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NSCLC is the most common primary origin of brain metastases (BMs). Approximately 10% to 20% of patients with NSCLC also present with BM at initial diagnosis, and BM will develop in around 40% of them during the course of their disease.[1] The incidence of BM is increasing on account of improved and more frequent brain imaging and also because of more effective systemic treatments resulting in longer overall survival (OS). In recent years major changes in the management of advanced NSCLC, including in patients with BM, have taken place. They include the introduction of immune checkpoint inhibitors (ICIs), which have significantly modified the therapeutic landscape. Improved OS rates have been achieved with newly available programmed death 1 (PD-1) (nivolumab and pembrolizumab) and PD-1 ligand 1 (PD-L1) (atezolizumab and durvalumab) inhibitors.[2–5] Regarding focal treatment for patients with BM, there is a practice change away from whole brain radiotherapy (WBRT).[6] Given the high local control rates and a low toxicity profile, stereotactic radiotherapy (SRT) delivery has increased in the past decades.[7]

There is a strong rationale to combine ICIs and radiotherapy (RT). Exposure to RT induces release of antigen from the tumor and danger signals that induce both local and distant anticancer immune response. However, the tumor microenvironment is typically immunosuppressive; therefore, additional modulation of the immune response using immunotherapy may be necessary to generate durable immune responses in patients treated with RT. Furthermore, ionizing radiation may increase expression of PD-L1 on the surface of tumor cells and revert acquired resistance to PD-1 blockade immunotherapy by limiting T-cell exhaustion.[8,9] Several preclinical studies have suggested synergistic effects of RT and PD-1/PD-L1 inhibitor.[8,9] Nevertheless, the optimal timing of ICIs and RT is still being debated. A preclinical study from Manchester showed that RT delivered concurrently with an PD-1 inhibitor resulted in improved antitumor effects compared with administration of the anti–PD-1 after RT.[10] However clinical evidence regarding the timing of RT and ICIs is scarce. In a subanalysis of a phase I study (Keynote-001), patients who received any RT before pembrolizumab had better outcomes than patients who did not receive RT (median OS 10.7 months versus 5.3 months, respectively, hazard ratio [HR] = 0.58, $p = 0.026$). However, no details on the delivery of cranial RT were provided.[11]

An important clinical concern in patients with BM is the possible increased risk of toxicity with the administration of an ICI before, during, or after brain irradiation. However, there is paucity of prospective data specifically related to the combination of ICIs and RT in patients with NSCLC that can help guide our clinical practice. In a nonrandomized phase II trial evaluating pembrolizumab in untreated or progressive BM, 18 patients with PD-L1–positive NSCLC with 46 BMs were included. Six patients had previously received WBRT and five had received SRT. Some patients received more than one RT course to the brain, and for RT it was not reported if any had both WBRT and SRT. Target lesions were defined as new lesions or those that progressed after RT (lesions before cranial RT were not included in the analysis). Hence, in patients with NSCLC who had previously received cranial RT, only three target lesions (all after WBRT, none after SRT) were analyzed. Six of 18 patients with NSCLC demonstrated a response to pembrolizumab

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within the brain, but none of the three lesions in patients progressing after initial WBRT responded to an ICI. No neurological grade 3 or higher toxicities were reported.[12] Generally, in pivotal ICI trials, patients with untreated BM have not been included, and patients with previously treated stable BM (6%–22.2% of patients) have not been analyzed.[2–5] However, specific safety results for patients with BM were reported in a pooled analysis of five trials with the PD-L1 inhibitor atezolizumab. Five percent (79 of 1452 patients) had previously treated, stable BM. The incidence of all adverse events (AEs) and serious AEs was similar between the patient groups with and without BM; however, neurological AEs were numerically higher in those with BM (all neurological AEs: 18% versus 9%; neurological serious AEs: 6% versus 3% [no grade 4–5]; and treatment-related grade 3 neurological AEs: 1% versus 3%).[13] The most common treatment-related AEs were headache and dizziness. No data were provided on the toxicity profile of ICIs according to the type of previous brain irradiation and the time interval between brain irradiation and ICIs. Despite the paucity of prospective data, a recent European survey on BM management in patients with NSCLC reported that many physicians are continuing anti–PD-1/PD-L1 therapy during SRT (129 of 462 [28%]) or WBRT (102 of 462 [22%]).[14]

In this issue of the *Journal of Thoracic Oncology*, Hubbeling et al. provide important insights into the combination of brain irradiation and ICIs in patients with NSCLC, with a specific focus on the sequencing and timing of cranial RT and the ICI. Brain RT–related AEs were retrospectively compared between 50 ICI-treated patients with NSCLC (31%) and 113 ICI-naive patients with NSCLC (69%). More than one RT course was allowed, and overall, 94 patients received SRT (70% of ICI-treated and 52% of ICI-naive patients), 28 patients received partial brain RT (16% of ICI-treated and 18% of ICI-naive patients, with most [66%] receiving it postoperatively), and 101 received WBRT (58% of ICI-treated and 64% of ICI-naive patients). ICI-treated patients received more RT courses (>1 course: 43% of ICI-negative versus 64% of ICI-treated patients [$p = 0.02$]), and more SRT sessions (a median of two SRT sessions in ICI-treated patients versus one in ICI-naive patients [$p = 0.003$]) than did ICI-naive patients. In terms of timing, RT was most frequently administered before (n = 31) or concurrently with (n = 20) the ICI. It should be noted that the definition of concurrent administration was delivery of RT 4 weeks or less before or after ICI. At a median follow-up duration from first RT treatment of 16 months (range 1–140 months), no significant difference was observed in the rate of all-grade RT-related AEs (including treatment-related imaging change) between ICI-treated and ICI-naive patients. For any particular cranial RT type, the incidence of grade 3 or higher AEs was 8% to 13% across treatment groups. The most frequently observed grade 3 or higher AEs in ICI-positive patients were headache (n = 2), anorexia (n = 2), and cognitive disturbance (n = 2). Importantly there were also no significant differences in rates of AEs based on the sequencing of RT and ICI.[15]

The authors should be congratulated for providing detailed data on a large cohort to date of patients with NSCLC treated with cranial RT and an ICI. Two other retrospective studies focusing on the outcome of patients with NSCLC with BM who received both RT and an anti–PD-1/PD-L1 inhibitor did not report severe neurological toxicity.[16,17] However, it should be emphasized that evaluating toxicity retrospectively is challenging, as it can be difficult to distinguish, for example, radiation necrosis (RN) or pseudoprogression from brain progression. A recently published retrospective series reported higher RN risks when combining ICI and SRT in patients with BM. Among 480 patients with BM (289 [61%] of 480 NSCLC) who had been treated with SRT, 115 (24%) received an anti-PD1 (nivolumab or pembrolizumab) or an anti–cytotoxic T-lymphocyte associated protein 4 (ipilimumab). Patients treated with ICI had a significantly higher rate of symptomatic RN after adjustment for tumor type (HR = 2.6, $p = 0.004$). Risk of neurotoxicity was highest for patients with melanoma treated with ipilimumab (HR = 4.7, $p = 0.01$).[18] Another point for discussion is whether assessing toxicity by using the Common Terminology Criteria for Adverse Events scale is the most clinically relevant way of assessing the safety of the combination of an ICI and cranial irradiation. Specific neurocognitive tests and quality of life data should ideally be reported, but this is rarely done outside the context of prospective trials. As highlighted by Hubbeling et al., small heterogeneous selected data sets of patients are not sufficient to draw firm conclusions on the safety of the combination of cranial irradiation with an ICI. In particular, it should be noted that in their study, only 20 patients received cranial irradiation concurrently with an ICI.[15]

Many questions regarding the combination of an ICI and brain irradiation remain unanswered and should ideally be tested in a prospective fashion. The impact of steroids, which are frequently prescribed for BM symptom management, in this group of patients is unknown. There are no prospective data on the influence of tumor histologic type or type of ICI used (PD-1/PD-L1 or cytotoxic T-lymphocyte associated protein 4 inhibition) on the risk of ICI-RT–induced neurotoxicity. Optimal timing and dose fractionation is currently under investigation in prospective trials enrolling patients with NSCLC with BM. Concurrent ICI and brain RT administration (starting during the first ICI cycle) is being

evaluated in three ongoing North American trials. The first (NCT02858869) is a phase I trial testing three different schemes of brain SRT (30 Gy in five fractions, 27 Gy in three fractions, or 21 Gy in a single fraction) with pembrolizumab in patients with NSCLC or melanoma. The second is a phase I/II (NCT02696993) nonrandomized trial evaluating nivolumab with or without ipilimumab with either SRT (at a dosage prescribed by the treating physician) or WBRT in patients with NSCLC. The third is a phase II trial from Canada (NCT02978404) enrolling patients with renal cell carcinoma or NSCLC who will receive radiosurgery (15–20 Gy in a single fraction) during the first cycle of nivolumab. Another important question is how best to assess response after SRT and an ICI and differentiate between progression, possible RN, or pseudoprogression. This question is being addressed in a phase II study evaluating magnetic resonance imaging with ferumoxytol as a contrast agent after combination treatment (NCT03325166). Finally, given that brain response rates were comparable to extracranial response rates in the study by Goldberg et al., whether ICI without RT is a valid option for patients with NSCLC with asymptomatic BM should be evaluated. Ultimately, ancillary studies are needed to validate companion predictive biomarkers at the cellular (tumor microenvironment composition), genomic (mutational/neoantigen load), and peripheral (blood and stools) levels. This will allow oncologists to better select patients who could benefit from promising but expensive therapeutic combinations.[8,9]

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