The discovery of treatable molecular targets in the adenocarcinoma histologic subtype of non-small cell lung cancer (NSCLC) with approved drugs is the most conspicuous and exciting development in the treatment of advanced lung cancer (1,2). No molecular targets treatable with drugs with proven efficacy have been described for squamous or small cell lung cancer (3). However, in adenocarcinomas, a number of mutations and gene fusions have been identified that drive cancer growth. These oncogenic targets guide treatment selection for specific patient subsets and the concept of “personalized therapy” has transformed the standard of care. There are four key components of personalized therapy. The first is the presence of an oncogenic target that drives cancer growth. Second is a predictive biomarker that detects the presence of the target. The third component is a drug that blocks the driver mutation with manageable normal tissue toxicity. The fourth essential step is well conducted clinical trials that confirm treatment efficacy showing a clinically worthwhile benefit. So far, treatment efficacy has been confirmed for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and V-ROS avian UR2 sarcoma virus oncogene homolog (ROS1) (1,2). Because of the success of targeted therapies in NSCLC patients with druggable mutations, the survival with metastatic NSCLC in these groups is approximately double that of patients without them. Molecular profiling (primarily in non-squamous cancers) has become standard in clinical practice. B-Raf proto-oncogene serine/threonine kinase (BRAF) mutations and ret proto-oncogene (RET) fusions are under investigation in ongoing clinical studies (4). The success of cancer genomics research in transforming the clinical care of patients with lung cancer is a notable achievement, but even within the adenocarcinoma histologic subtype, less than one third of patients have a druggable target. Moreover, almost all patients develop resistance to ongoing targeted therapy so the treatment is palliative. Moving personalized therapy into the curative adjuvant setting is a notion that captures the imagination of lung cancer investigators.

In 2009, the French cooperative thoracic intergroup launched the TASTE (tailored post-surgical therapy in early stage NSCLC) randomized phase II trial to assess the feasibility of patient-tailored treatment in surgically resected stage II or IIIA non-squamous lung cancers (5). Patients in the control arm (N=74) received four standard-dose courses of cisplatin plus pemetrexed (CP). In the customized treatment arm (N=76), patients with activated EGFR mutations were to receive erlotinib for one year; ERCC-1 negative patients received four CP courses, whereas ERCC-1 positive cases received no chemotherapy and were followed only. The objective of the trial was to demonstrate the feasibility of customized adjuvant chemotherapy based on biomarker analysis within a 2-month post-surgery window of treatment. Secondary objectives were tolerability, compliance with adjuvant therapy and biomarker distribution. The overall success rate of the trial, defined as the percentage of patients with complete biomarker status able to start adjuvant treatment within 2 months of surgery was 80%. Of the 127 patients allocated to CP, 82% received four cycles with good tolerability. However, the EGFR mutation rate found in the study was lower than the investigators expected. Seven patients (9.2%) received erlotinib in the customized arm for a
median exposure of 344 days. With respect to the ERCC-1 biomarker predicting resistance to platinum, the study immuno-histochemistry was positive in 25.3% vs. 44% in the IALT study (6). Disconcertingly, in an effort to comprehend this difference, the investigators found that the monoclonal antibody reagent was unable to distinguish between the four isoforms of the ERCC-1 protein, whereas only one isoform has full capacity for nucleotide excision repair (7). The ERCC-1 readouts were totally unreliable and for this reason the study was terminated and plans for a phase III study were scrapped. Sixteen patients not given adjuvant chemotherapy because of the flawed ERCC-1 biomarker were potentially harmed. Nevertheless, the investigators should be congratulated for their innovative efforts to move personalized therapy forward into the curative adjuvant setting. However, as a practical matter it is “back to the drawing board” for design of customized studies acknowledging what is now known about strengths and weaknesses of biomarker analysis and the potential of targeted therapy to enhance or replace standard adjuvant chemotherapy regimens.

With respect to the reliability of biomarkers in personalized medicine, the safest ground is the performance of genetic tests for detection of EGFR, ALK and ROS-1 (4). The reliability of immuno-histochemical biomarkers is another matter. At the 2014 ESMO conference, a poignant paper was presented by Seymour et al. on the prognostic and predictive biomarkers described in adjuvant chemotherapy for resected NSCLC trials by the LACE-Bio group (8). Based on retrospective analyses, eight immunohistochemical (IHC) biomarkers had been reported to be of predictive or prognostic value. The IHC biomarkers included ERCC-1, lymphoid infiltrate, mucin, β tubulin, P27, FASL, FAS/FASL and BAX. Over 3,000 specimens from the IALT, ANITA, and NCIC CTG BR 10 studies were re-examined to determine if the predictive/prognostic biomarker could be validated. In the end, LACE-Bio failed to validate all IHC biomarkers previously reported to be predictive of chemotherapy benefit and only two could be confirmed as prognostic (mucin for DFS and β-tubulin for OS). Some of the tests were performed again on the same specimen and were often discordant with the original result. Although inexpensive and widely available, IHC based assays other than for ALK are usually misleading and require validation before implementation in trials of personalized therapy for NSCLC.

There is some data in 2015 for efficacy of molecularly targeted therapy given after surgical resection of NSCLC. In a multicenter phase II study of two years of adjuvant erlotinib in resected early-stage NSCLC that were EGFR mutation positive, Pennell et al. (9) reported on 100 patients (45% stage I, 27% stage II, 28% stage IIIA). The 2-year DFS was 89% and the authors concluded that EGFR mutation positive NSCLC treated with adjuvant erlotinib have an improved 2-year DFS compared to historical controls. Of 24 recurrences, 22 occurred after stopping erlotinib (median 12 months) suggesting that adjuvant erlotinib may be beneficial. However, the BR 19 phase III randomized study of gefitinib vs. placebo in resected NSCLC showed no difference in the entire non-selected population for OS (HR 1.24; 95% CI, 0.94-1.64; P=0.14) or DFS (HR 1.22; 95% CI, 0.93-1.61; P=0.15) between the arms (10). For 15 patients that were mutation positive the HR was 1.84 for DFS and 3.16 for OS for gefitinib vs. placebo. Although this study was prematurely closed, the authors concluded that gefitinib was unlikely to be of benefit. At the ASCO 2014 meeting, the first results of a randomized, double-blind phase III trial of adjuvant erlotinib vs. placebo following complete resection with or without adjuvant chemotherapy in patients with stage IB-IIIA was presented (11). The RADIANT study included 623 patients on the erlotinib arm and 350 on placebo. In the entire unselected patient population, adjuvant erlotinib did not prolong the primary endpoint of DFS. In an subset analysis of EGFR mutation positive disease that included 102 patients on erlotinib and 59 patients on placebo, the HR for DFS was 0.61 (0.38-0.98; P=0.039) and for OS HR 1.09 (0.55-2.16; P=0.81) (12). Although the data on OS are limited, the overlapping survival curves do not look encouraging. From the data at hand, it looks like EGFR tyrosine kinase inhibitors may delay recurrence but not prevent it. With the higher incidence of EGFR mutation in Asian populations, this region will lead the way with prospective randomized trials comparing adjuvant EGFR directed therapy vs. standard chemotherapy. The West Japan Oncology Group is doing an adjuvant study to compare two years of adjuvant gefitinib with vinorelbine and cisplatin chemotherapy (WJOG 6014L). In United States, the Alchemist trial schema calls for 6,000-8,000 patients with stage IB, II and IIIA resected NSCLC to undergo central EGFR and ALK genotyping. For those EGFR positive, there is a comparison of erlotinib vs. placebo for 2 years (N=410) and for ALK-rearranged 2 years of crizotinib will be compared with placebo (N=360). Those without molecular alterations will be followed after adjuvant therapy creating a repository of tissue and outcome
data for later study of biomarkers.

At a more basic level, the choice of a chemotherapy regimen for adjuvant therapy is associated with practice variations. The best quality of evidence from randomized trials of chemotherapy vs. a control group is for the vinorelbine and cisplatin regimen (13,14). The TASTE investigators used pemetrexed and cisplatin because this regimen has less hematologic toxicity (5). Indeed, pemetrexed and cisplatin exhibited an excellent safety profile that allowed 82% of patients to receive four standard-dose cycles, a rate superior to published delivery of vinorelbine and cisplatin (15). Proponents of pemetrexed regard it as a targeted therapy with thymidylate synthase as a relevant biomarker (16). Based on the phase III study by Scagliotti et al. (16) comparing gemcitabine and cisplatin vs. pemetrexed and cisplatin, the pemetrexed combination is widely accepted as being more efficacious in treatment of advanced NSCLC with non-squamous histology. So what is wrong with extrapolating from stage IV disease to the adjuvant setting especially to a regimen that is supposedly more efficacious and better tolerated with more reliable chemotherapy administration? There are a number of factors that require careful consideration.

The small survival improvement seen with pemetrexed-cisplatin compared to gemcitabine cisplatin in non-squamous patients was observed in a non-stratified subset analysis (the stratification parameter was for histologic vs. cytologic biopsy, not histologic subtype) (16). Another phase III randomized trial by Grønberg et al. (17) of carboplatin-pemetrexed vs. carboplatin gemcitabine showed no difference in survival in the non-squamous histologic subset. More importantly, there are now five randomized trials that have compared platinum-pemetrexed to another platinum doublet in an advanced NSCLC patient population that was exclusively non-squamous and none have shown a hint of superior efficacy for platinum-pemetrexed in response rate, time to progression or overall survival (18-22). Not all these trials are powered to show small differences in survival, but the consistency of the negative results in all prospective randomized trials make the likelihood of superior efficacy of pemetrexed-platinum in non-squamous lung cancer very questionable. With respect to extrapolating results in stage IV disease to the adjuvant setting, there are other pitfalls. Oncologists that treat colorectal cancer know that FOLFOX and FOLFIRI are of the same effectiveness in the metastatic setting (23,24). However, in the adjuvant setting FOLFOX is effective in increasing the cure rate (25) whereas FOLFIRI is not (25).

Extrapolating chemotherapy selection from stage IV to the adjuvant setting is not without hazards and it is better to have actual data from large adjuvant trials. Some data exists on platinum and pemetrexed in the adjuvant setting but this is limited to an evaluation of drug delivery and toxicity as the trial is underpowered to examine survival outcomes (26). There are practice variations with respect to selection of chemotherapy regimens and many oncologists are comfortable to choose regimens that are not evidence-based in the adjuvant setting. Generally speaking, Canadian oncologists do not do this and cisplatin and vinorelbine with level 1 evidence of efficacy remains standard (14).

What are the prospects for improving the cure rate of early stage small cell lung cancer using biomarkers and molecularly targeted therapy? Our experience has taught us that we must be cautious with IHC biomarkers. With respect to the more reliable genetic tests, the familiar pie diagram of druggable driver mutations for adenocarcinoma has not changed recently. Although it may be an overstatement to say that discovery of new molecular targets for NSCLC has “hit the wall”, it is clear that the rate of progress has stalled. In 2015, the most exciting research in targeted therapy of NSCLC is not identification of new targets but better treatment of already known targets like EGFR mutations with third-generation inhibitors and ALK mutations with second-generation drugs. The low hanging fruit has been picked. For squamous lung cancer, the molecular battlefield is complex and bleak with no molecular targets identified that can be treated with a demonstrated worthwhile improvement in survival and certainly no biomarkers worth testing for guidance of adjuvant therapy (27). In the United States, ECOG 1505 completed accrual in Sep 2013 testing the addition of bevacizumab to adjuvant chemotherapy in resected NSCLC. Most of us would be astonished, if the result was different than that observed for the addition of bevacizumab to chemotherapy for resected colorectal cancer (28).

Clearly, it is difficult to improve the cure rate of resected early stage NSCLC using biomarkers and molecularly targeted therapy. On the other hand, there is only one example where adjuvant treatment of a resected epithelial malignancy has been improved with a (non-hormonial) molecularly targeted therapy. Trastuzumab plus adjuvant chemotherapy for operable breast cancer stands alone as the only such proven therapy in all of cancer medicine (29).

For lung cancer, there is considerable excitement with emerging results of immunotherapy with checkpoint inhibiting antibodies in advanced disease. There is an
intriguing possibility that the high antigenic load from many mutations in NSCLC may be an asset for adjuvant immunotherapy studies where the burden of residual disease is low. The National Cancer Institute of Canada Clinical Trials Group is planning such a study but it will be a number of years before results will be available.

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