Asian Thoracic Oncology Research Group Expert Consensus Statement on Optimal Management of Stage III NSCLC

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Received 5 August 2019; revised 24 October 2019; accepted 24 October 2019
Available online - 13 November 2019

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Disclosure: Dr. W.L. Tan reports travel/conference reimbursement from Boehringer Ingelheim, outside the submitted work. Dr. Chua reports personal fees from Varian Medical Systems, AstraZeneca, and Brainlab, outside the submitted work. Dr. Lin reports personal fees from BeiGene, Roche, and Novartis, outside the submitted work. Dr. Lee reports honoraria for delivering invited lectures and educational talks from AstraZeneca, Roche, Eli Lilly, Merck Sharp & Dohme, Bristol Myers Squibb, and Novartis, during the conduct of the study and outside the submitted work. Dr. Tho reports honorarium from AstraZeneca, MSD, Boehringer Ingelheim, Roche, and Eli Lilly, outside the submitted work. Dr. Ho reports personal fees from AstraZeneca EGFRTm NSCLC First-Line (FLAURA) Advisory Board Meeting, outside the submitted work. Dr. Yang reports honorarium for speech and attending advisory board from Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech, Chugai, MSD, Pfizer, Novartis, BMS, Ono pharmaceuticals, and AstraZeneca; personal fees for advisory board participation from Astellas, Merck Serono, Celgene, Merrimack, Yuhan Pharmaceuticals, Daichi Sankyo, Hansoh Pharmaceuticals, Takeda Pharmaceuticals, Blueprint Medicines, and G1 therapeutics, outside the submitted work. Dr. Soo reports grants and personal fees from AstraZeneca, and Boehringer Ingelheim, personal fees from BMS, Lilly, Merck, Novartis, Pfizer, Roche, Taiho, Takeda, Yuhan, outside the submitted work. Dr. Mok reports leadership and is shareholder of Hutchison ChImed, and Sanomics; leadership in ASO, ASCO, and CSCSO; leadership, grants, and personal fees from AstraZeneca; grants and personal fees from Roche/Genentech, Pfizer, Merck Sharp & Dohme, Novartis, SFL, and Bristol-Myers Squibb; non-financial support from GeneDecode; grants from Clovis Oncology, and Xcyvere; personal fees from Boehringer Ingelheim, Lilly, Merck Serono, Vertex Pharmaceuticals, Oncogenex, Celgene, Ignyta, Cirina, Fishawack Facilitate, Takeda Oncology, Janssen, OrigMed, Hengrui Therapeutics, Sanofi-Aventis R&D, Yuhan Corporation, PriIME Oncology, Amoy Diagnostics, Loxo-Oncology, ACEA Pharma, Alpha Biopharma Co., Ltd., CStone Pharmaceuticals, IQVIA, InMed Health, InMed Medical Communication, Virtus Medical Group, Bioidetics Ltd., and Bayer, outside the submitted work. Dr. DSW Tan reports grants and personal fees from Novartis, Bayer, AstraZeneca, and Pfizer; personal fees from Boehringer Ingelheim, Celgene, Eli-lilly, Loxo, Merck, Roche, and Takeda; and grants from GlaxoSmithKline, outside the submitted work. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2019.10.022

Journal of Thoracic Oncology Vol. 15 No. 3: 324-343
ABSTRACT
Stage III NSCLC represents a heterogeneous disease for which optimal treatment continues to pose a clinical challenge. Recent changes in the American Joint Commission on Cancer staging to the eighth edition has led to a shift in TNM stage grouping and redefined the subcategories (IIIA–C) in stage III NSCLC for better prognostication. Although concurrent chemoradiotherapy has remained standard-of-care for stage III NSCLC for almost 2 decades, contemporary considerations include the impact of different molecular subsets of NSCLC, and the roles of tyrosine kinase inhibitors post-definitive therapy and of immune checkpoint inhibitors following chemoradiotherapy. With rapid evolution of diagnostic algorithms and expanding treatment options, the need for interdisciplinary input involving multiple specialists (medical oncologists, radiation oncologists, pulmonologists, radiologists, pathologists and thoracic surgeons) has become increasingly important. The unique demographics of Asian NSCLC pose further challenges when applying clinical trial data into clinical practice. This includes differences in smoking rates, prevalence of oncogenic driver mutations, and access to health care resources including molecular testing, prompting the need for critical review of existing data and identification of current gaps. In this expert consensus statement by the Asian Thoracic Oncology Research Group, an interdisciplinary group of experts representing Hong Kong, Korea, Japan, Taiwan, Singapore, Thailand, Malaysia, and Mainland China was convened. Standard clinical practices for stage III NSCLC across different Asian countries were discussed from initial diagnosis and staging through to multi-modality approaches including surgery, chemotherapy, radiation, targeted therapies, and immunotherapy.

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Keywords: Asian; Consensus statement; Stage III NSCLC

Introduction
NSCLC comprises 85% of all lung cancer, and one-third of patients with NSCLC have stage III disease at diagnosis.1 Median overall survival (OS) for stage III NSCLC was less than 2 years with an expected 5-year survival of only 15%.1 With positron-emission tomography (PET) scans and magnetic resonance imaging (MRI) of the brain, patients with minimal distant disease are now reclassified as stage IV instead of stage III. This stage migration inadvertently leads to better outcomes for stage III disease, as shown in recent studies.2,3 Even within stage III NSCLC, outcomes can be diverse — with 5-year OS for stage IIIA ranging from 15% to 35% and stage IIIB ranging from 5% to 10%.4 Until recently, there have been few advances in stage III NSCLC. Radiation dose escalation, induction, and consolidation chemotherapy have all failed to improve outcomes. Immune checkpoint inhibitors (ICIs) have revolutionized treatment for metastatic/recurrent patients, and the introduction of consolidation durvalumab in unresectable stage III NSCLC has resulted in a paradigm shift for stage III disease.5 At the same time, with the emergence of targeted therapies, precision biomarkers in stage IV are also gaining traction in stage III disease due to promising responses with biomarker-directed treatments. This is particularly relevant in Asia where targetable oncogenes (e.g., epidermal growth factor receptor mutations [EGFRm]) are more prevalent compared to Caucasian populations.6

The prevalence of these oncogenes and smoking prevalence makes NSCLC found in Asian patients intrinsically distinct from that found in Caucasian patients. Health care factors such as access to care and availability of resources also differ between Asian and Caucasian communities, and significantly impact on real-world management of patients. As such, the Asian Thoracic Oncology Research Group (ATORG) convened an expert panel representing Hong Kong, Korea, Japan, Taiwan, Singapore, Thailand, Malaysia, and Mainland China to provide guidance for optimal management of stage III NSCLC adapted to the Asian NSCLC community, as well as to define important research priorities.

Methods
The ATORG expert panel consisted of lung cancer physicians from radiation oncology, pathology, thoracic surgery, and medical oncology. Available scientific data and literature, including meta-analyses, randomized controlled trials, prospective nonrandomized clinical trials, and observational studies, pertaining to the clinicopathologic staging and various multimodality treatment approaches for stage III NSCLC were reviewed and discussed in detail. Particular attention was given to studies with Asian populations and recommendations were made in the context of the Asian clinical landscape, considering the unique genomic landscape and diversity in health care factors. A consensus statement was then agreed upon for each discussion point among the panel members, with the strength of evidence and grade of recommendation (adapted from the European Society for Medical Oncology Consensus and clinical practice guidelines, defined in Supplementary Table 1) indicated in parentheses.7

Clinical Definition of Stage III NSCLC
NSCLC is currently staged by the eighth edition TNM staging system, which differs from the seventh edition in several aspects (summarized in Fig. 1).8
Patients with NSCLC should undergo initial radiographic imaging with PET-computed tomography (CT) scan (preferred) or chest, abdomen, and pelvis CT scan plus whole-body bone scan. The recommended workup for resource-limited regions is included in Supplementary Table 2. False-positive results for nodal involvement on PET-CT can be seen in mycobacterium tuberculosis (TB) — which is particularly relevant in Asia where pulmonary TB is endemic.9 We highlight a case which illustrates the challenge of differentiating neoplastic from infective/inflammatory etiology due to TB in the workup of NSCLC in Asia, emphasizing the importance of pathologic confirmation for accurate staging (Supplementary Fig. 1).

As patients with stage III disease are more likely to harbor occult metastases at an incidence of 24% to 51%, particularly intracranial involvement, MRI (preferred) or CT brain is recommended to exclude brain metastasis.10 Early detection of brain metastases can enable early treatment before onset of complications (e.g., neurologic deficits or seizures). Lymph node status should be assessed via a combination of PET-CT and/or minimally invasive techniques such as endobronchial ultrasound (EBUS), mediastinoscopy, or thoracoscopy if local expertise is available. In patients with bulky N2 disease (e.g. >2 to 3 cm in short-axis diameter by CT, evidence of extracapsular nodal involvement, and involvement of more than two lymph node stations), minimally invasive techniques may not be routinely needed.11,12 EBUS biopsy for pathologic confirmation is preferred for initial mediastinal staging.13 The extent of mediastinal lymph node involvement is important for determining the appropriate treatment strategy, for example, surgery followed by adjuvant chemotherapy ± radiotherapy (RT) versus concurrent chemoradiotherapy (CCRT) followed by immunotherapy.

**ATORG Consensus**

PET-CT for pretreatment staging is ideal, but minimally, a CT scan of the chest, abdomen, pelvis, and brain, and a bone scan should be performed [I, A]. EBUS is preferred for initial mediastinal staging for pathologic confirmation of N2 disease compared to mediastinoscopy [I, A]. Pathologic mediastinal staging may not be routinely needed for multilevel or bulky N2 disease after multidisciplinary evaluation except in cases where it impacts on the decision for surgery or radical RT [V, A]. Infective etiology should be considered, especially in Asia where diseases such as TB are endemic [V, A]. Complex cases should be discussed at multidisciplinary discussions for consensus on combined-modality approaches [V, A].

**Figure 1.** Evolving definition of stage III (American Joint Committee on Cancer [AJCC] seventh and eighth editions). AJCC changes from the seventh to the eighth edition are highlighted here. In terms of stage III, tumor size of 5 to 7 cm and tumor size of 7 cm or more are upstaged from T2b to T3 and from T3 to T4, respectively. Tumor involvement of the diaphragm is also upstaged from T3 to T4. However, tumor involvement of the main bronchus within 2 cm to carina is downstaged from T3 to T2. Prognostic groupings have also changed with T3N3 or T4N3 now classified as a newly designated stage IIIC.

<table>
<thead>
<tr>
<th>AJCC 7th</th>
<th>AJCC 8th</th>
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<tbody>
<tr>
<td><strong>T1a</strong></td>
<td>IA</td>
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<tr>
<td>≤2 cm</td>
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<tr>
<td><strong>T1b</strong></td>
<td>IA</td>
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<td>IIB</td>
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<td>&gt;6-7 cm</td>
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<tr>
<td><strong>T3</strong></td>
<td>IIB</td>
</tr>
<tr>
<td>&gt;6-7 cm</td>
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<tr>
<td><strong>T4</strong></td>
<td>IIA</td>
</tr>
<tr>
<td>Any size with invasion of mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina</td>
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<thead>
<tr>
<th>AJCC 7th</th>
<th>AJCC 8th</th>
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<tbody>
<tr>
<td><strong>T1a</strong></td>
<td>IA1</td>
</tr>
<tr>
<td>≤2 cm</td>
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<tr>
<td><strong>T1b</strong></td>
<td>IA2</td>
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<tr>
<td>&gt;1-2 cm</td>
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<tr>
<td><strong>T1c</strong></td>
<td>IA3</td>
</tr>
<tr>
<td>&gt;2-3 cm</td>
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<tr>
<td><strong>T2</strong></td>
<td>IB</td>
</tr>
<tr>
<td>Invades main bronchus without carina</td>
<td></td>
</tr>
<tr>
<td>Partial or total atelectasis/pneumonitis</td>
<td></td>
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<tr>
<td>&gt;3-4 cm</td>
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<tr>
<td><strong>T2b</strong></td>
<td>IIA</td>
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<tr>
<td>&gt;4-5 cm</td>
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<tr>
<td><strong>T3</strong></td>
<td>IIB</td>
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<tr>
<td>&gt;6-7 cm</td>
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<tr>
<td><strong>T4</strong></td>
<td>IIA</td>
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<tr>
<td>&gt;7 cm</td>
<td></td>
</tr>
<tr>
<td>Or any size with invasion of mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina</td>
<td></td>
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</tbody>
</table>
Pathologic Definition of Stage III NSCLC
Pathologic examination provides precise information for staging and management of stage III NSCLC, and there are several noteworthy clinical scenarios.

Adequacy of Mediastinal Nodal Sampling in Suspected Early-Stage NSCLC
Despite adequate preoperative mediastinal staging for clinical early-stage patients, 4.5% of patients are found to have pathologic stage III disease due to mediastinal nodal metastasis detected intraoperatively (incidental/unforeseen N2). The American Joint Committee on Cancer (AJCC), Union for International Cancer Control (UICC), and International Association for the Study of Lung Cancer (IASLC) recommend that at least six lymph nodes/stations should be removed or sampled; three of these nodes/stations should be mediastinal, including the subcarinal nodes, and three should be hilar-intrapulmonary lymph nodes/stations for proper pathologic nodal staging. Either systematic nodal dissection or lobe-specific mediastinal nodal sampling is adequate to detect incidental N2 disease. Patients with microscopic N2 disease represent a subgroup with better prognosis compared to macroscopic disease.

Multiple Lung Tumors
When patients present with multiple lung nodules, infection and other benign lesions (e.g., inflammatory granulomas) must be excluded first. For multiple malignant lung tumors, the differentiation between separate tumor nodules (intrapulmonary metastasis) and a second primary tumor is clinically relevant in affecting staging and therapeutic options. Stage I/IIA diseases, including T3 (separate tumor nodules in the same lobe) N1, and T4 (separate tumor nodules in a different ipsilateral lobe) N0/1, may be downstaged if multiple tumors are confirmed to be second primary tumors. In this case, molecular testing (at least for EGFRm) for each of the multiple primaries should be considered. Comprehensive histologic assessment is a promising yet complex tool to distinguish separate tumor nodules from second primary tumors and is helpful in patients with multiple lung tumors.

Testing for Predictive Biomarkers
Activating EGFRm is a frequent oncogenic driver event among Asian patients with NSCLC. A systemic review and global map of EGFRm incidence by ethnicity in lung adenocarcinoma (MutMapII) showed that 47% of tumors from the Asia-Pacific subgroup harbored EGFRm compared to 15% in the European subgroup. Sensitizing EGFRm in NSCLC include predominantly exon 19 deletions and exon 21 L858R point mutations (together representing 85% to 90% of EGFRm), and other less common mutations such as exon 19 insertions, p.L861Q, p.G719X, and p.S768I. The first two should be determined, at a minimum, for EGFRm testing in resource-limited regions. Two recent randomized trials, ADJUVANT/CTONG1104 and EVAN, showed superior outcomes with adjuvant EGFR tyrosine kinase inhibitors (TKIs) (gefitinib and erlotinib, respectively) when compared with adjuvant chemotherapy. Therefore, EGFRm testing for surgically treated stage III NSCLC is encouraged, whereas the role of routine adjuvant EGFR TKI continues to be debated.

The role of programmed death ligand 1 (PD-L1) immunohistochemistry as a predictive biomarker for stage III NSCLC has not been defined. In the PACIFIC study, limitations in its use include testing of PD-L1 on pretreatment tumor samples instead of post-CCRT samples, tissue collection at diagnosis was not mandatory and not all patients had known PD-L1 status, and the lack of stratification by PD-L1 expression. However, regardless of PD-L1 expression, consolidation durvalumab after CCRT in unresectable stage III disease has shown progression-free survival (PFS) and OS benefit in the PACIFIC study in the intention-to-treat population, gaining approval of the U.S. Food and Drug Administration (FDA) and regulatory authorities in many other countries including Canada, Switzerland, and Australia and in Asia (Japan, Malaysia, Singapore, and India). Yet, the European Medicines Agency has restricted the use of durvalumab for patients with PD-L1 expressing tumors (≥1%), based on an unplanned post hoc analysis that could not show a convincing OS benefit in PD-L1-negative tumors. This European Medicines Agency decision has been disputed by an international expert panel based on several caveats regarding analysis of PD-L1 expression in the PACIFIC trial and major concern that patients with unknown or negative PD-L1 status will be denied access to durvalumab.

ATORG Consensus
Comprehensive histological assessment is helpful to distinguish separate tumor nodules (intrapulmonary metastasis) from second primary tumors among patients with multiple lung tumors [IV, B]. The role of predictive biomarker testing is still being investigated in stage III NSCLC; however, given the high prevalence of EGFRm and the potential impact on treatment decisions, molecular testing at least for sensitizing EGFRm is encouraged for facilitation of discussion with patients regarding optimal management of stage III disease [II, C]. The role of PD-L1 as a predictive biomarker in stage III NSCLC
needs to be further interrogated in a planned prospective study. Patients with unknown or negative PD-L1 status should not be excluded from consolidation durvalumab [I, A].

**Standard of Care in Resectable Versus Unresectable Stage III NSCLC**

**Defining Resectability**

The role of surgery in stage IIIA-N2 NSCLC has engendered much controversy due to diversity of clinical practice, driven in part by heterogeneity of disease, access to relevant expertise, as well as paucity of randomized trials to address some key issues (e.g., neoadjuvant versus adjuvant therapy). Although it is generally accepted that patients with nonbulky (defined as less than 3 cm), discrete, or single-level N2 involvement may be the best candidates to undergo resection as part of a multimodality approach. There remains no widely agreed-upon definition of resectability.26,27 For patients whose likelihood of N2 involvement is at least moderate, such as tumors with central location or size greater than 3 cm, a thorough preoperative staging workup is mandatory.28,29 Positive mediastinal findings need pathologic confirmation, except for multilevel infiltrative LN involvement. These patients are not candidates for upfront curative-intent surgery (Fig. 2).

**Role of Surgery in Stage III NSCLC**

**Resected NSCLC With Incidental N2 Disease.** For patients with intraoperatively identified N2 involvement, if a complete resection can be achieved, major pulmonary resection with mediastinal lymph nodes dissection should proceed as planned, followed by cisplatin-based doublet adjuvant chemotherapy with or without RT.30 Data surrounding postoperative RT (PORT) is mixed31; limited evidence suggests a potential survival benefit with PORT in incidental N2 disease (Table 1), and it should be offered in select patients for whom the benefit of improved locoregional control outweighs the risk of excess toxicity.32,33 When indicated, it should be delivered using modern RT techniques and given sequentially after chemotherapy instead of CCRT as in the case of incomplete resection, to minimize toxicity.59

**Surgery in Patients With Proven N2 Disease.** Upfront surgical resection for preoperatively identified nonbulky or bulky N2 patients is controversial. Although some North American guidelines do not encourage upfront surgery, upfront resection of N2 disease is more commonly adopted in Asia.60,61 Reasons for this include the relatively favorable prognosis of Asian patients with NSCLC and the increasing efficacy of contemporary treatment approaches.62 Given the expanding role for combinatorial approaches with chemotherapy and/or immunotherapy with radical RT, there is also concern about applying evidence generated from trials, for example, PACIFIC in which patients recruited were predominantly bulky, multilevel N2 disease. For patients with minimal N2 involvement who undergo upfront surgery, ongoing prospective trials may help address the role of adding ICIs to current adjuvant strategies (NCT 02273375, NCT 02595944, and NCT 02504372), as well as identify any synergistic interaction with mediastinal RT.

![Figure 2. Spectrum of stage III with focus on N2. A schematic diagram showing heterogeneity of stage III NSCLC with different presentations and subgroups (stage IIIA/B/C) depending on the tumor and nodal status, which can be categorized into resectable, potentially resectable, and unresectable disease. A1–4 depicts the Robinson classification for stage IIIA disease. The red triangle represents the spectrum of nodal involvement ranging from incidental/microscopic to macroscopic, then increasing levels of disease bulk, from single level to multi-levels of nodal involvement.](image-url)
Neoadjuvant Chemotherapy Followed by Surgery in Stage III Disease. The role for neoadjuvant chemotherapy before surgery remains controversial. Several trials have shown a trend towards improved survival but patient numbers were small (Table 1). A meta-analysis in patients with resectable NSCLC showed a trend favoring neoadjuvant chemotherapy (hazard ratio [HR] = 0.65; 95% confidence interval [CI]: 0.41–1.04) in the subset with stage III disease, but this was not statistically significant.63 Yet, an updated meta-analysis of 13 randomized trials has shown significant OS benefit in patients who received neoadjuvant chemotherapy in addition to surgery, including those with stage III NSCLC.64

Neoadjuvant Chemoradiotherapy Followed by Surgery. INT-0139, comparing CCRT with neoadjuvant CCRT followed by surgery in N2 NSCLC, showed longer PFS but no survival benefit with surgery. However, a survival advantage was observed in patients who did not undergo pneumonectomy.44 The favorable outcomes for patients undergoing neoadjuvant CCRT followed by non-pneumonectomy surgery is corroborated in Asian patients in Samsung Medical Center where patients who achieved pathologic downstaging of N2 disease following neoadjuvant CCRT have improved outcomes irrespective of initial cN2 bulk/extent.45-48 Several trials addressed whether preoperative CCRT was better than neoadjuvant chemotherapy in stage III NSCLC, showing that adding RT did not improve survival although it increased mediastinal downstaging (Table 1).45-48 Incorporating surgery into management of stage III NSCLC should ideally be performed in high-volume institutions with an experienced multimodality team. Appropriate patient selection is key, and surgery should be preplanned through a multidisciplinary discussion to determine the best timing for local treatment (surgery ± radiation), and to minimize any breaks in RT if neoadjuvant chemoradiotherapy strategy is determined. Lobectomy with systemic mediastinal lymph nodes dissection is preferred over pneumonectomy because the latter carries higher surgical risk after chemoradiation.44

Neoadjuvant TKI Followed by Surgery and Adjuvant TKI. Feasibility and potential efficacy of neoadjuvant TKI has been shown in EMERGING-CTONG 1103, a recent phase II Chinese study which compared neoadjuvant/adjuvant erlotinib versus gemcitabine-cisplatin chemotherapy in untreated, EGFRm-positive (EGFRm+) stage IIIA-N2 NSCLC.52 Following neoadjuvant erlotinib, there is a trend towards higher objective response rate (54.1% versus 34.3%, p = 0.092), R0 resection rate (73.0% versus 62.9%, p = 0.358) and lymph node downstaging (10.8% versus 2.9%, p = 0.185), compared with chemotherapy. PFS was significantly longer with neoadjuvant/adjuvant erlotinib (21.5 versus 11.4 months; HR = 0.39; p < 0.001) than chemotherapy. Despite being an overall negative study as its primary endpoint of objective response rate was not met, it provides rationale for considering neoadjuvant EGFR TKI in patients with EGFRm+ disease and supports the concept of biomarker-directed treatment for stage III NSCLC. Besides erlotinib, there is currently no data to support the use of second- or third-generation EGFR TKIs. Neoadjuvant gefitinib and osimertinib are being investigated in ongoing clinical trials (NEGOTIATE/ NCT02347839 and NCT03433469, respectively) (Supplementary Table 3). If neoadjuvant EGFR TKIs are to be considered before surgery, erlotinib may be an option, but it requires careful benefit/risk discussion with the patient.

ATORG Consensus

All patients considered potentially resectable should be discussed in a multidisciplinary meeting [V, A]. A thorough preoperative staging workup is mandatory, including a PET/CT, brain MRI, and pathologic confirmation of suspicious mediastinal lymph nodes [I, A]. In patients who have undergone upfront resection for incidental N2 disease, adjuvant chemotherapy, with or without RT, can be offered to all stage III patients who are suitable irrespective of mutational status [I, A]. If surgery is considered for select patients with N2 disease, this should ideally be a lobectomy with mediastinal lymph node dissection, preplanned with either neoadjuvant chemotherapy or chemoradiotherapy, and should ideally be performed in high-volume centers with experienced trimodality teams [I, A]. Postoperative RT should be considered for pathologic N2 disease in patients in whom the benefit of improved locoregional control outweighs risk of excess toxicity [IV, B]. Neoadjuvant EGFR-TKI before surgery is not standard but erlotinib may be considered in stage III-N2 patients with sensitizing EGFRm before surgery, as another treatment option, after multidisciplinary evaluation [II, C].

CCRT Versus Sequential Chemoradiotherapy for Unresectable Stage III NSCLC

CCRT is the standard treatment for unresectable stage III NSCLC with a meta-analysis of six clinical trials showing an absolute OS benefit of 4.5% at 5 years when CCRT is compared to sequential chemoradiation.1,67 A summary of clinical trials regarding combined modality treatments in unresectable stage III NSCLC is included in Table 1. As shown, Asian and EGFRm+ NSCLC patients are under-represented in these studies. Recommended chemotherapeutic regimens in either concurrent or sequential setting include two to four cycles of platinum-
Table 1. Summary of Bimodality and Trimodality Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Population Characteristics</th>
<th>N</th>
<th>Asian (%)</th>
<th>IIA (%)</th>
<th>IIIB (%)</th>
<th>Treatment arms</th>
<th>OS (mo)</th>
<th>PFS (mo)</th>
<th>TRM (%)</th>
<th>Other Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>PACIFIC</td>
<td>Unresectable stage III/IIIB</td>
<td>713</td>
<td>26.9</td>
<td>52.9</td>
<td>44.7</td>
<td>A) CCRT + aPD-L1</td>
<td>NR</td>
<td>17.2</td>
<td>4.4</td>
<td>36.7% patients had unk PD-L1 status</td>
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<tr>
<td></td>
<td></td>
<td>Unselected for PD-L1 status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B) CCRT</td>
<td>28.7</td>
<td>5.6</td>
<td>6.4</td>
<td></td>
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<tr>
<td>2008</td>
<td>PROCLAIM</td>
<td>Unresectable stage III</td>
<td>598</td>
<td>20.4</td>
<td>47.2</td>
<td>52.3</td>
<td>A) CCRT-Ch (Cis + pemetrexed)</td>
<td>26.8</td>
<td>11.4</td>
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<tr>
<td></td>
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<td>Nonsquamous only</td>
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<td></td>
<td></td>
<td></td>
<td>B) CCRT-Ch (Cis + etoposide)</td>
<td>25.0</td>
<td>9.8</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Liang et al</td>
<td>Unresectable stage III</td>
<td>191</td>
<td>100</td>
<td>25.1</td>
<td>74.9</td>
<td>A) CCRT +/- consolidation Ch (Cis + etoposide)</td>
<td>23.3</td>
<td>14.0</td>
<td>4.2</td>
<td>G≥2 RP higher in carbo + paclitaxel arm  G≥3 esophagitis higher in carbo + etoposide arm</td>
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<td>Unselected for PD-L1 status</td>
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<td></td>
<td></td>
<td>B) CCRT +/- consolidation Ch (carbo + paclitaxel)</td>
<td>20.7</td>
<td>12.0</td>
<td>5.2</td>
<td>Patients recruited in multiple centers across Mainland China</td>
</tr>
<tr>
<td>2007</td>
<td>RTOG 0617</td>
<td>Unresectable stage III</td>
<td>424</td>
<td>2.4</td>
<td>64.9</td>
<td>35.1</td>
<td>A) CCRT-Ch (74 Gy)</td>
<td>20.3</td>
<td>9.8</td>
<td>3.9</td>
<td>53.5% 3DCRT, 46.5% IMRT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unselected for EGFRm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B) CCRT-Ch (60Gy)</td>
<td>28.7</td>
<td>11.8</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unselected for EGFRm</td>
<td>465</td>
<td>2.8</td>
<td>65.4</td>
<td>34.6</td>
<td>C) CCRT-Ch + C25</td>
<td>25.0</td>
<td>10.8</td>
<td>4.2</td>
<td>43.8% with available EGFR H-score (21.6% &gt;200)</td>
</tr>
<tr>
<td>2005</td>
<td>KCSG-LU05-041</td>
<td>Unresectable stage III</td>
<td>420</td>
<td>100</td>
<td>22.1</td>
<td>77.4</td>
<td>A) CCRT-Ch</td>
<td>21.8</td>
<td>9.1</td>
<td>2.9</td>
<td>Patients recruited from Korea, Taiwan, and Mainland China</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unselected for EGFRm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B) CCRT</td>
<td>20.6</td>
<td>8.1</td>
<td>0</td>
<td>Squamous 29.6%, ADC 31.3%</td>
</tr>
<tr>
<td>2001</td>
<td>SWOG 50023</td>
<td>Unresectable stage III</td>
<td>243</td>
<td>0.8</td>
<td>48.1</td>
<td>51.9</td>
<td>A) CCRT-Ch + consolidation gefitinib</td>
<td>23.0</td>
<td>8.3</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unselected for EGFRm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B) CCRT-Ch</td>
<td>35.0</td>
<td>11.7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>CALGB 39801</td>
<td>Unresectable stage III</td>
<td>366</td>
<td>0</td>
<td>49.0</td>
<td>47.0</td>
<td>A) Ch-CCRT</td>
<td>14.0</td>
<td>8.0</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medically or surgically</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B) CCRT</td>
<td>12.0</td>
<td>7.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>inoperable</td>
<td>577</td>
<td>2.0</td>
<td>42</td>
<td>57.0</td>
<td>A) CCRT (Cis + vinblastine + 60 Gy)</td>
<td>17.0</td>
<td>3.6</td>
<td>3.2</td>
<td>2% study patients were stage II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Included stage II –IIIB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B) CCRT (Cis + etoposide + 69.6Gy twice daily RT)</td>
<td>15.6</td>
<td>3.6</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>1984</td>
<td>CALGB 8433</td>
<td>T3 or N2 (stage III based on staging criteria defined at time of study)</td>
<td>155</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>A) Ch-RT</td>
<td>13.8</td>
<td>8.2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B) RT</td>
<td>9.6</td>
<td>5.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Year</td>
<td>Accrual Started Study</td>
<td>Population Characteristics</td>
<td>N</td>
<td>Asian (%)</td>
<td>IIIA (%)</td>
<td>IIIB (%)</td>
<td>Treatment arms</td>
<td>OS (mo)</td>
<td>PFS (mo)</td>
<td>TRM (%)</td>
<td>Other Study Details</td>
</tr>
<tr>
<td>------------</td>
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<td>-------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| 2004       | ESPATUE 42                  | Potentially resectable IIIA (N2) and selected IIIB | 161 | NA        | 34.2     | 65.8     | A) Ch-CCRT-Sx (45 Gy at 1.5 Gy twice daily)        | 5-y OS: 44%  
B) Ch-CCRT (45 Gy at 1.5 Gy twice daily followed by boost to 65 - 71 Gy) | 5-y OS: 40%  
B) Ch-CCRT (45 Gy at 1.5 Gy twice daily followed by boost to 65 - 71 Gy) | 5-y PFS: 32%  
B) Ch-CCRT (45 Gy at 1.5 Gy twice daily followed by boost to 65 - 71 Gy) | Ch: 0.4  
CCRT: 0.4 | 6.2  
2.5 | Of 81 patients allocated to Sx, 70 (86.4%) received surgery (pneumo 32.9%, lobec 59.7%)  
R0 resection 94.3% | |
| 1994       | EORTC 0894143               | Potentially operable IIIA (N2) | 332 | NA        | 100      | 0        | A) Ch-Sx                                          | 16.4    | 9.0     | 3.9     | Of 167 allocated to Sx, 154 (92.2%) received surgery (pneumo 47%, lobec 38%)  
R0 resection 50% |
| 1994       | INT 0139                    | Potentially operable IIIA (N2) | 396 | NA        | 100      | 0        | A) CCRT-Sx (45 Gy)                                | 23.6    | 12.5    | 7.9     | Of 202 allocated to Sx, 164 (81.2%) received surgery (pneumo 32.9%, lobec 59.8%)  
R0 resection 71.3% |
| 2003       | IFCT-0101                   | Operable IIIA (N2)           | 46  | NA        | 100      | 0        | A) CCRT-Sx (carbo + paclitaxel + 46 Gy)           | NR      | 23.9    | 0       | 44 of 46 patients (95.7%) underwent Sx as planned (pneumo 50%, lobec 45%)  
80% of all Sx achieved a complete R0 resection. Similar in 3 arms: 80% [CCRT-Sx, carbo-paclitaxel] vs. 76.5% [CCRT, Cis - vinorelbine] vs. 71.4% [Ch-Sx] |
| 2001       | SAKK 16/00                   | Operable IIIA (N2)           | 232 | NA        | 100      | 0        | A) Ch-RT-Sx                                       | 37.1    | 12.8    | 0       | 193 of 232 patients (83.2%) underwent Sx as planned (pneumo 22.8%, lobec 60.6%)  
86.0% of all Sx achieved a complete R0 resection. Similar in both arms: 90.9% [Ch-RT-Sx] vs. 80.9% [Ch-Sx] |
| 2000       | WJTOG 9903                  | Operable IIIA (N2)           | 60  | 100       | 100      | 0        | A) CCRT-Sx                                        | 39.6    | 12.4    | 0       | 51 of 60 patients (85%) underwent Sx as planned (pneumo 2.0%, lobec 84.3%) |

(continued)
<table>
<thead>
<tr>
<th>Year</th>
<th>Accrual Started</th>
<th>Study</th>
<th>Population Characteristics</th>
<th>N</th>
<th>Asian (%)</th>
<th>IIA (%)</th>
<th>IIIB (%)</th>
<th>Treatment arms</th>
<th>OS (mo)</th>
<th>PFS (mo)</th>
<th>TRM (%)</th>
<th>Other Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>GLCCG 48</td>
<td>524</td>
<td>Potentially operable</td>
<td>92</td>
<td>33.4</td>
<td>66.6 N:</td>
<td>21.6</td>
<td>A) CH-CCRT-Sx +/- RT (45 Gy at 1.5 Gy twice daily. A further 24 Gy at 1.5 Gy twice daily after surgery if margins positive or unresectable) B) Ch-Sx-RT (conventionally fractionated RT: 54 Gy, 68.4 Gy if margins positive)</td>
<td>A) 15.7</td>
<td>R0 resection group: 23.3</td>
<td>B) 10.0</td>
<td>296 of 524 (56.5%) patients underwent Sx as planned (8.1% had an exploratory thoracotomy, while pneumo 35.1%, lobec 50.7%) 80.4% of all Sx achieved a complete R0 resection Rate of R0 improved with addition of CCRT: 69% [Ch-CCRT-Sx +/- RT] &gt; 55% [Ch-Sx-RT] a</td>
</tr>
<tr>
<td>1995</td>
<td>INT 0160 49</td>
<td>110</td>
<td>T3-4 or N0-1 SS NSCLC</td>
<td>1</td>
<td>T3: 71</td>
<td>T4: 29</td>
<td>0</td>
<td>A) CCRT-Sx-Ch</td>
<td>33.0</td>
<td>NA</td>
<td>2.3</td>
<td>88 of 110 (80%) patients underwent Sx as planned (pneumo 3.4%, lobec 80.8%) 75.5% had a complete R0 resection Patients recruited from Japan 52 of 62 (83.9%) patients underwent Sx as planned (pneumo 13.5%, lobec 86.5%) 84.6% of all patients achieved a complete R0 resection - Rate of R0 vs. 77.4% [Sx] b</td>
</tr>
<tr>
<td>1993</td>
<td>JCOG 9209 10</td>
<td>62</td>
<td>IIIA (N2) resectable patients</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>A) Ch-Sx</td>
<td>17</td>
<td>5-y PFS: 10%</td>
<td>0</td>
<td>52 of 62 (83.9%) patients underwent Sx as planned (pneumo 13.5%, lobec 86.5%) 84.6% of all patients achieved a complete R0 resection - Rate of R0 vs. 77.4% [Sx] b</td>
</tr>
<tr>
<td>1989</td>
<td>Rosell et al 15</td>
<td>60</td>
<td>IIIA resectable patients</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>A) Ch-Sx-RT</td>
<td>22</td>
<td>12</td>
<td>NA</td>
<td>65% N2, 13.3% of pre-op chemo patients had satellite lung nodules Single station (50%): multiple station N2 (50%) Patients recruited in multiple centers across Mainland China N2: 97.1% Patients recruited in multiple centers across Mainland China</td>
</tr>
<tr>
<td>2019</td>
<td>EMERGING-CTONG1103 12</td>
<td>72</td>
<td>Selected EGFRm+ NSCLC Potentially resectable stage IIIA-N2</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>A) TKI-Sx-TKI</td>
<td>45.8</td>
<td>21.5</td>
<td>0</td>
<td>65% N2, 13.3% of pre-op chemo patients had satellite lung nodules Single station (50%): multiple station N2 (50%) Patients recruited in multiple centers across Mainland China N2: 97.1% Patients recruited in multiple centers across Mainland China</td>
</tr>
<tr>
<td>2012</td>
<td>EVAN 14</td>
<td>102</td>
<td>Selected EGFRm+ NSCLC. Completely resected, path staged IIIA</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>A) Sx-TKI (erlotinib) B) Sx-Ch</td>
<td>NR</td>
<td>42.4</td>
<td>0</td>
<td>65% N2, 13.3% of pre-op chemo patients had satellite lung nodules Single station (50%): multiple station N2 (50%) Patients recruited in multiple centers across Mainland China N2: 97.1% Patients recruited in multiple centers across Mainland China</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Year</th>
<th>Accrual Started</th>
<th>Study</th>
<th>Population Characteristics</th>
<th>N</th>
<th>Asian (%)</th>
<th>IIA (%)</th>
<th>IIIB (%)</th>
<th>Treatment arms</th>
<th>OS (mo)</th>
<th>PFS (mo)</th>
<th>TRM (%)</th>
<th>Other Study Details</th>
</tr>
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<tbody>
<tr>
<td>2011</td>
<td>ADJUVANT</td>
<td>23</td>
<td>Selected EGFRm+ NSCLC.</td>
<td>222</td>
<td>100</td>
<td>64.4</td>
<td>0</td>
<td>A) Sx-TKI (gefitinib) B) Sx-Ch</td>
<td>Not mature</td>
<td>Not mature</td>
<td>28.7a</td>
<td>N2: 64.4% Patients recruited in multiple centers across Mainland China</td>
</tr>
<tr>
<td>2007</td>
<td>RADIANT</td>
<td>53</td>
<td>Selected for EGFR protein expression by IHC or EGFR amplification by FISH</td>
<td>973</td>
<td>17.0</td>
<td>15.5</td>
<td>0.2</td>
<td>A) Sx-TKI (erlotinib) B) Sx-placebo</td>
<td>Not mature</td>
<td>Not mature</td>
<td>50.5</td>
<td>46.4 1) 48.2 1) EGFRm+: 28.5 2) 95.4% had a known EGFRm status. 16.5% had an activating EGFRm, of which 22.4% had IIIA disease</td>
</tr>
<tr>
<td>2002</td>
<td>BR19</td>
<td>503</td>
<td>Unselected for activating EGFRm</td>
<td>503</td>
<td>1.8</td>
<td>13.3</td>
<td>0</td>
<td>A) Sx-TKI (gefitinib) B) Sx-placebo</td>
<td>61.2</td>
<td>50.4</td>
<td>2.0</td>
<td>71.4% had a known EGFRm status. 3.0% had an activating EGFRm</td>
</tr>
<tr>
<td>1995</td>
<td>Big Lung trial</td>
<td>381</td>
<td>Completely resected I-IIIA</td>
<td>NA</td>
<td>26.0</td>
<td>7.9</td>
<td>0</td>
<td>A) Sx-Ch +/- RT B) Sx +/- RT</td>
<td>33.9</td>
<td>27.0</td>
<td>3.1</td>
<td>14% received PORT</td>
</tr>
<tr>
<td>1995</td>
<td>IALT</td>
<td>1867</td>
<td>Completely resected I-III</td>
<td>NA</td>
<td>39.0</td>
<td>0.3</td>
<td>0</td>
<td>A) Sx-Ch +/- RT B) Sx +/- RT</td>
<td>32.6</td>
<td>24.7</td>
<td>0.5</td>
<td>30.6% received PORT</td>
</tr>
<tr>
<td>1994</td>
<td>ANITA</td>
<td>840</td>
<td>Completely resected I-IIIA</td>
<td>NA</td>
<td>38.7</td>
<td>0.5</td>
<td>0</td>
<td>A) Sx-Ch +/- RT B) Sx +/- RT</td>
<td>65.7a</td>
<td>36.3a</td>
<td>1.7</td>
<td>28% received PORT</td>
</tr>
<tr>
<td>1994</td>
<td>ALPI</td>
<td>1088</td>
<td>Completely resected I-IIIA</td>
<td>NA</td>
<td>28.5</td>
<td>0</td>
<td>0</td>
<td>A) Sx-Ch +/- RT B) Sx +/- RT</td>
<td>43.7</td>
<td>20.7</td>
<td>0.9</td>
<td>43.2% scheduled for PORT</td>
</tr>
<tr>
<td>2006</td>
<td>National Cancer Database PORT study</td>
<td>4483</td>
<td>Completely resected pathologic stage IIIA (pN2) treated with adj Ch Treated from 2006 - 2010, identified from the National Cancer Database</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>A) Sx + Ch + RT (≥45 Gy) B) Sx + Ch</td>
<td>45.2a</td>
<td>NA</td>
<td>NA</td>
<td>Pneumo 8.3%, lobec 79.1%</td>
</tr>
</tbody>
</table>

(continued)
### Table 1. Continued

<table>
<thead>
<tr>
<th>Year</th>
<th>Accrual Started</th>
<th>Study</th>
<th>Population Characteristics</th>
<th>N</th>
<th>Asian (%)</th>
<th>IIA (%)</th>
<th>IIIB (%)</th>
<th>Treatment arms</th>
<th>OS (mo)</th>
<th>PFS (mo)</th>
<th>TRM (%)</th>
<th>Other Study Details</th>
</tr>
</thead>
</table>
| 1988 | SEER Database  | PORT  | Completely resected stage II-III who received a pneumonectomy or lobectomy Patients who underwent Sx from 1988 – 2002, identified within the SEER database | 7465 | 5.8 | 36.7 | 15.2 | A) Sx + RT  
B) Sx | N0: HR = 1.1 | NA | N1: HR = 1.1 | NA | N2: HR = 0.86 | 48.1% of patients were stage II  
26.6% of patients were N2  
Pneumo 20.8%, lobec 79.2% |

Summary of selected bi- and tri-modality trials (n = 30) for stage III NSCLC. Outcomes include median OS and median PFS in months. As shown here, Asian NSCLC is under-represented in most study populations and practice changing trials, yet represents a unique molecular profile distinct from Caucasian NSCLC. This highlights the need to consider the current treatment paradigm for stage III NSCLC in the Asian context.

3DCRT, three-dimensional conformal radiation therapy; ADC, adenocarcinoma; Adj, adjuvant; aPD-L1, anti-Programmed death-ligand 1; C225, cetuximab; carbo, carboplatin; CCRT, concurrent chemoradiotherapy; Ch, chemotherapy; cis, cisplatin; EGFRm, Epidermal growth factor receptor mutation; FISH, fluorescence in situ hybridization; HR, hazard ratio; IHC, immunohistochemistry; IMRT, intensity-modulated radiotherapy; lobec, lobectomy; NA, not available; NR, not reached; OS, overall survival; Path-staged, pathologically staged; PD, progression of disease; PD-L1, programmed death ligand 1; PFS, progression-free survival; pneumo, pneumonectomy; PORT, postoperative radiotherapy; pre-op, preoperative; RT, radiotherapy; SEER, Surveillance, Epidemiology, and End Results program; Sx, surgery; TRM, treatment-related mortality; unk, unknown.

*Statistically significant difference.

*Median survival not reported.

Unplanned exploratory post-hoc analysis: Median survival of induction CCRT patients who underwent a lobectomy compared with a matched cohort of definitive CCRT patients.

Unplanned exploratory post-hoc analysis: Median survival of induction CCRT patients who underwent a pneumonectomy compared with a matched cohort of definitive CCRT patients.

Analysis based on patients, eligible for treatment, allocated to each study arm. Includes patients who were deemed unresectable after induction treatment and did not go on to receive surgery.

Unplanned exploratory post hoc analysis: Median survival of patients who underwent a complete resection compared across both treatment arms.
Table 2. Recommendations for Concurrent Chemoradiotherapy for Stage III NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Histology Type</th>
<th>Concurrent Chemotherapy Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG 9019 (phase II) 65</td>
<td>Squamous and nonsquamous</td>
<td>Cisplatin 50 mg/m² on days 1, 8, 29, and 36; Etoposide 50 mg/m² on days 1-5, 29-33 of RT</td>
<td>2 cycles of consolidation cisplatin-etoposide if no PD, every 4 weeks a</td>
</tr>
<tr>
<td>RTOG 9410 (phase III) 40</td>
<td>Squamous and nonsquamous</td>
<td>Cisplatin 50 mg/m² intravenously on days 1, 8, 29, and 36; Oral etoposide 50 mg twice a day on RT days 1-5, 8-12, 29-33, 36-40.</td>
<td>Nil</td>
</tr>
<tr>
<td>RTOG 9410 (phase III) 40</td>
<td>Squamous and nonsquamous</td>
<td>Cisplatin 100 mg/m² on days 1 and 29; Vinblastine 5 mg/m² per week x 5 weeks</td>
<td>Nil</td>
</tr>
<tr>
<td>Czech Republic randomized study 69</td>
<td>Squamous and nonsquamous</td>
<td>Cisplatin 80 mg/m² on day 1, and vinorelbine 25 mg/m² at the 1st and 4th cycles (12.5 mg/m² during the 2nd/3rd cycles) on days 1, 8, and 15 of a 28-day cycle (max 4 cycles of chemotherapy)</td>
<td>Nil</td>
</tr>
<tr>
<td>RTOG 0617 36 (phase III)</td>
<td>Squamous and nonsquamous</td>
<td>Paclitaxel 45 mg/m² and carboplatin (AUC 2) weekly</td>
<td>2 cycles of consolidation paclitaxel 200 mg/m² and carboplatin AUC 6, every 21 days b</td>
</tr>
<tr>
<td>CALGB 39801 (phase III)</td>
<td>Squamous and nonsquamous</td>
<td>Paclitaxel 50 mg/m² and carboplatin (AUC 2) weekly, x 7 weeks</td>
<td>Nil</td>
</tr>
<tr>
<td>PROCLAIM 64 (phase III)</td>
<td>Nonsquamous</td>
<td>Cisplatin 75 mg/m² on day 1 and pemetrexed 500 mg/m² on day 1, every 21 days x 3 cycles</td>
<td>4 cycles of consolidation pemetrexed 500 mg/m², every 3 weeks a</td>
</tr>
</tbody>
</table>

Radical thoracic radiotherapy regimen involves 60 - 70 Gy in daily fractions of 1.8 - 2 Gy. Recommendations include common chemotherapeutic regimens used and recommended prescription dose for radical thoracic RT.

Addition of consolidation chemotherapy following a full course of cisplatin-based chemoradiation is not standard, but may be acceptable with the weekly paclitaxel-carboplatin regimen as the weekly dose is not considered adequate treatment.

For patients getting consolidation durvalumab after concurrent chemoradiotherapy, consolidation paclitaxel and carboplatin chemotherapy may not be required.

AUC, area under the curve; RT, radiotherapy.

Based compound coupled with another agent such as etoposide, taxane, or pemetrexed (Table 2). A phase III trial showed non-inferiority but better tolerability with pemetrexed compared to etoposide, in combination with cisplatin, making it an ideal option in nonsquamous histology. There is some evidence that CCRT with carboplatin and paclitaxel in the Asian context may result in higher rates of radiation pneumonitis and should be used with caution, especially in large-volume disease.

The eligibility for CCRT should be assessed primarily on the patient’s fitness and appropriateness for high-dose thoracic RT concurrent with platinum-based chemotherapy, with a minimum requirement that patient’s Eastern Cooperative Oncology Group performance status is at least 1. Advanced age alone should not be an absolute contraindication because there is no evidence to suggest that carefully selected older patients fare worse from CCRT. Patients who are not eligible for CCRT should be considered for sequential chemoradiation instead. CCRT with single-agent platinum-based chemotherapy cannot be recommended as superiority over sequential cisplatin-doublet chemoradiation has not been shown. For those who are not able to tolerate chemotherapy, definitive RT alone is an alternative, albeit with inferior outcomes. Patients with T4 (separate lung nodules in ipsilateral lobes) and N2-3 disease should still be considered for radical RT, leveraging on advanced radiotherapy techniques. For stage III patients who are not candidates for surgical resection or definitive chemoradiation, first-line pembrolizumab monotherapy has been U.S. FDA-approved for patients with PD-L1 tumor proportion score greater than or equal to 1% and negative for EGFR or anaplastic lymphoma kinase (ALK) mutations based on results of Keynote 042. However, there are concerns regarding the adoption of pembrolizumab monotherapy for patients with PD-L1 tumor proportion score 1% to 49%. Apart from Hong Kong and China, this indication has not been approved in many parts of Asia (including Korea, Japan, Taiwan, Singapore, Thailand, and Malaysia).

Dosimetric Considerations for RT. In the setting of chemoradiotherapy, the recommended radical RT dose is 60 to 70 Gy delivered in daily fractions of 1.8 to 2 Gy. Dose escalation to 74 Gy resulted in inferior survival in RTOG 0617 and is therefore not recommended. In the setting of RT alone, accelerated hypofractionated RT has been shown to be superior to conventional fractionated RT in a meta-analysis and may be considered. Currently, accelerated RT is not widely practiced in Asia in part due to concerns surrounding the management of acute toxicities in resource-limited settings. Dosimetric constraints to adjacent normal tissue must be respected (Supplementary Table 4). In addition, radiation dose to the heart increases cardiotoxicity and may negatively impact survival and should therefore be minimized. The panel acknowledges the limitations of
dosimetry alone in predicting severe radiation pneumonitis (RP). For example, an estimated 3% to 5% of definitive CCRT patients will still develop grade 3 or greater RP. Therefore, other factors such as age and presence of interstitial pulmonary fibrosis should also be considered. Incorporating all these factors, a risk assessment tool, which was validated in Japanese CCRT patients, predicted grade 3 or greater RP better than dosimetry alone and may be helpful in patient selection. Although lung function tests quantify baseline lung function, it is not useful in predicting severe RP.

Role of Prophylactic Cranial Irradiation. Prophylactic cranial irradiation after CCRT may reduce the development of symptomatic brain metastases but is not routinely recommended due to a lack of OS benefit.

**ATORG Consensus**

Patient selection for combined modality treatment should include performance status, comorbidities including pulmonary function, and appropriateness for high-dose thoracic RT concurrent with platinum-based chemotherapy; advanced age alone should not be an absolute contraindication [I, A]. Concurrent chemoradiotherapy, consisting of two to four cycles of cisplatin-based doublet chemotherapy with radical-dose RT delivering 60 to 70 Gy in 1.8- to 2-Gy daily fractions is recommended. All dose constraints to normal tissue should be met [I, A]. Sequential chemoradiotherapy may be considered for less-fit patients who are not candidates for standard CCRT [I, A]. For patients who are not chemotherapy-eligible, definitive thoracic RT alone is an alternative [I, A]. Patients who are not amenable to surgical resection or radical RT should be considered for systemic treatment [I, A]. There is no role for prophylactic cranial irradiation in stage III NSCLC [I, A].

**Current and Emerging RT Modalities**

Delivery of high-dose thoracic RT requires appropriate organ motion evaluation, which typically involves a four-dimensional CT simulation with or without respiratory gating. Delineation of internal target volumes, as defined in International Commission on Radiation Units and Measurements Report 62, should be incorporated to account for tumor motion. In resource-limited regions where four-dimensional CT is not available, increased margins (typically 12 mm longitudinally, 7 mm axially) should be applied for planning target volume expansions to account for uncertainties attributed to respiratory motion. Emphasis should be placed on quality assurance and dose reproducibility because poor RT delivery can directly impact outcomes. In large parts of Asia, however, trained radiation personnel and equipment remain in short supply, creating great disparity in access to good quality RT.

When available, intensity-modulated radiation therapy (IMRT) is preferred over older techniques. In a subgroup analysis from RTOG 0617, IMRT patients had larger treatment volumes but experienced less grade 3 or greater RP (7.9% versus 3.5%, \( p = 0.039 \)) and achieved lower heart doses, which was significantly associated with OS and cardiotoxicity. Furthermore, when compared to three-dimensional conformal RT (3DCRT), IMRT patients reported less clinically meaningful decline in quality-of-life outcomes up to a year post treatment. Taken together, IMRT offers better dosimetric coverage of the target while reducing dose to normal structures and is therefore recommended, particularly in large-volume disease. The addition of daily image guidance may improve delivery and outcomes further. In resource-limited settings where IMRT is not available, standard 3DCRT should be used.

Proton beam therapy (PBT) has not shown superiority over IMRT, but its dosimetric advantages, particularly in reducing heart and lung doses, may in theory be clinically meaningful in patients with large tumors or background interstitial lung disease (Supplementary Fig. 2). Thoracic PBT is extremely sensitive to motion, tissue density heterogeneity, and set-up uncertainties, and should be delivered with caution.

**ATORG Consensus**

High-dose thoracic RT requires appropriate organ motion management and robust quality assurance for the planning and delivery process [I, A]. Where available, modern RT techniques should be used. IMRT with good image guidance may improve outcomes in select patients with a large volume of disease [I, B]. In resource-limited regions where IMRT is not available, standard 3DCRT should be used. There is no clear evidence guiding the use of PBT in stage III [II, C].

**Role of Immunotherapy for Stage III NSCLC**

The phase III PACIFIC trial was based on the rationale that CCRT promotes immunogenic cell death of tumor cells and synergizes with anti-programmed death 1/PD-L1 blockade to enhance antitumor immunity. In this study, patients with unresectable stage III disease were randomly assigned to durvalumab (10 mg/kg given every 2 weeks for 12 months) or placebo as consolidation therapy 1 to 42 days after CCRT. Patients were unselected for tumor PD-L1 expression status. Durvalumab significantly improved OS (not reached versus 28.7 months, \( HR = 0.68, p = 0.0025 \)) and PFS (17.2 versus 5.6 months, \( HR = 0.51; 95\% CI: 0.41–0.63 \)) compared to placebo. These improved outcomes were driven by both improved local control (duration of response: not reached [durvalumab] versus 18.4 months
Chemotherapy in Setting of Chemoradiation

Induction Chemotherapy and Consolidation Chemotherapy in Setting of Chemoradiation

Adding induction or consolidation chemotherapy to definitive CCRT for unresectable stage III NSCLC has not shown a survival advantage but may add toxicity (Table 1). However, the panel accepts that in select cases, additional cycles of chemotherapy before or after CCRT may be appropriate.

Management of EGFR/ALK-Positive Stage III NSCLC

TKIs have consistently shown superior response rates and PFS in incurable stage IIIB and IV disease. The role of adjuvant TKI has therefore been examined in the curative setting. Three early large adjuvant trials were conducted but unfortunately did not select for driver mutation patients and were therefore negative (Table 1). More recently, the ADJUVANT/CTONG1104 trial randomized completely resected II-IIIA (N1 or N2) EGFRm+ patients to 2 years of adjuvant gefitinib or four cycles of chemotherapy with cisplatin and vinorelbine. Median PFS was significantly longer with gefitinib (28.7 versus 18.0 months) but OS data are not yet mature. In the subgroup analysis N2 patients seemed to derive more benefit than N1. Importantly, TKI offered better tolerability with fewer dose reductions compared to chemotherapy. These results are echoed by another phase II trial (EVAN) in stage IIIA resected patients who were randomized to erlotinib versus platinum doublet chemotherapy. Yet, ADJUVANT/CTONG1104 presented limitations, as in the intention-to-treat population the Kaplan-Meier curves of the two treatment groups converged at about 36 months, and nonprogressors seemed absent in either group, suggesting that gefitinib as adjuvant therapy might not be curative but merely delayed disease recurrence in patients with high-risk disease (N1- to N2-positive). Several ongoing trials are addressing if newer third-generation EGFR TKIs are superior in the adjuvant setting (ADAURA/NCT02511106). Adjuvant ALK TKIs are also being explored in ALCHEMIST (NCT02194738), whereas other trials are looking at the addition of adjuvant TKI (icotinib) to chemotherapy (ICTAN/NCT01996098 and NCT02125240/ICWIP) (Supplementary Table 3). However, stage III-specific results will be limited as these patients formed only a subgroup in these studies. To date, only the first-generation EGFR TKIs (gefitinib and erlotinib) have data to support their use as adjuvant therapy for postoperative EGFRm+ N2 disease, whereas second- and third-generation TKIs remain experimental. Therefore, if adjuvant EGFR TKIs are to be considered, first-generation TKIs should be used.

Notably in the PACIFIC study, EGFRm+ patients represented only 6% of all patients. We expect the rate of EGFRm+ patients in Asia to be higher than represented by the trial. In the subgroup analysis, the HR for [placebo] and reduction in distant metastases. Most frequent adverse events resulting in discontinuation of durvalumab were pneumonitis (4.8% [durvalumab] versus 2.6% [placebo]), RP (1.3% [durvalumab] versus 1.3% [placebo]), and pneumonia (1.1% [durvalumab] versus 1.3% [placebo]). Serious adverse events including death were not significantly different between durvalumab and placebo.

Whereas PACIFIC has established consolidation durvalumab as a new standard-of-care in unresectable stage III NSCLC, it is not yet widely reimbursable in Asia and hence not routinely offered. In the PACIFIC trial, only 27% of patients were Asians. Notably, in the Japanese subset of PACIFIC, median PFS was significantly improved with consolidation durvalumab (HR = 0.49, p = 0.020), consistent with that of the overall study. Although rates of RP leading to discontinuation of durvalumab for the Japanese subset was similar to the overall population, RP of any grade was generally higher (placebo: 60% [Japanese] versus 24.8% [overall]; durvalumab: 73.6% [Japanese] versus 33.9% [overall]) suggesting a more radiosensitive phenotype.

There remain unanswered questions from PACIFIC, such as patient selection — PD-L1 expression (assessed pre-chemoradiotherapy) was not useful to discriminate, EGFRm+ patients were too few to draw conclusions regarding the benefit of durvalumab, and data on ALK rearrangements was not reported. Although optimal timing between CCRT and durvalumab was not determined, there appeared to be greater PFS improvement in patients receiving durvalumab earlier (≤2 weeks after CCRT). In stage III patients who undergo sequential chemoradiation or resection post-chemoradiotherapy, the role of ICI is being investigated in multiple prospective clinical trials (Supplementary Table 3).

**ATORG Consensus**

Consolidative durvalumab for 12 months after completion of concurrent chemoradiotherapy should be considered in unresectable stage III NSCLC [I, A]. Optimal sequencing of ICI post-sequential chemoradiotherapy or post-resection remains an open question and requires prospective evaluation [V, C].

**Role of Induction and Consolidation Chemotherapy or Targeted Therapy in Stage III NSCLC**

**Induction Chemotherapy and Consolidation Chemotherapy in Setting of Chemoradiation**

Despite the strong results in the PACIFIC trial, there remains uncertainty regarding the role of adjuvant immunotherapy in NSCLC. Although PFS was significantly improved in the PACIFIC trial, OS was not statistically significant. Further, OS data have not yet matured in the PACIFIC trial. The role of adjuvant immunotherapy has therefore been examined in the setting of surgery. Three early large adjuvant trials are addressing if adjuvant immunotherapy (durvalumab) is superior in the adjuvant setting (ADJUVANT/CTONG1104). Adjuvant ALK TKIs are also being explored in ALCHEMIST (NCT02194738), whereas other trials are looking at the addition of adjuvant TKI (icotinib) to chemotherapy (ICTAN/NCT01996098 and NCT02125240/ICWIP) (Supplementary Table 3). However, stage III-specific results will be limited as these patients formed only a subgroup in these studies. To date, only the first-generation EGFR TKIs (gefitinib and erlotinib) have data to support their use as adjuvant therapy for postoperative EGFRm+ N2 disease, whereas second- and third-generation TKIs remain experimental. Therefore, if adjuvant EGFR TKIs are to be considered, first-generation TKIs should be used.

Notably in the PACIFIC study, EGFRm+ patients represented only 6% of all patients. We expect the rate of EGFRm+ patients in Asia to be higher than represented by the trial. In the subgroup analysis, the HR for...
PFS in the EGFRm+ population was 0.76 but CIs were wide, 0.35 to 1.64, because of the small sample size. The role of immunotherapy in EGFRm+ patients remains uncertain — in the advanced/metastatic setting, although second-line studies did not reveal OS benefit with ICI compared to single-agent chemotherapy, an exploratory analysis from the IMpower150 trial revealed OS and PFS benefit in the EGFRm+ patient subset with the quadruplet combination of carboplatin-paclitaxel-bevacizumab-atezolizumab versus carboplatin-paclitaxel-bevacizumab, but after prior EGFR TKI therapy. Therefore, there is ongoing debate surrounding the use of consolidation durvalumab in EGFRm+ patients with unresectable stage III NSCLC post-CCRT. However, they should not be excluded from this option and careful discussion about the risk-benefit ratio is warranted.

Given the efficacy of TKIs in oncogene-driven NSCLC and the high prevalence of targetable oncogenes (EGFR and ALK translocations) in Asian patients, incorporating TKI in the definitive treatment of stage III disease may be an alternative strategy and these approaches are being explored in ongoing studies (Supplementary Table 3). For instance, the use of maintenance osimertinib versus placebo following definitive chemoradiation is being evaluated in a phase III randomized study (NCT03521154). Although this does not answer the question of whether osimertinib can replace durvalumab in the EGFRm+ population, it may provide another treatment option for EGFRm+ patients.

Finally, it is unclear if the use of EGFR TKIs in patients who have either received or are planned for CCRT and ICI will be associated with higher toxicity. Previous studies have indicated unacceptably higher pneumonitis rates when EGFR TKI is used concurrently with durvalumab and caution is advised. Another question is whether EGFR TKI in combination with radical thoracic RT instead of chemotherapy would be the strategy to improve outcomes in stage III disease. An ongoing phase II trial (WJOG6911L) is investigating the efficacy and tolerability of gefitinib concurrent with thoracic RT in patients with unresectable stage III EGFRm+ NSCLC (Supplementary Table 3). Enrollment in prospective clinical trials for these EGFRm+ stage III patients is the key to resolving unanswered questions.

**ATORG Consensus**

Induction or consolidation chemotherapy in addition to definitive chemoradiotherapy in unresectable stage III NSCLC are not routine approaches for stage III but may be acceptable in select cases [II, B]. Adjuvant TKI for 2 years may be considered for stage III, node-positive patients with EGFRm+ who have undergone curative resection, if they are unsuitable candidates for adjuvant chemotherapy, after multidisciplinary evaluation [II, B]. If adjuvant EGFR TKIs are to be considered outside of a clinical trial, first-generation EGFR TKIs should be used [II, B]. Unresectable stage III patients with EGFRm+ should not be excluded from consideration for consolidation durvalumab post definitive chemoradiotherapy.

**Figure 3.** Proposed clinical algorithm for stage III NSCLC. Defining resectability is crucial to determining subsequent multimodality management of stage III NSCLC. All patients considered potentially resectable should be discussed in a multidisciplinary meeting. Thorough preoperative staging workup, including a PET/CT, brain MRI, and pathologic confirmation of suspicious mediastinal lymph nodes is mandatory. If surgery is considered in carefully selected patients, this should be preplanned with either neoadjuvant chemotherapy, chemoradiotherapy, or TKI and should ideally be performed in high-volume centers with experienced trimodality teams. Actionable alterations are highly prevalent in Asia and some such as EGFR mutations are becoming more relevant in management of stage III disease. The role of other alterations and biomarkers such as ALK-rearrangements and PD-L1 remains to be elucidated. ChemoRT, chemoradiotherapy; CT, computed tomography; MRI, magnetic resonance imaging; PD-L1, programmed death ligand 1; PET, positron-emission tomography; RT, radiotherapy; TKI, tyrosine kinase inhibitor.
Follow-Up of Stage III NSCLC After Radical Treatment

Following definitive therapy, patients should be followed up with a CT scan of the chest/upper abdomen (including adrenals), in addition to routine history and physical examination. As most failures occur within the first few years of treatment, imaging should be performed 3- to 6-monthly for the first 3 years, 6-monthly for next 2 years, then annually thereafter. Routine PET-CT scans for surveillance is not recommended but may be considered when abnormalities are detected on CT scan. In the case of suspected relapse/recurrence, pathologic
confirmation is advised particularly if there has been a long interval after radical treatment.

Conclusion and Summary of Consensus Statements

Treatment for stage III NSCLC involves a multidisciplinary approach and we have provided a framework for this, tailored to the Asian context (Fig. 3; Table 3). Strategies to improve survival outcomes for this heterogeneous group of patients remain a perennial challenge. As treatment paradigms for NSCLC in both metastatic and non-metastatic settings continue to evolve rapidly in the era of precision oncology, stratification strategies that recognize intrinsic biological tumor differences should be explored so that treatment algorithms can be adapted to specific populations. In Asia, more efforts are needed to set up collaborative real-world databases and develop prospective randomized trials in the region to better characterize the unique demographics of Asian patients with NSCLC.

Acknowledgments

This meeting was only supported by an unrestricted educational grant from AstraZeneca.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the Journal of Thoracic Oncology at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.10.022.

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