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Expert consensus recommendations on biomarker testing in metastatic and non-metastatic non-small cell lung cancer in Asia

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Abstract:

Most published guidelines for genomic biomarker testing in non-small cell lung cancer (NSCLC) reflect the disease epidemiology and treatments readily available in Europe and North America. However, 60% of annual global NSCLC cases occur in Asia, where patient characteristics, tumor molecular profiles, and treatments vary greatly from the Western world. For example, mutations in the epidermal growth factor receptor (EGFR) occur at a higher prevalence in Asia than in other world regions. Although medical associations such as IASLC, ESMO, and ASCO have described principles for tumor genomic biomarker testing in NSCLC, there is a need for recommendations specific for Asia. This report provides consensus recommendations for NSCLC biomarker testing from Asian lung cancer experts, for clinicians working in Asia to improve patient care. These recommendations are divided into non-metastatic and metastatic forms of adenocarcinoma and squamous cell carcinoma. Biomarker testing approaches for actionable genetic alterations in EGFR, ALK, ROS1 and others are discussed. Owing to the higher prevalence of EGFR mutations in Asia, the experts emphasized the need for EGFR testing to include not just common mutations (exon 19 deletions & L858R substitutions) but also other uncommon EGFR mutations. In addition to the assessment of biomarkers in tumor tissue, the role of assessing tumor biomarkers by liquid biopsy are also discussed.

Keywords: Non-small cell lung cancer, ctDNA, biomarkers, adenocarcinoma, squamous carcinoma, liquid biopsy
Introduction:
Asia contributes 60% to the world’s 2 million annual lung cancer cases.\textsuperscript{1-3} Although lung cancer mortality has been steady or decreasing in Western countries, it has been increasing in Asia for the past two decades.\textsuperscript{4} This may be attributed to several factors, including the epidemiology and molecular characteristics of lung cancer as well as treatment inaccessibility in Asia.

While smoking is the leading cause of lung cancer in both Western and Asian countries, among non-smokers, the cause of lung cancer is still largely unknown. Risk factors such as indoor coal burning, cooking fumes, outdoor air pollution, infections and family history of cancer may play an important role in the development of lung cancer in Asia.\textsuperscript{4-6} There is noticeable difference in the smoking rate in lung cancer patients by sex and by country within Asia. In a study by Mitsudomi et al in a cohort of Japanese patients with lung cancer, as many as 83% of female patients were never-smokers, compared with only 10% of male patients. In contrast, data from the Western world shows that most people with lung cancer are smokers irrespective of the sex of the patients.\textsuperscript{7}

The molecular characteristics of lung cancer in Asia, particularly lung adenocarcinoma, are also significantly different from Western populations. Mutations in \textit{EGFR} can be detected in 10-15\% of lung adenocarcinoma in Caucasian patients but can be found in up to 60-70\% of lung adenocarcinomas diagnosed in Asian never-smokers.\textsuperscript{4,8,9} On the other hand, \textit{KRAS} mutations, the most common oncogenic driver in lung adenocarcinoma in Caucasian patients (26\%), occur in less than 10\% of Asian lung adenocarcinomas.\textsuperscript{10} The prevalence of other well-characterized genomic drivers appears to be similar in Asian and non-Asian lung adenocarcinomas. A pooled analysis of 2,126 non-smoking Asian patients with lung adenocarcinoma identified \textit{EGFR} mutations in 74\%, \textit{ALK} rearrangements in 6\%, \textit{ROS1}
rearrangements in 0.8%, \textit{ERBB2 (HER2)} mutations in 4%, and \textit{RET} rearrangements and \textit{MET} exon 14 skipping in 1% each of the studied subjects.\textsuperscript{11}

In recent years, there has been a major shift in the management of NSCLC, from non-specific treatments such as chemotherapy to targeted therapies. In tumors with driver alterations, targeted therapy significantly improves patient outcomes and quality of life. Therefore, screening NSCLC for a range of recommended predictive and prognostic biomarkers has become a necessary step.\textsuperscript{12}

While tumor tissue including cytological specimens is the traditional standard for the detection of mutations, adequate material may not be available for testing after initial histological or cytological diagnosis. In such cases, re-biopsy may be necessary, which may not be feasible for all patients. Liquid biopsy is gaining acceptance due to its relative non-invasiveness and potential to overcome the limitations of tumor heterogeneity. Liquid biopsy assays are dependent on tumor DNA shedding into the bloodstream, which may be less common for patients with lower tumor burden or tumors limited to sanctuary sites such as the central nervous system. Furthermore, as with all DNA-dependent assays, sensitivity for the detection of complex genomic alterations such as rearrangements and large introns may be lower than with protein-based or RNA-based technologies. Despite the concern that ctDNA-based technologies may falsely attribute alterations from clonal hematopoiesis of indeterminate potential (CHIP) as having tumor origin, common CHIP-associated alterations and actionable NSCLC genomic alterations are largely mutually exclusive.\textsuperscript{13} Nevertheless, overall detection rates of clinically informative genomic biomarkers are similar for ctDNA panel testing and standard tissue testing.\textsuperscript{14,15} Table 1 captures commonly used testing methods in NSCLC.
With the growing number of genomic alterations that can inform the choice of targeted therapies, international guidelines for biomarker testing in NSCLC have been established by ASCO, CAP-IASLC-AMP, NCCN and ESMO. For the most part, the recommendations are largely aligned, however they were created predominantly in the context of non-Asian countries. One of the few guidelines that focused on Asian lung cancer patients was issued by ESMO in collaboration with the Chinese Society of Clinical Oncology; the Japan Lung Cancer Society also has a guideline on biomarker assessment. These described testing guidelines for \textit{EGFR}, \textit{BRAF}, \textit{ALK}, \textit{ROS1} and PD-L1, but emerging diagnostic techniques and therapeutics were not the focus.

Countries in the vast Asia-Pacific region present high variations in access to diagnostic tests and targeted medicines (Supplementary table 1); treatment decisions are strongly influenced by the availability of technology and resources to cover their costs. In Japan, chest x-ray with sputum cytology is recommended as lung cancer screening for smokers, while there is no policy for lung cancer screening in countries such as Singapore, India and Vietnam. Regarding the availability of emerging targeted therapies, health authority approval and reimbursement is different from country-to-country but generally lag behind Europe and the US (Supplementary table 1).

Therefore, the application of current Western guidelines in this context, while potentially desirable, is not consistently practical for most Asian patients with lung cancer. In the IASLC survey on molecular testing in lung cancer, 64\% of respondents from Asia expressed that less than half of their lung cancer patients undergo molecular testing. While the barriers to testing are diverse, the lack of recommendations that consider the unique epidemiology of lung
cancer and accessibility to technology may be one of contributing factors. Therefore, a pragmatic approach to lung cancer biomarker testing in Asia is warranted.

This consensus on biomarker testing for NSCLC in Asia is the result of extensive discussions among experts from several Asian countries. The experts discussed the needs and perceptions around biomarker testing in metastatic and non-metastatic NSCLC, provided insights on the use of various testing platforms, and reached consensus during the six online meetings. We received editorial support from a company strictly under the direction of the authors. All the authors approved in writing, after multiple rounds of review, the content of this paper. The goal of this consensus is to help ensure patients receive the newest available therapy and improve the quality of care so that the best possible outcomes for Asian lung cancer patients can be achieved.

1. Recommendations for biomarkers testing of non-metastatic NSCLC

The demographics of patients with lung cancer have changed in the past decade. With further implementation of lung cancer screening, we hope that a stage migration from metastatic to earlier stages of disease will also be observed.

The stage at presentation typically breaks down to the following: stage I 10%, stage II 20%, stage III 30%, and stage IV 40%. The majority of patients present with advanced stage or metastatic disease, which reduces the patient’s chances of survival with current therapies. However, it is also true that there is a great heterogeneity in terms of stage at presentation even within Asia. For example, stage I accounts for 40% of newly diagnosed NSCLC cases in Japan.

Based on the presumption that detection of tumor molecular abnormalities as soon as possible after diagnosis will lead to a significantly longer survival, biomarker detection strategies have been tested for potential value in the early detection of lung cancer or
prognostic and therapeutic guidance through the main methodologies implemented. These include detection of genomic changes by PCR (Polymerase Chain Reaction) or Next Generation Sequencing (NGS) and detection of over-expressed proteins by immunohistochemistry (IHC).

In this section, we discuss the biomarkers used in clinical practice as predictive, and prognostic biomarkers after diagnosis has been confirmed.

**Recommendations (Figures 1 and 2)**

- **Non-metastatic resectable NSCLC**
  - **Adenocarcinoma**
    - Stage IA: *EGFR* and PD-L1 testing as routine are not recommended at this time
    - Above stage IA: Evaluate *EGFR* status by PCR at diagnosis. If the tumor is positive for either *EGFR* mutation or PD-L1>1%, follow the local treatment recommendations. *(Figure 1).*
  - **Squamous cell carcinoma:** *EGFR* testing as routine is not recommended at this time for stages IA – IIIA, and PD-L1 testing is not recommended for stage IA.

- **Non-metastatic unresectable NSCLC**
  - If the patient is fit for definitive chemoradiotherapy, then consider evaluating for PD-L1 status (regardless of histology) and *EGFR* mutation (adenocarcinoma only) and follow local treatment recommendations *(Figure 2).*
  - If the patient is unfit for definitive chemoradiotherapy, then follow testing recommendations for metastatic disease.
In the case of unresected tumors, tissue biopsy used for diagnosis can be used for biomarker assessment.

A turnaround time of approximately 3 weeks for test results from resected tumors is acceptable while ≤ 2-week turnaround time is preferred for unresectable cases due to the urgency of treatment.

2. Recommendations for biomarker testing of metastatic NSCLC

2.1 Biomarker testing before initial therapy

2.1.1 Adenocarcinoma

2.1.1.1 Initial testing for patients with metastatic adenocarcinoma

2.1.1.2 Steps if initial testing does not provide an informative biomarker for adenocarcinoma

2.1.2 Squamous cell carcinoma

2.1.2.1 Initial testing for patients with squamous cell carcinoma

2.1.2.2 Steps if initial testing does not provide an informative biomarker for squamous cell carcinoma

2.2 Biomarker testing at disease progression

Test performance will vary due to different sensitivities, specificities, and characteristics of the samples themselves (age, preservation conditions, tumor cellularity, etc.). Clinicians should be aware of test performance, and workflows for testing should be validated by external quality control programs.28

Tumor tissue is the preferred source of material for confirmation of the diagnosis of metastatic NSCLC and for initial biomarker testing; however, sometimes its availability can be a limiting factor. In such cases, tissue should be prioritized for biomarker assessment that can be performed only with tissue, such as PD-L1 testing. For patients who meet clinical requirements, re-biopsy can be considered to obtain additional tumor tissue prior to initial treatment. However, such procedures are not feasible for all patients and could add to
morbidity, costs, and delays in treatment. In this consensus the term tissue biopsy also includes cytology specimens.

Analysis of circulating tumor DNA (ctDNA) has emerged as an effective and promising tool for genomic profiling in metastatic NSCLC. Evaluation of ctDNA can be particularly useful in situations where tissue biopsy is not safely obtainable due to poor physical condition of the patient or inaccessible tumor biopsy location. Although specificity and positive predictive value are generally high, the sensitivity compared to tissue-based methods may be lower when small quantities of DNA are shed from the tumor into the bloodstream. Nevertheless, detection rates of actionable genomic biomarkers are similar between NGS-based ctDNA assays and tissue-based methods. In addition to identifying oncogenic driver mutations which can be treated with targetable therapy in the treatment naïve advanced NSCLC setting, ctDNA might prove useful in novel ways including monitoring during an advanced NSCLC patient's treatment course (real-time monitoring) and determining mechanisms of resistance to therapy. A liquid biopsy may detect the presence of a genomic biomarker associated with NSCLC (e.g., EGFR mutation or ALK rearrangement) before a cellular-based diagnosis is obtained; however, the panel did not address whether targeted therapy should be initiated without supportive histology or cytology results.

2.1 Biomarker testing before initial therapy

2.1.1 Adenocarcinoma

2.1.1.1 Initial testing for patients with metastatic adenocarcinoma

The selection of biomarkers for testing before initial therapy for advanced-stage lung adenocarcinoma depends on the known prevalence of specific genetic alterations, availability of targeted therapies, access to technology (single-gene or panel testing), and reimbursement of diagnostic procedures and therapies.
Along with PD-L1, clinicians should assess for driver alterations in *EGFR, ALK*, and *ROS1* simultaneously. Depending on the resources and therapeutic products available, potentially informative or actionable alterations should also be assessed in other genes (*BRAF V600E, RET, MET* exon 14 skipping, *KRAS, ERBB2, NTRK*).

A variety of molecular testing approaches can be utilized, keeping in mind their advantages and limitations. Local laboratory testing of *EGFR* hotspot mutations can provide fast results and has the potential to identify most tumors with driver mutations in areas with a high probability of *EGFR* alterations. However, hotspot testing, even with perfect sensitivity, can miss less common but actionable *EGFR* alterations and do not cover all possible pathogenic insertions and deletions. Because *EGFR* mutations are highly prevalent in lung adenocarcinoma in Asia, uncommon mutations in *EGFR* may occur more frequently than common alterations in other genes. Therefore, whenever feasible, *EGFR* assessment should include not only exon 19 deletions and L858R but also other activating point mutations and exon 20 insertions.

As the number of genes that need to be assessed for NSCLC patients at diagnosis is continuously expanding due to efficacious therapies, pressure to use the available tissue sample judiciously becomes imperative. Therefore, when assessing for alterations in multiple genes, simultaneous testing that incorporates next-generation sequencing (NGS) from a single sample is preferred, whenever feasible, so as not to exhaust available tumor specimens. While tissue is the preferred material, the turnaround time for results may be two weeks (preferred) or longer. In cases where tissue may not be available, liquid biopsy-based single gene or NGS testing can be an option. Using plasma, single-gene testing can be completed in under one week; comprehensive testing can be completed in under two weeks.
For assessing gene rearrangements in \textit{ALK}, \textit{ROS1}, and other genes, test sensitivity is greater with protein-based or RNA-based technologies than with NGS of tumor-derived DNA. As tumor mutation burden (TMB) is not yet an established marker for immune checkpoint inhibitors in NSCLC and microsatellite instability (MSI) high is a rare occurrence in NSCLC, both of these biomarkers currently should not be routinely evaluated.

\textbf{Recommendations (Figure 3)}

- All patients with lung adenocarcinoma should be tested simultaneously for PD-L1 and driver alterations in \textit{EGFR}, \textit{ALK}, \textit{ROS1}.
  
  \hspace{1em} \textbf{Consideration:} Whenever possible, clinicians must wait for the results of driver biomarker testing before commencing first-line treatment. Treatment decisions should not be based solely on PD-L1 results.

- When available, tumor tissue should be used for genomic testing. However, if tissue is not available, or re-biopsy is not practical, ctDNA testing should be considered.

- Recommended approaches for testing: PCR based for \textit{EGFR}, IHC for \textit{ALK} and \textit{in situ} hybridization (ISH) or IHC for \textit{ROS1} rearrangements. Consider other methodologies such as NGS when it is necessary to cover a broad array of alterations.

- \textit{EGFR} testing should assess all common and uncommon driver mutations, including exon 20 insertions. PCR alone may miss some pathogenic alterations; therefore, NGS should be considered.

- If targeted therapies are available, test for potential alterations in all relevant genes prior to initial treatment (in addition to \textit{EGFR} mutations and \textit{ALK} and \textit{ROS1} rearrangements, assess for \textit{BRAF V600E}, \textit{MET} exon 14 skipping, \textit{KRAS} and \textit{ERBB2} mutations, \textit{RET} and \textit{NTRK} rearrangements).
  
  \hspace{1em} \textbf{Consideration:} If multiple genes will be tested, consider a panel test rather than sequential single testing for individual biomarkers.
• The preferred turnaround time for obtaining test results is $\leq 2$ weeks.
• Routine testing for tumor mutational burden (TMB) and microsatellite instability (MSI)-high status is not recommended.

2.1.1.2. Steps if initial testing does not provide an informative biomarker for metastatic adenocarcinoma
Genomic driver alterations are anticipated in more than 60% of lung adenocarcinoma cases in Asia; this can be as high as 90% in non-smokers.\textsuperscript{11} As driver mutations are usually mutually exclusive in treatment-naïve NSCLC, the presence of any driver mutation suggests the absence of another driver, and testing can be considered complete.\textsuperscript{14} Given the high prevalence of driver mutations in Asian patients with lung adenocarcinoma, there remains a reasonable probability that an actionable genomic biomarker may still be present even if initial testing failed to detect one.

The success of biomarker testing depends on several technical factors, and limitations in the type of test undertaken. The quantity and quality of the representative tissue samples and handling of the test material may all contribute to lack of detection of tumor DNA or a false negative result.\textsuperscript{30} For biopsy specimens, a single sample may not represent a complete genomic profile of a potentially heterogeneous tumor.\textsuperscript{31} For plasma samples, ctDNA may not be detected when tumors are not shedding sufficient genetic material into the bloodstream or the tumor is limited only to sanctuary sites such as the brain.\textsuperscript{32} Hotspot tests are focused only on common loci of mutation and therefore may miss other uncommon but potentially actionable alterations, including insertions and deletions. For these reasons, the lack of detection of a driver mutation following initial testing does not rule out the presence of an actionable genetic alteration. Whenever practical, follow-on testing should be conducted before the initiation of first-line treatment when initial testing does not detect a clinically
informative driver mutation. Panel testing, using tissue or plasma, is preferred to assess for multiple biomarkers simultaneously and to optimize turnaround time.

**Recommendations (Figure 3)**

- In the absence of a driver mutation after initial testing (single-gene analysis of tissue or plasma), perform follow-on testing for genomic biomarkers.
  - **Consideration:** If an NGS-based panel (tissue or plasma) were used as initial testing, then follow-on testing is not routinely recommended.
  - **Consideration:** When follow-on testing is performed, an NGS-based panel (tissue or plasma) is preferred.

- For clinical situations that do not require immediate treatment, wait for results of follow-on testing before initiating therapy according to local treatment recommendations. Test turnaround time in this situation should be minimized (≤ 2 weeks).

- For clinical situations that require immediate treatment, follow local treatment guidelines for genetic driver-negative metastatic NSCLC.

### 2.1.2 Metastatic squamous cell carcinoma

The presence of genetic driver alterations in NSCLC with uniform squamous cell histology is uncommon. Driver mutations are more likely to be detected in tumors with mixed adenosquamous histology. In such cases, small tumor specimens from lung adenocarcinoma or mixed adenosquamous carcinoma may be misdiagnosed as pure squamous cell carcinoma. Therefore, a thorough pathologic evaluation of tumor specimens is required to confirm the diagnosis. If there is doubt regarding the histologic diagnosis, or clinical features more commonly associated with adenocarcinoma are present (non-smoker, younger age, peripheral location), biomarker testing should be considered. Although uncommon, MET exon 14
skipping has a similar prevalence in both squamous carcinoma and adenocarcinoma.\textsuperscript{14,35,36,37}

2.1.2.1 Initial testing for patients with metastatic squamous cell carcinoma

Recommendations:
- Test all patients for PD-L1 in tumor tissue.
- Test for \textit{EGFR} mutations in patients who are never or light smokers or based on clinical judgment.\textsuperscript{38} Consider testing for \textit{MET} exon 14 skipping (highly recommended if sarcomatoid histology present).\textsuperscript{39} Testing for other biomarkers at this step is not recommended.
  - \textbf{Consideration}: If there is clinical suspicion of adenosquamous carcinoma or squamous carcinoma with an adenocarcinoma component as exemplified by squamous cell carcinomas in the peripheral lung or those occurring in non-smokers, follow the recommended testing protocol for adenocarcinoma.
- \textit{EGFR} testing, when performed, should assess all common and uncommon driver mutations, including exon 20 insertions.
- When available, tumor tissue should be used for genomic testing. However, if tissue is not available or re-biopsy is not practical, ctDNA testing should be considered.
- The preferred turnaround time for obtaining test results is \( \leq 2 \) weeks.

2.1.2.2 Steps if initial testing does not provide an informative biomarker for squamous cell carcinoma

Recommendations:
- Follow-on testing is not required if initial genomic testing of squamous cell carcinoma did not detect a driver alteration.

2.2 Biomarker Testing at Disease Progression
Nearly all advanced stage NSCLC patients who have been treated with systemic therapy will eventually develop tumor progression/progressive disease (PD). After treatment with first- or second-generation EGFR TKIs, the most common cause (~50%) of resistance is the acquisition of EGFR T790M. Alterations associated with acquired resistance to third-generation EGFR TKI include point mutations in EGFR (C797X and others), MET amplification, ERBB2 amplification, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations, BRAF mutations, KRAS mutations, and small cell transformation. Similarly, disease progression and acquired resistance have also been demonstrated in patients harbouring ALK rearrangement-positive NSCLC, particularly those who have been treated with early-generation ALK TKIs. Each ALK-targeting TKI has a unique profile that is resistant to or can overcome specific acquired point mutations in ALK.

The IASLC recommends biomarker testing in EGFR mutated lung cancer patients whose disease has progressed following initial TKI therapy. Given its convenience and relatively rapid turnaround time, the IASLC recommends ctDNA based NGS testing as a first step; however, tissue biopsy is recommended if biomarker testing results are negative or if there is a strong suspicion of small cell transformation.

**Recommendations (Figure 4):**
- PD after 1st/2nd gen EGFR TKI: Test for EGFR T790M in ctDNA or newly acquired tumor tissue, if feasible. If no actionable biomarker is detected in ctDNA, perform a biopsy and test tissue for EGFR T790M and assess histology.
- PD after 3rd gen EGFR TKI: Consider NGS panel test of ctDNA or newly acquired tumor tissue, if feasible. If no actionable biomarker is detected in ctDNA, perform a biopsy and assess histology.
• PD after other (non-ICI) targeted therapy: Newly acquired actionable alterations are less common in this setting. If resources are not a constraint, consider NGS panel testing of ctDNA or newly acquired tumor tissue, if feasible.

• For PD on ICI and/or chemotherapy (no history of targeted treatment):
  a) If complete biomarker testing were performed in the past, with no finding of an actionable driver alteration: No additional biomarker testing recommended.
  b) If biomarker testing were performed in the past, with an actionable driver alteration detected: No additional biomarker testing recommended.
  c) If incomplete or no biomarker testing were performed in the past: Perform comprehensive NGS panel test of ctDNA or tumor tissue (archival or newly acquired).

• The preferred turnaround time for obtaining test results is ≤ 2 weeks.

Conclusions and future perspectives

Ongoing clinical trials are exploring the efficacy and safety of new therapies that target specific genomic alterations in NSCLC. As new targets are characterized and new treatments become available, the need to assess for the presence of genomic alterations and other biomarkers will increase so that physicians can apply precision medicine to patients who are most likely to benefit from it. This complexity requires effective diagnostic approaches. The testing platforms for genomic biomarkers have evolved over the years from standalone testing by RT-PCR, IHC and FISH to more comprehensive NGS panels which can assess several genes at once. Each of these testing platforms has its advantages and challenges. According to a global survey conducted by IASLC, less than half of lung cancer patients received any sort of molecular testing. The major barriers common to all geographic
regions were cost, quality, access, awareness, and turnaround time. Respondents also expressed their concerns regarding limitations of sample quality and interpretation of test results. Particularly in Asia, where the prevalence of genomic alterations in NSCLC is high but access to medicines and testing procedures is heterogeneous, a pragmatic, region-specific approach to testing must be implemented.

This expert group reached a consensus that relevant genomic alteration assessment is necessary at diagnosis as well as at disease progression, considering tumor histology and treatment history. At diagnosis, along with PD-L1, \textit{EGFR}, \textit{ALK} and \textit{ROS1}, other assessment for other driver alterations should be considered when relevant targeted therapies are available. At the time of disease progression on first-generation EGFR TKIs, assessment for the presence of \textit{EGFR} T790M is essential. For progression on third-generation EGFR TKIs, more comprehensive testing may be considered. For progression on other targeted therapies, physicians should consider the probability of identifying a potentially actionable alteration prior to testing. In general protocol for biomarker testing of advanced NSCLC depends on factors such as the clinical condition of the patient, prior treatment history, biomarker testing history, and access to relevant targeted therapies.

Tissue-based tests are preferred, but in cases of inadequate tissue samples or inconclusive results or when re-biopsy is not feasible, evaluation of plasma for ctDNA is a viable alternative. With an increasing number of genes to be assessed, comprehensive genomic profiling (using either tumor tissue or plasma) is becoming a more efficient method at the time of initial assessment, optimizing turnaround time for results and sparing tissue samples for other analyses.
The recommendations provided are intended to provide a practical approach to biomarker assessment for clinicians across Asia who treat patients with lung cancer. However, health care providers are also advised to consider the particulars of each individual patient, including clinical history and co-morbidities, accessibility to treatments and testing procedures.

An obvious limitation of this consensus is the relevance of the recommendation in the face of a rapidly evolving landscape of actionable biomarkers, treatments, and diagnostic platforms. Therefore, it is advisable to track the developments and follow the most recent literature for the optimal diagnostic and treatment options.

This consensus aims to provide practical recommendations for genomic biomarker testing in early and advanced stage NSCLC for Asian lung cancer patients. The timely diagnosis of the genomic alterations in NSCLC will help clinicians make more informed treatment decisions and ultimately improve patients’ outcomes.

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- Carmen Luz Vargas Malaga, AstraZeneca
References:


Figure Legends

Figure 1. Biomarker testing recommendations for non-metastatic resectable lung cancer
Figure 2. Biomarker testing recommendations for non-metastatic unresectable lung cancer
Figure 3. Biomarker testing recommendations for metastatic adenocarcinoma
Figure 4. Biomarker testing recommendations at disease progression

Table Legends

Table 1. Detection techniques for biomarkers in NSCLC
Supplementary table 1. Table depicting the availability of drugs across Asian countries
Figure 1.

Non-metastatic resectable lung cancer

EGFR*, PD-L1

EGFR mutation positive (Exon 19 del, L858R only)

EGFR mutation negative, PD-L1 positive (≥1%)

Both EGFR mutation and PD-L1 negative

Follow the approved treatment recommendations**

*if adenocarcinoma component is present

**According to the local protocols, treatment and clinical trials if available

Figure 2.

Non-metastatic unresectable lung cancer

If the patient is fit for definitive chemoradiotherapy

PD-L1, EGFR*

EGFR mutation positive (Exon 19 del, L858R only)

EGFR mutation negative PD-L1 positive (≥1%)

EGFR mutation negative and PD-L1 negative

Follow the approved treatment recommendations**

*if adenocarcinoma component is present

**According to the local protocols, treatment and clinical trials if available
Figure 3

Metastatic adenocarcinoma

Test for EGFR, ALK, ROS1 and PD-L1 simultaneously by single gene testing

Genetic driver alteration
NOT detected

Multiple gene panel testing

If patient's (sic) condition does not allow waiting for results, follow treatment guidelines for genetic driver-negative disease*

Genetic driver alteration detected

Follow approved treatment recommendations for relevant targeted treatment**

If patient's (sic) condition allows, wait for results before initiating 1st line treatment

Genetic driver alteration
NOT detected

PD-L1 positive

Follow approved treatment recommendations**

PD-L1 negative

*Use results from follow-on testing to guide treatment at 2nd line

**According to the local protocols, treatment and clinical trials if available

Figure 4.

Disease progression

Prior EGFR TKIs 1st/2nd generation

Prior EGFR TKIs 3rd generation

Prior Other targeted therapies (Non-ICI)

Prior non targeted therapies

Test for EGFR T790M in ctDNA and/or newly acquired tumor tissue, if feasible**

Consider NGS panel test by ctDNA and/or newly acquired tumor tissue, if feasible

NGS panel test for ctDNA or newly acquired tumor tissue is exploratory

Prior multigene panel testing in the past

No additional testing recommended

No Prior multigene panel testing in the past

For adenocarcinoma, consider multigene panel testing of ctDNA or archival or newly acquired tumor tissue*

**If any other actionable alteration can be put on a clinical trial

*No additional testing for squamous cell carcinoma if EGFR testing previously performed according to these recommendations.
Table 1: Detection techniques for biomarkers in NSCLC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Predictive alteration</th>
<th>Examples of mutations</th>
<th>Tests available</th>
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<tbody>
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<td><em>PD-L1</em></td>
<td>High expression</td>
<td>NA</td>
<td>IHC</td>
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<td>EML4-ALK</td>
<td>IHC, FISH, NGS, PCR</td>
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<td><em>ROS-1</em></td>
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<td>CD74-ROS1</td>
<td>IHC, FISH, NGS, PCR</td>
</tr>
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<td><em>BRAF</em></td>
<td>Point mutation</td>
<td>V600E</td>
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Abbreviations: *PD-L1*, Programmed Death-Ligand 1; *EGFR*, Epidermal Growth Factor Receptor; *ALK*, Anaplastic Lymphoma Kinase; *ROS-1*, C-Ros oncogene 1; *BRAF*, Serine/threonine-protein kinase B-Raf; *MET*, Mesenchymal-Epithelial Transition factor; *HER2*, Human Epidermal growth factor Receptor 2; *NTRK*, Neurotrophic Receptor Tyrosine Kinase; *RET*, Rearranged during Transfection; *KRAS*, Kirsten Rat Sarcoma Viral oncogene homolog; *PCR*, Polymerase Chain Reaction (This is a dynamic list, please refer to the available test in your region)
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Non-metastatic resectable lung cancer

EGFR mutation positive

EGFR mutation negative, MET amplificated

Both EGFR mutation and MET negative

Follow the approved treatment recommendations**

* If adenocarcinoma component is present
** According to the institutional treatment and clinical trial, if available
CRediT Statement

The recommendations put forward are a result of extensive discussions among experts from several Asian countries, under the aegis of the Lung Ambition Alliance (LAA). The experts are the authors for this manuscript and have contributed equally to the manuscript.

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