

SUBMISSION REQUEST TO THE NCCN GUIDELINES THORACIC PANEL

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To: NCCN Guidelines Panel: Non-Small Cell Lung Cancer

On behalf of the Independent Lung Cancer Patient Advocates (ILCPA), we respectfully request the NCCN Guidelines Panel Non-Small Cell Lung Cancer to review the enclosed data for revision of the NSCLC treatment guidelines/algorithms for oligometastases, oligorecurrence and oligoprogression to create additional NSCLC stage IV M1a and M1b treatment sub-categories for oligometastases, and corresponding new oligometastases, oligo-recurrence and oligoprogression NSCLC treatment guidelines and algorithms for the proposed new treatment subcategory.

Specific Changes: We recommend that the NSCLC treatment guideline algorithm “*NSCL-13 Initial Treatment Guidelines*” should be expanded to create additional Stage IV NSCLC M1a and M1b treatment sub-categories for oligometastases with the following corresponding proposed treatment guideline: “For carefully selected patients with ≤ 3 metastatic sites (oligometastases) (including, but not limited to, brain, lung, and adrenal gland), a limited total tumor burden/volume, otherwise limited thoracic disease which is resectable, otherwise treatable by definitive local therapy or controlled, and with good performance status, consideration may be given for aggressive curative or remittive intent treatment for primary and metastatic sites, including, but not limited to, surgical intervention and/or stereotactic radiotherapy, and systemic therapy; for revision of NSCLC treatment guideline algorithm “*NSCL-15 Therapy For Recurrence And Metastases*” to incorporate an oligorecurrence category with equivalent proposed Stage IV NSCLC treatment guideline/algorithm changes; for revision of NSCLC treatment guideline algorithms “*NSCL-17*”, “*NSCL-18*”, and “*NSCL-21*” to incorporate an oligoprogression category for patients treated with targeted therapies where remaining disease is otherwise controlled, with equivalent proposed Stage IV NSCLC treatment guideline/algorithm changes; and revision of any corresponding NSCLC NSCL-13, NSCL-15, NSCL-17, NSCL-18, and NSCL-21 treatment guideline/algorithm references to reflect these changes.

FDA Clearance: N/A

Rationale: Multiple studies have demonstrated Stage IV NSCLC Oligometastatic patients to be prognostically (w/*superior survival*) and therapeutically different from other Stage IV NSCLC patients, and have further demonstrated that definitive treatment with life prolonging or curative intent to all primary and metastatic sites can yield prolonged survival benefits in a significant subset of these patients, as well as in oligorecurrence and oligoprogression when remaining disease is otherwise controlled by targeted therapies, justifying creation of new treatment guideline/algorithm categories for oligometastases, oligo-recurrence, and oligoprogression, and corresponding revision/expansion of treatment guidelines and algorithms in order to better provide treating clinicians and Stage IV NSCLC patients with updated treatment pathways and recommendations in keeping with the expanding treatment options for this subgroup of patients.

The following articles are submitted in support of these proposed changes. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications:

1. Hung JY, Durrani HP, Aljumaily R, et al. **Oligometastatic non-small cell lung cancer treated with curative intent** [abstract]. *J Clin Oncol* 32, 2014 (suppl; abstr e19034). Institutional data base analysis ≥ 5 OM: “Our results indicate that curative intent treatment of OM-NSCLC can achieve prolonged median survival and 3-year survival potential in adenocarcinoma. Survival benefits in these patients also exceed what has been achieved with maintenance chemotherapy.”
2. Gridelli C, de Marinis F, Cappuzzo F, et al. **Treatment of advanced non-small-cell lung cancer with epidermal growth factor receptor (EGFR) mutation or ALK gene rearrangement: Results of an international expert panel meeting of the Italian association of thoracic oncology.** *Clinical Lung Cancer*. 2014;15(3):173-181doi:10.1016/j.clcc.2013.12.002. Review of literature. Continuation of EGFR TKI or crizotinib beyond oligoprogression manageable by local treatment may be clinically justified.
3. Schreiner W, [Semrau S](#), [Fietkau R](#), [Sirbu H](#). **Oligometastatic non-small cell lung cancer - surgical options and therapy.** *Zentralbl Chir*. 2014 May 8 [article in German]. Retrospective case series analysis. ≤ 2 synchronous/metachronous OM, 5 yr disease-free survivals 16.5 - 29.2%: “The therapeutic strategies for OM NSCLC have changed over the last decade from palliative to curative intent” “Surgery in OM NSCLC is feasible for primary tumor and for metastases. It is an effective option in the multimodal treatment in highly selected patients.”
4. Varela G, Thomas PA. **Surgical management of advanced non-small cell lung cancer.** *J Thorac Dis*. 2014 May;6(Supple 2):S217-S223. Review of literature. Solitary site prognosis re oligorecurrence: Favorable ≤ 2 lesions, Relatively Favorable 3 to 5 lesions. Re sync-OM: Relatively Favorable ≤ 2 lesions. “For stage IV oligometastatic cases, surgery can still be included when planning multimodality treatment.”
5. Ashworth, AB, Senan S, Palma DA, et al. **An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer.** *Clin Lung Cancer*. 2014 May 15. pii: S1525-7304(14)00077-1. doi: 10.1016/j.clcc.2014.04.003. ≤ 5 OM.

Five year OS: Metachronous metastases 47.8%; Synchronous metastases NO 36.2%, and synchronous metastases N1/N2 13.8%. Long term survival common in selected patients w/metachronous OM. Synchronous OM N1/N2 disease high risk group.

6. Endo C, Hasumi T, Matsumura Y, et al. **A prospective study of surgical procedures for patients with oligometastatic non-small cell lung cancer.** *Ann Thorac Surg.* 2014 Apr 17. pii: S0003-4975(14)00334-8. doi: 10.1016/j.athoracsur.2014.01.052. Multi-center trial, "Clinical T1-2N0-1 lung cancer with a single-organ metastatic lesion was a good candidate for surgical resection. A 5-year survival rate of about 40% can be expected, which could be comparable with that for stage II non-small cell lung cancer."
7. Sonobe M, [Yamada T](#), [Sato M](#), et al. **Identification of subsets of patients with favorable prognosis after recurrence in completely resected non-small cell lung cancer.** *Ann Surg Oncol.* 2014 Mar 17. Retrospective study. With limited # recurrent lesions w/out local recurrence of primary, good ECOG, PS & sufficient time to recurrence, local treatment was effective for achieving long term post-recurrence survival and even cure.
- 7a. Gan GN, Weickhardt AJ, et al., **Stereotactic Radiotherapy Can Safely and Durably Control Sites of Extra-CNS Oligoprogressive Disease in ALK-Positive Lung Cancer Patients on Crizotinib.** *Int J Radiat Oncol Biol Phys.* 2014 Mar 15;88(4):892-8. doi: 10.1016/j.ijrobp.2013.11.010. Epub 2014 Jan 22. ≤4 discrete sites of eCNS progression.
8. Yano T, Okamoto T, Haro A, et al. **Local treatment of oligometastatic recurrence in patients with resected non-small cell lung cancer.** *Lung Cancer.* 2013 Dec;82(431-5). Retrospective study, distant OM ≤3 sites: Conclusion: Local therapy is a choice for first-line treatment in patients with postoperative OM recurrence.
9. Griffioen, GH, Toguri D, Dachele M, et al. **Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors.** *Lung Cancer.* 2013 Oct;82(1):95-102. Two center retrospective review: "Radical treatment of selected NSCLC patients presenting with ≤3 synchronous metastases can result in favorable 2-year survivals. Favorable outcomes were associated with intra-thoracic disease status: patients with small radiotherapy treatment volumes or resected disease had the best OS."
10. Maclean J, Fersht N, Singhera M, et al. **Multi-disciplinary management for patients with oligometastases to the brain: results of a 5 year cohort study.** *Radiat Oncol.* 2013 Jun 27;8:156. 26% NSCLC. A subset of patients with OM brain disease would benefit from aggressive local treatment. Consideration should be given to defining specific management pathways for these patients within general oncology practice.
11. Yu HA, [Sima CS](#), [Huang J](#), et al. **Local therapy with continued EGFR tyrosine kinase inhibitor therapy as a treatment strategy in EGFR-mutant advanced lung cancers that have developed acquired resistance to EGFR tyrosine kinase inhibitors.** *J Thorac Oncol.* 2013 Mar;8(3):346-51. Retrospective study, ≤ 5 sites, found local therapy to treat OM in this context is well tolerated and associated with long PFS and OS.
12. Chang HJ, Ko HL, Lee CY, et al. **Hypofractionated radiotherapy for primary or secondary oligometastatic lung cancer using Tomotherapy.** *Radiat Oncol.* 2012 Dec 27;7:222. Retrospective review. Using tomotherapy in hypofractionation may be effective for primary/secondary lung OM, without causing significant toxicities. GTV more significant than # of metastatic lesions or organs in predicting survival.
13. Weickhardt AJ, Burke JM, Gan G, et al. **Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer.** *J Thorac Oncol.* 2012 Dec;7(12):1807-14. doi:10.1097/JTO.0b013e3182745948. Retrospective study, ≤ 4 sites.
14. De Ruyscher D, Wanders R, van Baardwijk A, et al. **Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450).** *J Thorac Oncol.* 2012 Oct;7(10):1547-55. ≤ 5 OM. "In this phase II study, long-term PFS was found in a subgroup of NSCLC patients with synchronous oligometastases when treated radically. Identification of this favorable subgroup before therapy is needed."
15. Lopez Guerra JL, Gomez D, Zhuang Y, et al. **Prognostic impact of radiation therapy to the primary tumor in patients with non-small cell lung cancer and oligometastasis at diagnosis.** *Int J Radiat Oncol Biol Phys.* 2012 Sep 1;84(1):e61-7. Institutional review, limited # of sites, ≤5 OM at diagnosis, TN stages: 4 cases IB, 2 IIA, 2 IIB, 29 IIIA, and 41 IIIB: Concluded Tumor Volume, KPS, and at least 63 Gy to primary tumor associated with improved OS in patients w/OM at diagnosis. "Our results suggest that a subset of such patients may benefit from definitive local therapy."
16. Congedo MT, Cesario A, Lococo F, et al. **Surgery for oligometastatic non-small lung cancer: long-term results from a single center experience.** *J Thorac Cardiovasc Surg.* 2012 Aug;14(2):444-52. Retrospective analysis, metastases ≤ 2 sites and ≤2 metastases in same site treated w/curative intent concluded: "Surgical treatment for selected stage IV NSCLC is feasible and safe. Furthermore, good survival can be expected in those patients in whom a complete resection of the primary tumor and radical control of the distant disease are accomplished."
17. Hanagiri T, Takenaka M, Oka S, et al. **Results of a surgical resection for patients with stage IV non-small cell lung cancer.** *Clin Lung Cancer.* 2012 May;13(3):220-4. Retrospective review, mets ≤5 sites. Distant metastasis 5 yr survival rate 30.1%. Conclusion "Selected patients who can undergo surgical resection for the primary tumor and effective local therapy for metastatic lesions still have a chance to obtain long-term survival. Surgical treatment for NSCLC with OM disease can be considered as one arm of multidisciplinary treatment."
18. Gomez DR, Niibe Y, Chang JY. **Oligometastatic disease at presentation or recurrence for non-small cell lung cancer.** *Pulm Med* 2012;2012:396592. Review/analysis of literature. "Oligometastatic NSCLC presents a unique opportunity for potential curative therapy." "Given the emerging biologic and clinical evidence that oligometastatic NSCLC is a separate disease entity when compared to widespread metastatic disease, ideally patients could receive selective aggressive local therapy based on their specific disease characteristics, similar to other oncologic scenarios in which personalized medicine is the ultimate goal."
19. Patel PR, Yoo DS, Njibe Y, et al. **A call for the aggressive treatment of oligometastatic and oligo-recurrent non-small cell lung cancer.** *Pulm Med.* 2012;2012:480961. Review/analysis of literature, HIGRT to known sites when surgical resection not possible in OM/oligo-recurrent NSCLS. "In a population of patients formerly considered rapidly terminal, these studies report five year overall survival rates of 13-22%."
20. Salah S, Tanvetyanon T, Abbasi S, et al. **Metastectomy for extra-cranial extra-adrenal non-small cell lung cancer solitary metastases: systematic review and analysis of reported cases.** *Lung Cancer.* 2012 Jan;75(1):9-14. Results indicated selected patients with extra-adrenal and extra-cranial metastasis have a change of long term survival (5-year OS approaching 50%) with surgical approach if the mediastinal LN are free of metastasis.
21. Cheruvu P, Metcalfe SK, Metcalfe J, et al. **Comparison of outcomes in patients with stage III versus limited stage IV non-small cell lung cancer.** *Radiat Oncol.* 2011 Jun 30;6:80 Retrospective review, ≤ 8 lesions. "Stage IV NSCLC is a heterogeneous patient population, with a selected cohort apparently faring better than Stage III patients."