Original Article

Singapore Cancer Network (SCAN) Guidelines for the Use of Systemic Therapy in Advanced Non-Small Cell Lung Cancer

The Singapore Cancer Network (SCAN) Lung Cancer Workgroup

Abstract

Introduction: The SCAN lung cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the use of systemic therapy in advanced non-small cell lung cancer (NSCLC) in Singapore. Materials and Methods: The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. Results: Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2014), the European Society of Medical Oncology (2014), the National Institute of Clinical Excellence (2012), the Scottish Intercollegiate Guidelines Network (2014) and Cancer Care Council Australia (2012). Recommendations on systemic treatment for advanced NSCLC were produced. Conclusion: These adapted guidelines form the SCAN guidelines 2015 for systemic therapy of advanced or metastatic NSCLC.

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Key words: ADAPTE process, Asian population, Chemotherapy, Targeted therapy

Introduction

Non-small cell lung cancer (NSCLC) ranks as one of the most frequent cancers in Singapore with a total of 6407 new cases diagnosed from 2008 to 2012.[1] It remains the most lethal of all cancers, being the top cause of cancer death in men and second most lethal cancer in women.[1] Majority of patients (74.5%) are in advanced stages (III/IV) at point of diagnosis.[1]

Over the past 2 decades, comprehensive genomic studies have led to significant advances in our understanding of the pathogenesis of NSCLC where therapeutically tractable molecular subgroups are increasingly delineated. Thus, NSCLC is no longer thought of as a single disease entity, but as several unique molecular and histological subtypes, each with peculiar clinical implications and potentially different standards of care.

The SCAN Guidelines for the Use of Systemic Therapy in NSCLC

The SCAN Guidelines are clinical practice guidelines for the use of systemic therapy in NSCLC. It excludes small cell lung cancer.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of NSCLC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of patients with NSCLC.

Guideline Recommendations/Development

The SCAN Lung Cancer Workgroup comprises a panel of 12 oncologists and 1 pharmacist from Singapore with special interests in the management of lung cancer. Membership of

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the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope for guideline development: adjuvant lung cancer treatment and advanced lung cancer treatment. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework[2] was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to answer the following 7 key areas of the management of advanced NSCLC to provide recommendations on best practice (Table 1):

1. Pathological reporting and molecular subtyping
2. First-line treatment options for epidermal growth factor receptor (*EGFR*) sensitising mutation-positive advanced NSCLC
3. First-line treatment options for advanced NSCLC harbouring anaplastic lymphoma kinase (*ALK*) gene rearrangement
4. First-line chemotherapeutic options for advanced NSCLC with no driver mutation
5. Role of maintenance chemotherapy
6. Second-line chemotherapeutic options
7. Subsequent lines of treatment options

Five international guidelines were selected for review (Supplementary Table 1):

- "NCCN Clinical Practice Guidelines in Oncology—Non-small Cell Lung Cancer Version 4.2014" by the National Cancer Comprehensive Network (NCCN, USA)[3]
- "Metastatic Non-Small Cell Lung Cancer (NSCLC): ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up" by the European Society for Medical Oncology (ESMO), 2012[4]
- "NICE Pathway—Treatment for Non-Small Cell Lung Cancer" by the National Institute for Health and Care Excellence (NICE, 2014)[5]
- "SIGN 137: Management of Lung Cancer" by the Scottish Intercollegiate Guidelines Network (SIGN), 2014[6]
- "Clinical Practice Guideline for the Treatment of Lung Cancer" by the Cancer Council Australia, 2012[7]

The strength of the evidence and grade of recommendation of the international guidelines are reported and summarised. These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of NSCLC, it will be reviewed earlier.

1. Pathological Reporting and Molecular Subtyping

In the past, all histological subgroups of NSCLC were treated uniformly. There was limited use in expanding additional efforts in pathological reporting of a biopsy sample. In recent years, we have seen a paradigm shift in lung cancer treatment to one that is individualised according to histological subtyping. For example, life-threatening toxicities such as haemoptysis are associated with the use of bevacizumab in the treatment of squamous cell carcinoma (SCC) of the lung[8] and pemetrexed shows benefit over gemcitabine-based platinum 2-drug chemotherapy in non-squamous NSCLC.[9] *EGFR* mutations and *ALK* gene rearrangements are almost exclusively seen in lung adenocarcinomas.[10] These genetic alterations have been well validated as targets for a molecularly directed systemic therapy. First-line treatment should an *EGFR*-sensitising mutation or *ALK* gene rearrangement be identified would be an *EGFR* tyrosine kinase inhibitor (TKI),[11-13] crizotinib[14] or ceritinib[15] respectively. Emerging local data supports *ALK* testing in parallel with *EGFR* testing. Crizotinib can also be considered in those who possess genetic alteration in the *Ros1* gene.[16]

Recommendations on Pathological Reporting and Molecular Subtyping

There is unanimous agreement among the workgroup

Table 1. Singapore Cancer Network (SCAN) Guidelines for Systemic Therapy of Advanced NSCLC

Pathological Reporting and Molecular Subtyping	
• Diagnosis made according to WHO classification.	Category IIA
• If non-squamous in histology (Category I), never or former light smokers squamous histology (Level IV, A), small biopsy specimen or mixed histology, testing for *EGFR* activating mutations and *ALK* testing are recommended.	Category I (non-squamous) Level IV, A (never or former light smokers squamous)
• The workgroup supports detection of *ALK* translocation by fluorescence in situ hybridisation (FISH) as standard, however immunohistochemistry (IHC) and RT-PCR-based methods can be used if validated and qualified.	Category IIA
• If possible, parallel testing for molecular aberration is preferable to avoid delay in treatment.	Workgroup consensus
• *ROS1* testing can be considered.	Category IIA
• The workgroup also supports NCCN endorsement of broader molecular profiling with the aims of identifying tractable mutations and informing patients on the availability of clinical trials.	Category IIA
• Rebiopsy at disease progression should be considered.	Category IIA
First-line *EGFR* Mutation Positive	
• Either of the *EGFR*-TKI—gefitinib, erlotinib or afatinib—should be considered in the treatment of advanced NSCLC harbouring *EGFR* sensitising mutations.	Category I
• Should the mutation be discovered in the midst of first-line treatment, the systemic therapy can be interrupted or first-line chemotherapy can be completed prior to starting *EGFR*-TKI.	Category IIA
First-line *ALK* Mutation Positive	
• Clinical trials.	Category IIA
• Consider crizotinib as first-line treatment for *ALK* gene rearranged advanced lung cancer. The workgroup recommends a discussion with patients on the cost implications of this option prior to mutational testing.	Category I
• May switch to ceretinib if intolerant to crizotinib.	Category IIA
First-line Chemotherapy, Driver Mutation Negative	
• In fit patients, platinum doublet chemotherapy is recommended in the first-line treatment of advanced NSCLC.	Category I
• In view of better outcomes with the use of pemetrexed in non-squamous histology and in considering cost effectiveness, the workgroup is of the opinion that pemetrexed/platinum chemotherapy is preferable in the first-line treatment of non-squamous advanced NSCLC.	Workgroup consensus
• Addition of bevacizumab to platinum doublet is an option in non-squamous histology.	Category IIA
• The use of bevacizumab as well as pemetrexed is limited to those non squamous in histology.	Category IIA
• There is insufficient evidence to support the use of cetuximab for which the workgroup unanimously does not recommended in this setting.	Workgroup consensus
Maintenance Chemotherapy	
• In patients with good performance status of 0 – 1, continuation of pemetrexed (is recommended in non-squamous NSCLC if stable disease or response is seen following induction chemotherapy).	Level I, B
• In patients with non-squamous histology and good PS 0 – 1, should first-line chemotherapy be non-pemetrexed based, then switch maintenance to pemetrexed can be considered (Level I, B).	Level I, B
• In patients with all histology, switch to erlotinib can be considered (Level I, B) however the workgroup recommends this only if a sensitising *EGFR* mutation is detected (workgroup consensus).	Level I, B Workgroup consensus
Second-line Chemotherapy	
• The workgroup committee recommends consideration of clinical trials.	Workgroup consensus
• Docetaxel or pemetrexed (restricted to non-squamous in histology) can be considered in fit patients as second-line treatment of advanced lung cancer.	Level I, B
Subsequent Lines of Chemotherapy	
• The workgroup recommends first the consideration of clinical trials.	Workgroup consensus
• Erlotinib can be considered in the treatment of advanced lung cancer beyond second-line chemotherapy in patients with unknown *EGFR* status or *EGFR*-WT who have not received *EGFR*-TKI.	Level II, B
• Given the burgeoning pipeline of novel therapeutics addressing either distinct genetic drivers or resistance mechanisms, molecular profiling for "actionable" alterations either from archival tissue, or a repeat biopsy is also a reasonable consideration.	Workgroup consensus

ALK: Anaplastic lymphoma kinase; EGFR: Epidermal growth factor receptor; NCCN: National Comprehensive Cancer Network; NSCLC: Non-small cell lung cancer; PS: Performance status; RT-PCR: Reverse transcription polymerase chain reaction; TKI: Tyrosine kinase inhibitors; WHO: World Health Organization; WT: Wild type

members in adopting both the ESMO and NCCN guidelines.

1. Pathological diagnosis should be made according to WHO classification (Category IIA). If non-squamous in histology (Category I), never or former light smokers squamous histology (Level IV, A), small biopsy specimen or mixed histology, testing for *EGFR*-activating mutations and *ALK* testing are recommended.
2. The workgroup supports detection of *ALK* translocation by fluorescence in situ hybridisation (FISH) as standard, however immunohistochemistry (IHC) and reverse transcription polymerase chain reaction (RT-PCR)-based methods can be used if validated and qualified.
3. If possible, parallel testing for molecular aberration is preferable to avoid delay in treatment.
4. *ROS1* testing can be considered and if positive treatment with crizotinib may be considered as per NCCN guidelines (Category IIA).
5. The workgroup also supports NCCN endorsement of broader molecular profiling with the aims of identifying tractable mutations and informing patients on availability of clinical trials (Category IIA).
6. Rebiopsy at disease progression should be considered.

2. First-line Treatment Options for *EGFR* Sensitising Mutation Positive Advanced NSCLC

A substantially higher proportion of mutations in the *EGFR* tyrosine kinase is observed in Asian populations. Tumours that possess mutations in *EGFR* are highly sensitive to TKIs. Randomised phase III studies on various TKIs—gefitinib,[17-21] erlotinib[22,23] and afatinib[12, 24] versus chemotherapy exist. *EGFR*-TKI treatment resulted in significantly increased overall response rates (ORR) (HR = 2.08; 95% CI, 1.75 to 2.46; $P \leq 0.0001$)[25] and in a meta-analysis of data from trials examining the role of *EGFR*-TKI in all major clinical settings, *EGFR*-TKI treatment was associated with a lower risk of disease progression in the first-line (HR = 0.43; 95% CI, 0.38 to 0.49; $P \leq 0.001$) and subsequent line setting (HR = 0.34; 95% CI, 0.2 to 0.6; $P \leq 0.001$).[26] To date, no phase III trial has demonstrated overall survival (OS) benefit with *EGFR*-TKI use.[26] This is likely confounded by treatment postprogression in both comparator arms.

Cost-effectiveness

The cost-effectiveness of *EGFR*-targeted therapy has been addressed in several papers.[27-29] Of particular note, in a local analysis of the cost-effectiveness of *EGFR* testing followed by first-line gefitinib and second-line chemotherapy in *EGFR* mutants versus the practice of no *EGFR* testing (e.g. by clinical phenotype alone), first-line chemotherapy followed by second-line gefitinib, it was demonstrated that the major driver of cost savings was not providing gefitinib to patients who are not likely to benefit supporting the implementation of *EGFR* mutation testing prior to initiation of first-line systemic therapy.[28] The calculated incremental cost and quality-adjusted life year (QALY) were USD $15,197 and 0.27 with an incremental cost effective ratio (ICER) of USD $56,916 per QALY.[28]

Recommendations on First-line Treatment Options for EGFR Sensitising Mutation Positive Advanced NSCLC

The workgroup committee unanimously recommends adopting NCCN guidelines.

1. Either of the *EGFR*-TKIs—gefitinib, erlotinib or afatinib should be considered in the treatment of advanced NSCLC harbouring *EGFR*-sensitising mutations (Category II).
2. Should the mutation be discovered in the midst of first-line treatment, the systemic therapy can be interrupted or first-line chemotherapy can be completed prior to starting *EGFR*-TKI (Category IIA).

3. First-line Treatment Options for Advanced NSCLC Harbouring *ALK* Gene Rearrangement

Around 5% of NSCLC tumours harbour a novel fusion oncogene echinoderm microtubule-associated protein-like 4 gene (*EML4*) fused with *ALK* gene. These tumours are highly sensitive to therapy with *ALK* inhibitors.

Crizotinib is a multikinase inhibitor of *ALK* tyrosine kinase, mesenchymal epithelial transition growth factor (c-MET) and *ROS1* receptor tyrosine kinase. When compared to second-line chemotherapy (pemetrexed or docetaxel) in a phase III randomised controlled trial, treatment with crizotinib was associated with a significantly higher response rate of 65% vs 20% ($P < 0.001$), progression-free survival (PFS) of 7.7 months versus 3 months (HR = 0.49; 95% CI, 0.37 to 0.64; $P \leq 0.001$) and improvement in global quality of life.[30]

Ceritinib is a second-generation *ALK* inhibitor with clinical activity demonstrated in patients whom have received prior crizotinib and in those who had not received crizotinib.[15]

Cost-effectiveness

The cost-effectiveness of *EML4-ALK* fusion testing and first-line therapy with crizotinib was analysed from the perspective of the Canadian public healthcare system. Molecular testing and first-line therapy with crizotinib cost an additional USD $208,708 per QALY gained compared

with standard of care with no testing and no crizotinib treatment.[31] The authors concluded that *EML4-ALK* fusion molecular testing and targeted therapy with crizotinib in their setting of low prevalence of *EML4-ALK* fusion gene and the high cost of crizotinib is not cost-effective.[31]

Recommendations on First-line Treatment Options for Advanced NSCLC Harbouring ALK Gene Rearrangement

1. The workgroup unanimously recommends consideration of enrolment into clinical trials or to adopt NCCN guidelines for the consideration of crizotinib as first-line treatment for *ALK* gene rearranged advanced lung cancer (Category I). The workgroup recommends a discussion with patients on the cost implications of the option of crizotinib.
2. Patients who are intolerant to crizotinib may be switched to ceritinib (Category IIA).

4. First-line Chemotherapeutic Options for Advanced NSCLC Negative for Driver Mutation

Systemic platinum-based doublet chemotherapy is the preferred initial treatment option for patients with advanced NSCLC, good performance status and without a driver mutation. Chemotherapy in fit patients has been conclusively shown in a meta-analysis to improve OS when compared to best supportive care (HR = 0.77; 95% CI, 0.71 to 0.83; $P \leq 0.01$).[32] A randomised study comparing 4 platinum-based chemotherapy regimens showed no significant advantage of 1 regimen over the other.[33] More recently, evidence from a phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed showed similar efficacy, median OS (10.3 vs 10.3 months, HR = 0.94; 95% CI, 0.84 to 1.05) with better tolerability.[9] Importantly, a prespecified analysis of OS by treatment arm demonstrated a significantly better survival in patients with adenocarcinoma and large cell carcinoma treated with pemetrexed/cisplatin as compared to gemcitabine/cisplatin (12.6 months vs 10.9 months, HR = 0.84; 95% CI, 0.71 to 0.99; $P = 0.03$).

Subsequent trials have shown additional survival benefit with the addition of biologic agents such as bevacizumab. The Eastern Cooperative Oncology Group (ECOG) conducted a randomised study which showed a significant survival benefit of adding bevacizumab to paclitaxel plus carboplatin in the treatment of select patients with non-squamous NSCLC.[34] A systemic review and meta-analysis of trials adding bevacizumab to platinum-based chemotherapy in first-line treatment further confirms this survival benefit.[35]

The role of cetuximab, an *EGFR* monoclonal antibody in the first-line treatment for advanced NSCLC remains to be defined and has not been approved for use in this patient population.[36,37]

Cost-effectiveness

In a systematic review and economic evaluation of the clinical effectiveness and cost-effectiveness of first-line chemotherapy for advanced NSCLC, the preferred drugs for patients with advanced NSCLC are paclitaxel followed by gemcitabine and subsequently docetaxel.[38] In patients with non-SCC disease, pemetrexed/cisplatin is cost-effective with USD $53,238 per QALY gained.[38] In a cost-utility assessment of bevacizumab, the ICER of bevacizumab and chemotherapy when compared with chemotherapy alone was USD $560,000 per QALY.[39] Bevacizumab thus does not appear to be cost-effective when added to chemotherapy. There is no local data with regard to the cost-effectiveness of chemotherapy and or bevacizumab.

Recommendations on First-line Chemotherapeutic Options for Advanced NSCLC Negative for Driver Mutation

1. In fit patients, platinum doublet chemotherapy is unanimously recommended in the first-line treatment of advanced NSCLC (Category I).
2. In view of better outcomes with the use of pemetrexed in non-squamous histology and in considering cost-effectiveness, the workgroup is of the opinion that pemetrexed/platinum chemotherapy is preferable in the first-line treatment of non-squamous advanced NSCLC (workgroup consensus).
3. Bevacizumab when added to chemotherapy is an option (Category IIA).
4. The use of bevacizumab as well as pemetrexed is limited to those non-squamous in histology.
5. There is insufficient evidence to support the use of cetuximab for which the workgroup unanimously does not recommend in this setting (workgroup consensus).

5. Role of Maintenance Chemotherapy

Maintenance therapy is started immediately after first-line therapy with aims of prolonging tumour response or stable disease.

Trials using bevacizumab in combination with first-line platinum-based chemotherapy have continued bevacizumab as maintenance therapy after completion of 4 to 6 cycles of chemotherapy. In the pivotal randomised phase III trial comparing paclitaxel and carboplatin chemotherapy alone versus paclitaxel carboplatin bevacizumab, addition of bevacizumab was shown to improve OS (12.3 months vs 10.3 months, HR = 0.79; 95% CI, 0.67 to 0.92; $P = 0.003$), PFS (6.2 months vs 4.5 months, HR = 0.66; 95% CI, 0.57 to 0.77; $P < 0.001$) and response rates (35% vs 15%, $P < 0.001$) in patients with advanced non-squamous NSCLC. Out of 407 patients, 215 (53%) continued with bevacizumab

monotherapy with 107 (50%) receiving more than 5 cycles of monotherapy.[34]

Maintenance pemetrexed has been studied in 2 large trials.[40-42] "Switch maintenance" was examined in a randomised double-blinded international study where monotherapy pemetrexed versus placebo was commenced following 4 cycles of platinum-based chemotherapy. A switch to pemetrexed maintenance significantly improved PFS (4.3 months vs 2.6 months, HR = 0.5; 95% CI, 0.42 to 0.61; $P \leq 0.0001$) and OS (13.4 months vs 10.6 months, HR = 0.79; 95% CI, 0.65 to 0.95; $P = 0.012$).[41] In the PARAMOUNT trial, 539 advanced non-squamous NSCLC patients who received 4 cycles of pemetrexed-cisplatin induction therapy with no disease progression were randomly assigned to receiving continuation maintenance with pemetrexed plus best supportive care or with placebo plus best supportive care. Final OS analysis showed a statistically significantly longer OS of 13.9 months versus 11 months (unadjusted HR = 0.78; 95% CI, 0.64 to 0.96; $P = 0.0195$). In this trial, maintenance pemetrexed was well tolerated with no new safety findings.[42]

Cost-effectiveness

Cost-effectiveness of pemetrexed as first-line maintenance therapy was assessed by an American group as well as NICE. The American paper showed that in the subgroup of patients with non-squamous histology, the incremental cost per life year gained was USD $122,371 when compared to observation.[43] The ICERs as estimated by the manufacturer's model submitted to NICE were USD $51,289 per QALY for the non-squamous population.[44]

Recommendations on the Role of Maintenance Chemotherapy

1. In patients with good performance status of 0 – 1, continuation of pemetrexed is unanimously recommended in non-squamous NSCLC if stable disease or response is seen following induction chemotherapy (Level I, B).
2. In patients with non-squamous histology and good performance status of 0 – 1, should first-line chemotherapy be non-pemetrexed based, then switch of maintenance to pemetrexed can be considered (Level I, B).
3. In patients with all histologies, switch to erlotinib can be considered (Level I, B). However, the workgroup recommends this only if a sensitising *EGFR* mutation is detected (workgroup consensus).

6. Second-line Chemotherapeutic Options for Advanced NSCLC

Docetaxel dosed at 75 mg/m^2 has been shown to offer clinically meaningful benefit to patients with advanced NSCLC who have failed platinum-containing chemotherapy.[45, 46] A randomised phase II trial comparing docetaxel dosed at 100 mg/m^2 reduced to 75 mg/m^2 after a protocol amendment versus best supportive care in 103 patients showed a longer duration of survival for the chemotherapy arm (7 months, 95% CI, 5.5 to 9 months vs 4.6 months, 95% CI, 3.7 to 6 months; $P = 0.047$). When compared separately, patients who were treated with docetaxel at 75 mg/m^2 had significantly better survival than those treated with best supportive care (log-rank test; $P = 0.01$).[46] TAX 320 is a phase III randomised study of 373 patients comparing docetaxel dosed at 100 mg/m^2 or 75 mg/m^2 versus a control of vinorelbine or ifosfamide.[45] Patients treated with docetaxel dosed at 75 mg/m^2 every 3 weeks had significantly greater 1-year survival than those with control treatment (32% vs 19%; $P = 0.025$).

A subsequent randomised phase III trial comparing pemetrexed versus docetaxel as second-line treatment in patients with advanced NSCLC showed equivalent efficacy outcomes by way of OS (8.3 months vs 7.9 months; HR = 0.99; 95% CI, 0.82 to 1.2; $P = 0.226$), PFS and overall response rates (9.1% vs 8.8%).[47] The side effect profile of pemetrexed was favourable in comparison to docetaxel.[47] A secondary analysis further identified differing efficacy for pemetrexed over docetaxel in patients with non-squamous histology.[48]

Cost-effectiveness

Cost-effectiveness of second-line chemotherapy has been assessed. Docetaxel was associated with significantly lower treatment period cost and was more favourable with regards to cost-utility ratio as compared to pemetrexed. When compared to best supportive care, the cost utility of docetaxel was USD $35,668 per QALY whilst the cost utility per QALY for pemetrexed was USD $44,770.[49]

Recommendations on Second-line Chemotherapeutic Options for Advanced NSCLC

1. The workgroup committee unanimously recommends consideration of clinical trials.
2. Docetaxel or pemetrexed (restricted to non-squamous in histology) can be considered in fit patients as second-line treatment of advanced lung cancer (Level I, B).

7. Subsequent Lines of Chemotherapy for Advanced NSCLC

There is 1 randomised controlled trial that studied the role of erlotinib after failure of first- or second-line chemotherapy.[50] In this international, phase III randomised

double-blinded, placebo controlled trial, 731 patients who had received 1 or 2 prior lines of chemotherapy were randomly assigned in a 2:1 ratio to receive erlotinib or placebo. The primary endpoint of OS was met (6.7 months vs 4.7 months, HR = 0.7 95%; CI, 0.58 to 0.85; P <0.001). There were significantly more overall responses in the erlotinib group (8.9% vs <1%; P <0.001). The median PFS was significantly longer in the erlotinib group (2.2 months vs 1.8 months, HR = 0.61; 95% CI, 0.51 to 0.74; P <0.001). We are however mindful that patients enrolled on this trial are unselected and therefore extrapolation of this data in the current era of molecular subtyping must be done so with care. Nevertheless, this trial did provide clinically meaningful prolongation of survival despite heavy pretreatment of 50% of the enrolled patients.

Recommendations on Subsequent Lines of Chemotherapy for Advanced NSCLC

1. The workgroup unanimously recommends to first consider clinical trials.
2. Erlotinib can be considered in the treatment of advanced lung cancer beyond second-line chemotherapy in patients with unknown *EGFR* status or *EGFR*-WT who have not received *EGFR* TKI (Level II, B).
3. Given the burgeoning pipeline of novel therapeutics addressing either distinct genetic drivers or resistance mechanisms, molecular profiling for "actionable" alterations either from archival tissue, or a repeat biopsy is also a reasonable consideration (workgroup consensus).

All recommendations are unanimous.

Conflicts of Interest

Dr A Chang reports receiving advisory board fees from Pfizer, Celgene and BMS and lecture fees from MSD, Pfizer and BMS; Dr DSW Tan, receiving research funding from Novartis and advisory board fees from Novartis, Boerhinger Ingelheim and Pfizer; Dr WL Yeo, serving on advisory boards of Roche and Bayer; Ms L Chew, Dr TM Chin, Dr SS Leong, Dr HL Lim, Dr EH Lim, Dr RA Soo, Dr T Tan and Dr CK Toh have nothing to disclose.

Workgroup Members

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Reviewers

Invited reviewers were Gilberto Lopes, MD, MBA, Oncoclinicas Group, Brazil; Fergus Macbeth, MA, DM, FRCP, Wales Cancer Trials Unit, Cardiff University, UK.

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Supplementary Table 1. International Guidelines for the Systemic Therapy of Advanced NSCLC

Guideline Title	**NCCN Guidelines Version 2.2014 Non-Small Cell Lung Cancer**	**Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines**	**NICE Guidance** **1. The Diagnosis and Treatment of Lung Cancer (Update of NICE Clinical Guideline 24) (CG 121)** **2. Lung Cancer (Non-Small Cell) – Erlotinib (TA162)** **3. Lung Cancer (Non-Small Cell, First-Line Treatment) – Pemetrexed (TA181)** **4. Lung Cancer (Non-Small Cell) – Pemetrexed (Maintenance) (TA190)** **5. Lung Cancer (Non-Small Cell, First-Line) – Gefitinib (TA192)** **6. Lung Cancer (Non-Small Cell, *EGFR*-TK Mutation Positive) – Erlotinib (First-Line) (TA258)** **7. Lung Cancer (Non-Small Cell, Anaplastic Lymphoma Kinase Fusion Gene, Previously Treated) – Crizotinib: Guidance (TA296)**	**Clinical Practice Guidelines for the Treatment of Lung Cancer**
Date Released	11 April 2013	October 2012	1. Issue date: April 2011 2. Issue date: November 2008, reviewed December 2012 3. Issue date: September 2009, reviewed July 2010 4. Issue date: June 2010, reviewed November 2012 5. Issue date: July 2010, reviewed April 2013 6. Issue date: June 2012 7. Issue date: September 2013	January 2014
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	European Society for Medical Oncology (ESMO)	National Institute of Health and Clinical Excellence (NICE), United Kingdom	Clinical Guidelines Network Cancer Council Australia Commissioned by Australian Government
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Recommendations developed from discussion at consensus conferences. Group decision-making that seeks the consensus of experts and the fulfillment of objectives.Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO).	Open and transparent consultation process which allows individuals, patient groups, charities and industry to comment on recommendations.	Working party develops clinical questions, searches literature, formulates recommendations and write guideline chapters. Content is uploaded to Guidelines Wiki and undergoes public consultation prior to update. Annual working party meeting to review changes made by authors.
Target Population	All adults with non-small cell lung cancer	All adults with non-small cell lung cancer	All adults with non-small cell lung cancer	All adults with non-small cell lung cancer

ALK: Anaplastic lymphoma kinase; BSC: Best supportive care; EGFR: Epidermal growth factor receptor; IASLC: International Association for the Study of Lung Cancer; IHC: Immunohistochemistry; NSCLC: Non-small cell lung cancer; PS: Performance status; SRE: Skeletal-related events; WHO: World Health Organization
Note: The above summary is focused on systemic therapy for advanced NSCLC only.

Supplementary Table 1. International Guidelines for the Systemic Therapy of Advanced NSCLC (Cont't)

Guideline Title	**NCCN Guidelines Version 2.2014 Non-Small Cell Lung Cancer**	**Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines**	**NICE Guidance** **1. The Diagnosis and Treatment of Lung Cancer (Update of NICE Clinical Guideline 24) (CG 121)** **2. Lung Cancer (Non-Small Cell) – Erlotinib (TA162)** **3. Lung Cancer (Non-Small Cell, First-Line Treatment) – Pemetrexed (TA181)** **4. Lung Cancer (Non-Small Cell) – Pemetrexed (Maintenance) (TA190)** **5. Lung Cancer (Non-Small Cell, First-Line) – Gefitinib (TA192)** **6. Lung Cancer (Non-Small Cell, *EGFR*-TK Mutation Positive) – Erlotinib (First-Line) (TA258)** **7. Lung Cancer (Non-Small Cell, Anaplastic Lymphoma Kinase Fusion Gene, Previously Treated) – Crizotinib: Guidance (TA296)**	**Clinical Practice Guidelines for the Treatment of Lung Cancer**
Diagnosis	Pathological diagnosis: • Establish histologic subtype with adequate tissue for molecular testing (consider rebiopsy if appropriate). • *EGFR* mutation and *ALK* testing as part of multiplex/next generation sequencing. • Mutation testing if non-squamous and in non-smoker squamous or small biopsy specimens or mixed histology.	Pathological diagnosis: • WHO and IASLC classification of adenocarcinoma. • Specific subtype necessary. • Obtain sufficient tissue. • Rebiopsy at disease progression. • *EGFR* mutation status in non-squamous histology. • *EGFR* testing not recommended in patients with confident squamous histology except never/former light smoker. • Discuss *EML4-ALK* testing in non-squamous histology if crizotinib available.	Ensure adequate samples taken without unacceptable risk to the patient to permit pathological diagnosis including tumour subtyping and measurement of predictive markers.	Due to therapeutic implications, important to classify histologic subtype of NSCLC as accurately as possible to enable distinction between adenocarcinoma and squamous cell carcinoma.
Systemic Therapy	First-line: • Doublet chemotherapy • Bevacizumab + chemotherapy* • Cetuximab/vinorelbine/cisplatin First-line (poor PS/elderly) If PS 2 • Gemcitabine • Vinorelbine • Taxanes • Platinum-based combination	First-line: • Platinum-based combination chemotherapy • 4 – 6 cycles • Cisplatin is platinum of choice • Pemetrexed‡ • Bevacizumab§ • Cetuximab • Non-platinum-based combination chemotherapy only if platinum contraindicated.	First-line: • Platinum combination with third-generation drugs (docetaxel, gemcitabine, paclitaxel, vinorelbine). • Single agent third-generation. • Pemetrexed + cisplatin – in adenocarcinoma of large cell carcinoma.	First-line: • Third-generation platinum-based combination chemotherapy (with vinorelbine, paclitaxel, docetaxel, gemcitabine). • Cisplatin preferred to carboplatin for patients with high tumour burden and symptoms for purpose of inducing a response. However, this benefit may be offset by its greater risk of toxicity.

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	If PS 3 – 4 • BSC First-line (activating *EGFR* mutations • Erlotinib† • Afatinib† First-line (*ALK* rearrangement) • Crizotinib†	First-line (poor PS): If PS 2 • Gemcitabine • Vinorelbine • Taxanes • Platinum-based combination If PS 3 – 4 and absent *EGFR* sensitising mutation • BSC First-line (elderly) • Platinum combination if PS 0 – 1 • Single agent in selected PS 2 First-line (activating *EGFR* mutations) • Erlotinib • Gefitinib First-line (*ALK* rearrangement) • Crizotinib	• Erlotinib – recommend if *EGFR* mutation and manufacturer provides at discounted price (confidential) under patient access scheme. • Gefitinib – recommended if *EGFR* mutation and manufacturer provides at fixed price agreed under patient access scheme (GBP 12,200 per patient irrespective of duration).	• Cisplatin/pemetrexed recommended in preference to cisplatin/gemcitabine in patients with non-squamous histology. • Cisplain/gemcitabine preferred to cisplatin/pemetrexed in patients with squamous histology. • Non-platinum third-generation doublet (e.g. gemcitabine/paclitaxel) is an alternative for patients unsuitable for platinum-based therapy. • First-line combination chemotherapy should be stopped at disease progression or after 4 cycles. • Bevacizumab (15 mg/kg) + chemotherapy‖ • Cetuximab + cisplatin/vinoreline¶ First-line (unfit for combination chemotherapy): • Gemcitabine • Vinorelbine • Docetaxel • Paclitaxel

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Supplementary Table 1. International Guidelines for the Systemic Therapy of Advanced NSCLC (Cont't)

Guideline Title	NCCN Guidelines Version 2.2014 Non-Small Cell Lung Cancer	Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines	NICE Guidance 1. The Diagnosis and Treatment of Lung Cancer (Update of NICE Clinical Guideline 24) (CG 121) 2. Lung Cancer (Non-Small Cell) – Erlotinib (TA162) 3. Lung Cancer (Non-Small Cell, First-Line Treatment) – Pemetrexed (TA181) 4. Lung Cancer (Non-Small Cell) – Pemetrexed (Maintenance) (TA190) 5. Lung Cancer (Non-Small Cell, First-Line) – Gefitinib (TA192) 6. Lung Cancer (Non-Small Cell, *EGFR*-TK Mutation Positive) – Erlotinib (First-Line) (TA258) 7. Lung Cancer (Non-Small Cell, Anaplastic Lymphoma Kinase Fusion Gene, Previously Treated) – Crizotinib: Guidance (TA296)	Clinical Practice Guidelines for the Treatment of Lung Cancer
				First-line (elderly) • Vinorelbine • Docetaxel • Gemcitabine • Weekly paclitaxel/carboplatin First-line (activating *EGFR* mutations) • *EGFR*-TKI
	Maintenance: Continuation • Bevacizumab* • Cetuximab • Pemetrexed* • Bevacizumab + pemetrexed* • Gemcitabine Switch • Pemetrexed • Erlotinib • Docetaxel#	Maintenance: • Pemetrexed** • Erlotinib†† • Bevecizumab & cetuximab not recommended	Maintenance: • Pemetrexed – recommended in non-predominantly squamous and non-progressive disease following platinum-based chemotherapy.	Maintenance: • Pemetrexed‡‡ • Docetaxel • Erlotinib
	Second-line: PS 0 – 2 • Pemetrexed* • Docetaxel • Gemcitabine • Erlotinib	Second-line: • Pemetrexed‡ • Docetaxel • Erlotinib§§ • Crizotinib|||	Second-line: • Docetaxel • Erlotinib – if provided at an overall cost equal to that of docetaxel • Crizotinib – not recommended. Can be continued in those already taking crizotinib.	Second-line: • Docetaxel¶¶ • Erlotinib • Pemetrexed##

ALK: Anaplastic lymphoma kinase; BSC: Best supportive care; EGFR: Epidermal growth factor receptor; IASLC: International Association for the Study of Lung Cancer; IHC: Immunohistochemistry; NSCLC: Non-small cell lung cancer; PS: Performance status; SRE: Skeletal-related events; WHO: World Health Organization
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Supplementary Table 1. International Guidelines for the Systemic Therapy of Advanced NSCLC Cont't)

Guideline Title	NCCN Guidelines Version 2.2014 Non-Small Cell Lung Cancer	Metastatic Non-Small Cell Lung Cancer: ESMO Clinical Practice Guidelines	NICE Guidance 1. The Diagnosis and Treatment of Lung Cancer (Update of NICE Clinical Guideline 24) (CG 121) 2. Lung Cancer (Non-Small Cell) – Erlotinib (TA162) 3. Lung Cancer (Non-Small Cell, First-Line Treatment) – Pemetrexed (TA181) 4. Lung Cancer (Non-Small Cell) – Pemetrexed (Maintenance) (TA190) 5. Lung Cancer (Non-Small Cell, First-Line) – Gefitinib (TA192) 6. Lung Cancer (Non-Small Cell, *EGFR*-TK Mutation Positive) – Erlotinib (First-Line) (TA258) 7. Lung Cancer (Non-Small Cell, Anaplastic Lymphoma Kinase Fusion Gene, Previously Treated) – Crizotinib: Guidance (TA296)	Clinical Practice Guidelines for the Treatment of Lung Cancer
	PS 3 – 4 • BSC Subsequent-lines: • Docetaxel • Pemetrexed* • Erlotinib • Gemcitabine	Subsequent-line: • Erlotinib§§	Subsequent-line: • No recommendation	Subsequent-line: • Erlotinib
Bone Metastases	Not specified	To reduce SRE: • Zolendronic acid • Denosumab	Not specified	Not specified
Palliative Care	Recommended	Recommend early palliative care intervention.	Recommend early palliative care intervention.	Not specified
Smoking Cessation	Recommended	Recommended	Recommended	Not specified

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Note: The above summary is focused on systemic therapy for advanced NSCLC only.

*Non-squamous only.

†Interrupt or complete first-line chemotherapy if mutation discovered during first-line chemotherapy. In case of *EGFR* mutation, erlotinib/afatinib may also be added to current chemotherapy.

‡Restrict to non-squamous tumours.

§Combined with paclitaxel-carboplatin regimen in non-squamous.

‖In non-squamous histology and selected patients.

¶In tumours shown to express *EGFR* by IHC.

#Squamous only.

**Restrict to non-squamous tumours as switch or continuation maintenance.

††All histologies in particular patients with activating *EGFR* mutation tumours who have not received *EGFR*-TKI as first-line.

‡‡Non-squamous histology.

§§All histologies in particular patients with activating EGFR mutation tumours who have not previously received *EGFR*-TKI.

‖‖Crizotinib should be considered in presence of *ALK* rearrangement if not received as first-line.

¶¶Preferred in squamous histology.

##Preferred in non-squamous histology.