Lung cancer is the most common cause of cancer-related mortality in the United States, causing more deaths than breast, colon, and prostate cancer combined. Approximately 80% of lung cancer cases are non–small cell lung cancer (NSCLC; ref. 1). Of these, one third, or 40,000 patients in the United States annually, present with locally advanced or stage III disease. Stage III disease represents a heterogeneous group of patients consisting of several distinct substages (Table 1). However, all are characterized by a high rate of subsequent distant metastases following treatment with surgery or radiotherapy alone (2). As a result, clinical research efforts in stage III disease have focused on combined modality therapy, incorporating chemotherapy with thoracic radiation and/or surgery. Incorporation of novel therapeutic agents (NTA) in the management of stage III NSCLC will require a careful assessment of their potential in substituting for or enhancing the efficacy of modalities currently used.

Conceptually, locally advanced lung cancer can be thought of as a two-compartment model: a local-regional compartment in the chest and a distant compartment harboring potential micrometastases. At the most basic level, treatment with radiation therapy is directed toward the intrathoracic tumor burden, whereas chemotherapy works to eradicate systemic microscopic metastatic deposits below current levels of detection by computerized tomography scanning or positron emission imaging with fluorodeoxyglucose. Chemotherapy may contribute a radiosensitizing effect locally, as well as providing cytoreduction of bulky locoregional disease. Recently, a third compartment, the brain sanctuary, has assumed an increasingly important role in determining long-term patient outcome following combined modality therapy in stage III NSCLC. In many reports, isolated brain recurrence is being observed in ~20% of cases, raising the issue of whether prophylactic cranial irradiation should be used after completion of chemoradiotherapy, similar to standard practice in limited stage small cell lung cancer (3). Cancer must be eradicated from all three compartments to achieve long-term survival.

Four different treatment paradigms have emerged in recent years for application of chemoradiation (Fig. 1): sequential, concurrent, induction chemotherapy followed by concurrent chemoradiation, and concurrent chemoradiation followed by consolidation chemotherapy (4). Sequential approaches to chemoradiotherapy (5), in which chemotherapy precedes thoracic radiation, generally improve outcome by reducing distant failure rates, with no improvement in local control when compared with radiotherapy alone (6). In contrast, with concurrent chemoradiotherapy strategies, chemotherapy may play either a radiosensitizing role designed to improve local control or a cytotoxic role by eradicating distant micrometastases, or both, depending on the timing and doses of chemotherapy used. An example is provided by the trial of Schaake-Koning et al. (7) in which low-dose daily cisplatin improved survival solely by increasing local control without reduction in the rate of distant metastases. In view of these observations, concurrent chemoradiotherapy paradigms integrating both radiosensitizing agents and dose levels of...
chemotherapy effective against micrometastases may prove to be most efficacious.

Each approach offers potential advantages and disadvantages for the incorporation of NTAs into the paradigm. NTAs may theoretically play a similar role to that of chemotherapy because in addition to addressing distant micrometastases, some NTAs also possess radiosensitizing properties that could assist in local control.

Integration of Novel Therapeutic Agents into Chemoradiation Paradigms: Conceptual Issues

Despite the improvements in outcome achieved by using combinations of chemoradiation in unresectable stage III NSCLC, the great majority of these patients eventually succumb to their cancer. Furthermore, with current chemoradiation approaches, both local disease control within the thorax and distant micrometastases remain significant challenges. Therefore, careful consideration must be given to exactly what role a NTA is being asked to play in the combined modality therapy setting. Does the NTA have single-agent activity in NSCLC? Does it have radiosensitizing properties, or is its proposed role to be solely in control of distant micrometastases? What is the “best fit” for the NTA in the chemoradiation paradigms shown in Fig. 1? For example, is the agent best utilized as maintenance therapy, sequenced after chemoradiation, or added to an established chemoradiation regimen during the concurrent phase? Is the potential benefit from the NTA of sufficient magnitude that it can be proposed as a substitute for chemotherapy, delivered in combination with radiotherapy? Most importantly, it is essential that carefully planned correlative science accompany clinical trials to determine the biological effects of the NTA and its contribution to efficacy and/or toxicity.

Integration of Novel Therapeutic Agents into Chemoradiation Paradigms: Ongoing and Planned Clinical Trials

A wide array of NTAs is currently being evaluated in NSCLC. This review will highlight selected examples for which there are preclinical and/or clinical data to support their study in the combined modality setting in stage III NSCLC, including (a) signal transduction modulators directed against numerous molecular targets, (b) antiangiogenesis agents, (c) hypoxic cytotoxins, and (d) inhibitors of cyclin-dependent kinases.

Signal transduction modulators of the epidermal growth factor receptor pathway. The epidermal growth factor receptor (EGFR), a member of the HER or Erb-B family of type I receptor tyrosine kinases, is implicated in the development and progression of cancer (8). EGFR is expressed in many normal human tissues and activation of this proto-oncogene results in overexpression in many types of human tumors. Recently, small molecule tyrosine kinase inhibitors (TKI, gefitinib and erlotinib) and monoclonal antibodies (cetuximab) directed against EGFR have been shown to be efficacious in the treatment of advanced NSCLC and colon cancer, respectively (9).

Because the EGFR TKIs gefitinib and erlotinib have been found to be active in patients with NSCLC after failure of primary therapy, these agents have been added to chemoradiation regimens in advanced NSCLC in order to improve local control and survival.

**Table 1. Clinically distinct subgroups within stage III NSCLC**

| Stage IIIA | T3N1 | Tumor invasion of chest wall or near carina, with involved peribronchial or hilar lymph nodes |
| Stage IIIA | T1-3N2 | Prognosis and therapy determined by the involved ipsilateral mediastinal lymph nodes |
| Stage IIIB | T4N0-2 | Locally invasive primary tumor (excluding malignant pleural effusion) without involved contralateral or supraclavicular lymph nodes |
| Stage IIIB | T1-4N3 | Prognosis and therapy determined by the involved contralateral or supraclavicular lymph nodes |
| Stage IIIB | T4N0-3 | Malignant pleural effusion (T4), treated as stage IV |

**Fig. 1.** Chemoradiotherapy paradigms in stage III NSCLC.
frontline therapy, it was a logical step to combine them with chemotherapy. However, four large randomized trials of chemotherapy with or without gefitinib or erlotinib (INTACT 1 and 2, TRIBUTE, and TALENT) failed to show any benefit of the combination for response rate, progression-free survival, or overall survival (10–13). The negative results of these trials represented a major setback for the field of NSCLC research. Several questions remained unanswered: Why did these trials fail? Are the results of these trials generalizable to anti-EGFR monoclonal antibody therapies? How do we best use EGFR inhibitors of either type (TKIs or monoclonal antibodies) in advanced NSCLC?

Possible explanations for the negative results of the INTACT, TRIBUTE, and TALENT trials include, but are not limited to, (a) lack of patient selection for a predictive marker of response; (b) incorrect dose, schedule, or sequence of drugs; (c) potential antagonistic interaction between concurrent EGFR TKI and chemotherapy; or (d) a combination of these and other factors. Despite previous reports of preclinical synergism between EGFR TKIs and chemotherapy, more recent in vitro and in vivo studies of concurrent administration have suggested antagonism when compared with sequential administration of EGFR TKIs and chemotherapy (14). In an in vitro model (Fig. 2), the greatest degree of apoptosis is achieved when the chemotherapeutic agent docetaxel and erlotinib are administered sequentially rather than concurrently. Similarly, in vivo data from a xenograft study are supportive of the concept of antagonism (Fig. 3). In this NSCLC experimental model, daily administration of gefitinib plus paclitaxel (D) achieves no better growth inhibition than either single agent alone (B or C). However, gefitinib given in pulse doses of 250 mg/kg on days 1 and 2 with the same schedule of paclitaxel (E) results in smaller average tumor volumes and increases the number of mice that are tumor free (15). This data suggests that antitumor activity of EGFR TKIs and chemotherapy may be schedule dependent.

These results have prompted considerable debate about how best to incorporate EGFR inhibitors into chemoradiotherapy paradigms in stage III NSCLC. If antagonism does exist with concurrent administration, then sequential administration of EGFR TKIs before or after concurrent chemoradiotherapy (as in Fig. 1) is a logical approach. In the Southwest Oncology Group, a previous phase II trial (S9504) provided the basis for consolidation chemoradiotherapy following chemoradiotherapy. In S9504, concurrent thoracic radiation together with cisplatin/etoposide was followed by three cycles of consolidation docetaxel. In 83 patients with stage IIIIB disease, the median survival was 26 months and the 3-year survival 37%, comparing very favorably to Southwest Oncology Group historical controls (S9019) and available literature in this patient subset (16). Based on these encouraging results, the current Intergroup phase III trial (S0023) randomizes patients with unresectable stage III NSCLC to receive concurrent chemoradiotherapy and consolidation docetaxel, followed by maintenance gefitinib or placebo (Fig. 4). This study design avoids potential antagonism of gefitinib with chemotherapy or radiotherapy, and the toxicity profile of gefitinib suggests that it may be well tolerated for long-term maintenance therapy (17).

Alternatively, other studies are exploring the use of EGFR TKIs given concurrently with thoracic radiotherapy or chemoradiotherapy, based on the rationale that the INTACT trials were negative due to failure to select for a predictive marker of efficacy rather than antagonism. In this regard, Cancer and Leukemia Group B 30106 is a stratified phase II trial testing gefitinib concurrently with thoracic radiation alone in patients with a performance status of 2 or with >5% weight loss, and concurrently with chemoradiotherapy in patients with performance status of 0 to 1 (18). All patients receive induction carboplatin/paclitaxel and gefitinib as well as maintenance gefitinib. Similarly, a University of Chicago National Cancer Institute Consortium phase I trial is investigating the maximum tolerated dose of erlotinib given concurrently with two different chemoradiation regimens (induction chemotherapy followed by concurrent chemoradiation or concurrent chemoradiation followed by consolidation chemotherapy; ref. 19).

Lastly, it remains unclear whether the concerns described above pertain to monoclonal antibodies, such as cetuximab. In contrast to data with EGFR TKIs in the INTACT trials, cetuximab is effective in combination with concurrent chemotherapy in colorectal cancer (20). Moreover, the addition of cetuximab to radiation has recently been shown to be superior to radiation alone for locally advanced head and neck cancer (21). Based on these results, the Radiation Therapy Oncology Group is currently conducting a phase II study of cetuximab, carboplatin, paclitaxel, and radiotherapy in unresectable stage III NSCLC. A SWOG protocol in development will explore this approach with a combination of cetuximab given concurrently with thoracic radiation and weekly docetaxel in a defined population of patients with poor risk stage III NSCLC.

Angiogenesis inhibitors. Vascular endothelial growth factor (VEGF) is an endogenous angiogenic factor involved in both normal angiogenesis and the neovasculature associated with malignancy. In NSCLC, increased VEGF expression is associated with a poor prognosis and is inversely correlated with wild-type p53 (22). An anti-VEGF monoclonal antibody, bevacizumab, inhibits tumor-associated angiogenesis, growth, and metastasis in a dose-dependent manner. Preclinical studies have also shown synergistic antitumor activity for anti-VEGF antibody in combination with chemotherapy. Clinical trials have confirmed encouraging activity of bevacizumab in combination with

Fig. 2. Sequence-specific activity of erlotinib plus docetaxel: quantitation of apoptosis (%Sub-G1) by flow cytometry in a NSCLC cell line, A549 (14).

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chemotherapy in patients with metastatic NSCLC (23), and a randomized trial showed improved survival with the combination by comparison with chemotherapy alone in advanced-stage colorectal cancer (24). An ongoing phase II trial is evaluating bevacizumab in combination with paclitaxel/carboplatin and thoracic radiotherapy in stage III NSCLC.

Thalidomide was one of the earliest antiangiogenic agents to be tested in clinical trials. It is of historical interest because of its well-known teratogenicity, as evidenced by the stunted limb growth observed in children whose mothers took thalidomide as an antiepileptic during pregnancy (25). One hypothesis was that these thalidomide-induced limb defects were due to angiogenesis inhibition in fetal limb buds. There has been a renewed interest in thalidomide during the past decade for its potential antineoplastic activity, initially noted in multiple myeloma (26). Thalidomide is currently being evaluated in an Eastern Cooperative Oncology Group phase III trial in which patients with unresectable stage III NSCLC are randomized to concurrent carboplatin/paclitaxel and radiation therapy with or without thalidomide.

**Hypoxic cytotoxins.** Tirapazamine, a hypoxic cell cytotoxin now undergoing clinical evaluation, shows preclinical synergism with chemotherapy and radiation (27, 28). Under aerobic conditions, such as in normal tissue, tirapazamine is inactive; however, it is bioactivated under hypoxic conditions. In an initial phase III trial in stage IV NSCLC (CATAPULT 1), tirapazamine in combination with cisplatin resulted in improved survival compared with cisplatin alone (29). In addition, it has shown promising clinical activity in combination with radiotherapy and cisplatin in head and neck cancer (30). Unfortunately, a subsequent phase III trial failed to confirm the superiority of tirapazamine plus chemotherapy versus chemotherapy alone (31). Present hopes for clinical utility of tirapazamine rest with ongoing trials using it in combination with radiotherapy. In stage III NSCLC, an ongoing trial of the NCI-sponsored California Cancer Consortium is testing tirapazamine in combination with concurrent carboplatin/paclitaxel and thoracic radiotherapy.

**Cell cycle modulating agents.** Tumor cell killing by ionizing radiation varies across the cell cycle. Cells are most radiosensitive in G2-M and most radioresistant in S phase. Therefore, agents that can increase cell numbers in G2 and block cells from entering S phase may be potential radiosensitizers. Similarly, many chemotherapy agents are cell cycle specific. NTAs that modulate the cell cycle offer tremendous potential as sensitizers for cell cycle–specific chemotherapeutic agents and radiotherapy. UCN-01, a staurosporine analogue isolated from Streptomyces, is an early example of this class of agents. UCN-01 was originally developed as an inhibitor of protein kinase C, but antitumor activity is more likely related to independent effects on cyclin-dependent kinase inhibition and cell cycle modulation. UCN-01 shows potent in vitro and in vivo activity against a variety of tumor types. In addition, UCN-01 markedly potentiates the cytotoxicity of several chemotherapeutic agents, including cisplatin. The mechanism of potentiation may be related to p53-independent abrogation of the typical G2 arrest induced by cisplatin (32). In NSCLC, UCN-01 is reported to enhance cisplatin-induced cytotoxicity 100-fold in a cell line in which UCN-01 alone is ineffective (33). Phase I trials of UCN-01 as a single agent have now been completed, and trials investigating combinations of UCN-01– and platinum-based chemotherapy will be initiated in the near future.

### Summary

The development of combination chemotherapy and radiation therapy regimens over the past two decades has resulted in improved outcomes for stage III NSCLC. The use of NTAs with chemoradiation regimens for stage III NSCLC holds promise for improved outcomes with limited toxicity. However, the optimal integration of NTAs into current chemoradiation paradigms has yet to be determined. The preclinical rationale and early clinical experience of NTAs in chemoradiation regimens have been presented here to develop a conceptual framework for further laboratory and clinical study.

### Open Discussion

**Dr. Everett Vokes:** You mentioned G1 cell cycle arrest. Doesn’t C225 also cause G1 arrest? Then, you do have a contradiction with the clinical realities. There is the head and neck cancer trial that had a positive result with C225.  

**Dr. Gandara:** Yes, I agree, and that’s why if these trials with cetuximab all turn out to be positive, then there is something different about EGFR monoclonal antibodies compared with the tyrosine kinase inhibitors, just as there is with the monoclonal antibody trastuzumab, which is additive with chemotherapy. For example, an immunologic response could be initiated through the monoclonal antibody that would not occur with a tyrosine kinase inhibitor.
Dr. Thomas Lynch: Dr. Johnson, for the patients with EGFR mutations who present with locally advanced disease, what are your thoughts on a trial design that might be a reasonable way to approach that group of patients? 

Dr. Bruce Johnson: I think we need a prospective trial with the agent by itself so you know what the antitumor activity is. So, take a group of patients who have the mutation and have predominantly local disease, then treat them with concurrent radiation plus just the EGFR inhibitor.

Dr. Gandara: I didn’t include that issue in my talk because you convinced me the mutation only occurs in 2% of our lung cancer patients in the United States, so we would have to do that trial in Japan.

Dr. Lynch: Two percent? Pasi Jänne’s data presented at ASCO was 13% in those with metastatic disease. The question is how frequent is it in locally advanced disease?

Dr. Johnson: In the publication for our group, it was 2% [Science 2004;304:1497–500]. We have another study in press of 250 patients and there the mutation runs ~10%.

Dr. Lynch: The question is whether those patients present more often metastatically or more often with isolated nodules. I don’t think we know if the stage distribution of EGFR mutants is the same as that of the whole population of lung cancer patients, although the hints we have so far suggest there is probably not a huge difference.

Dr. Joan Schiller: If it is only 10% though, it’s going to be very difficult to do such a study. 

Dr. Lynch: It’s going to be incredibly difficult to do that. It becomes a Japanese question.

Dr. Karen Kelly: Paul Bunn made a comment to me the other day that there was no difference in overall survival in the TRIBUTE trial between the patients who had EGFR mutations and those who did not. Is that true?

Dr. Johnson: Of the ~30 patients who had EGFR mutations, the survival is similar so far whether they got erlotinib or not. But there have only been four deaths in each group, so in terms of long-term outcome it is unknown as yet. If they had EGFR mutations and if they did or did not get erlotinib, the outcome of the people with advanced disease was dramatically different than those without mutations.

Dr. Vokes: If you take out those patients with the mutation, what happens to the rest of the group?

Dr. Lynch: The response rates in survival were not dramatically different in the group that had mutations and received erlotinib.

Dr. Gandara: Actually, the progression rate was dramatically different. If you did not have the mutation and you got concurrent erlotinib and chemotherapy, you had twice the progression rate compared with chemotherapy alone.

Dr. Lynch: You mean you did worse with the mutation? There was a higher response rate, 27% versus 21%.

Dr. Gandara: Yes. The response rate was higher, but the progression rate was dramatically higher if you got the combination and had no mutation.

Dr. Lynch: With all of these data, just like with the analysis we are doing with INTACT, it is a subset of a subset of a subset. It is retrospective, and you don’t know the characteristics of the patients who you happen to have tumor on. Are those patients reflective of the entire group of people we see with metastatic disease? That is one of the concerns we have until we have prospective studies going forward.

Dr. Johnson: In the subset analyses of TRIBUTE, the take-home message to me is that the nonsmoker cohort has a dramatically different outcome from the smokers in that the median survival of the nonsmokers was 22 months compared with 10 months for the smokers. That is information we can actually use in treating patients.

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Integration of Novel Therapeutics into Combined Modality Therapy of Locally Advanced Non-Small Cell Lung Cancer

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