Stage IV nonsmall cell lung cancer treatment: oligometastatic disease and disease progression, untangling the knot

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Shareable abstract (@ERSpublications)
This article summarises the currently available data and emphasises the questions and perspectives in oligometastatic disease NSCLC https://bit.ly/4fgk10i

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Abstract

Stage IV nonsmall cell lung cancer (NSCLC) is a heterogeneous group of patients for whom systemic therapy is decided based on tumour-biological cancer features (histology, PD-L1 expression, genomic alteration, metastatic sites) and patient characteristics (performance status, comorbidities). In most instances, some kind of systemic treatment is proposed, for which immunotherapy-based or targeted therapies are considered the standards of care in 2024. Oligometastatic NSCLC represents a specific concept during the biological spectrum from localised to metastatic disease in which only a limited number of metastatic sites can be documented. Based on this assumption, prospective and a few randomised phase II studies have been performed, which suggested that adding a local ablative treatment to the systemic one can be a new option for selected stage IV NSCLC. The European Organisation for Research and Treatment of Cancer (EORTC) and the European Society for Radiotherapy and Oncology (ESTRO) supported efforts to define oligometastatic NSCLC to unify the semantics within the thoracic oncology community. This article summarises the currently available data and emphasises the questions and perspectives in oligometastatic disease NSCLC in European patient cohorts.

Introduction

Nonsmall cell lung cancer (NSCLC) is the leading cause of cancer death worldwide. More than 50% of the patients are diagnosed at an advanced or metastatic stage for which only palliative treatment (meaning with no curative intent) can be proposed [1]. Three revolutions have marked the metastasised NSCLC journey during the past 50 years. First, cisplatin was the first antineoplastic drug to improve survival in stage IV NSCLC. The second revolution was the discovery of actionable genomic alterations, the first to be identified were activating mutations of the epidermal growth factor receptor (EGFR). Thereafter, many other actionable mutations or translocations were discovered but still represent only a minority of tumours in European populations. The third recent revolution was linked to the discovery of the immune checkpoint [2], which led to a Nobel prize. Programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA4) inhibitors were rapidly introduced in routine practice and radically changed our clinical guidelines and patients' prognoses in stage IV NSCLC.

Relating to tumour biology in stage IV NSCLC, two theories paved the general metastatic cancer process. The first was proposed by Halsted [3] in 1894 as a continuum process through locoregional nodal extension. The second was published by Keynes [4] in 1954, suggesting that cancer is a systemic disease

with widespread extension and micrometastases. Between these two settings, an intermediate state was presented by Hellman [5] in 1994. Following a general overview of modern systemic therapies in stage IV NSCLC, this review presents the specific aspects of oligometastatic disease (OMD) in NSCLC focusing on definitions, specific treatment strategies and questions regarding the future prospects of systemic treatments in European OMD NSCLC patient cohorts.

Current treatment strategies

Stage IV NSCLC patients have a low survival rate and little chance of cure. The first therapeutic aim is to prevent disease progression and improve quality of life. At this stage, treatment strategies are planned in line with the patient's performance status, comorbid diseases, patient preference, and histopathological features, including actionable molecular alterations, predicted response to immune-targeted treatment approaches and access to treatment. Patients should undergo PD-L1 immunohistochemistry and molecular testing for activating mutations/translocations. Several oncogenic driver mutations are identified for which targeted therapy improves survival outcomes, for example, EGFR, anaplastic lymphoma kinase (ALK), ROS1, BRAF-V600, rearranged during transfection oncogene (RET), and neurotrophic tyrosine kinase receptor (NTRK). When tumours exhibit one of these alterations, targeted therapies became the preferred option, showing a better toxicity profile and disease control than systemic chemotherapy [6].

EGFR mutations are a heterogeneous group, they include mutations sensitive to tyrosine kinase inhibitors (TKIs) (*e.g.* del 19, L858R, G719X) but also mutations of resistance, such as T790M (resistant to first/second generation EGFR TKIs) or most of the exon 20 mutations (resistant to the available first to third generation EGFR TKIs) and for which specific inhibitors are in development. In first-line, improvement in progression-free survival (PFS) was obtained with first (gefitinib, erlotinib, icotinib) or second (afatinib, dacomitinib) generation drugs. Osimertinib, a third generation TKI targeting the T790M mutation, demonstrated better effectiveness and tolerance than previous TKIs and is now the preferred drug [7]. Furthermore, an European Medicines Agency (EMA)-approved combination of ramucirumab, an anti-vascular endothelial growth factor, and erlotinib may be considered as an alternative first-line treatment option in cases of classical activating EGFR mutations (del19 or L858R) [8]. Crizotinib was the first US Food and Drug Administration (FDA)-approved TKI used in ALK rearrangement. Second (brigatinib, alectinib) and third (lorlatinib) generation TKIs showed clear improvements over crizotinib for both overall disease control and intracerebral activity [9–11]. In most European countries, alectinib or brigatinib and, eventually, lorlatinib are the first-line therapeutic options in this group of patients. EGFR mutations and ALK translocations are the most frequent actionable molecular alterations. Rare mutations or translocations are subject to targeted therapies currently available in our armamentarium, either in the first or subsequent lines of treatment, depending on local reimbursement criteria. Crizotinib and entrectinib are recommended for ROS1 translocation [12].

Vemurafenib and dabrafenib demonstrated significant clinical activity against BRAF-V600 mutations. The combination of the BRAF-inhibitor dabrafenib and the MEK-inhibitor trametinib resulted in an improved response rate as well PFS compared with dabrafenib monotherapy. Therefore, dual blockage of the RAS–RAF–MEK–EKR signal chain is recommended as the first choice in NSCLC with BRAF-V600 mutations [13].

NTRK is a rare translocation for which new targeted therapies such as larotrectinib or entrectinib are active and available in Europe [14]. Further developments are ongoing, and active drugs are available, such as tepotinib (EMA approved) for MET exon 14 skipping or sotorasib (EMA approved) and adagrasib for KRAS-G12C mutation, or being tested for new genomic alterations as neuregulin 1 (NRG1) or nuclear protein in testis midline 1 (NUTm1).

However, in Europe patients with driver oncogenic alterations only represent a limited group among all stage IV NSCLC, emphasising the need for other therapeutic options in most of the cases.

Immunotherapy alone or in combination with chemotherapy is the new standard of care in metastatic NSCLC without molecular alterations, with prospective studies reporting significant improvement in PFS and overall survival (OS) over chemotherapy. Despite the PD-L1 expression level predicting clinical benefit, significant survival increases were achieved in all strata. Improvements were more pronounced in high expressers (PD-L1 $\geqslant$50%) in comparison with other groups (PD-L1 1–49% and <1%). Those results were obtained regardless of the line of treatment. Different agents (pembrolizumab, atezolizumab, cemiplimab) as single-agents or in combination with platinum-based regimens are now accepted by the EMA in Europe [15, 16]. As the first-line therapy, a single-agent should be preferred for tumours with PD-L1 $\geqslant$50% [17] and chemo-immunotherapy for the other groups.

Despite all the therapeutic advances, chemotherapy remains central in stage IV NSCLC as a first-line therapy with or without immune checkpoint inhibitors (ICI) in wild-type tumours (*i.e.* tumours without molecular alterations), for salvage therapy, and after exhaustion of targeted therapies. The most common regimen comprises 4–6 cycles of platinum-based combinations. However, platinum-free alternatives are available for patients with contraindications (*i.e.* old patients, those with poor performance status), such as vinorelbine, gemcitabine, or docetaxel monotherapies [6].

Local therapies, such as surgery and mainly radiotherapy, provide a significant rate of clinical benefit in controlling, for example, bone and brain metastases, superior vena cava syndrome, or painful chest wall involvement. New radiotherapeutic techniques are implemented in routine practice, like stereotactic approaches for limited brain, adrenals or lung metastases, and eventually, in some cases, for bone or liver involvement [18].

The oligometastatic concept

The term OMD was coined by Hellman and Weichselbaum [5] to describe an intermediate state between loco(regional) and metastatic tumours with potential interest in adding locally ablative therapy (LAT) to systemic treatment. The authors argued that tumour cells in a primary tumour might gradually gain the ability to invade distant sites, representing the "seed and soil" concept involving the capability of tumours cells to seed and the receptivity of the organs to host metastatic cells (soil). By definition, "oligometastatic" means a limited number of metastases and organs involved [19]. The implication of the OMD concept in therapeutic achievements was demonstrated in clinical series when one or two metastatic sites are considered in an approach including local therapies [20]. However, there were considerable variations in the definition of synchronous OMD (at the time of cancer diagnosis). In an attempt to substantiate and harmonise definitions, the European Organisation for Research and Treatment of Cancer (EORTC) published a consensus report based on a systematic review which schematised the definition of synchronous OMD in NSCLC, limiting the number of organs involved to three and the number of metastases to five [21]. The multidisciplinary expert panel emphasised the need for an extensive workup, including fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) and brain magnetic resonance imaging, as well as the prerequisite that introducing an ablative treatment may modify the course of the disease. Diffuse bone marrow and serosal involvements, not amenable to local therapy, are not considered oligometastases. In this definition, locoregional hilar-mediastinal lymph node infiltration adjacent to the primary tumour (N1–3) is not counted as a separate site. Importantly, this definition was proposed to be used in clinical trials, allowing meaningful comparisons across studies. Nevertheless, the acceptance of this definition is not universal, and some are proposing LAT in patients presenting with more than five metastases, providing that all can be treated with LAT. A prospective cohort or randomised trials are needed to determine with a high level of evidence the best threshold defining synchronous OMD.

Apart from the synchronous OMD, three other "oligo" situations may occur according to the EORTC consensus statement [22]:

1) Genuine OMD represents both synchronous OMD and oligorecurrence OMD (*i.e.* a limited number of distant metachronous metastases) with the latter defined as limited recurrence >6 months after optimal local control of a localised tumour.

2) Induced OMD is used to label oligoprogression, a limited number of progressive sites/metastases after systemic treatment administration.

3) Oligopersistent OMD relates to an active, persistent limited number of sites/metastases after response to the systemic treatment.

For a better understanding, a prospective cohort study (EORTC-ESTRO Oligocare) aiming to highlight the management of these scenarios is underway [23].

The synchronous OMD: the role of LAT in addition to systemic therapies

The synergy between LAT and systemic therapies for managing synchronous OMD in NSCLC has been a dynamic area of investigation during the past two decades. The first prospective report supporting this concept was published in 2002 [24]. LAT, such as stereotactic body radiation therapy (SBRT)/stereotactic ablative radiotherapy (SABR) or surgery combined with systemic treatments, have been shown to improve PFS and OS in patients with oligometastatic NSCLC in around 10 phase II studies; the data were summarised in a systematic review [25].

Three landmark phase II randomised studies provided the first high-level evidence to support adding LAT (SBRT/SABR) to systemic therapy in synchronous/metachronous OMD (table 1). The first multicentre

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TABLE 1 Select landmark trials in synchronous oligometastatic disease (OMD) for nonsmall cell lung cancer (NSCLC), exploring locally ablative therapy (LAT) to treat OMD in patients with tumours without driver mutations

Trial identifier, first author [ref.]	Study name	Study design	Patient characteristics	Participants, n	Intervention	Clinical outcomes
NCT01725165, Gomez [26, 27]	Local consolidative therapy *versus* maintenance therapy or observation for patients with oligometastatic NSCLC without progression after first-line systemic therapy	Randomised, phase II	1–3 metastatic sites (lymph node metastases count as a metastatic site) after first-line chemotherapy	49	Maintenance therapy or observation *versus* radical therapy of primary plus SABR or surgery	PFS 14.2 *versus* 4.4 months (p=0.022) OS 41.2 *versus* 17.0 months (p=0.017) Longer survival after progression for the LAT group No additional toxicity G3 observed
NCT02045446, Iyengar [28]	Maintenance chemotherapy *versus* consolidative SBRT plus maintenance chemotherapy for stage IV NSCLC	Randomised, phase II	1 metastatic site after first-line chemotherapy	30	Maintenance chemotherapy *versus* consolidative SBRT +maintenance chemotherapy for stage IV NSCLC	PFS 9.7 *versus* 3.5 months (p=0.01) Toxicity similar in both arms Fewer recurrences in SBRT arm
NCT01446744 Palma [29]	Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR COMET phase II randomised trial	Randomised; phase II (multiple tumour types, n=18 with lung cancer)	1–5 metastatic sites	99 Lung n=18 Breast n=18 Colorectal n=18 Prostate n=18	SABR to all metastatic sites *versus* palliative standard of care	PFS 11.6 *versus* 5.4 months (p=0.001) Initial OS 41 *versus* 28 months (p=0.090) Long-term 5-year OS 42.3% *versus* 17.7 (p=0.006) No differences in QoL between arms

SABR: stereotactic ablative radiotherapy; SBRT: stereotactic body radiation therapy; PFS: progression-free survival; OS: overall survival; LAT: locally ablative therapy; QoL: quality of life.

prospective randomised trial randomised OMD patients without disease progression after first-line systemic therapy (four cycles of platinum-based chemotherapy or 3 months of anti-EGFR/anti-ALK therapy) to maintenance therapy *versus* LAT consisting of surgery, radiotherapy, or both [26, 27]. The authors found improved PFS (11.9 months *versus* 3.9 months in the study and control groups, respectively, after a median follow-up of 12 months; p=0.0054), as well as improved long-term OS (median OS 41.2 months in favour of the LAT group *versus* 17.0 months in the control group; p=0.017). The study recruitment was halted early due to the significant improvement with consolidative local therapy. Second, Iyengar *et al*. [28] randomised patients following induction systemic treatment between a control group receiving maintenance chemotherapy only *versus* the intervention group treated with SBRT plus maintenance chemotherapy. EGFR- or ALK-mutated tumours were excluded. The trial also closed prematurely due to significantly better PFS in the consolidative local SBRT treatment arm (9.7 months *versus* 3.5 months; p=0.01), while toxicity levels were similar between both groups. Third, in the SABR-COMET trial [29], 99 patients with OMD in different primary tumour sites were enrolled, 18 of whom had oligometastatic NSCLC. A significant difference in 5-year OS was noted between the arm with SABR and standard of care combined (42.3%) *versus* the control arm with standard of care alone (17.7%). The authors reported 20% more adverse events (grade 2+) in the SBRT arm than in the control group, including three deaths in the SABR arm (4.5%).

Current first-line treatment strategies differed significantly for tumours with activating genomic alterations and there was a need for specific trials in this setting. The SINDAS trial was the first published phase III randomised controlled trial evaluating the role of first-generation TKIs (*e.g.* gefitinib or erlotinib) alone or with upfront SBRT for all synchronous OMD sites in patients with EGFR-driven OMD NSCLC [30]. Interim analyses showed that PFS in the TKI-only group was 12.5 months *versus* 20.2 months in the upfront SBRT combined with TKI group (p<0.001), OS was 17.4 *versus* 25.5 months (p<0.001). SBRT was not associated with an increase in the rate of adverse events. The SINDAS trial indicated that upfront SBRT may be a promising strategy in synchronous EGFR mutation-positive patients planned for first-line TKIs. Nevertheless, the results of this trial must be compared with the increased effectiveness of osimertinib as a third-generation TKI in stage IV NSCLC with EGFR mutation [7]. The exact place of LAT needs to be confirmed in further prospective trials given that the enhanced systemic effect of the third-generation TKI may obviate the need for general application of LAT in this specific OMD setting. A growing number of prospective studies are ongoing to test the addition of LAT in oligometastatic NSCLC with or without actionable oncogenic alterations (table 2).

The best timing to provide local treatment in OMD NSCLC remains debated [31]. The timing is actively being investigated by the Optimal Intervention Time of Radiotherapy for Oligometastatic Stage IV Non-small Cell Lung Cancer (OITROLC; ClinicalTrials.gov identifier: NCT02076477) investigators in China. OITROLC is a multicentre phase III trial that compares upfront or subsequent local therapy in synchronous OMD NSCLC patients. Patients in the upfront arm receive concurrent chemoradiotherapy followed by two cycles of chemotherapy, while patients in the subsequent arm receive two cycles of chemotherapy followed by concurrent chemoradiotherapy. The primary outcome is response rate at 3 months, while PFS, quality of life and grade ⩾3 toxicities are secondary outcomes.

In anticipation of numerous phase III trial results in the coming years, a recent American Society for Radiation Oncology/European Society for Radiotherapy and Oncology clinical practice guideline on the treatment of oligometastatic NSCLC was released to frame recommendations for the treatment of OMD NSCLC [32]. A patient-centred multidisciplinary approach for all decision-making regarding the potential integration of definitive local treatment strategies with radiotherapy and/or surgery was recommended.

LAT plays a significant role in managing synchronous oligometastatic NSCLC, both with and without driver mutations, and can be used in conjunction with systemic therapies to improve patient outcomes. Numerous randomised phase III clinical trials are currently underway to confirm the role of LAT in oligometastatic NSCLC further and it is hoped they will contribute valuable perspectives on optimising the management of OMD NSCLC.

The oligoprogression state

Despite promising results from the individual multimodal treatment of patients with metastatic NSCLC, most of them experience progression sooner or later. Due to the individual pretreatment, no general recommendation can be given for the progression. Therefore, different patterns of progression must be viewed differently.

Current therapeutic options for systemic progression in pretreated OMD NSCLC patients

In cases of generalised systemic recurrence after initial curatively intended OMD therapy (surgery or radiotherapy-based), which is not treatable with a local approach, systemic therapy will be offered.

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TABLE 2 Selected ongoing enrolling clinical trials in oligometastatic nonsmall cell lung cancer (OM-NSCLC) exploring the addition of local ablative therapy (LAT) and its timing to treat oligometastatic disease (OMD) in tumours with and without driver mutations

Clinical trial identifier	Study name	Study design	Patient characteristics	Intervention	Clinical outcomes
Selected clinical trials in sOMD-NSCLC without driver mutations					
NCT05278052 (TARGET-02)	Standard maintenance therapy *versus* local consolidative radiation therapy and SMT in OM-NSCLC	Randomised phase III	1–3 metastases in 1 organ, or 1–5 excluding the primary tumour and regional nodes	Standard maintenance therapy+SBRT 2028 *versus* standard maintenance therapy alone	OS
NCT02417662 (SARON)	Stereotactic ablative radiotherapy for oligometastatic NSCLC	Randomised, phase III	NSCLC synchronous oligometastatic (<3) EGFR/ ALK-negative or unknown mutation status	Platinum-based chemotherapy alone±conventional radiotherapy or SBRT	OS
Selected clinical trials in sOMD-NSCLC with driver mutations					
NCT03391869 (LONESTAR)	LCT after nivolumab and ipilimumab for immunotherapy-naïve patients with metastatic NSCLC – strategic alliance: BMS	Randomised, phase III		LAT after nivolumab and ipilimumab for immunotherapy-naïve patients with metastatic NSCLC	
NCT03410043 (NORTHSTAR)	Osimertinib, surgery and radiation therapy in treating patients with stage IIIB or IV NSCLC with EGFR mutations	Randomised, phase II	Stage IIIB/IV EGFR mutant NSCLC not amenable to curative intent therapy	LAT (surgery radiation and/or ablation) to target lesions after induction osimertinib *versus* osimertinib alone	PFS
NCT03965468 (CHESS)	Immunotherapy, chemotherapy, radiotherapy and surgery for synchronous oligometastatic NSCLC	Single arm, phase II	1–3 (at least 1 extracerebral)	Induction with durvalumab, platinum-based including carboplatin and paclitaxel, and SBRT followed by definitive local therapy and continuation of durvalumab until disease relapse or up to 1 year	PFS
Selected clinical trials with upfront and consolidative LAT for sOMD-NSCLC					
NCT02076477 (OITROLC)	The optimal intervention time of radiotherapy for oligometastatic stage IV NSCLC	Randomised two arm, prospective, phase III	Synchronous, 1–5 metastases	Upfront LAT with concurrent chemoradiation to all disease sites followed by two cycles of platinum-doublet chemotherapy *versus* initial two cycles of platinum-doublet chemotherapy followed by LCT with chemoradiation	Short-term effects, response rate 3 months after treatments
NCT03827577 (OMEGA)	Local ablative therapy in oligometastatic NSCLC	Randomised, phase III	Metachronous and synchronous, 1–3 metastases	Resection of primary NSCLC plus LAT to all metastases *versus* standard of care chemotherapy	OS up to 60 months

sOMD: synchronous OMD; SMT: standard maintenance therapy; SBRT: stereotactic body radiation therapy; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; OS: overall survival; PFS: progression-free survival; LCT: local consolidation therapy.

The choice of drugs depends on previous exposures to chemotherapy and immunotherapy, and the time interval between ending systemic treatment and relapse, with 6 months being the commonly applied threshold. Patients who have only received LAT or had adjuvant or consolidative therapy >6 months ago might be reinduced with a classical first-line platinum doublet, provided their general condition is good, and eventually combined with a checkpoint inhibitor. For earlier relapses or progression under first-line systemic treatment, a taxane, ultimately combined with an anti-angiogenic agent, is the standard second-line regimen in patients not yet exposed to checkpoint inhibitors [33, 34]. In patients pretreated with a TKI, a re-biopsy should be performed to detect resistance mechanisms and adapt the therapeutic strategy.

Therapeutic options for oligorecurrence, oligoprogression and oligopersistence in pretreated OMD NSCLC patients

In contrast to general systemic progression, LAT may be considered in progressing patients in whom the number of progressive metastatic sites appears limited. Three situations need to be discussed: 1) oligorecurrence, 2) oligoprogression and 3) oligopersistence.

1) Oligorecurrence refers to the appearance of new metastatic sites >6 months after loco(regional) treatment with the intent to cure according to the EORTC consensus statement [22]. When possible, pathological confirmation is required to confirm malignancy and to exclude secondary cancer. Overall, the same approach can be considered as for synchronous OMD. As an example, both synchronous OMD and oligorecurrence (*i.e.* metachronous OMD) in NSCLC were included in the abovementioned trial undertaken by Gomez *et al.* [26, 27].
2) Oligoprogression is the singular progression of a previously existing tumour manifestation after response to the systemic treatment [22]. If technically possible, a biopsy should be carried out to detect resistance mechanisms to the current therapy in activating genomic alterations and to exclude histological transformation or second malignancy. The proof of concept was recently validated in a phase II randomised trial including lung and breast cancer patients [35]. Oligoprogressive patients (⩽5 progressive metastases), on first-line systemic therapy were randomised between the standard of care with or without SBRT. The primary end-point was PFS with prespecified subgroup analysis according to the disease site. Among 106 patients, 59 had NSCLC, of whom 86% had wild-type tumour. As for other phase II studies in synchronous OMD [26–28], recruitment was halted early based on a planned positive interim analysis. Globally, the study was positive on the primary end-point with a median PFS of 3.2 months (95% CI 2–4.5 months) in the standard-of-care group and 7.2 months (95% CI 4.5–10 months) in the SBRT group (p=0.0035). Interestingly, the difference in PFS was only observed in the NSCLC patients (median PFS 10 months (95% CI 7.2 months to not reached) *versus* 2.2 months (95% CI 2–4.5 months) (HR 0.41; 95% CI 0.22–0.75; p=0.0039) suggesting that LAT effectiveness in oligoprogressive patients cannot be extrapolated in all cancer types. Toxicity in the experimental arm was detected in 9 (16%) patients presenting with grade 2 or worse toxicities, including gastrointestinal reflux disease, pain exacerbation, radiation pneumonitis, brachial plexopathy and low blood counts. In the case of oligoprogression, the question remains about the interest in continuing the same systemic therapy when adding LAT. This is particularly important in patients with activating genomic alterations when other highly active targeted therapies are available for delaying exposure to chemotherapy. This concept is currently examined in clinical trials such as HALT (ClinicalTrials.gov identifier: NCT03256981) or ROSE (NCT05089916).
3) Oligopersistence refers to the presence of a limited number of ongoing active OMD despite individual multimodal therapy. This concept is challenging in its definition as it can be interpreted differently according to the type of systemic pretreatment, considering chemotherapy, immunotherapy or targeted therapies separately. Many questions arise, such as the maximal number of metastases and sites, the time interval for considering the "persistent site" as resistant to the treatment, and the way of assessing the resistance. As an example, persisting activity during immunotherapy on FDG-PET/CT can be linked to active neoplastic disease but also to inflammatory processes needing pathological confirmation before considering LAT in this setting. At the time writing, we do not have clinical data allowing definite recommendations. These patients must be discussed on a case-by-case basis in multidisciplinary consultations, including (pneumo)-oncologists, surgeons and radiation oncologists.

Perspectives and questioning in oligometastatic processes

It is important to emphasise that most published clinical trials in OMD NSCLC were performed before the immunotherapy era, and before the accessibility of, or even the knowledge about, activating genomic alterations and directed targeted therapies. In most instances, systemic therapy was not pursued beyond LAT completion [26–28], while major long-term results are described with immunotherapy (provided for up to 2 years in randomised trials) [15] or targeted therapies administered continuously for months or

years. The role of LAT in this new era must be confirmed in an ongoing phase III trial, such as SARON (ClinicalTrials.gov identifier: NCT02417662), as well as the determination of the optimal duration of the systemic treatment.

Out of major changes in the therapeutic schedules, new targets and new therapeutic designs have been discovered that certainly will impact the future management of OMD NSCLC. A summary of these major novelties is presented in the following paragraphs.

Bispecific antibodies are engineered to present with two binding sites, allowing multiple targets and a potential increase in efficacy of each individually blocked target. Amivantamab is a fully human Fc-active immunoglobulin G1 (IgG1) directed against both epidermal growth factor (EGF) and MET receptors. Amivantamab has a low fructose backbone to enhance binding to FcγRIIIa/CD16a on natural killer cells, monocytes and macrophages, triggering antibody-dependent cell-mediated cytotoxicity. Early phase trials showed promising results in EGFR exon 20 insertions. In the first-line, amivantamab was tested in association with chemotherapy *versus* chemotherapy alone [36]. The primary outcome (PFS) was met, with a median PFS of 11.4 months (95% CI 9.8–13.7 months) *versus* 6.7 months (95% CI 5.6–7.3 months) (HR 0.40, 95% CI 0.30–0.53; p<0.001). In second-line therapy, in patients with classical EGFR mutations (del19 and L858R) after osimertinib failure, chemotherapy was tested against amivantamab–chemotherapy and amivantamab–lazertinib–chemotherapy regimens. Lazertinib is a third-generation EGFR TKI with potent intracranial activity. Both arms with amivantamab were superior to chemotherapy with regards to PFS [37]. Amivantamab–lazertinib was compared to osimertinib as first-line therapy in patients with classical EGFR mutations and showed better PFS. The data for OS were immature [38]. These results must be set in the perspective of the SINDAS phase III trial [30]. Yet, survival data in the FLAURA trial [7] showed better survival rates in non-OMD NSCLC treated by osimertinib alone than in the group receiving LAT and a first generation EGFR TKI.

Antibody–drug conjugates (ADCs) are a novel class of antineoplastic drugs that use monoclonal antibodies, allowing the selection of a target located on the surface of cancer cells, and deliver a payload, a cytotoxic component. A host of targets and associated ADCs are being developed against Trop2, HER2, HER3, c-MET, EGFR, PTK7, mesothelin (MSLN), B7-H3, tissue factor, AXL, NaPi2b, CEACAM5, ROR2 and ITGB6 [39]. Currently, only trastuzumab–deruxtecan is approved by the EMA and FDA for treating HER2 overexpressing or HER2-mutant NSCLC. Trastuzumab–deruxtecan showed, in second-line, after progression on chemotherapy, a 55% objective response rate, a median duration of response of 9.3 months (95% CI 5.7–14.7 months), a median PFS of 8.2 months (95% CI 6.0–11.9 months) and a median OS of 17.8 months (95% CI 13.8–22.1 months) [40].

Cell therapy is a generic term that encompasses several new techniques, such as chimeric antigen receptor (CAR) T-cells, stem cells, cytokine-induced killer cells and tumour-infiltrating lymphocytes. Several targets have been identified, including EGFR, MSLN, prostate stem cell antigen and mucin 1, but efficacy has been limited in NSCLC due to several challenges posed by solid tumours. These challenges include the difficulty in reaching solid tumours and the specificity of the tumour microenvironment that can stop CAR T-cells from progressing [41].

When observing the major advances in stage IV NSCLC treatment, many questions remain regarding integrating new therapies and new techniques in OMD NSCLC.

- First, there is still no consensus on what really defines LAT. In most studies, the aim was to treat locally with the intent to control the cancer site definitively. This can be obtained through surgery or stereotactic radiotherapy, but also with conventional radiotherapy, eventually combined with chemotherapy, brachytherapy, radiofrequency ablation or chemo-embolisation.
- The second question is regarding the optimal LAT. No clinical study has compared the different LAT options; they allowed the investigator to determine the best approach according to the treated site. Additional factors like patient fitness for certain LAT modalities as well as patient preferences may lead to best individualised LAT approaches.
- The time for proposing LAT remains debatable. In synchronous or metachronous OMD, we can argue that the treatment strategy should be discussed as front-line and that non-progressing patients should be offered LAT after induction systemic therapy. By contrast, if an OMD approach is not considered front-line, we are facing oligopersistent disease for which the best time for proposing LAT is a case-by-case discussion, complexified by the long-term duration of immunotherapy and targeted therapies.
- Also, a question remains concerning the systemic treatment duration after LAT administration. Is LAT just added to the systemic treatment that will continue according to standards, or can we stop or reduce its intensity after LAT?

Finally, we must consider some limitations in the clinical trials. Most randomised studies were stopped early due to positive results in interim analyses; overall, the number of patients is limited, and large phase III trials proposing current standard therapies with ICIs or targeted therapies are absolutely needed to provide a high level of evidence in confirmatory studies. All the patients in clinical trials were highly selected. Oncologists must be cautious in applying the current data in routine practice without any reflection about risks and benefits. We can suggest that any patient for whom an OMD approach is considered must be discussed in multidisciplinary consultations and must be treated in specialised centres.

Conclusions

OMD is a recent concept introduced two decades ago, suggesting an intermediate state between loco (regional) and metastatic diseases. Many small size, phase II trials showed potential interest in adding a LAT to standard-of-care systemic treatment in synchronous and metachronous OMD, while we are expecting further data in oligopersistent and oligoprogressive disease in the near future. The current data must be confirmed in large phase III trials, taking into consideration the recent therapeutic advances with ICIs and targeted therapies that have revolutionised the patient's prognosis. The complexity of therapeutic decisions will probably increase soon, when bispecific antibodies and ADCs will be part of our armamentarium for treating stage IV NSCLC.

Conflict of interest: T. Berghmans declares the following interests: consultancy for InhaTarget; Advisory Board participation for Bayer, Janssen, Merck, BMS and Roche; investigator for Pfizer, Merck, AstraZeneca, Novartis, Peregrine and Amgen; and a travel grant from Takeda. None of these represents a potential conflict of interest relating to this article. T.G. Blum declares the following interests: talks for AstraZeneca, BMS, MSD and Roche with payments to his hospital employer; personal and institutional funding from EU-granted Consortia (EU IMI OPTIMA, EU IHI IDERHA, EU4Health SOLACE). None of these represents a potential conflict of interest relating to this article. D. Kauffmann-Guerrero declares the following interests: talks for AstraZeneca, Pfizer, Boehringer-Ingelheim, Novartis and Roche; Advisory Board participation for Boehringer-Ingelheim, MSD, BMS, Pfizer, Roche, Janssen and Takeda. None of these represents a potential conflict of interest relating to this article. The remaining authors have no conflicts to declare.

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