tumours (HR 1.14, 95% CI 0.84–1.55; p=0.40). Patients with ERCC1-positive tumours who did not receive adjuvant chemotherapy survived longer than those with ERCC1-negative tumours (adjusted HR for death 0.66, 95% CI 0.49–0.90; p=0.009).[18] The result suggested that completely resected ERCC1-negative NSCLC would benefit from a cisplatin-based adjuvant chemotherapy, whereas those with high ERCC1 levels were less likely to benefit. The rationale was that DNA damaged by cisplatin was unable to undergo repair, resulting in greater tumour cell death. In another study, Simon et al. evaluated the effect of intratumoural ERCC1 expression on survival in NSCLC patients who underwent surgical resection for cure.[19] Using realtime polymerase chain reaction (RT-PCR) analysis of ERCC normalised to 18S ribosomal RNA expression, an ERCC1 value of 50 revealed a statistically significant difference in median survival for patients with ERCC1 expression of >50 (94.6 months) compared with patients with ERCC1 expression of <50 (35.5 months, p=0.01). The value of ERCC1 has yet to be tested prospectively, but there are several randomised prospective clinical trials (Southwest Oncology Group [SWOG] S0720, Tailored post-surgical therapy in early-stage NSCLC [TASTE] and International tailored chemotherapy adjuvant [ITACA]) testing the utility of ERCC1 as a biomarker in adjuvant NSCLC treatment (see below).

Ribonucleotide Reductase M1

The regulatory subunit of ribonucleotide reductase M1 (RRM1) is essential for nucleotide excision repair. RRM1 expression was studied

in patients with early-stage NSCLC who had only undergone resection with no adjuvant chemotherapy.[20] In this study, patients with high RRM1 expression had a median disease-free survival exceeding 120 months compared with patients with low RRM1 expression who had a median survival of 54.5 months (HR for disease progression or death in the high expression group, 0.46; p=0.004). The overall survival was more than 120 months for patients with tumours with high levels of RRM1 expression and 60.2 months for those with low levels of RRM1 expression (HR for death, 0.61; p=0.02).

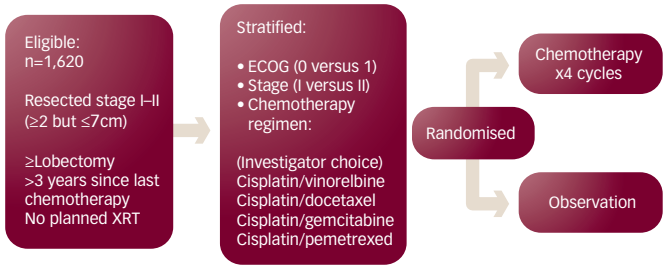
RRM1 is the molecular target of gemcitabine and high levels of RRM1 have been linked to gemcitabine-resistance in advanced NSCLC. A small prospective phase II clinical trial in patients with locally advanced, non-resectable NSCLC revealed that RRM1 expression was significantly (p=0.002) and inversely correlated (r = -0.498) with disease response to platinum plus gemcitabine.[21] A randomised phase III trial of 170 patients who received either gemcitabine versus gemcitabine plus carboplatin revealed that low RRM1 and ERCC1 expression was significantly correlated with disease response (r = -0.41; p=0.001 for RRM1; r = -0.39; p=0.003 for ERCC1). A model for response prediction that included RRM1, ERCC1 and the treatment arm was highly predictive of the treatment response observed (p=0.0005). RRM1 expression appears to correlate with ERCC1 expression (p<0.001) in both early- and late-stage NSCLC and improves the prognostic utility.[17,19] The SWOG S0720 trial listed below will use the levels of both RRM1 and ERCC1 expression in patients with resected stage I NSCLC to determine whether or not they should receive cisplatin plus gemcitabine as adjuvant chemotherapy versus observation.

Epidermal Growth Factor Receptor

The utility of single-agent tyrosine kinase inhibitors (TKIs) as first-line therapy in patients with advanced NSCLC (stage IIIB or IV) was demonstrated in the Iressa pan Asia study (IPASS) trial. IPASS was a phase III study that randomised never/light ex-smoking Asian patients who had never received therapy to receive either gefitinib or carboplatin/paclitaxel. It demonstrated a significant progression-free survival benefit for the gefitinib arm (HR = 0.74; p<0.0001).[22] This revealed that in carefully selected patients with advanced disease, gefitinib may be superior to chemotherapy. By contrast, a phase III trial using gefitinib (Iressa survival evaluation in lung cancer [ISEL] trial) as second- or third-line therapy in patients with advanced NSCLC did not reveal a statistical advantage over placebo in an unselected population.[23] Another TKI, erlotinib, was originally approved for second- or third-line monotherapy in advanced NSCLC after a randomised, placebo-controlled, phase III study (BR.21) demonstrated an increase in survival for these patients from 4.7 to 6.7 months.[24]

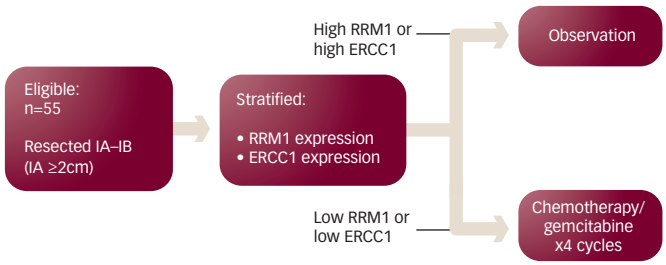
Following on from the mixed success of the use of TKIs as a therapy in patients with advanced NSCLC, their use in maintenance and adjuvant therapies was tested. The SWOG 0023 trial enrolled unresectable stage III NSCLC patients to evaluate gefitinib as a maintenance therapy following definitive concurrent cisplatin/etoposide and consolidative docetaxel.[25] This trial was a randomised, placebo-controlled trial in an unselected patient population and resulted in an unexpected survival detriment for gefitinib. Owing to the negative gefitinib trials SWOG 0023 and ISEL, the double-blinded, prospective randomised placebo-controlled phase III trial JBR.19 using gefitinib was closed early. This study was designed to investigate the role of adjuvant gefitinib in resected stage IB–IIIA NSCLC. In this under powered study, gefitinib did not improve disease-free and overall survival. Subgroup analysis

Figure 1: CALGB 30506 Trial Overview



Primary end-point: overall survival.
CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; XRT = radiotherapy.

Figure 2: SWOG S0207 Trial Overview



Primary end-point: feasability of pharmacogenomics-based treatment.
SWOG = Southwest Oncology Group

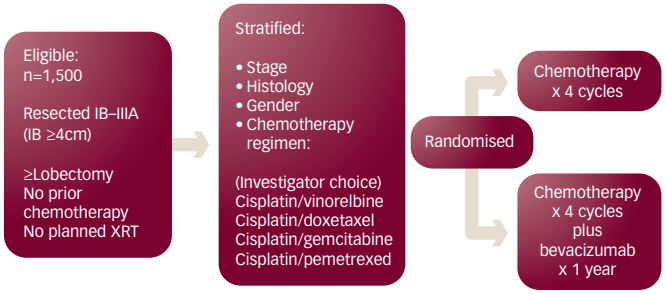
showed that KRAS mutation status, epidermal growth factor receptor (EGFR) by fluorescence *in situ* hybridisation (FISH) or EGFR sensitising mutation status were neither prognostic nor predictive of survival. The focus has now shifted from gefitinib to erlotinib. The Randomised double-blind trial in adjuvant NSCLC with Tarceva® (RADIANT), which requires EGFR overexpression to be detected by IHC, will investigate the role of erlotinib in the adjuvant setting. In addition, there are ongoing non-randomised studies exploring the use of adjuvant erlotinib in patients with EGFR mutations in resected NSCLC (TASTE and Massachusetts General Hospital trials discussed below). Despite the promising results seen with use of the EGFR TKIs as first-line therapy in those with EGFR mutations, their role as adjuvant therapy even in this setting remains investigational.

Although EGFR mutations are being used to predict who will respond to TKIs,[26] the utility of evaluating EGFR expression using IHC or FISH analysis is controversial. Although there are data to suggest that increased EGFR copy number detected by FISH predicts responsiveness to antibody therapy, there is no clear predictive value of EGFR FISH for treatment with TKIs.[27–30] Although FISH is not being explored in the adjuvant setting, EGFR copy number or increased EGFR expression detected by IHC are undergoing further evaluation in phase III biomarker validation studies for erlotinib (NCCTG-N0723 – closed) and cetuximab (SWOG S0819) in patients with advanced NSCLC.

p53

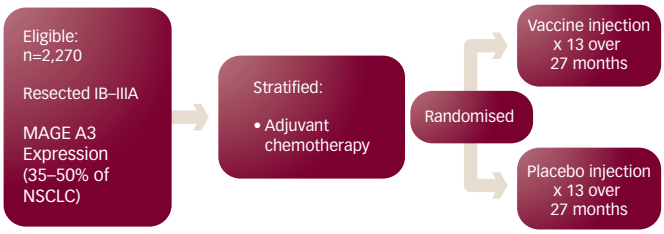
The mutation or loss of p53 can lead to genomic instability resulting in an aggressive tumour with a poor prognosis. There have been many meta-analyses looking at both p53 protein levels and mutational status as a prognostic marker. In the JBR.10 trial, overexpression of p53 protein detected by IHC was a marker for poor prognosis but the p53 mutational status was not prognostic for survival.[31] Overexpression of p53 protein evaluated by IHC predicted survival

Figure 3: ECOG 1505 Trial Overview



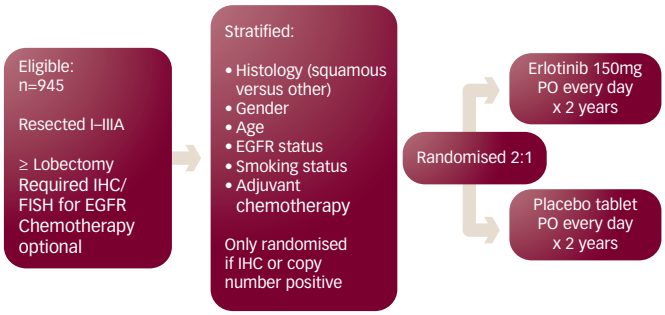
Primary end-point: overall survival.
ECOG = Eastern Cooperative Oncology Group; XRT = radiotherapy.

Figure 4: MAGRIT Trial Overview



Primary end-point: disease-free survival.
MAGRIT = MAGE-A3 as Adjuvant, Non-Small Cell Lung Cancer Immunotherapy; NSCLC = non-small-cell lung cancer.

Figure 5: RADIANT Trial Overview



Primary end-point: disease-free survival. EGFR = epidermal growth factor receptor; FISH = fluorescence in situ *hybridisation; IHC = immunohistochemistry; PO = orally; RADIANT = Randomized Double-blind Trial in Adjuvant NSCLC with Tarceva.*

benefit from adjuvant chemotherapy, but the p53 mutation was not a predictive marker for adjuvant chemotherapy. The utility of this marker for adjuvant therapy is therefore indeterminate at this time.

Insulin-like Growth Factor Receptor 1

The prognostic role of insulin-like growth factor receptor 1 (IGF1R) expression in surgically resected NSCLC was recently undertaken.[32] IGF1R expression was evaluated by IHC in tissue microarray sections. Although a positive IGF1R expression was significantly associated with squamous cell histology, there was no difference in survival between the positive and negative groups. Therefore, IGF1R expression does not appear to be a prognostic factor in resected NSCLC patients. If IGF1R targeted agents prove to have some efficacy in advanced stage NSCLC, they are likely to be further investigated in early-stage disease.

Breast Cancer 1

Breast cancer 1 (BRCA1) is a member of the DNA mismatch repair pathway. Overexpression of BRCA1 correlates with poor overall survival in patients with completely resected, chemotherapy-naive NSCLC.[33] BRCA1 messenger RNA (mRNA) expression has been linked to resistance to DNA-damaging reagents, such as cisplatin and etoposide, while functioning as a sensitiser to antimicrotubule drugs, such as taxanes and vinca alkaloids. BRCA1 mRNA expression is being evaluated as a method to customise adjuvant chemotherapy in the Spanish customised adjuvant trial (SCAT) trial (see below).[34]

Thymidylate Synthase

In a randomised phase III trial comparing pemetrexed/cisplatin with gemcitabine/cisplatin, survival was superior in patients with non-squamous histology receiving the pemetrexed-based regimen.[35,36] Using the histological classification for a therapeutic decision led the US Food and Drug Administration (FDA) to limit pemetrexed therapy to only patients with nonsquamous NSCLC. The treatment outcome difference using pemetrexed in different histologies is likely to be due to an underlying difference in thymidylate synthase (TS). TS is an enzyme that is important for DNA biosynthesis and a target of fluoropyrimidine- and pemetrexed-based therapies. Low TS expression levels have been associated with a better response to pemetrexed.[37,38] Although TS mRNA expression is on average lower in groups of patients with non-squamous histologies compared with squamous histologies, there is significant overlap of expression ranges in individual patient tumours. Further analysis of the relationship between chemotherapy and TS is being studied prospectively in the international ITACA phase III trial.

Class III β-tubulin

Tubulins are a family of globular proteins that make up microtubules in cells. They are important for many aspects of the cell, including structure, movement, mitosis and vesicular transport. The expression of class III β-tubulin (βTubIII) was studied in the JBR.10 study. IHC was performed for βTubIII on 265 out of 482 resected tumour specimens, and a high level of expression was correlated with a better relapse-free survival and overall survival in patients who received the adjuvant chemotherapy.[39] A high expression of βTubIII correlates with resistance to antimicrotubule reagents.[40] Further prospective studies are needed to validate the utility of βTubIII. Although to date most of the aforementioned biomarkers have not been integrated into practice, there are numerous ongoing clinical trials to address the utility of these genetic biomarkers for clinical treatment decisions.

Genomic and Proteomic Signatures

Several gene expression signatures containing non-overlapping genes may provide predictive information on clinical outcome. Recently, a 15-gene signature was identified in patients from the JBR.10 trial observation arm that separated the group into high-risk and low-risk subgroups with significantly different survival (HR 15.02, 95% CI 5.12 to 44.04; p<0.001; stage I HR 13.31; p<0.001; stage II HR 13.47; p<0.001).[41] The genetic signature was validated in four separate microarray data sets. The same signature predicted survival of those patients with early-stage, completely resected NSCLC who received adjuvant cisplatin/vinorelbine. This demonstrates the potential to select patients with early-stage (IB–II) NSCLC that are most likely to benefit from adjuvant chemotherapy with cisplatin/vinorelbine but it needs further validation. Multiple other gene signatures are under investigation. In addition to genomic signatures, studies using proteomics have been developed to classify which patients might respond to receptor TKIs.[42–45] Although this is used in advanced NSCLC, the same proteomic signatures are now being applied to

early-stage NSCLC. Proteomic signatures still need validation using prospective studies.

Prospective Clinical Trials Using Biomarkers to Predict Utility of Adjuvant Therapy

Cancer and Leukemia Group B 30506 Trial

The Cancer and leukemia group B (CALGB) 30506 trial is a randomised phase III trial to determine the potential overall survival benefit of adjuvant chemotherapy in patients with NSCLC of 2–7cm without nodal involvement randomised to chemotherapy compared with observation (see *Figure 1*). Patients in the trial will be randomised to observation or to three cisplatin-doublet chemotherapies. High-quality fresh frozen lung cancer tumour tissue will be collected and processed from multiple institutions for gene expression array generation. The primary objective is to determine whether any gene expression patterns can be correlated with the effect of adjuvant chemotherapy for overall survival. Other biomarkers are also being investigated.

Southwest Oncology Group S0720 Trial

The Southwest Oncology Group (SWOG) S0720 is a phase II clinical trial using the expression of ERCC1 and RRM1 to determine adjuvant therapy in patients with stage IA or IB NSCLC (see *Figure 2*). After surgery patients are assigned to one of two arms based on RRM1 and ERCC1 gene expression analysed using automated quantitative analysis (AQUA) technology. Arm I includes patients who have high RRM1 and ERCC1 expression who will be observed post-operatively. Arm II includes patients who have low RRM1 and ERCC1 expression who will receive gemcitabine and cisplatin for four cycles. The primary objective is to assess the feasibility of assigning adjuvant treatment based on tumoural RRM1 and ERCC1 gene expression and to estimate the two-year disease-free survival of these patients. The trial will also to explore the relationship between RNA and RRM1 and ERCC1 protein expression, and the relationship between RRM1 and ERCC1 expression in the formalin-fixed and paraffin-embedded tumour specimens.

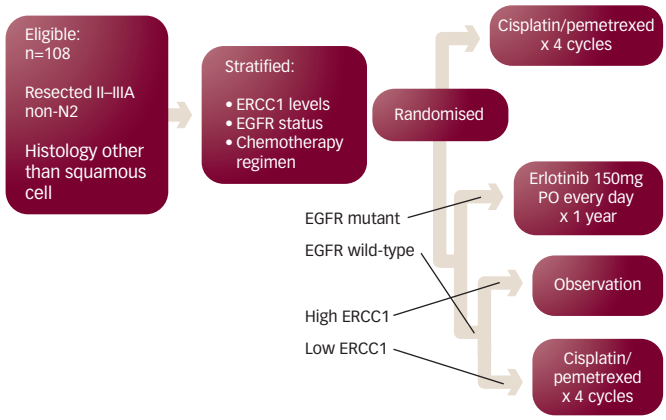
Eastern Cooperative Oncology Group 1505 Trial

The Eastern Cooperative Oncology Group (ECOG) 4599 and Avastin in lung cancer (AVAiL) phase III clinical trials for patients with advanced NSCLC demonstrated a benefit from the addition of bevacizumab to first-line chemotherapy.[46–48] Based on these positive results in advanced NSCLC, the ECOG 1505 trial is an ongoing clinical trial to investigate the role of bevacizumab in the adjuvant setting for patients with resected stage IB (at least 4cm in size) to IIIA NSCLC (see *Figure 3*). The trial is not based on any biomarkers for enrolment stratification because none have been validated for the antivascular endothelial growth factor treatment strategies, but extensive correlates are planned and all patients will have tumour tissue collected and blood drawn and banked from multiple time-points.

Melanoma-associated Antigen 3 Adjuvant Non-small-cell Lung Cancer Immunotherapy Trial

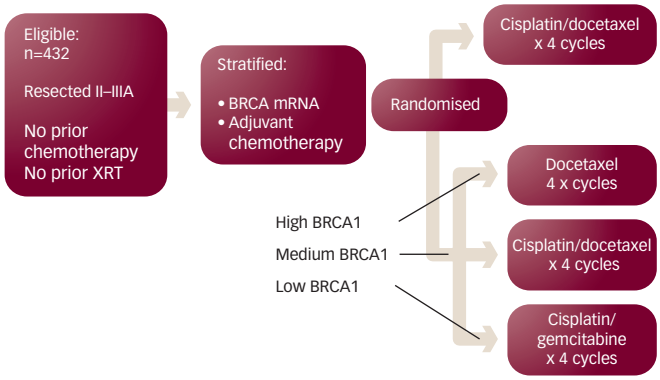
The role of vaccines in NSCLC is as yet unproven and remains an area of active investigation. Melanoma-associated antigen 3 (MAGE-A3) is a tumour antigen in 30–50% of resected lung cancers. The MAGE-A3 adjuvant NSCLC immunotherapy trial (MAGRIT) is investigating the use of the MAGE-A3 vaccine in patients with completely resected stage IB, II and IIIA NSCLC that express the MAGE-A3 antigen (see *Figure 4*). The target accrual is 2,270 patients to find over 1,400 who will be eligible for the vaccination based on MAGE-A3 expression. The vaccination will be given 13 times over 27 months. Patients will be followed every

Figure 6: TASTE Trial Overview



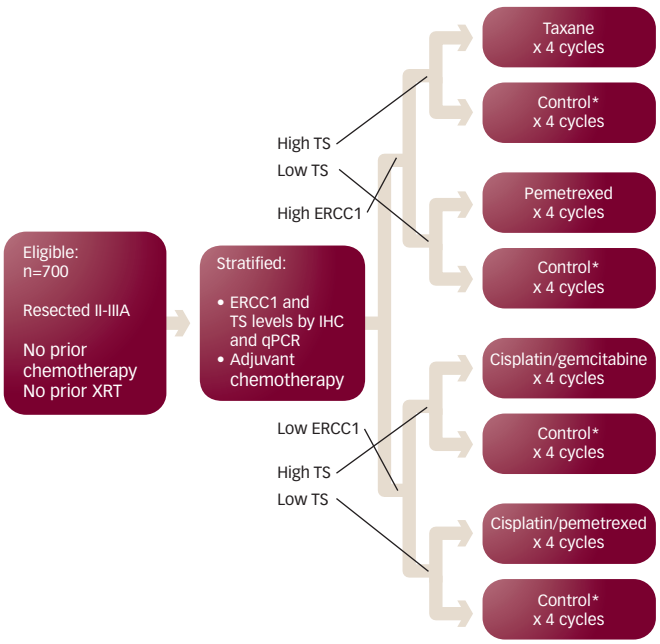
Primary end-point: feasibility followed by disease-free survival. EGFR = epidermal growth factor receptor; PO = orally; TASTE = Tailored post-surgical therapy in early stage NSCLC.

Figure 7: SCAT Trial Overview



Primary end-point: overall survival.
BRCA1 = Breast cancer 1; mRNA = messenger RNA; SCAT = Spanish customised adjuvant trial; XRT = radiotherapy.

Figure 8: ITACA Trial Overview



*Primary end-point: overall survival. *Control = Investigator choice of a Cisplatin-based doublet.*
ITACA = International tailored chemotherapy adjuvant trial; mRNA = messenger RNA; qPCR = quantitative PCR; TS = thymidylate synthase; XRT = radiotherapy.

six months for five years and then annually until year 10. The primary end-point is disease-free survival.

Randomised Double-blind Trial in Adjuvant Non-small-cell Lung Cancer with Tarceva Trial

The RADIANT trial is a phase III clinical trial designed to evaluate the role of erlotinib in the adjuvant treatment of patients with resected stage IB–IIIA NSCLC (see *Figure 5*). The adjuvant trial is a double-blind, placebo-controlled study that randomised 945 patients to either two years of daily oral erlotinib therapy at 150mg/day or placebo. Only patients with EGFR-positive tumour tissue detected by either FISH or IHC were randomised. Before randomisation, patients were allowed to receive up to four cycles of platinum-based adjuvant chemotherapy. Correlates of the study include EGFR FISH and mutational status. RADIANT has completed accrual and we are awaiting results. Massachusetts General Hospital and the Dana Farber Cancer Institute are running a phase II non-randomised clinical trial evaluating erlotinib as an adjuvant therapy in patients with resected stage I–IIIA NSCLC with confirmed exon 19 deletion mutations or exon 21 L858R point mutations in the EGFR.

Tailored Post-surgical Therapy in Early-stage Non-small-cell Lung Cancer Trial

The TASTE trial is enrolling patients for a randomised phase II/III adjuvant trial, evaluating the feasibility of standard versus customised treatment in stage II or IIIA non-N2, non-squamous NSCLC (see *Figure 6*). Patients are randomised to receive either standard chemotherapy consisting of cisplatin plus pemetrexed for four cycles (Arm A) or a customised drug treatment in Arm B. In Arm B, patients harbouring EGFR mutations will be treated with erlotinib. If they have wild-type or an undetermined EGFR status, patients will be tested for their levels of ERCC1. Those that have high ERCC1 levels will receive no treatment and be observed and those that have low ERCC1 levels will receive cisplatin plus pemetrexed for four cycles. The hypothesis is that patients receiving tailored adjuvant therapy will have better disease-free survival rates than patients in the control arm receiving standard chemotherapy therapy.

Spanish Customised Adjuvant Trial

The Spanish customised adjuvant (SCAT) trial uses the BRCA1 mRNA levels to customise therapy in patients with completely resected stage I–IIIA NSCLC (see *Figure 7*). The rationale for the trial is that patients with low BRCA1 mRNA levels have longer survival when treated with cisplatin-based chemotherapy,[49] whereas patients with high BRCA1 levels have longer survival when treated with taxane-based therapy.[50] Early-stage NSCLC patients with high BRCA1 levels had significantly worse survival.[33] The trial was designed to give patients with high BRCA1 levels docetaxel, patients with intermediate BRCA1 levels docetaxel/cisplatin, and patients with low BRCA1 levels cisplatin/gemcitabine. An interim analysis presented at the American Society of Clinical Oncology in 2008 showed that single-agent docetaxel had no detrimental effect on survival compared with docetaxel/cisplatin.

International Tailored Chemotherapy Adjuvant Trial

The International tailored chemotherapy adjuvant (ITACA) trial is a pharmacogenetic-driven phase III study based on both ERCC1 and TS testing (see *Figure 8*). The study selects adjuvant therapy for patients with resected stage II and IIIA NSCLC based on RT-PCR expression of ERCC1 and TS. ERCC1 and TS are scored as either high or low and the four possible combinations of expression levels are treated with different chemotherapy. The four chemotherapy possibilities are taxane (ERCC1 high and TS high), pemetrexed (ERCC high and TS low), cisplatin/gemcitabine (ERCC1 low and TS high) and cisplatin/pemetrexed (ERCC1 low and TS low). Each of the four customised chemotherapy regimens is being tested against a control arm consisting of a cisplatin-doublet of the investigator's choice.

Future Directions

The use of chemotherapy for the treatment of patients with resected NSCLC became the standard of care less than a decade ago; however, we appear to have reached a plateau in efficacy. The benefits of empiric treatment were modest with a 5–10% improvement in overall survival at five years. Increased interest in identifying biomarkers has led to retrospective analysis of biomarkers from completed trials. Close analysis of the adjuvant chemotherapy trials revealed that subgroups of patients carrying differential expression or mutation of a particular gene resulted in different outcomes. Those biomarkers are now being used in prospective randomised controlled clinical trials to determine if they have utility as predictive biomarkers. In addition, combinations of genes are being explored as a genetic profile for individualising therapy. With improved understanding of the basic biology behind NSCLC and more drugs targeting pathways actively contributing to tumour growth, we are beginning to enter the era of personalised adjuvant therapy. The results of these ongoing trials will hopefully lead to improved care for our patients in the near future. ■

1. Mountain CF, Revisions in the International System for Staging Lung Cancer, *Chest*, 1997;111:1710–7.
2. Arriagada R, Bergman B, Dunant A, et al., Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer, *N Engl J Med*, 2004;350:351–60.
3. Douillard JY, Rosell R, De Lena M, et al., Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial, *Lancet Oncol*, 2006;7:719–27.
4. Winton T, Livingston R, Johnson D, et al., Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer, *N Engl J Med*, 2005;352:2589–97.
5. Pignon JP, Tribodet H, Scagliotti GV, et al., Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group, *J Clin Oncol*, 2008;26:3552–9.
6. Burdett S, Stewart LA, Rydzewska L, A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer, *J Thorac Oncol*, 2006;1:611–21.
7. Burdett SS, Stewart LA, Rydzewska L, Chemotherapy and surgery versus surgery alone in non-small cell lung cancer, *Cochrane Database Syst Rev*, 2007:CD006157.
8. Holmes EC, Preoperative neoadjuvant therapy in non-small-cell lung cancer: open season? *J Natl Cancer Inst*, 1991;83:228–9.
9. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group, *BMJ*, 1995;311:899–909.
10. Chhatwani L, Cabebe E, Wakelee HA, Adjuvant treatment of resected lung cancer, *Proc Am Thorac Soc*, 2009;6:194–200.
11. Scagliotti GV, Fossati R, Torri V, et al., Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer, *J Natl Cancer Inst*, 2003;95:1453–61.
12. Waller D, Peake MD, Stephens RJ, et al., Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial, *Eur J Cardiothorac Surg*, 2004;26:173–82.
13. Gandara DR, Lara PN Jr, Mack P, et al., Individualizing therapy for non-small-cell lung cancer: a paradigm shift from empiric to integrated decision-making, *Clin Lung Cancer*, 2009;10:148–50.
14. Custodio AB, Gonzalez-Larriba JL, Bobokova J, et al., Prognostic and predictive markers of benefit from adjuvant chemotherapy in early-stage non-small cell lung cancer, *J Thorac Oncol*, 2009;4:891–910.
15. Ikeda N, Nagase S, Ohira T, Individualized adjuvant chemotherapy for surgically resected lung cancer and the roles of biomarkers, *Ann Thorac Cardiovasc Surg*, 2009;15:144–9.
16. Simon GR, Individualizing chemotherapy for non-small cell lung cancer (NSCLC) in the adjuvant and advanced setting: current status and future directions, *Curr Treat Options Oncol*, 2008;9:300–12.
17. Simon G, Sharma A, Li X, et al., Feasibility and efficacy of molecular analysis-directed individualized therapy in advanced non-small-cell lung cancer, *J Clin Oncol*, 2007;25:2741–6.
18. Olaussen KA, Dunant A, Fouret P, et al., DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy, *N Engl J Med*, 2006;355:983–91.
19. Simon GR, Sharma S, Cantor A, et al., ERCC1 expression is a predictor of survival in resected patients with non-small cell lung cancer, *Chest*, 2005;127:978–83.
20. Zheng Z, Chen T, Li X, et al., DNA synthesis and repair genes RRM1 and ERCC1 in lung cancer, *N Engl J Med*, 2007;356:800–8.
21. Bepler G, Kusmartseva I, Sharma S, et al., RRM1 modulated *in vitro* and *in vivo* efficacy of gemcitabine and platinum in non-small-cell lung cancer, *J Clin Oncol*, 2006;24:4731–7.

22. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma, *N Engl J Med*, 2009;361:947–57.
23. Thatcher N, Chang A, Parikh P, et al., Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer), *Lancet*, 2005;366:1527–37.
24. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al., Erlotinib in previously treated non-small-cell lung cancer, *N Engl J Med*, 2005;353:123–32.
25. Kelly K, Chansky K, Gaspar LE, et al., Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023, *J Clin Oncol*, 2008;26:2450–6.
26. Greulich H, Chen TH, Feng W, et al., Oncogenic transformation by inhibitor-sensitive and -resistant EGFR mutants, *PLoS Med*, 2005;2:e313.
27. Tsao MS, Sakurada A, Cutz JC, et al., Erlotinib in lung cancer – molecular and clinical predictors of outcome, *N Engl J Med*, 2005;353:133–44.
28. Hirsch FR, Varella-Garcia M, Dziadziuszko R, et al. Fluorescence *in situ* hybridization subgroup analysis of TRIBUTE, a phase III trial of erlotinib plus carboplatin and paclitaxel in non-small cell lung cancer, *Clin Cancer Res*, 2008;14:6317–23.
29. Hirsch FR, Herbst RS, Olsen C, et al., Increased EGFR gene copy number detected by fluorescent *in situ* hybridization predicts outcome in non-small-cell lung cancer patients treated with cetuximab and chemotherapy, *J Clin Oncol*, 2008;26:3351–7.
30. Hirsch FR, Dziadziuszko R, Varella-Garcia M, et al., First-generation epidermal growth factor receptor inhibitors in non-small cell lung cancer: clinical impact of the epidermal growth factor receptor fluorescence *in situ* hybridization assay, *J Thorac Oncol*, 2008;3:S138–42.
31. Tsao MS, Aviel-Ronen S, Ding K, et al., Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer, *J Clin Oncol*, 2007;25:5240–7.
32. Cappuzzo F, Tallini G, Finocchiaro G, et al., Insulin-like growth factor receptor 1 (IGF1R) expression and survival in surgically resected non-small-cell lung cancer (NSCLC) patients, *Ann Oncol*, 2010;21:562–7.
33. Rosell R, Skrzypski M, Jassem E, et al., BRCA1: a novel prognostic factor in resected non-small-cell lung cancer, *PLoS One*, 2007;2:e1129.
34. Cobo M, Massuti B, Morán T, et al., Spanish customized adjuvant trial (SCAT) based on BRCA1 mRNA levels, *J Clin Oncol*, 2008;26:Abstract 7533.
35. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies, *Oncologist*, 2009;14:253–63.
36. Scagliotti GV, Parikh P, von Pawel J, et al., Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer, *J Clin Oncol*, 2008;26:3543–51.
37. Chang MH, Ahn JS, Lee J, et al., The efficacy of pemetrexed as a third- or fourth-line therapy and the significance of thymidylate synthase expression in patients with advanced non-small cell lung cancer, *Lung Cancer*, 2010;69:6.
38. Righi L, Papotti MG, Ceppi P, et al., Thymidylate synthase but not excision repair cross-complementation group 1 tumor expression predicts outcome in patients with malignant pleural mesothelioma treated with pemetrexed-based chemotherapy, *J Clin Oncol*, 2010;28:1534–9.
39. Seve P, Lai R, Ding K, et al., Class III beta-tubulin expression and benefit from adjuvant cisplatin/vinorelbine chemotherapy in operable non-small cell lung cancer: analysis of NCIC JBR.10, *Clin Cancer Res*, 2007;13:994–9.
40. Gan PP, Pasquier E, Kavallaris M, Class III beta-tubulin mediates sensitivity to chemotherapeutic drugs in non small cell lung cancer, *Cancer Res*, 2007;67:9356–63.
41. Zhu YH, Chen JY, Yang GY, et al., Diagnostic value of transbronchial lung biopsies for acute and chronic rejection in lung transplant recipients [In Chinese], *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*, 2009;21:119–20.
42. Chung CH, Seeley EH, Roder H, et al., Detection of tumor epidermal growth factor receptor pathway dependence by serum mass spectrometry in cancer patients, *Cancer Epidemiol Biomarkers Prev*, 2010;19:358–65.
43. Carbone DP, Salmon JS, Billheimer D, et al., VeriStrat classifier for survival and time to progression in non-small cell lung cancer (NSCLC) patients treated with erlotinib and bevacizumab, *Lung Cancer*, 2010,69:337–40.
44. Amann JM, Lee JW, Roder H, et al. Genetic and proteomic features associated with survival after treatment with erlotinib in first-line therapy of non-small cell lung cancer in Eastern Cooperative Oncology Group 3503, *J Thorac Oncol*, 2010;5:169–78.
45. Salmon S, Chen H, Chen S, et al., Classification by mass spectrometry can accurately and reliably predict outcome in patients with non-small cell lung cancer treated with erlotinib-containing regimen, *J Thorac Oncol*, 2009;4:689–96.
46. Johnson DH, Fehrenbacher L, Novotny WF, et al., Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer, *J Clin Oncol*, 2004;22:2184–91.
47. Sandler A, Gray R, Perry MC, et al., Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer, *N Engl J Med*, 2006;355:2542–50.
48. Manegold C, Bevacizumab for the treatment of advanced non-small-cell lung cancer, *Expert Rev Anticancer Ther*, 2008;8:689–99.
49. Taron M, Rosell R, Felip E, et al., BRCA1 mRNA expression levels as an indicator of chemoresistance in lung cancer, *Hum Mol Genet*, 2004;13:2443–9.
50. Quinn JE, Kennedy RD, Mullan PB, et al., BRCA1 functions as a differential modulator of chemotherapy-induced apoptosis, *Cancer Res*, 2003;63:6221–8.
51. Kamal NS, Soria JC, Mendiboure J, et al.; International Adjuvant Lung Trial-Bio investigators, MutS homologue 2 and the long-term benefit of adjuvant chemotherapy in lung cancer, *Clin Cancer Res,* 2010;16(4):1206–15.
52. Filipits M, Haddad V, Schmid K, et al., Multidrug resistance proteins do not predict benefit of adjuvant chemotherapy in patients with completely resected non-small cell lung cancer: International Adjuvant Lung Cancer Trial Biologic Program, *Clin Cancer Res*, 2007;13(13):3892–8.