**Single-Fraction vs Multifraction Stereotactic Ablative Body Radiotherapy for Pulmonary Oligometastases (SAFRON II)**

The Trans Tasman Radiation Oncology Group 13.01 Phase 2 Randomized Clinical Trial

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**IMPORTANCE** Evidence is lacking from randomized clinical trials to guide the optimal approach for stereotactic ablative body radiotherapy (SABR) in patients with pulmonary oligometastases.

**OBJECTIVE** To assess whether single-fraction or multifraction SABR is more effective for the treatment of patients with pulmonary oligometastases.

**DESIGN, SETTING, AND PARTICIPANTS** This multicenter, unblinded, phase 2 randomized clinical trial of 90 patients across 13 centers in Australia and New Zealand enrolled patients with 1 to 3 lung oligometastases less than or equal to 5 cm from any nonhematologic malignant tumors located away from the central airways, Eastern Cooperative Oncology Group performance status 0 or 1, and all primary and extrathoracic disease controlled with local therapy. Enrollment was from January 1, 2015, to December 31, 2018, with a minimum patient follow-up of 2 years.

**INTERVENTIONS** Single fraction of 28 Gy (single-fraction arm) or 4 fractions of 12 Gy (multifraction arm) to each oligometastasis.

**MAIN OUTCOMES AND MEASURES** The main outcome was grade 3 or higher treatment-related adverse events (AEs) occurring within 1 year of SABR. Secondary outcomes were freedom from local failure, overall survival, disease-free survival, and patient-reported outcomes (MD Anderson Symptom Inventory–Lung Cancer and EuroQol 5-dimension visual analog scale).

**RESULTS** Ninety participants were randomized, of whom 87 were treated for 133 pulmonary oligometastases. The mean (SD) age was 66.6 [11.6] years; 58 (64%) were male. Median follow-up was 36.5 months (interquartile range, 24.8-43.9 months). The numbers of grade 3 or higher AEs related to treatment at 1 year were 2 (5%; 80% CI, 1%-13%) in the single-fraction arm and 1 (3%; 80% CI, 0%-10%) in the multifraction arm, with no significant difference observed between arms. One grade 5 AE occurred in the multifraction arm.

**CONCLUSIONS AND RELEVANCE** In this randomized clinical trial, neither arm demonstrated evidence of superior safety, efficacy, or symptom burden; however, single-fraction SABR is more efficient to deliver. Therefore, single-fraction SABR, as assessed by the most acceptable outcome profile from all end points, could be chosen to escalate to future studies.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT01965223


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Stereotactic ablative body radiotherapy (SABR) is a technique that allows precise delivery of high biological effective doses (BEDs) of radiation. In phase 2 randomized clinical trials of patients with oligometastatic disease, SABR has demonstrated an advantage in disease-free survival (DFS) and overall survival (OS) over standard systemic therapies alone.²,³ However, no high-level evidence or consensus is available on the optimal dose and fractionation schedule for SABR in oligometastatic disease.⁴ Single-fraction SABR is resource efficient to deliver and convenient from a patient perspective. However, this approach is not widely used because of theoretical concerns around safety and efficacy. In the context of the COVID-19 global pandemic, single-fraction schedules may be particularly attractive because they may reduce potential transmission risk compared with more protracted schedules.⁵,⁶ Two prior phase 2 randomized clinical trials in primary lung cancer have demonstrated that single 34-Gy⁵ or 30-Gy⁶ SABR in primary lung cancer had similar safety and efficacy to multifraction SABR. Pulmonary oligometastatic disease may pose additional complexity because of multiplicity in targets and heterogeneity in disease biology. The primary objective of the Trans Tasman Radiation Oncology Group (TROG) 13.01 Stereotactic Ablative Fractionated Radiotherapy Versus Radiosurgery for Oligometastatic Neoplasia to the Lung (SAFRON) II trial was to assess whether single-fraction SABR and multifraction SABR have an acceptable safety profile defined by the rate of high-grade treatment-related adverse events (AEs). Secondary objectives were to describe and compare patient-reported outcomes, clinical efficacy, cost-effectiveness, and immunogenicity of single-fraction SABR and multifraction SABR. The central hypothesis is that each treatment arm has an acceptable toxicity, efficacy, and quality-of-life profile, but single-fraction SABR is more efficient in delivery than multifraction SABR.

Methods

Study Design
This was a multicenter, open-label, phase 2 randomized clinical trial led by TROG in collaboration with the Australasian Lung Cancer Trials Group (ALTG). The study received ethics approval from the Peter MacCallum Cancer Centre. All participants provided written informed consent, and data were deidentified. Enrollment was from January 1, 2015, to December 31, 2018, with a minimum patient follow-up of 2 years (last patient visit in July 2020). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. The trial protocol, statistical analysis plan, and radiotherapy quality assurance manual can be found in Supplement 1.

Participants
The 90 eligible participants had 1 to 3 oligometastases to the lung from any nonhematologic malignant tumor located away from central structures (defined as 2 cm beyond the bifurcation of lobar bronchi and central airways). The maximum individual tumor size was 5 cm. Participants were 18 years or older and had an Eastern Cooperative Oncology Group performance status of 0 to 1, with all primary and extrathoracic disease controlled with local therapy. Key exclusion criteria were presence of germ cells and small cells, uncontrolled primary or extrathoracic disease, previous high-dose thoracic radiotherapy (defined as a BED¹₀ of 10 Gy [BED₁₀ₐ] of a total of 40 Gy), and receipt of systemic therapy within 3 weeks of treatment.

Interventions
Patients assigned to the single-fraction arm received 28 Gy, and patients assigned to the multifraction arm received a total dose of 48 Gy in 4 daily 12-Gy fractions of SABR delivered on nonconsecutive days during 2 weeks. These arms were theoretically biologically equivalent for tumor effects, with a BED₁₀ of 106 Gy in the single-fraction arm and 105 Gy in the multifraction arm. Treatment should have commenced within 4 weeks of randomization. Dose was prescribed so that the minimum dose (dose to 99% of the planning target volume [PTV]) should be 100% or more of the prescribed dose.6 Treatment techniques used are listed in eTable 1 in Supplement 2.

End Points
Safety was the primary end point, defined as grade 3 or higher treatment-related AEs occurring within 1 year of SABR. The AEs were classified according to the Common Terminology Criteria for Adverse Events, version 4.0. Secondary end points included patient-reported outcomes (symptom severity and interference using the MD Anderson Symptom Inventory–Lung Cancer [MDASI-LC]¹⁰ and health-related quality of life using the EuroQol 5-dimension visual analog scale [EQ-5D VAS]¹¹), freedom from local failure (FFLF) or freedom from distant failure, OS, DFS, and resource use. A modified DFS (mDFS) was also reported to account for salvage local therapies. For mDFS, progression that was salvaged with local treatment, such as SABR, thermal ablation, or surgery, was not counted as an event, and patients were followed up until progression that could not be salvaged with local therapy or death. All time-to-event end points were measured from the date of randomization to the date of the event of interest. Patients with disease progression were followed up for subsequent progression; therefore, distant failure was not a censoring event for FFLF, and local failure was not a censoring event for freedom from distant failure.

Key Points

**Question** Is single-fraction or multifraction stereotactic ablative body radiotherapy (SABR) optimal for the treatment of patients with 1 to 3 oligometastases to the lung?

**Findings** In this phase 2 randomized clinical trial that included 90 patients, the primary end point of severe toxicity was no different in the single-fraction arm (5%) than in the multifraction arm (3%). The secondary end points of efficacy, survival, and quality of life were also not different between the study arms.

**Meaning** Single-fraction SABR is of shorter duration and thus may be preferred from resource and patient perspectives.
Figure 1. CONSORT Diagram

Patients received 1 dose of 28 Gy (single-fraction arm) or 4 fractions of 12 Gy each (multifraction arm) to each oligometastasis.

Assessments
Patients were followed up at 4 weeks and at 3, 6, 9, 12, 16, 20, 24, 30, 36, 42, 48, 54, and 60 months after treatment, until the last patient reached the 24-month follow-up visit. At each visit a physical examination, medical history, Eastern Cooperative Oncology Group performance status, AEs, and patient-reported outcomes were recorded. From the 3-month visit onward, computed tomography surveillance and routine blood tests were performed at each visit. Pulmonary function tests were performed at 6 months and annually thereafter.

Sample Size
The sample size was calculated separately for each arm to assess the acceptable toxicity rate. We assumed the true rate of grade 3 or higher treatment-related AEs within 1 year was 5% ($P = .05$), and a rate of 17% or higher was unacceptable ($P = .17$). For a 1-sided exact test for proportion assuming a binomial distribution with an $\alpha$ of 10%, 80% power, and 15% dropout rate (originally assumed to be 8% but changed to 15% during trial recruitment based on observed dropout rate), the total sample size required to have 38 evaluable patients per arm was 45 patients per arm.

Immunologic Analysis
A subset of 18 patients treated at the Peter MacCallum Cancer Centre provided additional consent for translational analyses. Peripheral blood was collected at baseline (before SABR) and 24 hours and 1 month after SABR. Analysis of immune subsets, intracellular cytokine staining, and plasma cytokine assay was performed by cytometry by time of flights, fluorescence-activated cell sorting, and cytometric bead ar-ray assays as described in eMethods in Supplement 2 using previously described techniques.12

Statistical Analysis
A minimization algorithm with random element was used to balance the allocation to the treatment arms with respect to number of metastases (1, 2, or 3) and histologic subtype (colorectal or noncolorectal origin). The rate of grade 3 or higher treatment-related toxic effects at 1 year was estimated for each arm with an 80% 2-sided CI. The analysis of the primary end point was confined to participants who completed 1 year of follow-up. A sensitivity analysis was performed assessing the cumulative incidence of grade 3 or higher treatment-related AEs in all patients who commenced treatment. Death was considered a competing event, and patients whose last follow-up was before 1 year were censored at the date of last follow-up. The Cochran-Mantel-Haenszel test was used to compare the rate of grade 3 or higher treatment-related toxic effects between the arms, controlling for primary location (colorectal vs noncolorectal).

Median follow-up time was estimated using the reverse Kaplan-Meier method. Time-to-event outcomes were described using Kaplan-Meier methods with 95% CIs. Survival curves were compared between arms using the stratified log-rank test (stratified by number of metastases and histologic subtype), with hazard ratios (HRs) estimated using the stratified Cox proportional hazards model. Time to local failure was analyzed per patient and per lesion, clustered by patient. Local failure (per patient), regional failure, and distant failure were also described as cumulative incidence with death as a competing event.

The MDASI-LC and EQ-5D VAS were analyzed using general linear mixed models. The area under the curve (AUC) was compared between the arms using linear contrasts from the general linear mixed model. The AUC was calculated from baseline to 1 year; however, the model was built using all assessments. The linear mixed model included arm, time (as factor), and the interaction between arm and time as fixed effects with patients as a random effect. All statistical analyses were performed in R statistical software, version 3.6.1 (R Foundation for Statistical Computing).

Results
Ninety patients were randomized across 13 centers in Australia and New Zealand of whom 87 patients (mean [SD] age, 66.6 [1.6] years; 58 [64%] male) were treated for 133 pulmonary metastases. The CONSORT flowchart is shown in Figure 1. Two protocol violations occurred because of receipt of adjuvant systemic therapy after SABR (duration of <6 months); all other patients received SABR alone. Arms were well balanced; baseline characteristics are provided in the Table.

Radiotherapy Quality Assurance
All centers performed 2 benchmarking plans as part of trial accreditation: a single-lesion case and a dual-lesion case. Real-time radiotherapy quality assurance with preradiotherapy peer review for all cases was conducted. In total, 2837 variables were reviewed, with 2729 variables (96%) considered acceptable,
83 (3%) deemed to be minor protocol deviations, 12 (0.4%) considered to be major deviations, and 13 variables (0.5%) missing or not evaluable. Three cases were replanned after real-time peer review and proceeded to treatment.

Safety

A total of 38 patients in each arm were evaluable for the primary end point of grade 3 or higher AEs related to treatment within 1 year of SABR. The numbers of grade 3 or higher AEs related to treatment at 1 year were 2 (5%; 80% CI, 1%-13%) in the single-fraction arm and 1 (3%; 80% CI, 0%-10%) in the multifraction arm, with no significant difference observed between arms (P = .37). The findings of a sensitivity analysis that included all available follow-up to 1 year were almost identical (cumulative rate of grade ≥3 AEs of 5% [80% CI, 2%-10%] in the single-fraction arm and 2% [80% CI, 1%-7%] in the multifraction arm). One patient in the multifraction arm had grade 5 (death) treatment-related hypoxia and radiation pneumonitis within 3 months of SABR. This patient had 3 pulmonary metastases treated on a background of unrecognized interstitial lung disease. eFigure 1 in Supplement 2 describes the 30 most common AEs of any grade in all patients who commenced treatment. Radiation dermatitis was more common in the multifraction arm (n = 7) compared with the single-fraction arm (n = 0), with a difference of 16% (95% CI, 3%-30%); similarly, esophagitis was more common in the

### Table. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Single-fraction treatment (n = 45)</th>
<th>Multifraction treatment (n = 45)</th>
<th>Total (N = 90)</th>
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<tr>
<td>Age, mean (SD), y</td>
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<td>66.6 (12.0)</td>
<td>66.6 (11.6)</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (62)</td>
<td>30 (67)</td>
<td>58 (64)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (38)</td>
<td>15 (33)</td>
<td>32 (36)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index, median (range)</td>
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<td>5.0 (2.0-7.0)</td>
<td>5.0 (2.0-8.0)</td>
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<tr>
<td>Histopathologic subtype</td>
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<td></td>
<td></td>
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<tr>
<td>Adenocarcinoma</td>
<td>29 (64)</td>
<td>27 (60)</td>
<td>56 (62)</td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>3 (7)</td>
<td>7 (16)</td>
<td>10 (11)</td>
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<tr>
<td>Transitional cell carcinoma</td>
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<td>2 (2)</td>
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<tr>
<td>Other</td>
<td>13 (29)</td>
<td>9 (20)</td>
<td>22 (24)</td>
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<td>Location of primary tumor</td>
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<td></td>
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<td>2 (2)</td>
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<td>21 (47)</td>
<td>42 (47)</td>
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<td>3 (3)</td>
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<td>Kidney</td>
<td>6 (13)</td>
<td>4 (9)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Lung</td>
<td>4 (9)</td>
<td>6 (13)</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Melanoma</td>
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<td>5 (6)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1 (2)</td>
<td>3 (7)</td>
<td>4 (4)</td>
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<td>Other</td>
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<td>7 (16)</td>
<td>14 (16)</td>
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<tr>
<td>Lung lesion(s) considered medically inoperable</td>
<td>22 (50)</td>
<td>24 (56)</td>
<td>46 (53)</td>
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<td>No</td>
<td>22 (50)</td>
<td>19 (44)</td>
<td>41 (47)</td>
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<td>3</td>
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<td>31 (69)</td>
<td>58 (64)</td>
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<tr>
<td>1</td>
<td>18 (40)</td>
<td>14 (31)</td>
<td>32 (36)</td>
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<tr>
<td>No. of lung metastases present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>27 (60)</td>
<td>26 (58)</td>
<td>53 (59)</td>
</tr>
<tr>
<td>2</td>
<td>12 (27)</td>
<td>14 (31)</td>
<td>26 (29)</td>
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<tr>
<td>3</td>
<td>6 (13)</td>
<td>5 (11)</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Sum of target lesion diameters, mm</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
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<td>22.9 (17.1)</td>
<td>22.4 (14.4)</td>
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<tr>
<td>Median (range)</td>
<td>18.6 (7.8-56.0)</td>
<td>18.0 (5.0-95.0)</td>
<td>18.3 (5.0-95.0)</td>
</tr>
<tr>
<td>PET staged</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (29)</td>
<td>12 (27)</td>
<td>25 (28)</td>
</tr>
<tr>
<td>Yes</td>
<td>32 (71)</td>
<td>33 (73)</td>
<td>65 (72)</td>
</tr>
<tr>
<td>FEV1, mean (SD), L</td>
<td>2.6 (1.0)</td>
<td>2.5 (0.8)</td>
<td>2.6 (0.9)</td>
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<tr>
<td>FVC, mean (SD), L</td>
<td>3.8 (1.1)</td>
<td>3.5 (1.1)</td>
<td>3.6 (1.1)</td>
</tr>
<tr>
<td>FEV1/FVC actual, mean (SD), %</td>
<td>68.7 (13.7)</td>
<td>72.4 (8.2)</td>
<td>70.6 (11.3)</td>
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<tr>
<td>FEV1/FVC predicted, mean (SD), %</td>
<td>89.3 (15.3)</td>
<td>92.9 (11.8)</td>
<td>91.1 (13.6)</td>
</tr>
<tr>
<td>DLCO (uncorrected value), mean (SD), mL/min/mm Hg</td>
<td>20.1 (8.3)</td>
<td>20.1 (7.0)</td>
<td>20.1 (7.6)</td>
</tr>
</tbody>
</table>

Abbreviations: DLCO, monoxide diffusion capacity of the lung; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PET, positron emission tomography.

* Data are presented as number (percentage) of patients unless otherwise indicated.
multifraction arm (n = 8) compared with single-fraction arm (n = 1), with a difference of 16% (95% CI, 2%-31%).

**Efficacy**

The median follow-up was 36.5 months (interquartile range, 24.8-43.9 months). Efficacy outcomes (per-patient level) are depicted in Figure 2. No significant difference was found in the multifraction arm compared with the single-fraction arm for FFLF (HR, 0.5; 95% CI, 0.2-1.3; \( P = .13 \)). The median FFLF was not reached. The FFLF estimates in the multifraction arm were 95% (95% CI, 81%-99%) at 1 year and 80% (95% CI, 62%-90%) at 3 years. In the single-fraction arm, the FFLF estimates were 93% (95% CI, 79%-98%) at 1 year and 64% (95% CI, 46%-78%) at 3 years. A post hoc exploratory subgroup analysis found no evidence that the subgroup treatment effect was different between primary location (colorectal vs noncolorectal), tumor size greater than 3 cm or 3 cm or less, and radiotherapy technique in regard to FFLF (eFigure 2 in Supplement 2). Cumulative incidences of local, regional, and distant failure are given in eFigure 3 in Supplement 2.

No significant difference was found between the multifraction arm and the single-fraction arm for OS (HR, 1.5; 95% CI, 0.6-3.7; \( P = .44 \)). Median OS was not reached in either arm, with OS estimates in the multifraction arm of 93% (95% CI, 80%-98%) at 1 year and 67% (95% CI, 48%-81%) at 3 years and in single-fraction arm of 95% (95% CI, 83%-99%) at 1 year and 81% (95% CI, 64%-91%) at 3 years.

No significant difference was found between the multifraction arm and the single-fraction arm for DFS (HR, 1.0; 95% CI, 0.6-1.6; \( P > .99 \)) or mDFS (HR, 1.0; 95% CI, 0.6-1.7; \( P = .99 \)). The median DFSs were 13.2 months (95% CI, 10.1-17.2 months) for the multifraction arm and 14.3 months (95% CI, 9.7-21.4 months) for the single-fraction arm. Of 105 progression events, 47 (45%) were planned for further definitive local therapy. Of these, the local therapy modality was more radiotherapy in 73% and surgery in 27%. Twelve patients had local failure only, of whom 7 underwent salvage surgery. The median mDFS was 24.5 months (95% CI, 15.6- not estimable) in the multifraction arm and 24.4 months (95% CI, 16.4- not estimable) in the single-fraction arm. The median time to distant failure was 14.5 months (95% CI, 12.4-36.8 months) for the multifraction arm and 16.0 months (95% CI, 9.7- not estimable) for the single-fraction arm. Kaplan-Meier estimates per arm are given in eTable 2 in Supplement 2. At the end of follow-up, 44 patients (56% of patients with...
available data) received systemic therapy. In both the single-fraction and multifraction arms, 22 patients commenced systemic therapy, with a median time to initiation of systemic therapy of 21.4 months in the single-fraction arm and 22.9 months in the multifraction arm ($P = .72$).

**Patient-Reported Outcomes**

The MDASI-LC completion rate ranged from 90% to 100% for each visit within 1 year of SABR. Most patients had a baseline score of 0 to 1 in each of the MDASI-LC subscales (maximum possible score is 10, indicating the highest symptom burden or interference in daily life), and few scored higher than 5 (eFigure 4A in Supplement 2). The difference in the AUC ($\Delta$AUC) for each of the MDASI-LC subscales between the multifraction arm and single-fraction arm were not significantly different: core symptoms ($\Delta$AUC, $-0.12$; 95% CI, $-0.53$ to 0.28; $P = .55$), symptom interference ($\Delta$AUC, 0.02; 95% CI, $-0.58$ to 0.62; $P = .95$), symptom severity ($\Delta$AUC, 0.07; 95% CI, $-0.30$ to 0.44; $P = .71$), and total symptoms ($\Delta$AUC, $-0.07$; 95% CI, $-0.45$ to 0.31; $P = .70$). There was no clear evidence that the EQ-5D VAS differed between the multifraction arm and the single-fraction arm, with a $\Delta$AUC of 3.52 (95% CI, $-0.86$ to 7.90; $P = .12$). Change from baseline and difference between arms over time for each MDASI-LC and EQ-5D VAS subscale are depicted in eFigure 4B in Supplement 2.

**Translational Outcomes**

The systemic immune effects of SABR, regardless of regimen, were analyzed before and after treatment (eFigure 5A in Supplement 2). For most immune cell subsets, their frequency remained unchanged at 1 month after SABR relative to baseline (eFigure 6 in Supplement 2). However, the percentage of CD4+FoxP3+ T-regulatory (Treg) cells was significantly elevated from baseline to 1 month after SABR (Figure 3A). The percentage of cytotoxic T-lymphocyte-associated antigen (CTLA-4) (Figure 3B) and programmed cell death 1 (PD-1)
Figure 3C expressing CD4+ and/or CD4−CD8− T-cell subsets were also significantly increased in response to SABR. Plasma cytokine analysis found an increase in interferon (IFN) α2 from baseline or 24 hours to 1 month after treatment. Interleukin (IL) 1β decreased from baseline to 24 hours and increased to the 1-month time point. CCL2 levels increased from 24 hours to 1 month after treatment (eFigure 5B in Supplement 2). No change in IL-6, CXCL10, and sCD25 plasma levels were detected (eFigure 6 in Supplement 2). We then compared the change (from baseline to 1 month) in immune cell percentage between patients who received single-fraction vs multifraction regimens (eFigure 5C in Supplement 2). For single-fraction vs multifraction, significant differences were seen within CD4+ T-cell subsets and their T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT) expression and CD8+ T-cell subsets and their PD-1 or TIGIT expression (eFigure 5C in Supplement 2). Except for the CD4+ TEMRA (terminally differentiated effector memory cells), the single-fraction arm had a significantly higher percentage change than the multifraction arm (eFigure 5C in Supplement 2). The immune cell composition and plasma cytokine levels were compared between patients who were classified as disease free (responders) or who had progressed at the landmark date of the primary end point analysis (1 year after SABR). Relative to baseline, responders had a decreased percentage of PD-1+ and TIGIT+ Treg cells and a lower percentage of CTLA4+CD4+ effector memory T cells (Figure 4A) compared with those with disease progression. In addition, responders had an increase in the percentage of cluster abundance of circulating IFN-γCD4+ T cells, TNF+ natural killer cells, TNF+CD8+, and TNF+PD1+CD8+ T cells, suggesting increased effector function in those cells (Figures 4B).

Nine patients responded to SABR and 9 patients had disease progression within 1 year of follow-up. The baseline to 1-month median change in cluster abundance for patients who responded or progressed are shown. The bar shows the median change in cluster abundance during 1 month. The P values were determined by the Mann-Whitney U test. CTLA-4 indicates cytotoxic T lymphocyte–associated antigen; EM, effector memory; NK, natural killer; IFN, interferon; PD-1, programmed cell death 1; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain; TNF, tumor necrosis factor; and Treg, T regulatory.
Discussion

The TROG 13.01/ALTG 13.001 SAFRON II study is the first fully recruited randomized clinical trial to investigate the treatment of pulmonary oligometastases. This study has important implications for treatment selection in patients with pulmonary oligometastases, particularly in resource-constrained environments, such as countries strongly impacted by the COVID-19 global pandemic. We observed a rate of grade 3 or higher treatment-related AEs of 5% or less in both arms. No significant differences were found between the multifraction arm and the single-fraction arm for FFLF, OS, DFS, or mDFS. The only other randomized clinical trial available, to our knowledge, Pulmonary Metastasectomy Versus Continued Active Monitoring in Colorectal Cancer (PulMiCC),13 was a trial comparing surgical metastasectomy with observation in patients with pulmonary metastases from colorectal cancer. PulMiCC was terminated early because of poor accrual (N = 65). Control rates and progression rates were not reported in PulMiCC; however, the 4-year OS for the control group was 40% (95% CI, 26%-63%) and 43% (95% CI, 27%-66%) for those assigned to metastasectomy.13 This finding is comparable to our findings. The PulMiCC authors observed an initial and expected decrease in quality of life at 3 months after surgery, without any longer-term detriment to quality-of-life outcomes. In the SAFRON II trial, there was no detriment to quality of life observed throughout the assessment period (eFigure 3 in Supplement 2). The outcomes observed in this trial are consistent with the 3 prior single-arm phase 2 trials of metastasectomy14 and SABR15,16 for pulmonary oligometastases.

Fractionation of SABR has theoretical safety advantages. Despite the single-fraction arm in SAFRON II having a theoretically higher dose for late tissue effects (BEDc of 289 Gy vs BED2, 240 Gy for multifraction SABR), no excess high-grade toxic effects were observed, with any grade radiation dermatitis and esophagitis being lower in the single-fraction arm. This finding was similar to the findings of the 2 trials5,6 of single-fraction vs multifraction SABR for early-stage lung cancer. The dose prescription method in these studies5,6 resulted in an estimated peripheral dose to PTV being similar to that of SAFRON II (single dose of 28 Gy or 4 fractions of 12 Gy covering 99% of the PTV), perhaps a little lower in the Roswell Park trial26 (which did not use heterogeneity correction for a single dose of 30 Gy or 3 fractions of 20 Gy, covering 95% of the PTV), and perhaps a little higher in NRG/Radiation Therapy Oncology Group 0915 (single fraction of 34 Gy or 4 fractions of 12 Gy, covering 95% of the PTV). As expected, the lung cancer rates for SABR for primary lung cancer were higher, with both studies5,6 reporting local control rates at 2 years of at least 95% or higher in each arm. In this study, the 2-year FFLF was 73% for the single-fraction arm and 83% for the multifraction arm. A post hoc exploratory analysis suggested local failure events in the single-fraction arm were driven by patients with colorectal disease (eFigure 7 in Supplement 2). Although this study and the other 2 studies5,6 indicate that single-fraction SABR is a desirable option for lung tumors, a possible signal of higher propensity for local failure in patients with colorectal metastases receiving single-fraction treatment is hypothesis generating and could be investigated further in future trials.

In this study, we found that SABR can induce changes in the composition of circulating immune cells and potentially alter their functional status, as determined by changes in the abundance of immune checkpoint (PD-1, TIGIT, and CTLA-4)–expressing cells and plasma cytokine levels. The differential effects of multifraction vs single-fraction SABR on immune cell activity were not extensive, consistent with the clinical outcomes. Consistent with a previous study that investigated SABR and anti–CTLA-4 blockade,17 disease progression was associated with an increased abundance of circulating Treg cells expressing immune checkpoint molecules indicative of heightened regulatory function. In contrast, patients who were free of disease at 1 year after SABR also had T cells with increased cytokine secretion (TNF and IFN-γ) and PD-1 expression, possibly inclusive of tumor-responsive T cells. Taken together, these data suggest that SABR to pulmonary oligometastases drives systemic immune activation, and we postulate that this could be augmented with the addition of immune checkpoint blockade. The observed potential prognostic biomarker of response require further external validation.

Limitations

This study has several limitations. Interstitial lung disease was not an exclusion criterion at conception of the trial, and a single treatment-related mortality event in the multifraction arm could possibly have been avoided. Evaluation of safety of SABR in interstitial lung disease is currently being explored in the Assessment of Precision Irradiation in Early NSCLC and Interstitial Lung Disease trial.18 The SAFRON II trial was not histologic subtype specific and did not control for subsequent systemic therapy at relapse; therefore, despite the treatment arms being well balanced, a separation of OS curves late after SABR potentially favoring the single-fraction arm should be interpreted with caution. The sample size was limited for the correlative analyses, and findings should be validated in a larger cohort. To improve outcomes in this patient cohort, our findings suggest that both single-fraction and multifraction SABR could be candidates for exploration of radiotherapy and immunotherapy combinations. Several randomized clinical trials are currently investigating consolidation SABR after systemic therapies inclusive of immunotherapy.19-21

Conclusions

In this phase 2 trial of SABR in patients with pulmonary oligometastases, both the single-fraction and multifraction treatment arms had acceptable safety profiles and good efficacy outcomes. Neither of the arms had evidence of superior safety, efficacy, symptom burden, or immunogenicity compared with the other arm. Because the single-fraction treatment is of shorter duration and hence more efficient, this arm is a good candidate for escalation to future randomized clinical trials.
ARTICLE INFORMATION

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REFERENCES

Single- vs Multifraction Stereotactic Body Radiotherapy for Pulmonary Oligometastases

Invited Commentary

Managing Pulmonary Oligometastatic Disease With Stereotactic Body Radiation Therapy—Moving the Field Forward 1 Organ at a Time

Arya Amini, MD

The landscape for radiation oncologists treating patients with metastatic disease has drastically changed during the past decade. With multiple seminal works in the arena of oligometastatic disease, the combination of stereotactic body radiation therapy (SBRT)/stereotactic ablative radiation therapy (SABR) became an important treatment modality for patients with metastatic disease. We learned that we can improve progression-free and overall survival and potentially begin flattening Kaplan-Meier curves in metastatic disease through the combination of SBRT/SABR and promising systemic therapies. 1-3 In this issue of JAMA Oncology, Siva and colleagues4 report findings from the Trans Tasman Radiation Oncology Group (TROG) 13.01, a phase 2 randomized clinical trial that compared single-fraction vs multifraction SABR in patients with pulmonary metastases (Stereotactic Ablative Fractionated Radiotherapy Versus Radiosurgery for Oligometastatic Neoplasia to the Lung [SARON]) II). The study included 90 patients with a total of 133 pulmonary oligometastases (defined as ≤3 cm) with a maximum size of 5 cm and a noncentral location who were randomized to a single-fraction treatment of 28 Gy or a multifraction treatment of 48 Gy delivered at 12 Gy per fraction, with biologic effective doses at 10 Gy (BED10) of 106 Gy in the single-fraction arm and 105 Gy in the multifraction arm. The primary end point was grade 3 or higher treatment-related adverse events within 1 year of treatment completion. The study found no difference in grade 3 or higher toxic effects, which were overall relatively low at 3% for the multifraction arm and 5% for the single-fraction arm. One grade 5 toxic effect occurred in a patient who had underlying, unrecognized interstitial lung disease and had 3 lesions treated with multifraction SABR and unfortunately developing pneumonitis 3 months after treatment. The investigators additionally found no difference in freedom from local failure, disease-free survival, and overall survival between the 2 fractionation schemes. An additional novelty of this work is their analysis on the immunogenic effects of SABR in which they demonstrated expected changes in T-regulatory cells, cytotoxic T-lymphocyte–associated antigen, and programmed cell death 1 expression, which all had increased expression levels after SABR; differences of expression between the single-fraction and multifraction arms appeared to be similar. Finally, patient-reported outcomes appeared similar between the 2 groups. The authors concluded that both single-fraction and multifraction treatments are safe and effective, with the single-fraction treatment potentially being more convenient for patients.

The TROG 13.01 SAFFON II study4 answers the fundamental question that up to this point was not directly answered, whether SABR in 1 to 3 fractions can safely be delivered to multiple pulmonary metastases. The fundamental principle in oligometastatic disease based on the number of landmark studies published has been to use ablative doses of radiation to treat patients’ limited sites of disease. The Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) study5 challenged the dogma by expanding the definition of oligometastatic to 5 sites (albeit their study consisted of mostly ≤3 sites), opening the door to the idea that SABR can prolong survival in patients with metastatic disease and that benefit may apply to patients with more than 1 to 3 sites. We learned, however, from SABR-COMET that SBR can come at a cost of toxic effects because 3 patients in their study experienced grade 5 toxic effects. As we enter the new era of radiation oncology in oligometastatic and potentially polymetastatic disease, with SABR-COMET10,5 among others, trying to push the boundary of how we manage metastatic disease with local ablative therapy, groundbreaking work, such as TROG 13.01 SAFFON II,6 is critical in defining the safety and efficacy of treating multiple lesions in a single organ. TROG 13.01 SAFFON II not only demonstrated that treating up to 3 lung nodules is safe but, more importantly, that ablative doses...