Editorial

Utility of stereotactic ablative radiotherapy/stereotactic body radiation therapy in the setting of oligometastatic non-small cell lung cancer

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Oligometastatic disease treatment has become one of the highlights of radiation treatment in recent years. Phase II study results from UT Southwestern published in September 2017 in *JAMA Oncol* showed a near three-fold benefit to progression-free survival favoring local ablative radiation therapy, leading to a stopping in accrual earlier than anticipated (1). The study directly compared stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT), with maintenance chemotherapy versus maintenance chemotherapy alone, both arms after receiving induction chemotherapy. The study population was limited to patients with non-small cell lung cancer (NSCLC), including up to five metastatic lesions with no targetable mutations and no disease progression after induction chemotherapy. Patients in the SABR with chemotherapy arm had a progression free survival (PFS) of 9.7 months versus their chemotherapy alone counterparts of 3.5 months (P=0.01) without added toxicity. Such a stark contrast invokes the results of the recent PACIFIC trial, where a similar three-fold difference in PFS was also reported receiving adjuvant durvalumab, a programmed death-ligand 1 (PD-L1) inhibitor, after completion of chemoradiation in unresectable stage IIIA and medically inoperable stage IIIB NSCLC patients (2). The results were so impressive that usage of adjuvant durvalumab has become adopted into most current version of the National Comprehensive Cancer Network (NCCN) guidelines, as standard of care for medically inoperable stage IIIA–C NSCLC patients receiving chemoradiation (3). This rapid paradigm shift encourages further exploration into different ways to improve patient outcomes, especially considering new findings in the setting of oligometastatic disease.

The phase II study results from UT Southwestern are not alone in showing the efficacy of aggressively treating oligometastatic NSCLC with radiation therapy. There have been several similar studies that showed a benefit with local consolidative therapies (4,5). PFS was associated with patients receiving consolidative therapy and having targetable mutations, and the multi-center phase II trial spearheaded by MD Anderson looking at up to three oligometastases was also closed early to accrual for a similar three-fold difference in PFS, 11.9 months in the consolidative arm and 3.9 months in the maintenance systemic therapy arm (P=0.0054) (5). We will discuss targetable mutations, i.e., epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), in more detail later in this article. Interestingly, the UT Southwestern group also had a phase II single arm trial investigating SABR as second line therapy in conjunction with erlotinib for patients who had progressed through platinum chemotherapy (6). Median PFS was reported as 14.7 months and median overall survival (OS) as 20.4 months which are relatively improved compared to historical results without second line SABR. Erlotinib was administered for 1 to 3 weeks prior to the delivery

of SABR and then subsequently as maintenance therapy. Approximately half of the patients (13 of 24) were tested for the presence of an EGFR mutation, of which none were positive. Due to the lack of positive EGFR mutants, the authors believe that the improved PFS and OS can be attributed to the utilization of SABR. Their examination of survival between the remaining half of untested patients versus tested patients did not show significance; however, the trial was not originally designed nor powered to adequately compare such a difference. Since multiple phase II studies show promising results for consolidative SABR in NSCLC patients, the natural course is to develop phase III trials to further delineate details to potentially chance clinical practices as standard of care.

An important step in this direction is the appropriate stratification of patients with oligometastatic disease to help with management decisions. This issue is best exemplified by the new definitions of metastatic disease as per the AJCC 8th edition for staging NSCLC (7). While the prior 7th edition only separated M staging as M1a and M1b, there will now be a quantified status of extrathoracic disease. The 8th edition demarcates between a single site of extrathoracic metastasis as M1b and multiple sites as M1c. In addition, M1b disease will be classified as stage IVA NSCLC, while M1c disease will be stage IVB. Of note, M1a is unchanged and is also grouped as stage IVA.

To further separate patient groups based on prognostic factors, we can also look to the timing of the development of metastases. A meta-analysis covering multiple institutions proposed a stratification system based on metachronous versus synchronous metastases and regional nodal status, with metachronous metastases without evidence of regional nodal disease as having the best survival with reported 5-year OS of 47.8% (8). Patients with advanced nodal disease and synchronous metastases, i.e., heaviest disease burden at presentation, were associated with worse outcomes, including reported 5-year OS of 13.8%. In addition, patients with a histology of adenocarcinoma also showed improved survival (P=0.036), which historically have had better prognoses than their squamous cell counterparts, but also likely attributable to targetable mutations that respond to systemic therapy.

The current landscape of targetable mutations for oligometastatic NSCLC is primarily dominated by EGFR as well as ALK. For EGFR mutants, the majority of patients are treated with TKI, e.g., erlotinib, although there is also some usage of monoclonal antibodies, e.g., cetuximab, of which multiple studies have shown PFS benefit, but not OS benefit (9). There was, however, a reported OS benefit to having sequential EGFR-tyrosine kinase inhibitors (TKI) and chemotherapy compared to either treatment alone (10). Patients with echinoderm microtubule associated-protein like 4 (EML4)-ALK fusion rearrangement are similarly treated with TKI, e.g., crizotinib or ceritinib, including as first-line therapy which has been shown to have a benefit to PFS (11). RTOG 1306 is an ongoing phase II trial currently investigating locally advanced unresectable NSCLC of non-squamous histology comparing induction targeted therapy, erlotinib for EGFR mutants and crizotinib for ALK positive patients, followed by conventional chemoradiation versus no targeted therapy. Although targeted therapy shows great promise, the biggest concern is acquired resistance at which point the therapy loses its efficacy (12). There is limited data in regards to concurrent SABR and targeted therapy, so it is difficult to say at this time if such a treatment course is appropriate for patients without risking undue toxicity from co-administration (13). EGFR inhibitors in particular have been reported to have possibility of pulmonary toxicity which may limit ability to be employed concurrently with radiation therapy (14).

As with most disease sites, immunotherapy is being rapidly adopted for investigation in NSCLC. Again, the results of the PACIFIC trial were groundbreaking for immunotherapy in the adjuvant setting. The KEYNOTE-01 trial showed a significant effect of extracranial radiation preceding administration of pembrolizumab, manifested as a two-fold increase in survival, from 5.3 to 10.7 months for patients with advanced NSCLC (15). Although the data captured whether patients had received SABR or not, no direct analysis was reported. The study did examine whether the radiation was delivered with definitive or palliative intent as well as site of treatment including extracranial and thoracic. The majority of patients, roughly 80%, had PD-L1 status reported with improved PFS previously correlated with higher expressions of PD-L1. Unfortunately, the study did not report the relative timing in the sequence of events from radiation to start of pembrolizumab.

Since there have been several phase II trials showing a clinical benefit to consolidative SBRT, the next natural step would be to incorporate the findings related to these trials to design a future phase III trial. Ideally, the trial would address key questions with the role of SABR in oligometastatic NSCLC. Firstly, the timing of SABR, i.e., upfront *vs.* consolidative. Most studies, both prospective and retrospective have been designed with the rationale that systemic therapy is initiated first to treat a systemically

disseminated disease. Could there potentially be a benefit, however, to providing SABR for patients either as concurrent treatment with systemic therapy or even preceding it? The idea of eliminating any gross disease is always attractive in the mind of radiation oncologists since we can visualize a target for our treatment fields. At the very least, the ablation of disease burden has been associated with improved PFS. There may be, however, an additional benefit to treating oligometastases with the combination of SABR with immunotherapy where local ablative therapy has the potential of priming the immune system via the abscopal effect. The general consensus appears to be approximately five sites of extrathoracic disease for consideration of aggressive treatment. Secondly, we will have to identify the optimal therapy to complement SABR, which will likely be driven by a combination of molecular markers and histology. Potential scenarios include targeted therapies followed by SABR for non-squamous cell NSCLC patients and SABR followed sequentially by immunotherapy. Lastly, and arguably most importantly, can the PFS changes we see in the earlier phase II studies transcend mere PFS benefit and actually manifest as OS benefit?

Upcoming data from current trials will help shape our suggestions for future trial design. The ongoing NRG LU-002 study will shed more light on the value of SABR in addition to maintenance systemic therapy after first-line systemic therapy. The study includes docetaxel, gemcitabine, and pemetrexed, but does not allow for targeted therapies or immunotherapy. The radiation is delivered to both the metastatic disease sites, up to three lesions, as well as the primary site. The phase III trial primary endpoint is OS, so the results should provide us with considerably more evidence to guide our treatment of oligometastases.

Due to the promising results from the PACIFIC trial, the role of Durvalumab with SABR is a logical adoption. There is in fact, a phase IB clinical trial conducted by the University of Wisconsin-Madison (NCT03275597) and sponsored by AstraZeneca, that is exploring this very question (16). The trial is investigating the usage of dual checkpoint inhibitors, namely Durvalumab (PD-L1) and Tremelimumab (CTLA-4), in conjunction with SABR. SABR is delivered upfront, followed by adjuvant Durvalumab until progression and tremelimumab for up to four cycles (four cycles administered every 4 weeks). The trial has not yet started accruing, and has a targeted completion date in 2021. To delve further into the role of SABR with immunotherapy will be to determine not only the relative timing of SABR to immunotherapy delivery, but also the fractionation scheme for SABR. Determining the acceptable spectrum of one, three, or five fractions for streamlined delivery in the context of immunotherapy for oligometastatic patients will be critical for maximizing the clinical benefits of combining radiation with a systemic therapy that ostensibly depends on radiation to become even more effective than before.

Looking ahead, the results from the UT Southwestern study have "primed" our appetites for the rewarding potential of local ablative therapy in patients with oligometastatic NSCLC. Our next steps will be to discover a way to optimize the effects of systemic therapy with the added value of SABR. Time and time again, a multi-modality approach has been shown to be more often than not the most effective method for treating advanced disease. We live and work in an exciting era of constant paradigm changes and are excited for the opportunity to grow together in our integrated approach to cancer care.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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