



How to optimize the incorporation of immunotherapy in trials for oligometastatic non-small cell lung cancer: a narrative review

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Abstract: Patients with oligometastatic disease (OMD) non-small cell lung cancer (NSCLC) are considered as a subgroup of metastatic NSCLC that can obtain long-term survival or even cure. Oligometastatic refers to a state of a limited number of metastases in a limited number of organs. In clinical guidelines it is stated that patients with oligometastatic NSCLC can benefit from the addition of local radical therapy (LRT) to systemic therapy. With the introduction of minimally invasive surgery, advances in interventional radiology and stereotactic radiotherapy (SRT), LRT is becoming feasible for more and more patients. Furthermore, the introduction of immune checkpoint inhibitors (ICI) in the treatment landscape of advanced NSCLC has improved the survival of these patients. Importantly, the use of ICI in combination with LRT is also of interest in the subgroup of NSCLC patients with OMD. For example, it has been suggested that SRT may synergize with ICI as several preclinical studies reported an increased tumor antigen release, improved antigen presentation, and T-cell infiltration in irradiated tumors. In this narrative review, we describe the current evidence of immunotherapy treatment in OMD NSCLC, with a focus on future trial design and problems that need to be addressed.

Keywords: Clinical trials; immunotherapy; local radical therapy; non-small cell lung cancer (NSCLC); oligometastatic; radiotherapy

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Introduction

The majority of the patients with metastatic non-small cell lung cancer (NSCLC) without an oncogenic driver (i.e., most of the patients) will not reach a survival of 5 years (1). However, the outcome for this group of patients is also improving with the introduction of immune checkpoint inhibitors (ICI) as with the use of ICI, almost 20% of the patients are still alive at 5 years (2,3).

Another group of patients that can obtain long-term survival or even cure are those with oligometastatic disease (OMD) (4-9). "Oligometastatic" refers to a state of a limited number of metastases in a limited number of organs (10). In both the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines it is stated that patients with OMD can benefit from the addition of local radical therapy (LRT) to systemic therapy (11,12).

It is important to recognize that different types of OMD exist (for example synchronous, metachronous, oligopersistent/induced and oligoprogressive). Furthermore, different definitions for the term oligometastatic itself are used in clinical trials (e.g., maximum number of allowed metastases as well as maximum number of metastatic sites), so that trial comparisons are even more difficult (13). To better describe the different types and definitions of OMD, the European Organization for Research and Treatment of Cancer (EORTC) published two consensus recommendations: one on types of OMD (9 different types of OMD were identified according to for example time point of diagnosis in the disease course) and one on the required staging as well as the definition of synchronous OMD in NSCLC (14,15).

With the introduction of minimally invasive surgery, advances in interventional radiology and stereotactic radiotherapy (SRT), resulting in less treatment related toxicity, LRT is becoming feasible for more and more patients.

Hope to improve overall survival (OS) with the addition of LRT to systemic therapy comes also from two small randomized phase II trials (n=49 and n=29) including patients with NSCLC and synchronous OMD, without progression on induction systemic therapy (no ICI). The addition of LRT showed significant improvements in progression free survival (PFS) with hazard ratios (HR) of 0.35 and 0.30, respectively (4,9). One of these trials also showed an impressive gain in OS (17.1 vs. 41.2 months, respectively) (4). However, the long-term impact of LRT in

OMD remains unknown, mainly due to the low numbers of patients in the two randomized trials and the short follow-up time in the study of Iyengar *et al.* (9.6 months) (4,9). It should be acknowledged that in both trials the aim was to include a larger number of patients, but because the planned interim analysis showed such a large increase in PFS in the study of Gomez *et al.*, the institutional review board did not consider it ethical to continue the trial. Subsequently, the trial of Iyengar had also to be prematurely closed. Ideally, larger randomized phase III trials are needed to know the long-term impact of a radical treatment on the OS of patients with oligometastatic NSCLC. Importantly, the only prospective trial (single arm phase II, n=39) with follow-up data beyond 5 years, in patients not selected according to initial response to systemic treatment and before the era of ICI, showed a disappointing 5- and 6-year OS (7.7% and 2.5%, respectively) (5). Therefore, both local and systemic treatments for patients with NSCLC and OMD should be optimized. As stated above, ICI have revolutionized the treatment of NSCLC and the use of ICI in combination with LRT is also of interest in the subgroup of NSCLC patients with OMD. For example, it was suggested that SRT may synergize with ICI since several preclinical studies reported an increased tumor antigen release, improved antigen presentation, and T-cell infiltration in irradiated tumors (16).

In this narrative review, we describe the current evidence of immunotherapy treatment in OMD NSCLC, with a focus on future trial design and problems that need to be addressed. For this narrative review, a broad non-systematic search of the literature was performed to identify trials in OMD as well as ICI related biomarkers. The search was performed on PubMed (last search date Sept 15, 2020), as well as the meeting libraries of the largest oncological conferences (World Conference on Lung Cancer, American Society for Clinical Oncology, European Society for Medical Oncology (last search date Sept 15, 2020)). Only abstracts and full publications in English were considered eligible.

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-1065>).

Summary of available trial data on OMD NSCLC and ICI

Most of the reported trials in OMD NSCLC used as the systemic treatment component either chemotherapy or

tyrosine kinase inhibitors (TKI) (4,5,9,17,18). The first reported trial that evaluated ICI in OMD NSCLC, is a single arm phase II trial including patients with either synchronous or metachronous OMD (≤ 4 metastatic sites) (19). There was no limit on lines of therapy as long as the patient had not received a programmed death (ligand)1 (PD-[L]1) inhibitor, and inclusion criteria were not limited by PD-L1 or molecular status. LRT to all disease sites had to be completed before trial enrolment. Pembrolizumab 200 mg every 3 weeks (Q3W) was administered for a maximum of 8 cycles with the option to receive an additional 8 cycles if there was no disease progression after the first 8 cycles. Co-primary efficacy endpoints of the trial were PFS from start of LRT (PFS-L) and PFS from start of pembrolizumab (PFS-P). Forty-five of the 51 enrolled patients received pembrolizumab (14 had synchronous OMD). Thirty-two were PD-L1 evaluable with 34% PD-L1 $\geq 1\%$, 29 were evaluable for CD-8 T-cell infiltration, 52% had CD-8 T-cell infiltration of $>2.5\%$. Twenty-eight patients completed 8 cycles of pembrolizumab, 18 patients completed 16 cycles. With a median follow-up of 25.0 months, median PFS-L was 19.1 months (95% CI: 9.4–28.7) and median PFS-P was 18.7 months (95% CI: 10.1–27.1). Median OS was 41.6 months (95% CI: 27.0–56.2), 1- and 2-year OS rates were 91% and 78%, respectively. Both PFS and OS compare favorably with historical data (5). Clinical variables that were significantly associated with survival could not be identified, although there was a trend to a more favorable PFS-L in patients with metachronous OMD or positive PD-L1 status. Five patients experienced grade 3–4 treatment-related toxicity (one patient both a grade 3 and a grade 4 toxicity) (19). Several other trials are ongoing, these are summarized in *Table 1*. This trial summary also shows that comparison of trials is difficult regarding both the inclusion criteria as well as the endpoints. It is often even not clear which type of OMD is allowed (synchronous, induced, persistent, metachronous etc.).

As suggested by the trial results described above, the addition of ICI to LRT on all macroscopic tumor sites may boost the efficacy of LRT in OMD. However, several challenges in trial design and use of systemic therapy and LRT (radiotherapy as well as surgery) must be overcome before this approach can be broadly adopted in the daily clinical practice. These challenges are described below and are depicted in *Figure 1*.

Current challenges in the design of trials using immunotherapy in OMD NSCLC

Methodology

The rapid and remarkable advances in NSCLC disease management and treatment with immunotherapeutic agents have led to remarkable challenges in clinical trial methodology. So far, steps forward have been made, but still large gaps are present that need to be addressed (20).

As mentioned above there is no clear consensus on the definition of OMD itself, as well as on the types of OMD. The efforts made by international societies (14,15) have only been partially included in currently ongoing clinical trials. Clearly, this leads to a selection bias that hampers trial comparisons as well as the data interpretability. From *Table 1*, it is also clear that staging requirements [8 out of 16 summarized trials have no baseline imaging defined (clinicaltrial.gov data)] and the required molecular typing are not always specified.

A homogeneous study population is necessary for trials designed to be conclusive on the primary endpoint, whereas some heterogeneity is expected in trials designed to learn. These factors need to be assessed at the time the study objective and design are developed (21).

The main lesson for statisticians and methodologists is that setting a clear question is the first and key step to design a clinical trial. Often, trials fail to reach a conclusion because too many questions are asked in the same trial (21).

In OMD-immunotherapy trials, the key question is if adding LRT to immunotherapy is better than systemic treatment alone. Still, several questions need to be addressed: which is the best timing of LRT? What is the optimal duration of immunotherapy treatment? Is immunotherapy alone sufficient or does it need to be combined with chemotherapy or other drugs? If all these questions are put in the same trial, then clearly it will be difficult to have a strong and definitive conclusion. However, if few are chosen, then, with a proper study design, more knowledge could be generated (20).

Beyond the trial design question, researchers designing clinical trials in OMD also need to consider that OMD does not represent the majority of the diagnosed advanced NSCLCs.

Therefore, trials designed to conclude, typically phase III trials, must be properly shaped to reach the conclusion in an adequate timeframe. As it is expected that OS is prolonged

Table 1 Overview of ongoing immunotherapy in OMD NSCLC

NCT number/ name	Phase estimated enrollment	Type OMD included	Baseline staging required	Definition OMD	Treatment	Primary endpoint	Status
Synchronous							
NCT03965468, ETOP-CHESS	II; single arm; n=47	Synchronous	PET-CT; MRI brain; mediastinal staging recommended	Maximum of 3 metastatic sites, at least one has to be extra-cranial	Durvalumab-carboplatin-paclitaxel 4-6 cycles Q3W, SRT to all metastatic lesions start one week after start of chemo-ICI Restaging after 3 months, if no PD: LRT (surgery/ SRT) primary, followed by adjuvant durvalumab (maximum duration durvalumab from start: 1 year)	PFS at 12 months	Recruiting
Both meta- and synchronous or unspecified							
NCT04255836	II; single arm; n=35	Not specified	Not specified	≤5 mets, ≤3 metastatic organs	Durvalumab-carboplatin-paclitaxel or durvalumab- cisplatin-pemetrexed 4 cycles Q3W, followed by SRT, continuation of durvalumab for maximum of 2 years	PFS	Not yet recruiting
NCT03705403, IMMUNOSABR2	II; randomized, open label; 1st-3th line treatment eligible; n=126	All types	PET-CT or CT- chest/upper abdomen; MRI or CT brain	group: ≤5 mets, maximum of 2 brain mets; polymets group: 6-10 mets	Experimental arm: (SRT followed by L19-IL2 day 1, 3, 5 iv, Q3W, maximum of 6 cycles. ICI allowed to continue after L19-IL2 if this is SoC treatment for these patients Control arm: SoC according to local and national guidelines	PFS	Recruiting
NCT04486287	II; single arm; 2nd line; n=44	Not specified	Not specified	Not specified; "oligometastatic"	SRT before enrollment to all disease sites. No PD after SRT Sintilimab 200 mg iv Q3W until PD, or maximum of 12 months	ORR	Not yet recruiting
NCT03827577, OMEGA	Phase III; randomized, open label; n=195	Synchronous and metachronous	PET-CT; MRI brain	1-3 mets; single brain met not allowed	Enrollment and randomization either before start of systemic therapy or after 3 months of systemic therapy without PD. Experimental arm: LRT to all disease sites, SoC systemic therapy according to PD-L1, molecular status and local protocols Control arm: SoC systemic therapy according to PD-L1, molecular status and local protocols	OS	Recruiting

Table 1 (continued)

Table 1 (continued)

NCT number/ name	Phase estimated enrollment	Type OMD included	Baseline staging required	Definition OMD	Treatment	Primary endpoint	Status
NCT03557411	Phase II; single arm; n=42	“previously treated OMD”	Not specified	1–5 mets	SHR-1210 (anti-PD1), concurrent with hypofractionated radiotherapy Number of cycles and dose of SHR-1210 not specified	Grade ≥3 toxicity 6-month PFS	Recruiting
NCT04306926	Phase II; single arm; n=59	OMD with PD on first line chemo	Not specified	≤5 mets; primary tumor should be controlled	SRT 3 days before TQB2450 (anti-PD-L1) TQB2450 1200 mg iv Q3W, no maximum specified	PFS	Not yet recruiting
NCT03275597	Phase I; single arm; n=21	All types	Not specified	≤6 extracranial mets; brain mets may be treated before enrollment	SRT: 7 days (± 3 days) after SRT start durvalumab 1,500 mg Q4W, until PD, plus tremelimumab 75 mg Q4W maximum 4 cycles	Safety	Recruiting
NCT03275597	Phase Ib; single arm; n=21	All types	Not specified	≤6 extracranial mets; brain mets may be treated before enrollment	SBRT followed by durvalumab 1,500 mg Q4W until disease progression, and tremelimumab 75 mg Q4W for a maximum of 4 cycles	Safety	Recruiting
NCT03808662	Phase II; randomized, open label; n=160	Oligoprogressive breast cancer or NSCLC	Not specified	≤5 progressive lesions	Experimental arm: SRT to all oligoprogressive sites Comparator: SoC, including ICI if SoC	PFS	Recruiting
Trials allowing ICI and OMD, but not specifically focused on either OMD, or ICI in OMD							
NCT02417662, SARON	Phase III; randomized; open label; n=340	Synchronous, any systemic treatments, CT brain not only ICI	PET-CT; MRI / organs	≤5 mets, ≤3 metastatic organs	Experimental arm: SoC systemic therapy followed by radical radiotherapy (SRT or conventional) Control arm: SoC systemic therapy	OS	Recruiting
NCT03391869, LONESTAR	Phase III; randomized, open label; n=270	Consolidation, all types of metastatic NSCLC allowed, not only OMD	Not specified	Not specifically for OMD	Experimental A: nivolumab day 1, 15, 29 plus ipilimumab day 1 Q6W for maximum of 2 years Experimental B: nivolumab day 1, 15, 29 plus ipilimumab day 1 Q6W for 2 cycles, followed by consolidation LRT (surgery/radiotherapy) 14 days after completion of induction therapy. Adjuvant nivolumab/ipilimumab for a maximum of 2 years	OS	Recruiting

Table 1 (continued)

Table 1 (continued)

NCT number/ name	Phase estimated enrollment	Type OMD included	Baseline staging required	Definition OMD	Treatment	Primary endpoint	Status
NCT03774732, NIRVANA-LUNG	Phase III; randomized, open label; n=460	All types of metastatic NSCLC allowed, not only OMD	PET-CT; MRI/ CT brain	≤7 mets	Experimental arm: pembrolizumab-chemotherapy, till disease progression. Radiotherapy (preferably SRT for OMD) start C2D1 Control arm: pembrolizumab-chemotherapy, till disease progression Both arms: pembrolizumab Q3W or Q6W according to local standard	OS	Recruiting
NCT04405401, SUPPRESS- NSCLC	Phase II; randomized, open label; n=68	Oligoprogressive after any systemic treatment, not only ICI	Not specified	1–5 oligoprogressive lesions, maximum 3 organs; brain mets not counted	Experimental arm: SRT to oligoprogressive lesions and continue current systemic therapy Control arm: either switch to new line of systemic therapy, maintain current systemic therapy or BSC	PFS	Not yet recruiting
NCT02756793, STOP	Phase II; randomized; open label; n=54	Oligoprogressive after any systemic treatment, not only ICI	Not specified	1–5 oligoprogressive lesions, maximum 3 progressing mets in 1 organ	Experimental arm: SRT, discontinue systemic therapy (option to restart upon PD) Control arm: standard of care	PFS	Recruiting

No trials found specifically focussing on metachronous disease. OMD, oligometastatic disease; N, number; PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance imaging; met, metastasis; Q, every; W, week; SRT, stereotactic radiotherapy; chemo, chemotherapy; ICI, immune checkpoint inhibitor; PD, progressive disease; LRT, local radical therapy; PFS, progression free survival; SoC, standard of care; iv, intravenously; ORR, objective response rate; PD-(L)1, programmed death (ligand)1; C, cycle; D, day; OS, overall survival; BSC, best supportive care.

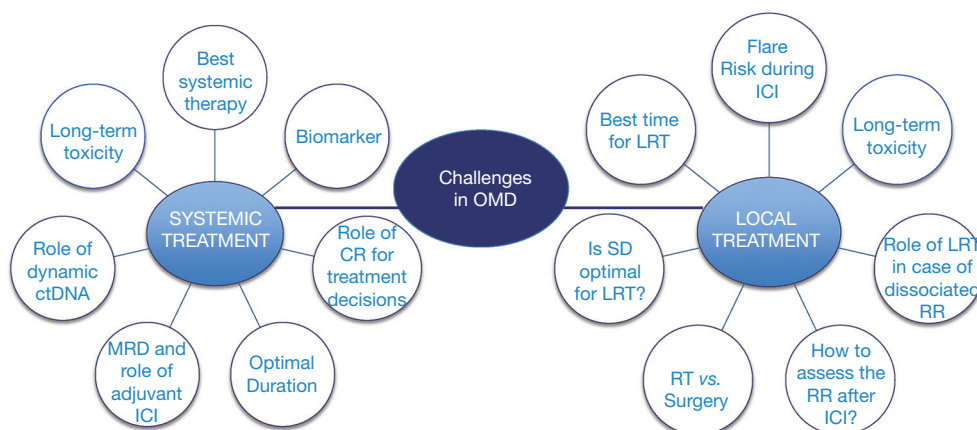


Figure 1 Challenges in the design of immunotherapy trials for OMD NSCLC. OMD, oligometastatic disease; CR, complete response; MRD, minimal residual disease; ICI, immune checkpoint inhibitor; ctDNA, circulating tumor DNA; LRT, local radical therapy; SD, stable disease; RR, response rate; RT, radiotherapy.

in this patient population, phase III trials are challenging. As a compromise, randomized phase II trials seem therefore to be the preferred design, both for exploratory and regulatory purposes (22). However, efforts should be made to not prematurely close these trials for accrual. As stated above, a major drawback of the two non-ICI randomized phase II trials in OMD NSCLC is that they were prematurely closed to accrual because of a major PFS improvement in the experimental arm, resulting in a small number of patients included per arm (4,9). Although in one trial a superior OS was found for the investigational arm (4), the low number of patients included limits the ability to conclude whether the addition of LRT is beneficial in OMD.

The problem of heterogeneity of the OMD definition could be addressed in basket trials. These are mostly made of single-arm phase II trials, usually on a homogeneous population. Basket trials could then be the first step to potentially divide different types of OMD and assess activity and preliminary efficacy of the evaluated treatment strategy(21). Another possibility in basket trials is to evaluate potential predictive biomarkers (e.g., molecular profiles) per type of OMD.

Once the objective is defined the primary endpoint should be chosen carefully. PFS has been mostly used as an endpoint since it provides an earlier assessment of efficacy, and it is not affected by subsequent treatments. Therefore, most immunotherapy trials in advanced disease use it as primary endpoint. However, the evaluation of PFS in patients treated with LRT can be challenging, especially in patients treated with radiotherapy. Pseudoprogression,

although rare, should also be considered. As atypical response patterns can occur with immunotherapy, attention should be paid to the criteria to define progression: RECIST criteria are still the standard criteria since iRECIST criteria, despite considering pseudoprogression, are not validated yet (23).

In principle, OS is the best endpoint for conclusive trials as it is not affected by bias and provides a long-term evaluation of the efficacy of the treatment strategy. OS data are so far lacking for OMD-ICI trials. A drawback of having OS as primary endpoint in ICI trials, is that survival improved significantly with ICI (even without the addition of LRT) compared with chemotherapy, resulting in a prolonged time to obtain the final data. Landmark analyses at 18 or 24 months of OS could and should be considered (21,22).

As an alternative, especially but not only for exploratory trials, the survival until progression to the following treatment (PFS-2) could be selected, although this is not a validated endpoint (21,22).

Response in terms of ORR, toxicity and quality of life (QOL) should be limited to secondary endpoints since these data are already mostly known, except maybe for long-term toxicity.

These endpoints could possibly also be assessed in real-world data registries, the best to provide large and real data. However, this type of datasets is usually affected by several biases related to for example selection for LRT, the lack of control, the heterogeneity of management and quality assurance that is difficult to be ensured (24).

Indeed, quality assurance is of a cornerstone relevance in combination trials since it needs to ensure and balance the best quality possible with feasibility in real practice (25). For example, lower volume surgical and radiation therapy departments are less experienced but if adequately trained could rapidly incorporate more complex rules whereas large volume departments might be challenged by longer procedures.

The biology of OMD has not yet been deeply studied and therefore clinical trials are precious tools for translational research based both on tumor and liquid biopsies.

The best systemic and locoregional partners in the treatment of OMD

The optimal management that should be used in an ICI trial enrolling NSCLC patients with OMD depends on both the type of OMD (synchronous, metachronous etc.) (15) as well as available biomarkers (e.g., PD-L1 status and molecular typing of the tumor). To date, for OMD, except for the oncogenic drivers, no biomarkers exist to select a certain systemic therapy. It is also not known whether the biomarkers (especially PD-L1) used in the general metastatic setting can also be applied to select the best systemic therapy for the subgroup of patients with OMD.

For example, a patient with oligoprogression on ICI probably does need other cancer directed therapy compared to a treatment naïve patient with synchronous OMD, as different resistance mechanisms will play a role (26,27). Moreover, a patient with an oncogenic driver will likely benefit less from ICI, as has been shown in the non-OMD metastatic setting (28). As most systemic treatment options exist in first line, these options will be discussed the most extensive here. Monitoring of patients and the optimal duration of systemic therapy is discussed below.

Systemic therapy for synchronous OMD

PD-(L)1 inhibitors have become standard of care in the first line treatment of patients with metastatic NSCLC, either as monotherapy or in combination with platinum-based chemotherapy regardless of the histologic subtype (11,12). Recently, in the USA, combinations of PD-L1 inhibition and cytotoxic T-lymphocyte associated protein 4 (CTLA4) inhibition have become available as new potential treatment strategies either as ICI-ICI combination only (nivolumab-ipilimumab for PD-L1 $\geq 1\%$), or in combination with 2 cycles of platinum-doublet chemotherapy (regardless

of PD-L1 expression) (12). Currently, only PD-L1 status [selection for pembrolizumab monotherapy], microsatellite instability (MSI, selection for pembrolizumab monotherapy (USA among others)] and tumor mutational burden [TMB, selection for pembrolizumab after progression on first line therapy (USA only)] are available to guide treatment decisions in the metastatic setting (11,12,29).

Local radical therapy

Importantly, most of the patients with OMD will eventually progress, often with widespread metastases. For NSCLC, no biomarkers exist that can distinguish true OMD from OMD that will progress to widespread metastatic disease. It could even be that some patients with true OMD only need LRT to all visible disease, without or only with a limited duration and intensity of systemic therapy. Other patients probably will need more intense and prolonged systemic therapy combined with LRT, and a subgroup probably will not benefit from LRT at all. The challenge both lies in identifying these groups as well as in selecting the optimal therapy for each group. Data obtained from colorectal liver metastases (47% synchronous) show that, within the subgroup of OMD, further subtyping can aid in distinguishing true OMD from OMD that later will transform to widespread metastases (30). The immune subtype in advanced colorectal cancer, with T-cell activation, IFN-inducible genes and increased cytotoxic T-cell infiltration was associated with a favorable survival, and even with recurrence most patients had only a localized recurrence, again amenable for LRT. The canonical subtype had a depletion of innate and adaptive immune signatures and (almost) no cytotoxic T-cell infiltration, the stromal subtype had increased epithelial-mesenchymal transition, reduced cytotoxic T-cells and pathway signatures of non-immune inflammation (30). It could be that the immune OMD subtype needs less immune stimulation or even no systemic therapy/immunotherapy compared with the others to obtain durable responses, but this has never been explored in NSCLC. In contrast, when extrapolating data from early-stage NSCLC, the combination of chemotherapy and ICI results in the highest rate of major pathological response (31-33). However, also in the neoadjuvant setting the optimal selection of patients for a specific systemic therapy is not well known.

Radiotherapy can act synergistically with ICI and is therefore an interesting LRT option to combine with immunotherapy (34-36). However, the optimal sequence of radiotherapy and immunotherapy as well as the optimal

radiotherapy dose, fractionation and irradiated volume are unclear (37,38).

Moderate doses per fraction (8–10 Gy) induced activation of anti-tumor T cells, an effect dependent on type I interferon induction within the tumor microenvironment, leading to increased cell death and possibly efficacy. For those reasons, hypofractionated RT at doses ranging from 5–20 Gy per fraction is believed to be better than conventionally fractionated RT of 2 Gy per fraction (39). Irradiating various lesions releases antigens and activates immune signals from different tumor microenvironments supporting the rationale to target several lesions instead of a single one (40). Depicting which irradiated lesions that may be more immunogenic is an area of active research. Given technological improvements, SRT of all macroscopic tumor sites could also be easier to perform and is potentially seen as an adequate aggressive approach in OMD (16). On the other hand, radiation can cause immunosuppression (36). It should also be evaluated whether lymph node irradiation is necessary, even in the context of involved lymph nodes, as lymph node irradiation reduces the immune response (41–43). Ionizing radiation could mobilize suppressive immune cells such as myeloid derived suppressor cells (MDSC), pro-tumorigenic M2 tumor associated macrophages (TAM) and FOXP3 regulatory T cells. The addition of different immunotherapy types to LRT may be of interest to boost the immune response. An example is L19-IL2: this randomized phase II IMMUNOSABR2 trial (NCT03705403) evaluates L19-IL2 combined with SRT in two groups of patients: oligometastatic (defined as a maximum of 5 metastatic sites) and limited metastatic (6–10 metastatic sites). There are no limitations on types of previous therapy if no more than two previous lines of therapy have been administered (44).

Both surgery and radiotherapy are mentioned as LRT option in clinical guidelines (11,12) and have been used in completed trials (4,5). The advantage of surgery is that the surgical specimen can be used for translational research. However, radiotherapy is non-invasive, and it could be that radiotherapy is a better LRT partner than surgery, as surgery induces a systemic inflammatory cytokine response. Of note, levels of circulating interleukin (IL)1, IL-6, IL-10 and tumor necrosis factor alfa are all increased after surgery, especially after non-minimally invasive surgery. Furthermore, video-assisted thoracoscopic surgery compared with thoracotomy resulted in less suppression of for example CD4 T-cells (45). Hopefully, the single arm phase II ETOP-CHESS trial (NCT03965468) translational

research part provides more data, as in this trial, induction chemo-ICI combined with SRT is given, followed by surgery of the primary tumor (if feasible, otherwise also SRT). Last, focus should also be on minimizing long-term toxicity of systemic therapies and LRT, as aim is to improve long-term survival in these patients. Importantly, approximately 30% of patients with metastatic NSCLC treated with PD-(L)1 inhibition experience late (>12 months after start of ICI) immune related toxicity (46). Furthermore, attention should be paid to the organ receiving LRT, as for example patients with brain metastases treated with ICI and SRT could develop symptomatic radiation necrosis as a late toxicity (47). Data for OMD NSCLC are not available yet.

Sequence of treatments

To complicate matters, the optimal sequence, (systemic followed by LRT, LRT followed by systemic, concurrent) and duration of therapy (e.g., short induction and/or extensive adjuvant) as well as the best LRT partner for systemic therapy are not well known. *In vivo*, the neo-adjuvant use of anti-CTLA4 followed by radiation resulted in superior survival compared with adjuvant use (48). Adjuvant anti-PD(L)1 could further improve outcomes (49), but the optimal sequence has not been evaluated in randomized trials.

Based on the results of the chemotherapy and TKI OMD trials, induction systemic therapy followed by LRT, compared with concurrent systemic therapy and LRT, seems to result in the most favorable survival (4,5,9). This is probably due to the selection of patients with tumors sensitive to systemic therapy. However, although cross-trial comparison is difficult, the phase II trial of Bauml *et al.*, using upfront LRT followed by pembrolizumab (19), resulted in similar PFS and OS data compared with the systemic therapy followed by LRT trials (4,9). Again, selection occurred as only those patients not progressing after LRT were included (19). (Please read another article by Shankar Siva, *et al.*, entitled “Local ablative therapies in oligometastatic NSCLC-upfront or outback?” of the series dedicated to this subject.)

Metachronous presentation/oligoprogression/oligorecurrence

In retrospective studies including patients treated with a TKI, the proportion of limited recurrences, in the form of oligoprogression, varies from 15% to 47% (50). This may be less (10–20%) in patients receiving ICI (51). Eradication

of oligoprogressive lesions by LRT could in theory allow the suppression of tumor clones resistant to systemic therapy. This could restore the overall sensitivity of the metastatic disease to the current systemic treatment which can thus be continued, alter the natural course of the disease, and therefore ideally prolong OS. Identifying the best treatment for patients initially responding to ICI but that are diagnosed with oligoprogression while on ICI treatment remains challenging. Oligoprogressive patients on ICI could theoretically continue their ICI after LRT (51,52). Trials in this setting are ongoing in oncogene-addicted NSCLC patients receiving TKI (e.g., HALT: NCT03256981) or in NSCLC patients receiving systemic therapy (e.g., SUPPRESS-NSCLC: NCT04405401) but data supporting this approach is limited in ICI treated patients. In a small retrospective study (n=26) including patients with acquired resistance to a PD-1 inhibitor, 88% had oligoprogressive disease (53). In the patients who received LRT [n=15 (58%); 11/15 continued the ICI], 2-year OS was 92%. It is however unknown if this strategy increases outcomes as compared with systemic treatment modifications and no LRT. Other similar encouraging results (one phase II trial, one retrospective series) were presented in an abstract form (54,55). Regarding systemic treatments, a patient with oligoprogression on ICI probably does need other cancer directed therapy compared to a treatment naïve patient with synchronous OMD as different resistance mechanisms will play a role (26,27). Moreover, a patient with an oncogenic driver such as epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) fusion will likely benefit less from ICI, as has been shown in the non-OMD metastatic setting (28). To complicate matters even further, it could be that biomarkers are different for the different OMD types (synchronous *vs.* metachronous). Several trials are ongoing evaluating the addition of LRT to systemic therapy in NSCLC patients with oligoprogressive disease (Table 1), but only one trial (NCT04485026) evaluates specifically the patient population oligoprogressive on ICI. Another trial (NCT03808662) also includes oligoprogressive patients with breast cancer, and patients are eligible if oligoprogressive on systemic therapy (not specific ICI).

Other challenges

OMD diagnosis and management requires a multidisciplinary evaluation.

For example, the site of metastasis is of key relevance

for multidisciplinary discussion. Liver metastases are for example often not treated with radical intent, but can however respond if treated with LRT. In a phase I trial comparing different fractionating doses on lung and liver metastasis with ipilimumab, systemic immune activation was high with high proportions of CD8+ cells and PD-1 activation after liver irradiation (56). This suggests that patients with liver metastases may be candidate to a multimodal LRT and ICI approach.

One of the challenges, particularly for patients on treatment with ICIs is to differentiate dissociated responses (growing lesion while others are in regression) from oligoprogression. Dissociated responses occurred in 7.5% of NSCLC patients treated with anti-PD1/PD-L1 agents (57). As for oligoprogression, no predictor of dissociated response has been identified. To optimize future treatment strategies, in such patients, tumor and blood samples must be performed to decipher the resistance mechanism before a LRT is applied.

ICI treatment can even result in a “tumor flare” phenomenon, which has been reported in patients with advanced cancer. A tumor flare is defined as an initial tumor expansion related to an immune-mediated inflammatory response by immune cells infiltrating the tumor (23), which can be confused with tumor progression. Importantly, misinterpretation could result in the avoidance of the use of potentially curative LRT. Of note, in patients with early-stage NSCLC treated with ICI, nodal immune flare has been reported in up to 11% of patients, changing the treatment plan in 9%. However, pathological evaluation of flared nodes revealed benign noncaseating granulomata (58), strongly supporting that invasive restaging procedures of sites of suspected progression on ICI can be required prior to definitive treatment decisions. The role of surgeons and radiation oncologists is particularly challenged by ICIs compared to other treatment strategies both in terms of efficacy but also in terms of safety. For example, from preliminary data, surgery can be technically more difficult after ICI treatment.

Optimal duration of treatment, monitoring of patients

As in metastasized disease in general, a matter of debate is how long patients with OMD should be treated with systemic therapy, how these patients should be monitored and whether there are markers that can be used to decide for a certain treatment duration.

In previously treated advanced NSCLC patients, there

is no evidence of a correlation between longer treatment duration and a longer survivorship. For example, 3-year OS is similar for patients treated with nivolumab (~18%) or pembrolizumab (~20%) independent of whether patients received treatment until progression or for a predefined maximum number of years (3,59-61). Furthermore, although the data is very limited, exploratory analyses have reported long-term survival even among patients with advanced NSCLC who did not complete the prespecified number of ICI cycles (3,62).

In contrast, the phase III CheckMate 153 trial included patients with advanced NSCLC, who completed nivolumab for 1 year, and assessed the efficacy of continuing nivolumab versus stopping the drug at 1 year of treatment. The trial reported that continuous treatment improved the PFS relative to those who discontinued the treatment at 1 year [24.7 vs. 9.4 months; HR 0.56 (95% CI: 0.37 to 0.84)] (63). However, this benefit was linked to the previous response rate to induction treatment, and the prolonged ICI strategy only benefitted patients who achieved a complete or partial response to induction nivolumab (HR, 0.46; 95% CI, 0.27 to 0.77), but not those patients with stable disease (HR, 1.01; 95% CI, 0.51 to 2.01). However, these data confirm that response on ICI is an important predictive marker of long term benefit with ICI. Although the CheckMate 153 study suggests that a prolonged treatment may have an impact on outcome, the study did not report potential clinical or biological parameters that were associated with clinical benefit, and that could aid in making treatment decisions.

Evidence for the possibility of a shorter treatment duration comes from non-metastatic disease. In the PACIFIC trial, including patients with locally advanced NSCLC treated with concurrent chemoradiation, consolidation therapy with durvalumab resulted in a survival benefit compared with placebo, despite the fact that only 43% of the patients enrolled were able to complete the planned 1-year of therapy (64,65). However, it is not known whether these patients would have had a longer survival if they could have completed the full year of consolidation therapy, and whether 1 year of adjuvant therapy is the right treatment duration at all. The optimal treatment duration with ICI becomes even more relevant for the patients with OMD obtaining a response, especially a complete response (CR) with ICI treatment. Furthermore, should these patients continue treatment with ICI and should/can these patients still receive LRT? In patients with metastatic melanoma, almost 20% stop treatment in the context of CR, as CR is the best marker

for long-term survival and minimal risk of relapse (66). Recently, an exploratory landmark analysis from the CheckMate 227 trial (nivolumab plus ipilimumab versus chemotherapy in advanced NSCLC patients) reported that 70% of responders [partial response (PR) or CR on ICI] at 6 months are alive at 3 years regardless of PD-L1 expression, supporting the correlation between response on ICI and OS in NSCLC (67). However, it remains unknown whether discontinuing treatment could be a potential strategy in this subset of NSCLC patients achieving a response on ICI as the treatment in the CheckMate 227 trial was until progression. Similarly, it remains unknown whether a CR in NSCLC has the same predictive value for stopping treatment as in melanoma, as CRs with systemic treatments in NSCLC are uncommon (~5%) (68). Furthermore, a CR by radiological RECIST criteria is different from pathology assessment, as RECIST can underestimate CR occurrence. For example, in the NADIM study, a 4.3% CR rate was found when using RECIST criteria after neoadjuvant chemotherapy plus nivolumab in early-stage NSCLC, which reached 59% by pathological evaluation (33). However, pathological assessment by re-biopsy is not always feasible in advanced NSCLC and the discrimination between CR and PR thus becomes a new challenge among patients with OMD treated with ICI. Although in early stage some studies have reported a correlation between the decrease in SUV in a fluodeoxyglucose positron emission tomography (FDG-PET) scan as a predictive for pathological response (69), in other trials such as the PRINCEPS trial, the metabolic response could not be correlated with pathological regression (70). Therefore, the correlation between metabolic and pathologic regression merits further prospective evaluation. To complicate matters, imaging alone cannot aid in deciding the duration of the systemic treatment in a patient who has also received LRT for OMD. Either the tumor is resected and not visible anymore, or radiation induced changes exist which are often difficult to distinguish from tumor residue or relapse.

New potential biomarkers, such as circulating tumor DNA (ctDNA) are also of interest for disease monitoring and to guide treatment decisions (71), specially among those OMD patients who receive local treatment strategies as ctDNA may detect minimal residual disease (MRD) following curative surgery, which correlates with risk of recurrence (72). Early data suggest that MRD diagnosed by detectable ctDNA after chemoradiation in stage III may help to decide which patients benefit the most of consolidation ICI (73). In a small series, patients with

undetectable ctDNA after chemoradiation had an excellent outcome independently of receiving consolidation ICI or not. However, patients with MRD post-chemoradiation who received consolidation ICI had significantly better survival compared with patients who did not receive consolidation treatment (73). If these data are confirmed, ctDNA may help to assess patients with a CR after local strategies and dynamic ctDNA evolution may help to personalize optimal treatment duration with ICI. CtDNA could also be of relevance for several situations where morphological imaging does not provide clear information about the response. Examples are sclerotic bone lesions, or fibrotic or nodular scars in liver or lungs that can replace previous metastases. Finally, dynamic changes in ctDNA upon receiving ICI are reported as useful tools for evaluating treatment efficacy (74). If validated prospectively in clinical trials, physicians would be able to select patients either for early discontinuation of ICI (no detectable MRD), or early treatment intensification (detectable MRD) (71). Data specific for patients with OMD treated with ICI and LRT do not exist to the best of our knowledge. Unfortunately, and in contrast with the studies mentioned above, in the phase II study of Gomez *et al.* (no ICI), only IL1 α was associated with improved outcomes. CtDNA metrics and baseline T-cell repertoire were not, although ctDNA decreased in patients treated with LRT, and T-cell changes were oligoclonal (75).

Finally, as stated before, cancer surgery may trigger a stress response leading to expansion of T-regs and M2 macrophages, and impaired NK-cell cytotoxicity, resulting in an overall immunosuppressive state (76), which can reduce the potential benefit of continuing ICI after surgery in OMD. This challenging question is even more relevant as adjuvant ICI is still under investigation in early-stage NSCLC in several ongoing clinical trials (e.g., PEARLS NCT02504372; BR31 NCT02273375; ANVIL NCT02595944; IMpower 010 NCT02486718; and CANOPY-A NCT03447769) (77). Therefore, due to lack of data about the survival benefit of adjuvant ICI one may also question the role of “adjuvant” treatment in OMD patients after induction systemic therapy followed by LRT strategies. Data, including the usefulness of pathological CR and MRD evaluation in selecting patients for adjuvant therapy are awaited and it is not clear whether these data can be extrapolated to OMD NSCLC. Therefore, the role of adjuvant treatment on OMD NSCLC patients who achieve a pathological CR after surgery without MRD on ctDNA remains an unresolved question (78).

Acquired resistance/translational research to be done in OMD trials

Recently, an immunotherapy resistance taskforce has defined primary resistance as those patients who have disease progression after receiving at least 6 weeks of exposure to ICI. The secondary resistance is defined as those patients who achieve a confirmed objective response (CR/PR) or prolonged stable disease (SD) of at least 6 months and then have disease progression in the setting of ongoing treatment (27). Different mechanisms for acquired resistance have been reported, such as clonal selection or clonal evolution of tumor cells with outgrowth of clones containing genetic changes imparting resistance to therapy, mutations in the interferon gamma response genes JAK1 and JAK2, and alterations in antigen presentation pathways, including downregulation and/or loss of beta-2-microglobulin (27).

Although definitions about primary and secondary resistance are relevant for future clinical trials, the genomic and immune heterogeneity in the tumor are not contemplated in these definitions, and these factors may impact the treatment responses. In advanced melanoma patients treated with ICI, heterogeneity in therapeutic responses via radiologic assessment was observed in the majority of patients as synchronous metastases only shared 60% of neoantigens (79). PD-L1 expression is the only predictive biomarker accepted for making treatment decisions in advanced NSCLC. However, for example in lung adenocarcinoma, the distribution of PD-L1 expression by anatomic sites varied, and the proportion of cases with high PD-L1 expression ($\geq 50\%$) was greater in lymph nodes than in bone metastases (30% *vs.* 16%). Indeed, the predictive value of PD-L1 expression on ICI response varied by organ, being predictive for lung and distant metastases, whereas it had decreased predictiveness for lymph node and bone metastases (80). Divergent spatial TMB variation occurs in one third of lung adenocarcinomas, and TMB was significantly lower in lymph node compared with other sites, leading to divergent TMB designation in 17% of the analyzed patients. Therefore, the tumor content and spatially divergent mutational profiles within a tumor are relevant factors influencing TMB estimation, revealing limitations of single-sample-based TMB estimations in a clinical context (81). Finally, several molecular alterations can be associated with differential PD-L1 expression. *KRAS* and *TP53* had the strongest correlations with high PDL1

expression, whereas *STK11*, *EGFR*, and *WNT* pathway alterations were associated with low PD-L1 expression abrogating the predictive value of PD-L1 for ICI (80). In patients with OMD NSCLC, anatomic site of metastatic disease and the co-occurrence of molecular alterations may have an influence on the radiological response upon ICI. These factors should be considered before excluding oligometastatic patients for local therapies in case of heterogeneous response on ICI. Importantly, future trials should incorporate extensive translational research part to investigate the challenges described above.

Conclusions

The addition of LRT to systemic therapy, especially ICI, results in encouraging survival data in early clinical trials. To compare clinical trials, a uniform definition of OMD types as well as OMD itself should be used. Current challenges lay in trial design, including type and duration of systemic therapy, the best timing and target type/number on which LRT should be applied, and follow-up. Trials should incorporate extensive translational research parts, so that patient selection for a certain type of therapy can be personalized and optimized.

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