Editorial Commentary

The PEMBRO-RT phase II randomized trial and the evolution of therapy for metastatic non-small cell lung cancer: a historical perspective

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Provenance: This is an invited article commissioned by the Section Editor Dr. Song Xu (Department of Lung Cancer Surgery, Tianjin Medical University General Hospital; Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Lung Cancer Institute, Tianjin, China).

Comment on: Theelen WSME, Peulen HMU, Lalezari F, *et al.* Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non–Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical TrialPembrolizumab Alone vs After Stereotactic Body Radiotherapy in Patients With Advanced NSCLCPembrolizumab Alone vs After Stereotactic Body Radiotherapy in Patients With Advanced NSCLC. JAMA Oncol 2019. [Epub ahead of print].

Submitted Oct 29, 2019. Accepted for publication Nov 05, 2019.
doi: 10.21037/atm.2019.11.42
View this article at: http://dx.doi.org/10.21037/atm.2019.11.42

Lung cancer kills more individuals than any other malignancy. In the United States alone, it is estimated that 142,670 patients with die of this disease during 2019 (1). In 1995, Hellman and Weichselbaum proposed the existence of "*a clinically significant state of disease termed oligometastases that was in between purely localized and widely metastatic*." (2). This term was to be used to describe patients with "metastases to a single or a limited number of organs". They believed that these patients were amenable to potentially curative therapy based on the occasional long-term survivor following local therapy (resection or radiotherapy) of these lesions. They went further to state that effective therapy required the technology to identify all lesions treated with multiple modalities integrating newer methods of surgery or radiation therapy often in conjunction with systemic therapy. This was a very important manuscript that expressed a philosophy of care and a road to future progress in the care of cancer patients with advanced stage non-small cell lung cancer (NSCLC). Most importantly, it pointed out the opportunity for long term survival in patients with stage IV disease.

One of the newer radiotherapy technologies used to treat patients with early lung cancers and metastases is stereotactic body radiotherapy (SBRT) also known as stereotactic ablative body radiotherapy (SABR). In contrast to conventional RT, SBRT includes greater precision in patient immobilization, treatment planning, and image guidance. Radiotherapy is directed to radiographically apparent disease alone. Generally, it includes five treatments or less with high doses per fraction resulting in high biologically effective doses (BED). SBRT has been shown very effective for early lung cancers (3-5). Additionally, SBRT has been used for oligometastatic cancer with success (6). Palma *et al.* performed a phase II trial including 99 patients with various oligometastatic (≤5 metastases) tumors (including NSCLC) randomized to either conventional systemic therapy or the same plus SBRT to all known metastatic lesions. The median survival was 28 months with conventional systemic therapy compared to 41 months who received conventional therapy plus SBRT (P=0.090). This met the primary statistical endpoint of the trial design. The benefit of longer survival came at the cost of adverse events (grade ≥2) that occurred in 29% of those who received SBRT compared to 9% with conventional therapy (P=0.026). Additionally, treatment-related deaths occurred in 4.5% after SBRT compared with 0% with conventional therapy.

Gomez *et al.* performed a randomized phase II trial

for patients with oligometastatic NSCLC that compared local consolidative therapy to maintenance therapy or observation (7). This trial enrolled patients with oligometastatic NSCLC (≤3 metastases) having no progression after systemic therapy. Patients were randomly assigned to maintenance therapy/observation or to local therapy (resection or radiotherapy) to all active sites of disease. The radiotherapy was quite varied and included both SBRT and conventional techniques. Often combinations of these modalities were used in the local therapy patients. The study was closed after only 49 patients were randomly assigned because of a significant benefit observed in the local therapy arm. The data revealed a significant survival benefit to the local therapy arm (median, 41.2 months compared to 17.0 months without it) (P=0.017). They concluded that patients with oligometastatic NSCLC who did not progress after front-line systemic therapy had better outcomes with the addition of local therapy.

Additionally, immunotherapy has had a major impact on the treatment and outcome of patients with metastatic NSCLC. One recent example was the long-term results of the KEYNOTE-001 trial that included 101 treatment naïve patients and 449 previously treated patients with stage IV, programmed death ligand 1 (PD-L1) expressing NSCLC (8). All patients were treated with various doses of pembrolizumab on this large trial. The 5-year OS was 23% for treatment-naive patients and 16% for previously treated patients. This was comparable to the 16% 5-year survival reported with nivolumab alone in previously treated patients with advanced NSCLC (9). Additionally, these results were much better than those from historical controls with stage IV NSCLC and comparable to patients with stage III disease treated with chemo-radiotherapy (10,11).

In addition to the findings summarized above, previous studies have found greater tumor antigen release, antigen presentation, and T-cell infiltration following the irradiation of tumors (12-17). This information led Theelen *et al.* to perform the PEMBRO-RT trial, a randomized phase II study that included 92 patients with advanced stage NSCLC (18). The goal of this trial was to assess whether the addition of SBRT to a single tumor lesion prior to pembrolizumab enhances response in stage IV NSCLC patients. Ninety-two patients were randomly assigned to receive either pembrolizumab (200 mg/kg every 3 weeks) administered alone or after SBRT to a single tumor lesion until progression, unacceptable toxicity, or a maximum of 24 months. In the SBRT arm, the first pembrolizumab dose was given ≤7 days after completion of SBRT, consisting of 3 doses of 8 Gy delivered on alternate days to a single safe and convenient tumor site but not the biopsy site. The 3-month response rate was 18% in the control arm *vs.* 36% in the SBRT arm (P=0.07). A significant improvement (64% *vs.* 40%; P=0.04) was observed in the disease control rate at 12 weeks in the SBRT arm. The median survival was 7.6 *vs.* 15.9 months [hazard ratio (HR), 0.66; P=0.16]. Subgroup analyses found the greatest benefit from the addition of SBRT to pembrolizumab occurred in patients with PD-L1-negative tumors. The benefit of SBRT with respect to survival occurred only in the PD-L1 negative subgroup (HR, 0.48; P=0.046). No increase in toxicity was observed in the SBRT arm. SBRT administered prior to pembrolizumab was tolerated well. In spite of a doubling of response rate occurred, this outcome didn't meet the pre-specified criteria for meaningful clinical benefit. Positive results were largely influenced by the PD-L1-negative patients, who had significantly improved survival. The authors concluded that a larger trial will be needed to determine whether SBRT activates the microenvironment potentiating the outcome of immunotherapy for stage IV NSCLC patients. This study is important in clearly identifying a patient subgroup (those with PD-L1 negative tumors) who appear to benefit from the use of radiotherapy to alter the tumor microenvironment potentiating the effects of pembrolizumab.

The studies described above have shifted the 5-year survival of patients with stage IV NSCLC from nearly zero to the range of 16% to 23%. More research will be required to further improve these results. This will require motivated investigators and patients participating in well-designed trials. The result of this trial leads one to believe that the inflammatory response following SBRT can be used to increase PD-L1 making the tumor microenvironment more favorable (especially for initially PD-L1 negative tumors) for a response to PD-L1 inhibitors. I agree with the authors' recommendation that this hypothesis be studied in a larger randomized study.

Acknowledgments

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Schild SE. The PEMBRO-RT phase II randomized trial and the evolution of therapy for metastatic non-small cell lung cancer: a historical perspective. Ann Transl Med 2019;7(Suppl 8):S294. doi: 10.21037/atm.2019.11.42

