Editorial Commentary

A first attempt to establish a definition of oligometastatic non-small cell lung cancer by a European consensus group

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Provenance: This is an invited article commissioned by the Section Editor Xiaozheng Kang (Department of Thoracic Surgery, Beijing Cancer Hospital, Peking University, Beijing, China).

Comment on: Dingemans AC, Hendriks LEL, Berghmans T, *et al*. Definition of synchronous oligo-metastatic non-small cell lung cancer - a consensus report. J Thorac Oncol 2019. [Epub ahead of print].

Submitted Nov 13, 2019. Accepted for publication Nov 21, 2019.
doi: 10.21037/jtd.2019.11.49
View this article at: http://dx.doi.org/10.21037/jtd.2019.11.49

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death worldwide, with metastatic NSCLC generally considered to be incurable and refractory and thus associated with a poor survival outcome (1). However, for a specific subset of metastatic NSCLC characterized by few metastatic lesions, known as oligometastatic disease, long-term survival can be empirically expected with local radical therapy. Indeed, the current versions of both the European Society of Medical Oncology (ESMO) guidelines and the National Comprehensive Cancer Network (NCCN) guidelines refer to this disease subset as a distinct entity to be treated with a specific strategy in order to potentially achieve long-term survival (2,3).

This stance is supported by a few prospective clinical trials that have suggested clinical benefit of ablative local therapy in combination with systemic chemotherapy, in comparison with systemic chemotherapy alone, for advanced NSCLC with a limited number of metastatic lesions (4,5). A randomized phase II trial performed by Gomez *et al.* thus showed a statistically significant benefit in terms of both progression-free survival (PFS) and overall survival (OS) for local consolidative therapy (radiotherapy or surgery, or both) compared with maintenance systemic therapy or observation alone in patients with oligometastatic NSCLC that did not progress after front-line systemic chemotherapy [median PFS of 14.2 months with a 95% confidence interval (CI) of 7.4–23.1 versus 4.4 months (95% CI, 2.2–8.3 months), P=0.022; median OS of 41.2 months (95% CI, 18.9 months–not reached) versus 17.0 months (95% CI, 10.1–39.8 months), P=0.017] (4). In addition, a randomized phase II study performed by Iyengar *et al.* found that consolidative radiotherapy resulted in a significantly longer PFS than did maintenance chemotherapy alone for oligometastatic NSCLC patients without disease progression after induction systemic chemotherapy (median PFS of 9.7 versus 3.5 months, P=0.01) (5). Of note, these two trials terminated patient accrual early as recommended by the local data safety and monitoring committees because of the significant improvement in survival outcome in their experimental arms (local radical therapy). However, the notion of this oligometastatic disease subset as a target for local therapy with radical intent has been controversial, given the lack of high-quality evidence such as that provided by large phase III trials as well as the heterogeneous definition of such disease in existing studies (6,7).

In an article published recently in *Journal of Thoracic Oncology*, Dingemans *et al.* propose a definition of synchronous oligometastatic NSCLC in order to support the achievement of long-term survival with local radical therapy (8). This consensus report of a pan-European multidisciplinary group of thoracic oncology experts represents the first attempt to provide a precise and official definition of oligometastatic NSCLC. The 35 authors include medical oncologists, radiation oncologists, pulmonologists, thoracic surgeons, and radiologists affiliated with various societies including the European

Organization of Research and Treatment of Cancer (EORTC), International Association for the Study of Lung Cancer (IASLC), European Respiratory Society (ERS), European Society for Radiotherapy & Oncology (ESTRO), and ESMO. The process to achieve consensus essentially consisted of three parts: (I) the sending of an online survey to members of each society to support formulation of the questions that would need to be discussed during a final consensus meeting; (II) a systematic and comprehensive review of previous retrospective and prospective studies to help establish the definition of synchronous oligometastatic NSCLC by the consensus meeting members; and (III) a discussion among the consensus group members of real-life cases to focus both agreement and disagreement on how to practically define synchronous oligometastatic NSCLC.

The final meeting of the 35 consensus group members was held in Dublin on 23 January 2018 and proposed a provisional definition of synchronous oligometastatic NSCLC as follows:

(I) Metastatic NSCLC with a maximum of five metastatic lesions involving a maximum of three organs, that can be treated with local radical therapy including both surgery and radiotherapy with acceptable toxicity in order to achieve long-term disease control including a cure.
(II) Histology and genomic background should not be considered.
(III) Mediastinal lymph node metastases are allowed but should not be counted as a metastatic site.
(IV) Bone marrow metastases and diffuse metastases such as meningeal, pericardial, pleural, and mesenteric metastases are not allowed.
(V) [^{18}F]Fluorodeoxyglucose-based positron emission tomography-computed tomography and brain imaging [preferably magnetic resonance imaging (MRI)] are mandatory (with MRI of the liver being recommended if the liver is the only site of metastasis), and pathological confirmation of at least one metastatic lesion is required unless the multidisciplinary treatment team decides that the risk outweighs the benefit.

This consensus statement on the definition of synchronous oligometastatic NSCLC is expected to standardize the inclusion criteria of future clinical trials and will help determine the treatment strategy for advanced NSCLC with a limited number of metastases in clinical practice. The statement was developed as the result of a multistep process with the input of many thoracic oncology experts, an appropriate approach given the limited evidence available. However, it should be noted that the definition is provisional and is not based on high-quality evidence. In particular, there was substantial disagreement on how many metastatic lesions should be allowed, an issue that needs to be clarified in future studies. Indeed, a maximum of three metastatic lesions had support at the consensus meeting, with the final number of five being based largely on the results of the systematic review, which revealed that most previous or ongoing clinical trials evaluating the efficacy of local radical therapy for synchronous oligometastatic NSCLC allowed recruitment of patients with more than three metastatic lesions. However, the proposed definition does not mean that more than three metastatic lesions can be successfully managed with local ablative therapy, and most of the patients in the previous randomized phase II trials who achieved positive results actually had less than three metastases (4,5). In addition, the proposed definition allows patients with actionable gene alterations, although such patients should be addressed independently because they may be able to achieve long-term survival with systemic targeted therapy alone. This issue was discussed at the consensus meeting, but the reasons for including these patients in the definition was not fully described. Furthermore, metachronous oligometastatic disease, also known as oligorecurrent disease, was not considered in this consensus report. These important issues should be addressed by future studies including clinical trials and meta-analyses.

The two randomized phase II trials performed by Gomez *et al.* and Iyengar *et al.* suggest the appropriateness of local ablative therapy for oligometastatic NSCLC, although the study results remain nondefinitive (4,5). The study by Gomez *et al.* thus included only 49 patients, with the difference in OS between the experimental and control arms possibly having been the result of allocation imbalance. Two patients who tested positive for an *ALK* fusion gene and who might potentially have achieved long-term survival by treatment with an ALK tyrosine kinase inhibitor (TKI) were recruited to the trial, and both of these individuals were allocated to the experimental arm, possibly resulting in a disproportionately longer survival in this arm (4). The study by Iyengar *et al.* recruited only patients without known driver oncogenes, but this trial included an even smaller number of patients (n=29) and has not yet reported OS data (5). Both of these previous trials also did not exclude patients with metachronous disease.

Four large randomized phase III trials—SARON

(NCT02417662), SINDAS (NCT02893332), OMEGA (NCT03827577), and HALT (NCT03256981)—are currently in progress for assessment of local ablative therapy combined with systemic therapy for patients with oligometastatic NSCLC. The results of these trials should inform selection of a definitive treatment strategy for such patients. The SARON and SINDAS trials in particular are notable. The SARON study is being conducted at ~30 hospitals in the United Kingdom and plans to recruit 340 NSCLC patients with one to three metastases (9). This trial excludes patients positive for known driver oncogenes—such those with *EGFR* mutations, *ALK* fusion genes, or *ROS1* fusion genes—and its findings will thus have been obtained with a relatively homogeneous population. After confirmation of disease control with two cycles of platinum-based induction chemotherapy, enrolled patients are randomly allocated either to the control arm for treatment with at least two additional cycles of maintenance chemotherapy alone or to the experimental arm for treatment with a maximum of two additional cycles of platinum-based chemotherapy followed by consolidative radiation therapy for all detectable lesions. One strong point of this trial is that the primary end point is OS. The SINDAS trial is currently under way in China and allows recruitment of patients with one to five metastatic sites. This trial is distinct in that only patients with *EGFR* mutation-positive NSCLC are enrolled, and its results will therefore not overlap with those of the SARON trial. The patients included in the SINDAS trial are randomly allocated to the control arm for treatment with a first-generation EGFR-TKI or to the experimental arm for treatment with stereotactic body radiation therapy (SBRT) for all lesions concurrently with and followed by administration of a first-generation EGFR-TKI. The planned number of participants is 200, and the primary end point is PFS. Many additional randomized phase II trials including those that allow recruitment of other cancer types are also ongoing (*Table 1*). The first results of most of these trials should be available from 2021 to 2023.

Recent advances in immunotherapy have resulted in changes to the standard of care for advanced NSCLC, with inhibitors of programmed cell death-1 (PD-1) or of its ligand PD-L1 having become essential components of first-line systemic therapy (10-13). A challenge now is to combine such immunotherapy with local ablative therapy in order to further improve the survival outcome of patients with oligometastatic NSCLC. The combination of local radical therapy with immunotherapy is rationally supported by the results of both preclinical and translational studies (14-17). A reduction in tumor burden achieved by local radical therapy thus has the potential to improve the functional status of antitumor T cells by limiting the T cell exhaustion induced by excessive antigen exposure, thereby increasing the susceptibility of residual cancer cells to PD-1/PD-L1 blockade therapy (14,15). In addition, radiation therapy may act in a synergistic manner with PD-1/PD-L1 inhibitors by inducing immunogenic cell death accompanied by the release of damage-associated molecular patterns from the dying tumor cells that promote the function of antitumor immune cells including antigen-presenting cells and cytotoxic lymphocytes (16,17). Indeed, a recent randomized phase II trial (PEMBRO-RT) found a significant improvement in tumor response as well as a trend toward a better PFS and OS in patients with metastatic NSCLC receiving SBRT at a single tumor site before treatment with the PD-1 inhibitor pembrolizumab compared with those treated with pembrolizumab alone (overall response rate of 36% versus 18%; median PFS of 6.6 versus 1.9 months; median OS of 15.9 versus 7.6 months), although enrollment for this trial was not limited to oligometastatic disease and the SBRT was not ablative, given that only a single lesion was targeted (18).

Several studies of local ablative therapy combined with systemic therapy including PD-1/PD-L1 inhibitors for oligometastatic NSCLC are currently ongoing (*Table 2*). Among these trials, the pilot results of a single-arm phase II study (NCT02316002) have already been reported (19). In this study, 45 patients were assigned to receive pembrolizumab for up to 1 year (until disease progression) after completion of local ablative therapy including surgical resection or radiotherapy. Enrolled patients were allowed to have undergone prior treatment with the exception of PD-1/PD-L1 inhibitor therapy, and patients with metachronous disease (oligometastatic recurrence after initial definitive therapy) were also allowed to participate, resulting in heterogeneity of the study population. Most patients (93%) had only one or two metastatic sites, although up to four such sites were allowed. The PD-L1 tumor proportion score (TPS) was known for 71% of patients, with only one-third of these patients being PD-L1 positive (PD-L1 TPS of ≥1%), suggesting that the potential of most participants to respond to pembrolizumab therapy was low. The median PFS from the initiation of ablative therapy was 19.1 months (95% CI, 9.4–28.7 months), and the PFS rate at 36 months was ~40% to 50%. Median OS from the initiation of ablative therapy was 41.6 months (95%

Table 1 Ongoing randomized clinical trials comparing local ablative therapy combined with systemic therapy with systemic therapy alone in oligometastatic NSCLC

Trials	Trial number	Trial design	Country	Number of metastatic sites	Major criteria	Estimated enrollment	Primary endpoint	Intervention	Estimated study completion year
Phase III									
SARON trial (Stereotactic Ablative Radiotherapy for Oligometastatic NSCLC. A Randomised Phase III Trial)	NCT 02417662	Randomized phase III	UK	≤3	Synchronous	340	OS	Control arm: Further 2 cycles of platinum-based chemotherapy with or without maintenance chemotherapy	2022
					No *EGFR*-mutation/*ALK*-fusion/*ROS1*-fusion No disease progression after 2 cycles of platinum-base chemotherapy			Experimental arm: Further 2 cycles of platinum-based chemotherapy followed by conventional RT or SBRT	
SINDAS trial (Tyrosine-kinase Inhibitor With or Without SBRT in Newly Diagnosed Advanced Staged Lung Adenocarcinoma)	NCT 02893332	Randomized phase III	China	≤5	Synchronous or metachronous *EGFR*-mutation positivity	200	PFS	Control arm: Gefitinib or Erlotinib Experimental arm: SBRT followed by Gefitinib or Erlotinib	2020
OMEGA trial (A Randomized Trial of Local Ablative Therapy *vs.* Conventional Treatment in Oligometastatic NSCLC)	NCT 03827577	Randomized phase III	Italy	≤3	Synchronous or metachronous Mutational status not considered	195	OS	Control arm: Standard systemic chemotherapy (platinum doublet, Targeted agent based on genetic testing, or immunotherapy according to PD-L1 expression level) Experimental arm: Standard systemic chemotherapy followed by surgical resection, SBRT, or RFA	2022
HALT trial (Targeted Therapy With or Without Dose Intensified Radiotherapy for Oligo-progressive Disease in Oncogene-addicted Lung Tumours)	NCT 03256981	Randomized phase II/III	UK	≤3	OPD following initial response to TKI treatment Actionable mutation positivity	110 (phase2/3)	PFS	Control arm: Continuation of initial TKI treatment Experimental arm: SBRT followed by readministration of initial TKI treatment	2021
Phase II									
CORE trial (A Randomised Trial of Conventional Care Versus Radioablation [SBRT] for Extracranial Oligometastases)	NCT 02759783	Randomized phase II/III	UK	≤3	Synchronous or metachronous Mutational status not mentioned Breast cancer, NSCLC, and prostate cancer	Not applicable (245 for overall cohort)	PFS	Control arm: Standard of care treatment at the discretion of local oncologist Experimental arm: SBRT followed by standard of care treatment at the discretion of local oncologist	2024

Table 1 *(continued)*

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Trials	Trial number	Trial design	Country	Number of metastatic sites	Major criteria	Estimated enrollment	Primary endpoint	Intervention	Estimated study completion year
Randomized Phase II Trial of Local Consolidation Therapy After Osimertinib for Patients With EGFR Mutant Metastatic NSCLC	NCT 03410043	Randomized phase II	USA	≤3 (as a prespecified subgroup)	Synchronous or metachronous *EGFR*-mutation positivity	Not applicable (143 for overall cohort)	PFS	Control arm: Osimertinib Experimental arm: Surgical resection or radiation therapy after induction therapy with osimertinib, followed by maintenance therapy with osimertinib	2022
PROMISE-004 (Precision Radiation for OligoMetastatIc and MetaStatic DiseasE [PROMISE]-004: Consolidative Use of Radiotherapy to Block Oligoprogression)	NCT 03808662	Randomized phase II	USA	≤5	Extracranial OPD following first-line systemic chemotherapy or TKI treatment Mutational status not considered Breast cancer, and NSCLC	Not applicable (160 for overall cohort)	PFS	Control arm: Standard of care per physician discretion Experimental arm: SBRT	2022
A Randomized Phase II Study Assessing the Efficacy of Local Consolidative Therapy for NSCLC Patients With Induced Oligometastatic Disease	NCT 01725165	Randomized phase II	USA	≤3 (after induction systemic therapy)	Synchronous or metachronous Mutational status not considered No disease progression after 4 cycles of platinum-base chemotherapy or TKI treatment	94	PFS	Control arm: Maintenance therapy per physician discretion Experimental arm: Surgical resection or radiation therapy followed by maintenance therapy per physician discretion	2019
A Phase II Randomized Study Assessing the Efficacy of SBRT in Patients With Oligometastatic Breast or Lung Cancer	NCT 03808337	Randomized phase II	USA	≤5	Synchronous or metachronous Mutational status not considered Breast cancer, and NSCLC	Not applicable (142 for overall cohort)	PFS	Control arm: Standard of care per physician discretion (including immunotherapy) Experimental arm: SBRT followed by standard of care per physician discretion	2022
Local Non-salvage Radiotherapy for Synchronous Oligometastatic NSCLC: A Multicenter, Randomized, Controlled, Phase 2 Study	NCT 03119519	Randomized phase II	China	≤5	Synchronous Mutational status not considered	148	PFS	Control arm: Standard platinum-based chemotherapy or TKI treatment Experimental arm: Standard platinum-based chemotherapy or TKI treatment followed by radiation therapy	2021

NSCLC, non-small cell lung cancer; UK, the united kingdom; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; OS, overall survival; RT, radiation therapy; SBRT, stereotactic body radiotherapy; PD-L1, programmed cell death-ligand 1; RFA, radiofrequency ablation; OPD, oligoprogressive disease; TKI, tyrosine kinase inhibitor; PFS, progression-free survival.

Table 2 Ongoing trials for local ablative therapy combined with PD-1/PD-L1 inhibitors in oligometastatic NSCLC

Trials	Trial number	Trial design	Country	Number of metastatic sites	Major criteria	Estimated enrollment	Primary endpoint	Intervention	Estimated study completion year
Phase II Study of Pembrolizumab After Curative Intent Treatment for Oligometastatic NSCLC	NCT 02316002	Phase II	USA	≤4	Synchronous or metachronous	51	PFS	Surgical resection or RT followed by pembrolizumab	2022
LONESTAR trial (Randomized Phase III Trial of Local Consolidation Therapy After Nivolumab and Ipilimumab for Immunotherapy-Naive Patients With Metastatic NSCLC)	NCT 03391869	Randomized phase III	USA	≤3 (as a pre-specified subgroup)	Synchronous or metachronous No *EGFR*-mutation/*ALK*-fusion	Not applicable (270 for overall cohort)	OS	Control arm: Nivolumab + ipilimumab Experimental arm: Surgical resection or RT after induction therapy with nivolumab + ipilimumab, followed by maintenance therapy with nivolumab + ipilimumab	2022
Comprehensive Stereotactic Body Radiotherapy to All Sites of Oligometastatic NSCLC Combined With Durvalumab (MEDI4736) and Tremelimumab Dual Immune Checkpoint Inhibition	NCT 03275597	Phase I	USA	≤6	Synchronous or metachronous No *EGFR*-mutation/*ALK*-fusion	21	Safety	SBRT followed by durvalumab + tremelimumab	2021
CHESS trial (A Multicentre Single Arm Phase II Trial Assessing the Efficacy of Immunotherapy, Chemotherapy and Stereotactic Radiotherapy to Metastases Followed by Definitive Surgery or Radiotherapy to the Primary Tumour, in Patients With Synchronous Oligo-metastatic NSCLC)	NCT 03965468	Phase II	Europe	≤3	Synchronous No *EGFR*-mutation/*ALK*-fusion/*ROS1*-fusion	47	PFS	Platinum-doublet + durvalumab + SBRT followed by definitive surgical resection or RT of the primary tumor, and maintenance therapy with durvalumab	2021
WJOG11118L TRAP OLIGO trial (Phase II Study of Multidisciplinary Therapy Combined with Pembrolizumab for Patients with Synchronous Oligometastatic NSCLC)	Not yet registered	Phase II	Japan	≤3	Synchronous No *EGFR*-mutation/*ALK*-fusion/*ROS1*-fusion/*BRAF*-mutation	30	PFS	Platinum-doublet + pembrolizumab followed by surgical resection or RT, and maintenance therapy with pembrolizumab	2025

PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; NSCLC, non-small cell lung cancer; PFS, progression-free survival; EGFR, epidermal growth factor receptor; RT, radiation therapy; ALK, anaplastic lymphoma kinase; OS, overall survival; SBRT, stereotactic body radiotherapy.

CI, 27.0–56.2 months), with the OS rate at 36 months being ~70%. The survival outcome achieved in this trial was thus superior to that observed in the studies by Gomez *et al.* and Iyengar *et al.* (4,5). In addition, the survival outcome was also superior to that for PD-L1 high-positive (PD-L1 TPS of ≥50%) NSCLC patients treated with pembrolizumab in the first-line setting in the KEYNOTE-042 trial (median PFS of 7.1 months; median OS of 20.0 months), although this latter trial included patients with non-oligometastatic NSCLC and therefore a potentially worse prognosis (20). These pilot data are promising, although they remain preliminary, and they should facilitate the design of further studies.

In summary, the recent article by Dingemans *et al.* of the European consensus group has proposed a first official definition of synchronous oligometastatic NSCLC in order to address an urgent need in the field of lung cancer research and treatment. This provisional definition should help clinicians to determine treatment strategy for their patients with a limited number of metastatic sites, standardize the inclusion and exclusion criteria of future clinical trials, and facilitate appropriate interpretation of results from studies of oligometastatic NSCLC. The upcoming results for many ongoing randomized clinical trials are needed before definitive conclusions can be drawn with regard to the best approach to achieving long-term survival in this subset of patients, with one such promising approach being the combination of immunotherapy and local ablative therapy.

Acknowledgments

We thank Taichi Miyawaki and Hirotsugu Kenmotsu at the Division of Thoracic Oncology, Shizuoka Cancer Center, for their kindly giving detailed information of WJOG11118L trial.

Footnote

Conflicts of Interest: K Haratani has received honoraria from AstraZeneca K.K. and Ono Pharmaceutical Co. Ltd.; lecture fees from AS ONE Corporation, AstraZeneca K.K., Bristol-Myers Squibb Co. Ltd., Chugai Pharmaceutical Co. Ltd., MSD K.K., and Pfizer Japan Inc.; and research funding from AstraZeneca K.K. K Nakagawa has received honoraria from Astellas Pharma Inc., AstraZeneca K.K., Bristol-Myers Squibb Co. Ltd., Chugai Pharmaceutical Co. Ltd., Clinical Trial Co. Ltd., Eli Lilly Japan K.K., MSD K.K., Nichi-Iko Pharmaceutical Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd., Pfizer Japan Inc., Reno. Medical K.K., and Sym Bio Pharmaceuticals Ltd.; research funding from A2 Healthcare Corp., AbbVie Inc., Astellas Pharma Inc., Bristol-Myers Squibb Co. Ltd., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co.Ltd., Eisai Co. Ltd., Eli Lilly Japan K.K., EP-CRSU Co. Ltd., GRITSTONE ONCOLOGY Inc., ICON Japan K.K., inVentiv Health Japan, MSD K.K., Linical Co.Ltd., Nippon Boehringer Ingelheim Co. Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co. Ltd., PAREXEL International Corp., Pfizer Japan Inc., Quintiles Inc., Taiho Pharmaceutical Co. Ltd., and Takeda Pharmaceutical Co. Ltd.; and consulting or advisory fees from Astellas Pharma Inc., Takeda Pharmaceutical Co. Ltd., and Ono Pharmaceutical Co. Ltd. M Takeda has received honoraria from Ono Pharmaceutical Co., Boehringer Ingelheim Japan Inc., Novartis Pharma K.K. Chugai Pharmaceutical Co. Ltd.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Haratani K, Takeda M, Nakagawa K. A first attempt to establish a definition of oligometastatic non-small cell lung cancer by a European consensus group. J Thorac Dis 2019;11(12):5635-5642. doi: 10.21037/jtd.2019.11.49