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Preamble

Authorization
The National Comprehensive Cancer Network (NCCN) supports and authorizes selected disease-specific expert oncology groups to develop Asia Consensus Statements which reflect regional differences in care, based upon the recommendations of the NCCN Clinical Practice Guidelines in Oncology™ ("NCCN Guidelines") and subject to approval by NCCN and representatives of NCCN’s panels.

Objectives
These statements are designed to provide clear documentation of modifications from the “parent” NCCN Guidelines, outlining those relating to genetic variation in the metabolism of agents or differences in the regulatory environments in participating Asian countries. The main objective of this initiative is the widespread provision and implementation of clinical resources that describe optimal, evidence-based treatment recommendations with the goal of ultimately improving the lives of patients in Asia with cancer.

Genesis and Development Process
This collaborative project was initiated by the NCCN and NCCN’s official representative in Asia, EMD Scientific Communication Ltd. Formation of individual, disease-specific panels of Asian experts is the first step towards the development of an NCCN Asia Consensus Statement for the respective tumor type. Additionally, an NCCN panel chair or member is nominated to participate in the discussion, development, and approval of resultant manuscripts. During each disease-specific consensus discussion, pertinent sections of the latest NCCN Guidelines are assessed for potential adaptation. The agreed-upon modifications of the recommendations of the NCCN Guidelines are documented, categorized, and supported with evidence wherever possible, and are validated and approved by the NCCN.

Background of Panel members
Each Panel comprises multidisciplinary specialists from different Asian countries who are involved in the patient care and management of the specific disease.

Consensus
Categorization of final consensus reached by the panel is based on the NCCN categories of evidence:

<table>
<thead>
<tr>
<th>Category</th>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>1</td>
<td>High</td>
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<tr>
<td>2A</td>
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<td>2B</td>
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<td>3</td>
<td>Any</td>
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*High level of evidence includes randomized, controlled clinical trials, and meta-analyses. Typically, high level evidence are published in peer-reviewed journals. Lower level evidence includes phase II studies, retrospective studies, and clinical experience of experts. Lower level evidence may also include preliminary results of potentially high level evidence (presented at major meetings but before peer-reviewed publication).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
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The statements contained herein reflect the consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these recommendations is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application of the Asia Consensus Statements and disclaims any responsibility for their application or use in any way. The statements are copyrighted by National Comprehensive Cancer Network. All rights reserved. These statements and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2009.

Application of this Document
The statements contained herein are with reference to the NCCN Clinical Practice Guidelines in Oncology™: Non-Small Cell Lung Cancer (v.2.2009). As such, for contextual comprehension of the statements, please refer to the version of the NCCN Clinical Practice Guidelines in Oncology™: Non-Small Cell Lung Cancer noted above. To view the most recent and complete versions of all NCCN Guidelines, please refer to the NCCN Guidelines in English at www.nccn.org. The NCCN Guidelines may not be reproduced in any form without the express written permission of NCCN. All rights reserved.

Limitations
In this preliminary component of a novel, ongoing exercise, the statements have been compiled by experts upon review of the NCCN Clinical Practice Guidelines in Oncology™: Non-Small Cell Lung Cancer (v.2.2009). As NCCN is committed to maintaining up-to-date NCCN Guidelines, NCCN and the Asian panel members are likewise committed to provision of a comprehensive Asia Consensus Statement which will be updated from time to time. Users of the NCCN Guidelines and Statements should note that the recommendations are applicable to 80 – 85% of the patients, and if less than 5% of the patients fall into a particular situation, there may not be any recommendations in the Guideline nor the Statement for these patients. In this case and at all times, clinicians are advised to use their own clinical judgment to determine the best way to manage each patient.
Non-Small Cell Lung Cancer Overview – The Asian Landscape

In addition to the never-smoked status being a good prognostic factor in NSCLC, a US retrospective population-based study has found Asian ethnicity (vs. Caucasians) to be a favorable prognostic factor for overall survival among smokers (HR=0.847, 95% CI: 0.794-0.904) as well as never-smokers (HR=0.861, 95% CI: 0.750-0.988).¹

The higher prevalence of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) sensitive mutations among Asians compared with Caucasians accounts for most of the differences in management of Asian and Caucasian patients. This subject is dealt with in detail under Statement 3. However, the number of cases with mutations insensitive to EGFR-TKI is increasing in Asia.

Being a reference uniquely for countries in Asia, issues closest to the heart of the practicing physician in Asia are addressed in this inaugural edition of the Statement. These issues include tuberculosis in lung cancer, the importance of epidermal growth factor receptor (EGFR) mutation status, and treatment outcomes in East Asian patients.

References:

Statement 1: Tuberculosis and lung cancer

As lung cancer and pulmonary tuberculosis (TB) may coexist, the possibility of underlying lung cancer should be considered in patients with clinical diagnosis of TB. It should also be noted that the presence of TB may interfere with the diagnosis, staging and treatment of lung cancer.

Discussion: Of the world’s estimated 9.27 million incident cases of TB in 2007, 55% were in Asia, with India as a leading contributor of 2 million cases. Coexistent lung cancer and pulmonary tuberculosis is thus not uncommon. As lung cancer can be masked by TB, this has important clinical implications. In India, it is not uncommon for lung cancer patients to be treated for tuberculosis initially. A recent retrospective study in Korea found that of 62 cases of coexistent lung cancer and TB, 37% of the cases were suspected clinically with TB or pneumonia but not lung cancer at admission. Cough with sputum was the most common symptom at admission, being present in 55% of all the cases. The authors of the study concluded that, particularly when an elderly man with a history of heavy smoking is suspected of TB, physicians should not overlook the possibility of coexisting lung cancer which although may not be clear in radiographic findings, warrants attention to detect lung cancer in the early stage.

From Indian studies, while lung cancer and tuberculosis share common symptoms, including fever, cough with expectoration, hemoptysis, weight loss and anorexia, other information can be suggestive of lung cancer, such as patient’s age, smoking history, mediastinal symptoms (e.g. hoarseness of voice, SVC obstruction and dysphagia).

References:
Statement 2: Revised algorithm for stage IV (M1: solitary site and disseminated)

Radiotherapy (RT) is recommended as a treatment option. The revised algorithm is as shown below.

[Cross ref: Guidelines Page NSCL-11]

For the management of this disease, RT is commonly practiced both in Asia and the West.

Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

See NCCN CNS Guidelines
Statement 3: EGFR mutation status and EGFR-TKI treatment

Statement background:

Several biomarkers have emerged as prognostic and predictive markers for NSCLC. Among these biomarkers, the evidence is strongest for epidermal growth factor receptor (EGFR), the 5’ endonuclease of the nucleotide excision repair complex (ERCC1), the proto-oncogene Kirsten-Rous sarcoma virus (K-ras), and the regulatory subunit of ribonucleotide reductase (RRM1). A \textit{prognostic} biomarker is a biomolecule that is indicative of patient survival independent of the treatment received; that is, the biomolecule is an indicator of the innate tumor aggressiveness. A \textit{predictive} biomarker is a biomolecule that is indicative of therapeutic efficacy; that is, there is an interaction between the biomolecule and therapy on patients’ outcome. [Ref: Guidelines Page MS-5]

Whether the presence of the EGFR exon 19 deletion (E19del) or exon 21 L858R mutation (the two most commonly found EGFR mutations) is prognostic of survival for patients with NSCLC, independent of therapy, remains to be proven, as prospective research results are still lacking. However, the presence of the EGFR E19del or L858R mutation is predictive of treatment benefit from EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy. The presence of K-ras mutations is prognostic of poor survival for patients with NSCLC when compared to absence of K-ras mutations, independent of therapy. Presence of K-ras mutations is also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR-TKI therapy. [Ref: Guidelines Page MS-5]

EGFR expression is detectable in approximately 80% – 85% of patients with NSCLC, and the levels of expression vary widely on a continual scale. Both E19del and L858R mutations result in activation of the tyrosine kinase domain, and both are associated with sensitivity to the small molecule TKIs, erlotinib and gefitinib. These mutations are found in approximately 10% of Caucasian patients and in 30% - 40% of Asian patients with NSCLC. [Reference: Guidelines Pages MS-5 to MS-6] Presence of EGFR-activating mutations represents critical biological factors for proper patient selection. [Ref: NSCL-A 2 of 2: Principles of Pathologic Review]

Due to the genetic difference resulting in the significantly higher response rate to EGFR-TKI therapy in the Asian population, the following recommendations are made:
3(A) For therapy of distant metastases involving the brain, EGFR-TKI as a treatment option (other than palliative external-beam RT) should be considered for patients with known EGFR-TKI sensitive mutation disease. (Category 2B) [Cross Ref: Guidelines Page NSCL-12]

**Discussion:**
Several studies have demonstrated the therapeutic potential of EGFR-TKIs, such as gefitinib, in the treatment of brain metastases from NSCLC.1-4

A Taiwanese study involving 76 NSCLC patients who were given oral gefitinib 250 mg daily irrespective of their performance status (PS), number of prior treatment regimens, and the presence of brain metastases, reported that there were no differences between patients with and without brain metastases in terms of progression-free survival (PFS, p=0.765) as well as overall survival (OS, p=0.223); overall median PFS was 5.0 months (95% CI, 3.5–6.6 months) while median OS was 9.9 months (95% CI, 4.9–14.8 months).1 The results also showed significantly longer PFS for patients with adenocarcinoma vs. those with non-adenocarcinoma (median PFS =7.3 vs. 2.9 months, p=0.001). In addition, patients with adenocarcinoma (p=0.006) and better PS (p<0.001) had a longer OS. As with previous EGFR-TKI studies, severity of skin toxicity in this study was found to be related to tumor response (p=0.007) and patient survival (p<0.001).

In a separate study, distinct therapeutic potential found against brain metastases compared with primary lung tumor and extracranial metastases suggests that molecular targeted therapy against EGFR could be an option for the treatment of brain metastases secondary to NSCLC which are refractory to conventional chemotherapy or radiation therapy.4

**References:**
3(B) Due to the predictive importance of EGFR mutation status in Asian patients, the algorithm for the treatment of recurrence and metastasis has been revised as follows:

[Cross Ref: Guidelines Page NSCL-13]

- **EGFR mutation status known**
  - **EGFR mutation positive**
    - Performance status 0 – 1: Treat with EGFR-TKI (category 1)
    - Performance status 2 – 4: Treat with EGFR-TKI (category 2A)
  - **EGFR mutation negative**
    - Performance status 0 - 1: Chemotherapy (category 1) or Bevacizumab + chemotherapy (if criteria met) or Cisplatin/pemetrexed (category 1) (if criteria met) or Cetuximab*/vinorelbine/cisplatin (category 2B) (if criteria met)
    - Performance status 2: Cetuximab*/vinorelbine/cisplatin (category 2B) (if criteria met) or Chemotherapy
    - Performance status 3-4: Best supportive care only (See NCCN Palliative Care Guidelines)
- **EGFR mutation status unknown**
  - East Asian never smokers, & adenocarcinoma
    - Treat with EGFR-TKI regardless of Performance status preferred (category 2B)
  - Others
    - Switch to another EGFR-TKI (category 3)

- **Progression after EGFR-TKI treatment**
  - Performance status 3-4: Best supportive care only (See NCCN Palliative Care Guidelines)

* **There is insufficient data supporting the use of cetuximab within the Asian population, especially nonsmoking adenocarcinoma or EGFR mutation positive patients. (Category 2B)**
Discussion:

Asian studies have further proven the predictive value of EGFR mutation on survival benefit from gefitinib.\(^1\-^3\) The landmark phase III IPASS study has also demonstrated superior efficacy, higher quality of life and similar symptom improvement rates, and a more favorable tolerability profile for the EGFR-TKI, gefitinib, compared with carboplatin/paclitaxel in Asian, chemonaïve, never or light ex-smokers with advanced NSCLC and adenocarcinoma histology.\(^4\)

In addition, a recent study in Japan reported that EGFR mutation-positive patients with poor performance status (PS 2 to 4) benefit from first-line gefitinib, with significant improvement in performance status and progression-free survival.\(^5\) As there previously has been no standard treatment for these patients with short life expectancy other than best supportive care, determination of EGFR-mutation status is recommended in this patient population; this study has provided some evidence that treatment with an EGFR-TKI for this group of patients is efficacious and feasible.

In contrast, a retrospective subgroup analysis of the FLEX study did not find survival benefits in Asian patients (n=121) treated with cetuximab + cisplatin/vinorelbine (CV), over those treated with CV alone (OS in months: 17.6 vs. 20.4, p=0.4992). However, preliminary results of prespecified subgroup analyses suggest a greater benefit in Caucasians independent of histology and a general better prognosis in Asians.\(^6\)

References:

3(C) Gefitinib is recommended as a treatment option for both second- and third-line therapies for patients with progressive advanced or metastatic disease. (For progressive disease, consensus for gefitinib treatment for performance status 0-2 patients is category 2A, while that for performance status 3-4 patients is category 2B.)

[Cross ref: Guidelines Page NSCL-15, NSCL-E 1 of 2]

**Discussion:**

Although a statistically significant difference in survival was not seen between gefitinib and placebo in the overall ISEL population, preplanned subgroup analyses showed significantly longer survival in the gefitinib group for never-smokers and patients of Asian origin. In a subgroup of patients of Asian origin with previously treated refractory advanced NSCLC, subset analysis from the phase III ISEL study showed that treatment with gefitinib was associated with a significant improvement in survival compared with placebo (hazard ratio [HR]=0.66; 95% CI=0.48-0.91; p=0.010; median survival= 9.5 vs. 5.5 months).

A retrospective ad hoc analysis of the same study showed improved survival among Indian patients (n=77). Compared with placebo group (n=20, 26%), gefitinib treatment resulted in longer median survival (6.4 vs. 5.1 months, p value not calculated), longer time to treatment failure (5.5mo vs. 3.0mo, p value not calculated), and higher objective response rate (14% vs. 0%).

Gefitinib was also generally well tolerated in patients with Asian origin in all studies, with rash and diarrhea being the most common adverse events.

The INTEREST study established non-inferior survival of gefitinib compared with docetaxel as the second line treatment, suggesting that gefitinib is a valid treatment for pretreated patients with advanced NSCLC.

The ISTANA study compared the efficacy of gefitinib and docetaxel in patients with advanced or metastatic NSCLC with prior platinum-based chemotherapy, and found that gefitinib treatment resulted in significantly higher PFS (p=0.0441) and objective tumor response rates (28.1% vs. 7.6%, p=0.0007), with lower rate of grade 3/4 adverse events reported in gefitinib group (21.0% vs. 27.6%).

As for patients with poor performance status (PS 2 to 4), the recent Japanese study reported that such patients who are EGFR mutation-positive benefit from first-line gefitinib, with significant improvement in performance status and progression-free survival. This first report provides some evidence on the feasibility for the treatment of these patients with short life expectancy for whom best supportive care was, prior to this, possibly the most cost-effective.
References:


In advanced disease, new agent platinum combinations have generated better clinical outcomes in Asians (especially never-smokers and/or EGFR mutation positive patients) compared with Caucasians: Overall response rate (~25-43% vs. ~25-35%), median survival (11.4-17.1 mo vs. 8-10 mo), 1-year survival rate (~41-60% vs. 30-40%) and 2-year survival rate (21.4-31.5% vs. 10-15%).

[Cross ref: Guidelines Page NSCL E 1 of 2]

Discussion:

Asian never-smokers and/or EGFR mutation positive patients have a different prognosis:

A phase II trial of gefitinib (250 mg/day) in NSCLC showed an objective response rate of 12-18%, and higher rates were found in Japanese patients, women, never-smokers, and patients with adenocarcinoma.\(^1\) In the phase III ISEL trial, best supportive care with gefitinib rather than placebo significantly prolonged median survival in patients of Asian origin (primarily from Taiwan, Thailand, Singapore, the Philippines, and Malaysia; 9.5 vs. 5.5 months, \(p=0.01\)) and never-smokers (8.9 vs. 6.1 months, \(p=0.012\)). Gefitinib treatment also led to significantly longer time to treatment failure in Asians (4.4 mo vs. 2.2 mo in placebo) than in those of non-Asian origin (0.86 [0.76-0.98] \(p=0.0197\)).\(^1,2\)

A recent phase III showed that pemetrexed/cisplatin (PC) is non-inferior to gemcitabine/cisplatin (GC) in first-line NSCLC, and PC resulted in better survival outcomes in East / South East Asian patients, compared with GC (HR=0.88).\(^3\) PC treatment also led to better median survival in East / South East Asian patients, compared with other races (13.8 months vs. 10.0 months in Caucasian vs. 9.9 months in all other races). In addition, East Asian patients (from South Korean and Taiwan) with non-squamous histology treated with PC had better overall survival (17.1 vs. 10.3 months), and better overall response rate regardless of histology (42.6% vs. 30.3%), compared with the overall population (African descent, Caucasian, East / South East Asian, and other races).\(^4\) PC is recommended by the NCCN Clinical Practice Guidelines in Oncology\(^\text{TM}\) for Non-Small Cell Lung Cancer (NSCL-E 1 of 2, V.2.2009) as first-line therapy in advanced-stage non-squamous NSCLC.

In a phase III Japanese study, the efficacies of irinotecan/cisplatin, paclitaxel/carboplatin, gemcitabine/cisplatin, and vinorelbine/cisplatin were compared. The four platinum-based combination regimens were shown to have similar overall response rates (30.1-33.1%) and median survival (11.4-14.0 months) in the patients.\(^5\)
References:


