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CLINICAL INVESTIGATION

Combination of SABR With Anti-PD-1 in Oligoprogressive Non-Small Cell Lung Cancer and Melanoma: Results of a Prospective Multicenter Observational Study

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Purpose: The percentage of patients with metastatic non-small cell lung cancer (NSCLC) and melanoma who benefit from anti–programmed cell death protein 1 (anti-PD-1) is low owing to resistance mechanisms. SABR has a role in oligoprogressive disease and can improve responses to anti-PD-1. This multicenter prospective observational study aimed to determine whether concomitant anti-PD-1 and SABR to oligoprogressive sites enhance tumor response in metastatic NSCLC and melanoma.
Methods and Materials: Patients with metastatic NSCLC or melanoma in progression to anti-PD-1 but continuing the same line owing to clinical benefit were referred for palliative SABR. All patients received concomitant pembrolizumab or nivolumab

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and SABR to 1 to 5 lesions, maintaining anti-PD-1 until further progression, unacceptable toxicity, or medical/patient decision. Objective response rate—complete responses and partial responses—was evaluated during all follow-up according to Response Evaluation Criteria in Solid Tumors 1.1. The abscopal response was evaluated 8 weeks after SABR as a ≥30% reduction in 1 to 2 predefined nonirradiated lesions.

Results: Of the 61 patients enrolled, 50 could be analyzed. With a median follow-up of 32.8 months, objective response rate was 42% (30% complete responses and 12% partial responses). Median progression-free survival was 14.2 months (95% confidence interval, 6.9-29 months). Median overall survival since SABR was 37.4 months (95% confidence interval, 22.9 months-not reached). Abscopal response was 65%, evaluated in 40 patients who fulfilled the criteria.

Conclusions: Combined anti-PD-1 and SABR in oligoprogressive metastatic NSCLC or melanoma can achieve high rates of response and extend the clinical benefit of immunotherapy by delaying further progression and a new systemic therapy. This approach should be assessed in larger randomized trials.

Introduction

Immunotherapy has significantly changed the prognosis of metastatic patients, especially in non-small cell lung cancer (NSCLC) and melanoma. Immune checkpoint inhibitors (ICI), particularly those targeting programmed cell death protein 1 (anti-PD-1) and its ligand (anti-PD-L1) have improved both progression-free survival (PFS) and overall survival (OS) in a subset of patients.[1-4] Unfortunately, the percentage that actually benefits from ICI remains low owing to several resistance mechanisms.[5-7] This issue has led to the investigation of different treatment combinations to overcome these resistances, such as dual ICI—for example, anti-PD-1 and anti−cytotoxic T-lymphocyte antigen 4—or ICI with chemotherapy (CT). Compared with ICI monotherapy, ICI + CT has improved the objective response rate (ORR), but at the expense of higher toxicity rates.[8,9] Moreover, elderly or unfit patients are usually unsuitable for these combinations and, therefore, exclusive treatment with ICI is their only option.[10,11]

In this context, the association of SABR with ICI (I-SABR) is becoming a very active field of research owing to the particular synergies of these 2 therapies.[12,13] SABR can improve responses by inducing a robust and effective immunogenic cell death—traditionally known as "abscopal response" (AR)[14]—with no increase in toxicity, therefore allowing for the safe continuation of ICI. This AR can induce distant responses in tumor sites that have received no local radiation owing to this immunogenic effect.[12,14,15] This combination has reported a clinical benefit in phase 2 randomized studies.[12,13] Furthermore, it has awakened an interest in oligoprogressive disease (OPD) as a tool for maintaining responses without the need for introducing new systemic lines.[16] Evidence for this scenario is already available in patients with CT or targeted therapies[17−19] but is still lacking for ICI. As previously seen with CT and targeted therapies, SABR could potentially help to delay the discontinuation of ICI, with a possible effect in PFS and OS.

We present the results of a prospective study that assessed the benefit of I-SABR in patients with metastatic NSCLC and melanoma who have experienced oligoprogression to ICI monotherapy. This study evaluates the effect of this combination in terms of ORR and correlates this benefit with PFS, OS, and time to next treatment (TTNT), while also attempting to clinically quantify the AR.

Methods and Materials

Participants

We conducted a prospective observational study at 4 hospitals in Spain from September 1, 2017, to August 1, 2020. The cohort consisted of patients ≥ 18 years of age with NSCLC or melanoma who were in confirmed progression (up to 5 lesions) to anti-PD-1 (pembrolizumab or nivolumab) but maintained the same ICI owing to clinical benefit,[20] regardless of the number of previous systemic lines or the presence of refractory/relapsed disease. These patients were referred to our department for palliative SABR. Exclusion criteria included: (1) Eastern Cooperative Oncology Group performance status of 3 to 4; (2) suspected pseudoprogression or hyperprogression to ICI; (3) severe autoimmune diseases; or (4) previous radiation therapy (RT) that might interfere with the study treatment. Patients who were recruited for the study but developed further progression and had the anti-PD-1 stopped before SABR were excluded from analysis. The study protocol was approved by the ethics committee of Dr Negrín University Hospital of Gran Canaria and followed the ethical standards of the Declaration of Helsinki.[21] All patients provided written informed consent before enrollment.

Study protocol

Before SABR, we selected 1 to 5 measurable lesions to treat and, if applicable, up to 2 nontarget lesions outside of the planned radiation field. All target lesions were in progression. The preferred order for choosing targets was: (1) all symptomatic lesions (up to 5); (2) visceral/nodal lesions; and (3) bone lesions.[22] Criteria for nontarget lesions included measurable visceral/nodal lesions.

SABR was administered with palliative and immunostimulatory intent by volumetric arc radiation therapy in 5 nonconsecutive fractions (fx) of 7 Gy, separated by at least

36 hours. In the case of brain metastases, reirradiation, or dose-limiting constraints, an alternative dose of 24 Gy in 3 fx was delivered. These 2 regimes were established based on the available evidence at the time of the design.[12,23,24] Tumor volumes larger than 65 cc received partial irradiation. Pembrolizumab and nivolumab were administered intravenously (at doses of 200 mg/kg every 3 weeks and 240 mg/kg every 2 weeks, respectively), concurrently with SABR and until further progression, unacceptable toxicity, or medical decision. Rechallenge with further courses of SABR after new oligoprogression was allowed if the patient maintained clinical benefit. If this rechallenge was successful and the patient was able to continue receiving the same anti-PD-1, we considered this an extension of clinical benefit and, therefore, we did not count it as a disease progression. Patients could receive a maximum of 3 SABR courses following this strategy. Response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 according to recommendations,[25] with computed tomography scan 2 months after SABR and subsequently every 3 months. Treatment response before and after SABR was evaluated by 2 independent radiologists who were masked for the sites selected for measuring AR. Confounding factors were assessed in the statistical analysis as described in the following corresponding section. Study size was determined by nonprobabilistic sampling, recruiting those patients referred to our department for palliative SABR who fulfilled the inclusion criteria. A fixed study size or relevant response rate could not be determined, as there were no previously published data on this particular clinical setting.

Study endpoints

The primary endpoint was the ORR, complete responses (CR) and partial responses (PR), which was evaluated in all sites of disease until the end of follow-up. Secondary endpoints included the AR, measured 2 months after SABR as a ≥30% reduction in the previously selected, nonirradiated lesions,[24] PFS, OS, local control (LC) (CR, PR, and stable disease), TTNT, and toxicity (according to common toxicity criteria or Common Terminology Criteria for Adverse Events version 4.0).

Assessment of variables

Certain quantitative variables were grouped to form categorical variables, but both continuous and grouped analyses were performed: (1) specific tumor histology was grouped into 3 categories (lung squamous, lung nonsquamous, and melanoma) to detect possible differences in the response to I-SABR; (2) the number of metastases was categorized as oligometastatic (up to 5 lesions) or polymetastatic (more than 5) according to the definition of oligometastatic disease by European Society for Radiotherapy and Oncology −American Society for Radiation Oncology guidelines[26]; (3) PD-L1 expression was grouped as ≥50%, 1% to 49%, and <1%, in accordance with the tumor proportion score; (4) to assess if previous RT or systemic treatments affected outcomes, these variables were categorized as yes/no and 1, 2, or ≥3, respectively; and (5) the number of irradiated sites was grouped as 1, 2, or ≥3 to assess if multisite irradiation had an influence on outcomes, as previous reports have suggested.[27]

Statistical analysis

Data were analyzed using SPSS version 26.0 (IBM) and RStudio 1.2 (https://cran.r-project.org), from March 31 to April 30, 2021. OS, PFS, LC, and TTNT were estimated with the Kaplan-Meier method. Data for patients who were alive were censored for OS at the time of the final follow-up. Data for those who were alive and had no tumor progression were censored for the evaluation of PFS and LC at the last assessment. PFS and OS stratified by the presence of AR were compared by applying the log-rank test. To control for confounding factors and assess the association of SABR with the various patient characteristics, we performed multivariate analysis based on Cox proportional hazard models. To select the variables for this model, we employed a stepwise algorithm by combining backward and forward search according to the Akaike information criterion metric. The final Cox model was fitted to satisfy the proportional hazards hypothesis test by removing nonproportional covariates. Two-sided $P \leq .05$ was considered statistically significant.

Results

Baseline characteristics

From September 1, 2017, to August 1, 2020, 61 patients who met the inclusion criteria were included in the study. Of these, 3 patients died before evaluation, 2 withdrew consent, 4 experienced clinical progression before SABR, and 2 had no evaluation at the closing of the study. Fifty patients were included in the final analysis, and none were lost during follow-up. Patient and treatment characteristics are described in Table 1. The median age was 64 years (range, 39-87) and 64% (n = 32) were men. The most frequent tumor histology was nonsquamous NSCLC. Sixty-four percent of patients (n = 32) had more than 5 metastases. Patients had received a median of 2 lines of systemic therapy before I-SABR (range, 1-4). Current ICI agent was balanced between pembrolizumab (54%, n = 27) and nivolumab (46%, n = 23). In addition to computed tomography scan, 64% of patients (n = 32) were evaluated with positron emission tomography. Before SABR, patients had received a median of 6 cycles of ICI (range, 2-43). Fifty percent (n = 25) were primary refractory to ICI. Tumor sites selected for SABR were mainly nodal and lung metastases. Median size for target lesions was 2.5 cm (range, 0.8-9.4 cm). Median size for

Table 1 Patient and treatment characteristics

Characteristic	Value
Sex	
Male	32 (64%)
Female	18 (36%)
Median age in years (range)	64 (39-87)
ECOG	
0	22 (44%)
1	24 (48%)
2	4 (8%)
Histologic features	
Lung (nonsquamous)	26 (52%)
Lung (squamous)	5 (10%)
Melanoma	19 (38%)
PD-L1 status	
<1%	5 (10%)
1%-49%	0 (0%)
≥50%	11 (22%)
Unknown	34 (68%)
Driver mutations	
Yes	4 (8%)
No	46 (92%)
Number of systemic therapy lines before SABR	
1	25 (50%)
2	18 (36%)
≥3	7 (14%)
Prior radiation therapy	
Yes	12 (24%)
No	38 (76%)
Metastatic stage	
Oligometastatic (1-5 lesions)	18 (36%)
Polymetastatic (>5 lesions)	32 (64%)
Current ICI agent	
Pembrolizumab	27 (54%)
Nivolumab	23 (46%)
Primary resistance to ICI	
Yes	25 (50%)
No	25 (50%)
Cycles of ICI before SABR	
Median (range)	6 (2-43)
Irradiated tumor sites	
Nodes	26 (34%)
Lung	20 (26%)
Bone	17 (23%)
Liver	4 (5%)
Other	9 (12%)
Number of irradiated sites	
1	31 (62%)
2	14 (28%)
≥3	5 (10%)
SABR dose	
35 Gy/5 fx	39 (78%)
24 Gy/3 fx	11 (22%)
Number of SABR courses	
1	31 (62%)
2	13 (26%)
3	6 (12%)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; fx = fractions; ICI = immune checkpoint inhibitor; PD-L1 = programmed cell death ligand 1.

nonirradiated lesions was 1.9 cm (range, 0.9-10 cm). Sixty-two percent of patients (n = 31) received a single SABR course.

Outcomes

Treatment results are summarized in Table 2. At the cutoff date of March 31, 2021, with a median follow-up of 32.8 months (range, 5-44.6), ORR was 42% (21/50 patients), consisting of 30% (n = 15) CR and 12% (n = 6) PR. Ten percent (n = 5) had stable disease (SD) and 48% (n = 24) had further progression. AR could be measured in 80% (40 patients). The missing 20% (10 patients) were either oligometastatic and had all their lesions irradiated (n = 7), or the previously selected lesions for evaluating AR were not measurable by RECIST after SABR (n = 3). Of these, 65% (n = 26) showed AR 8 weeks after SABR. The change from baseline for nontarget lesions in these patients is shown in Figure E1. LC in the irradiated sites at the end of follow-up was 84% (54% CR, 12% PR, and 11% SD). Median time to achieve best LC was 4 months (2-30). Median TTNT was 13 months (10.6 months-not reached). Only 32% (16 patients) required a new line of systemic therapy during follow-up. The clinical benefit of I-SABR over time in each patient is represented in Figure 1. At the end of follow-up, 8% of patients (n = 4) had completed ICI and were disease-free with no active treatment. These consisted of 2 oligometastatic melanomas, 1 polymetastatic melanoma, and 1 polymetastatic nonsquamous NSCLC. Three of these achieved a CR in the first 6 months after SABR and 1 (the polymetastatic melanoma) at 12 months. Thirty percent of patients in the cohort (n = 15)

Table 2 Response to treatment

Endpoint	n (%)
ORR	21/50 patients (42%)
Complete response	15 (30%)
Partial response	6 (12%)
Stable disease	5 (10%)
Progression disease	24 (48%)
AR at 8 wk	
Present	26/40 patients (65%)
Absent	14/40 patients (35%)
LC	64/76 lesions (84%)
Complete response	41 (54%)
Partial response	12 (16%)
Stable disease	11 (14%)
Progression disease	12 (16%)

Abbreviations: AR = abscopal response; LC = local control; ORR = objective response rate.

were still under the same anti-PD-1 agent. During follow-up, 6 patients who had disease recurrence after the discontinuation of anti-PD-1 after achieving a CR had the same agent reintroduced and had regained clinical benefit by the end of follow-up. Of these, 2 had completed all the expected anti-PD-1 cycles and 4 had requested treatment discontinuation because of personal preference.

In terms of survival, median PFS was 14.2 months (95% confidence interval [CI], 6.9-29 months). Two-year PFS was 35.9% (95% CI, 24.2%-53.2%). Median OS since the delivery of SABR was 37.4 months (95% CI, 22.9 months-not reached). Two-year OS from SABR was 60.3% (95% CI, 47.5-76.6%). Twenty-nine patients (58%) were alive at the time of analysis. Kaplan-Meier curves for PFS and OS from SABR are displayed in Figure 2. Patients with AR had a median PFS of 21.2 months (95% CI, 12.2 months-not reached) compared with 3 months (95% CI, 2.5 months-not reached) in those without it ($P < .0001$) (Fig. 2). No differences between tumor histology were observed (Fig. E2). Other treatment variables such as number of SABR courses and number or location of treated lesions did not seem to affect survival.

Subgroup analyses with multivariate regression for disease progression and death are presented in Figure 3. Primary refractory disease was associated with a higher risk of progression (hazard ratio [HR], 3.3; $P = .008$). The presence of AR was significantly associated with a lower risk of progressive disease (HR, 0.13; $P < .001$). As for death, squamous histology, male sex, and grade 2 toxicity were associated with a significantly higher risk. In contrast, oligometastatic status was associated with a decreased risk of death (HR, 0.22; $P = .049$).

The most common adverse effect after I-SABR was grade 1 to 2 asthenia in 16% of patients (n = 16%). Only 6% (n = 3) showed grade ≥3 toxic effects during follow-up: 1 nephritis and 2 transaminase elevations, which required the discontinuation of ICI. These, however, were not related to SABR, as they manifested in nonirradiated organs and were confirmed to be immune-related. No treatment-associated deaths occurred. Detailed data on toxicity are available in Table E1.

Discussion

Although ICI have improved the prognosis in some patients with metastatic disease, others present primary resistances

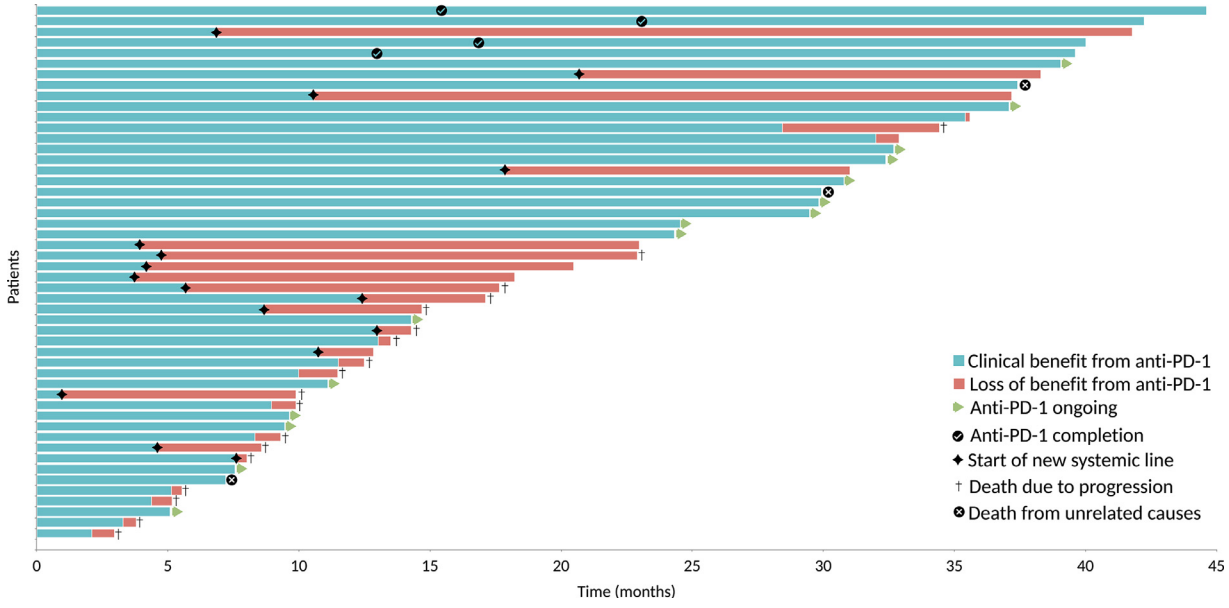


Fig. 1. Clinical evolution of each patient after immune checkpoint inhibitor SABR. *Abbreviation:* anti-PD-1 = anti–programmed cell death protein 1.

to treatment, and many develop resistant tumor subclones over time.[5-7] This has led the way for the combination of ICI with other therapeutic strategies that may improve response. The use of SABR in OPD has already reported a potential role in the delay of new lines of systemic treatment, mainly in metastatic NSCLC with driver mutations.[18,28,29] When combined with ICI, SABR can potentially have additional advantages by unleashing an immune response through the release of tumor-associated antigens.[30,15] To our knowledge, this is the first prospective study to evaluate the efficacy of SABR after progression to anti-PD-1 in patients with metastatic melanoma and NSCLC.

In terms of response, our results are consistent with those reported in the randomized I-SABR studies. We observed an ORR of 42% (21/50 patients) with 30% CR. The PEMBRO-RT trial reported an ORR of 36% in the experimental arm versus 18% in the control arm,[12] while the MD Anderson Cancer Center study showed 22% versus 25% when comparing RT/SABR plus ICI versus ICI, and the SABR arm reported an ORR of 38%.[13] It must be noted that we achieved a slightly higher ORR despite the fact that our cohort had worse baseline characteristics. The MD Anderson Cancer Center trial only included oligometastatic patients (up to 4 lesions), whereas 64% of our patients had more than 5 metastases. Fifty percent of our patients had already received ≥2 lines of systemic therapy before SABR versus only 28% in PEMBRO-RT. Furthermore, we achieved this ORR despite 50% of patients being primary refractory to ICI. For our study, we decided to evaluate ORR considering all lesions, including the irradiated ones. In a context of oligoprogression, control of the irradiated lesions can determine whether the patient is able to continue receiving the same line of ICI. We believe that this better reflects the reality of clinical practice. In contrast, the 2 previously mentioned studies excluded the radiated lesions when evaluating ORR. Although our definition could lead to an overestimation of ORR, our results seem to be in line with the published data. To minimize this, we decided to exclude SD from ORR, as in a context of oligoprogression this SD could be achieved by simply controlling the radiated lesions. Moreover, more than 60% of our cohort consisted of polymetastatic patients in which LC of 1 or a few sites could not probably mask systemic progression.

A randomized trial by Schoenfeld et al[31] included patients who had progressed to a line of anti-PD-1/L1 and randomized them to receive durvalumab plus tremelimumab alone or in combination with either low-dose (8 Gy in doses of 0.5 Gy

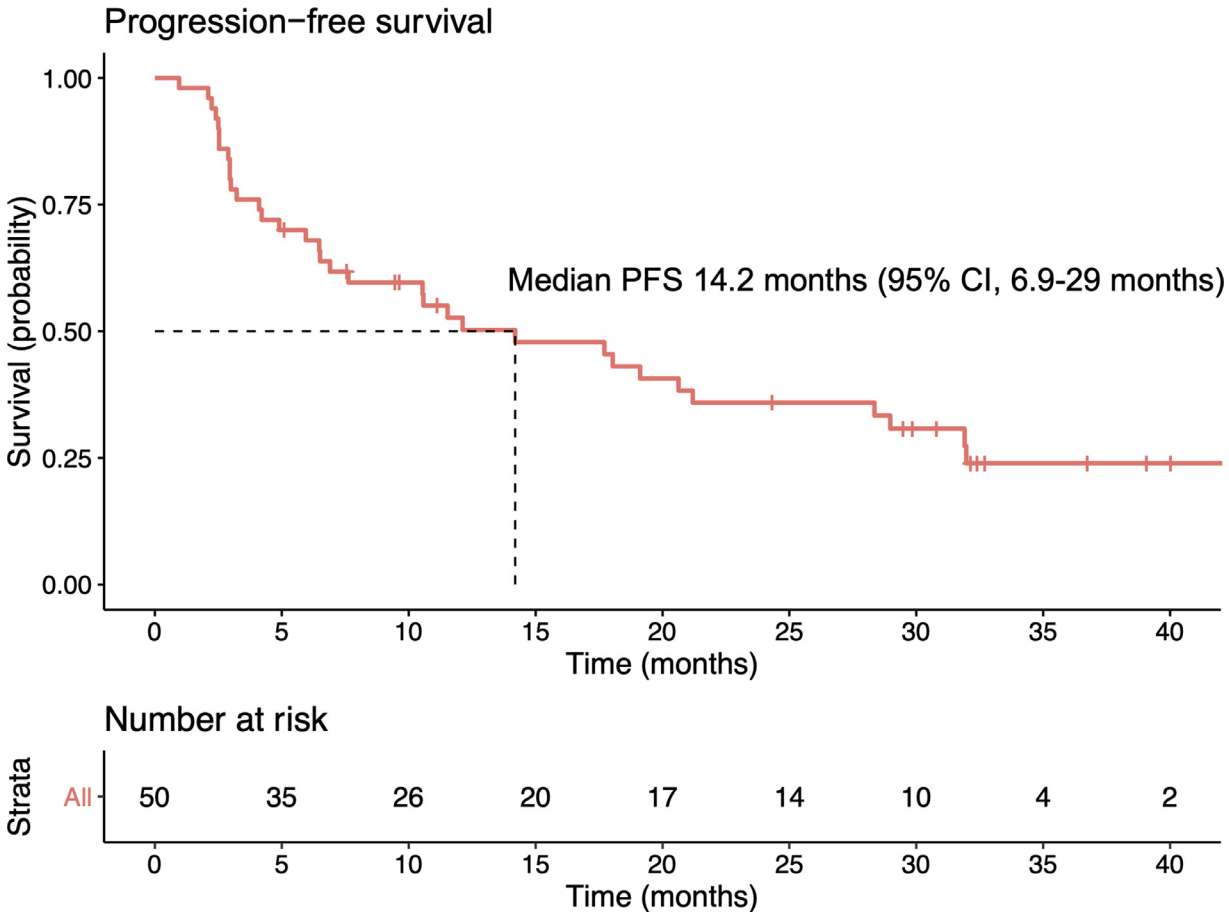
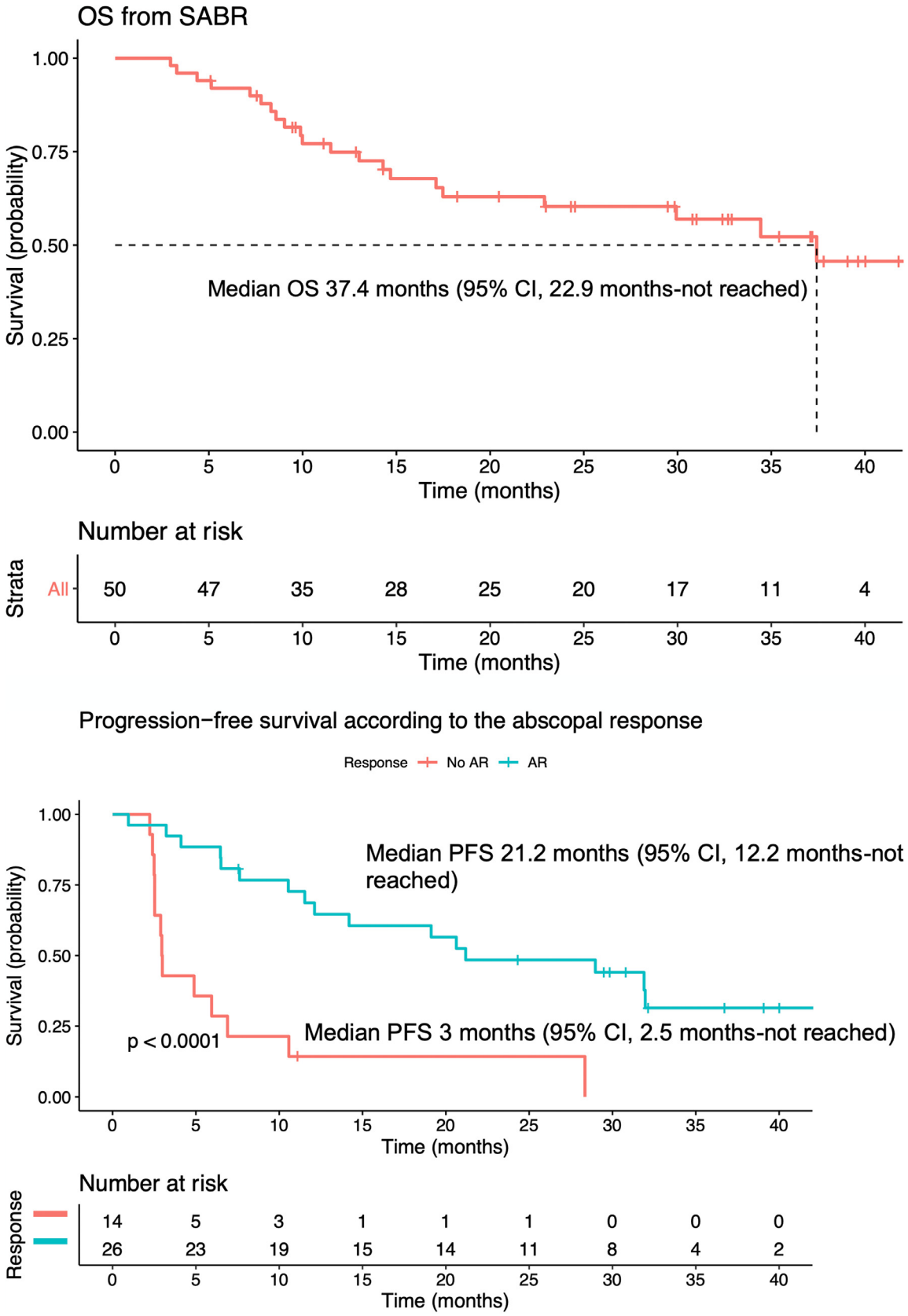


Fig. 2. Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS). (A) PFS. (B) OS. (C) PFS according to the presence of abscopal response. *Abbreviation:* CI = confidence interval.



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twice a day during the first 4 cycles of systemic therapy) or hypofractionated (24 Gy in 3 fx) RT. At the end of follow-up, no differences in ORR were observed between arms. Although this study contrasts with our results, baseline characteristics of patients, ICI agents, and SABR doses are different between studies, which highlights the need for further research. Although patients with NSCLC with PD-L1 >1% may achieve better responses,[32] we decided not to stratify patients according to their PD-L1 status. Given that recruitment started before first-line therapy with ICI was authorized in our country, many of our patients received ICI as second-line or had previously participated in randomized trials, so PD-L1 status was either not required or masked. Therefore, these data were missing in many cases. Even though PEMBRO-RT reported a greater benefit in the PD-L1 negative subgroup, this was not replicated in a posterior pooled analysis of the 2 randomized trials.[32]

Our median PFS of 14.2 months and median OS of 37.4 months are quite promising if we consider that these patients were already in progression to ICI, and more than half were polymetastatic. Driver mutations represented only 8% of cases, an incidence along the lines of current data.[33,34] Although the PEMBRO-RT trial found no significant benefit in PFS or OS, the mentioned pooled analysis did report increased PFS (median 9 vs 4.4 months, $P = .045$) and OS (median 19.2 vs 8.9 months, $P = .004$) in favor of the combination.[32] Furthermore, Bauml et al[14] reported a median PFS of 19.1 months in oligometastatic patients treated with local ablative treatment to all disease sites. I-SABR was effective in delaying the need of a new line of systemic therapy in our cohort. These results reinforce the relevant emerging role of ablative therapies such as SABR in OPD. Although no other results have been published with the combination of anti-PD-1, Iyengar et al[17] reported a very similar median PFS (14.7 months) in a phase 2 study that included 24 patients with oligoprogressive NSCLC who were treated with combined SABR and erlotinib. Considering that our cohort had a more unfavorable prognosis, the fact that we achieved a comparable benefit in PFS suggests that I-SABR, via the abscopal effect, might unleash more effective responses.

To determine the AR, we evaluated the response in 1 to 2 predefined nonirradiated lesions. Under these criteria, we observed a response in 26 out of the 40 patients who

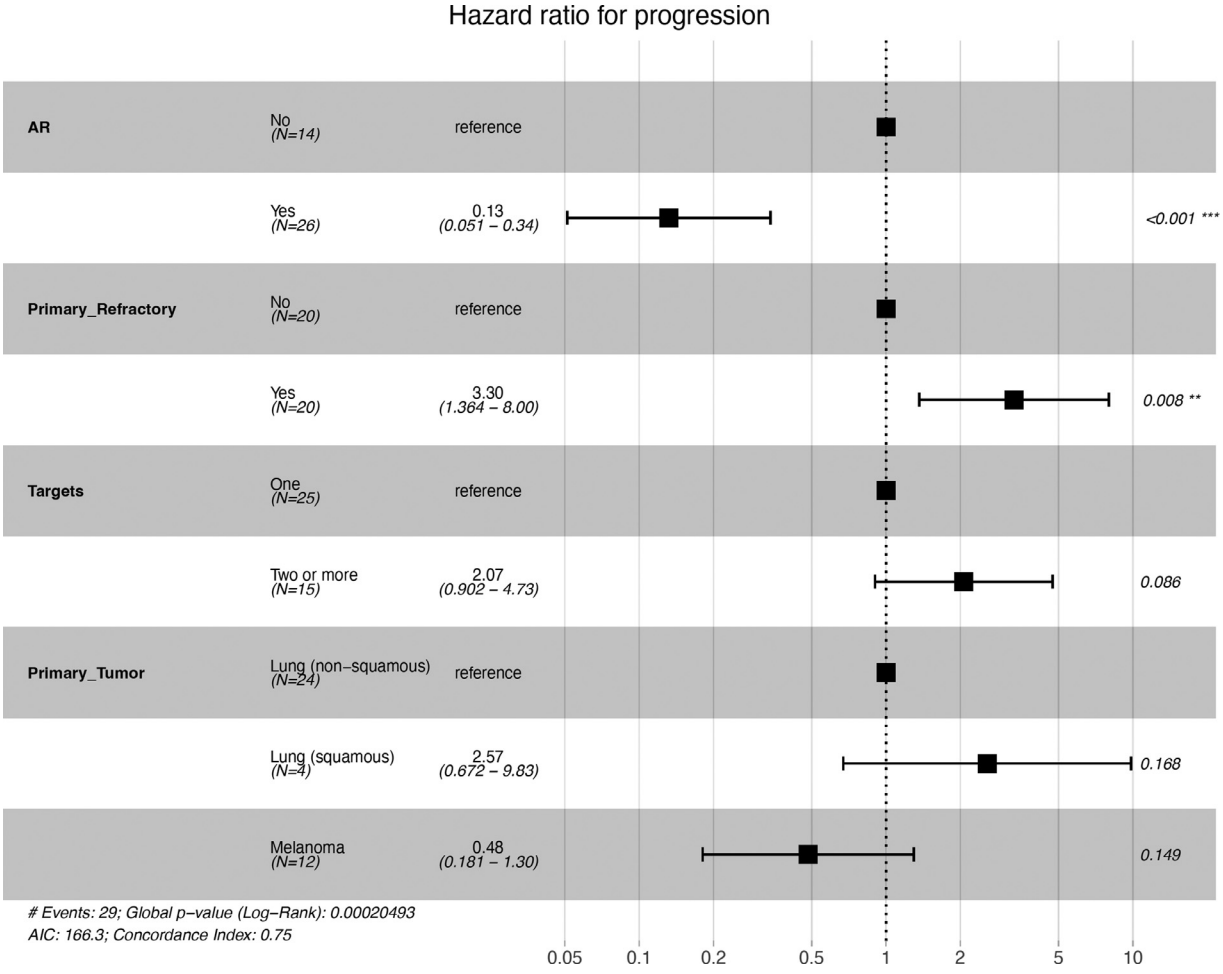

Fig. 3. Multivariate analysis for progression and death. (A) Multivariate analysis for progression. (B) Multivariate analysis for death. *Abbreviations:* AR = abscopal response; Base_Tox = base toxicity; Met_Status = metastatic status.

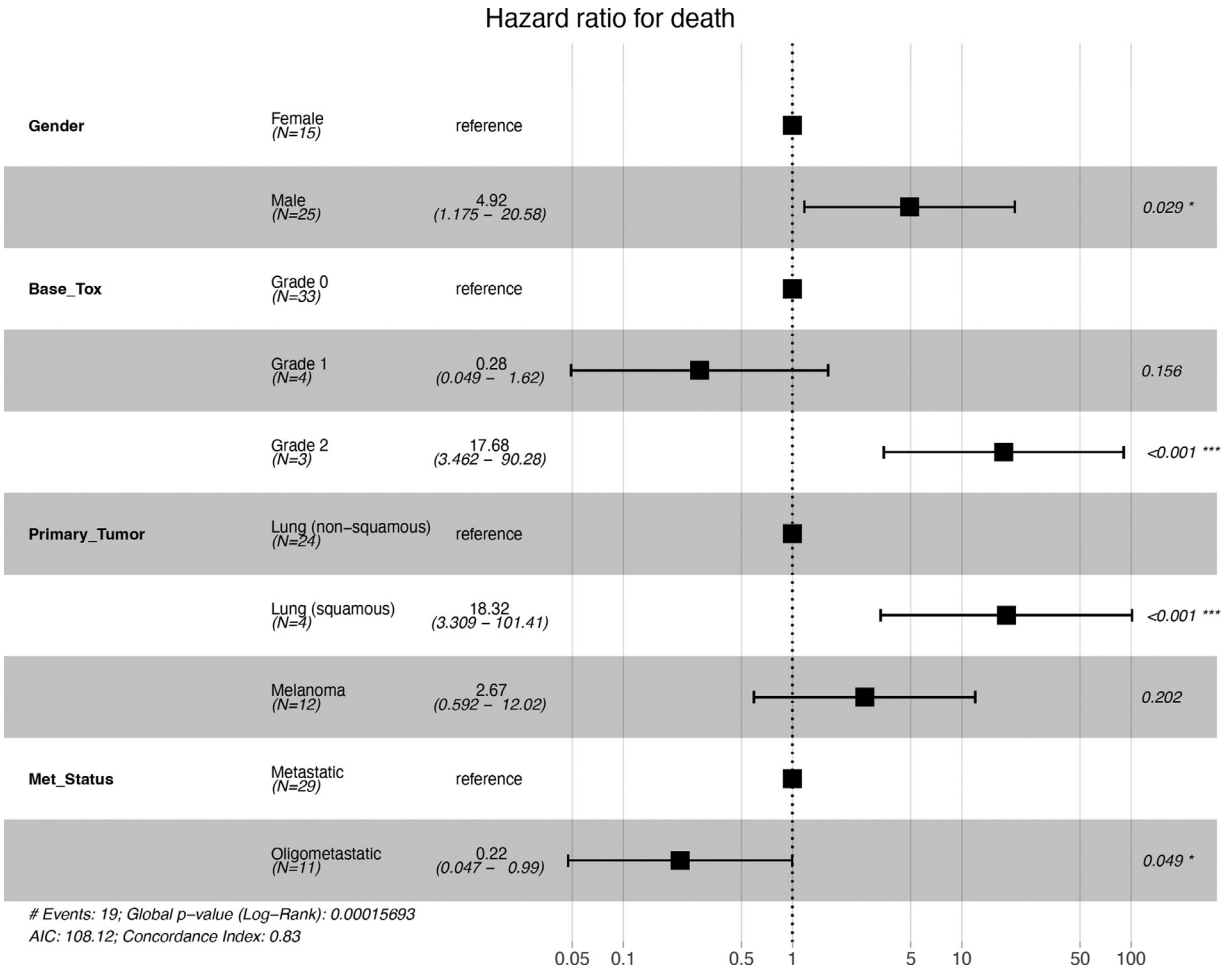

Fig. 3. Continued.

could be analyzed for this endpoint (65%). This AR is superior to that reported in the previously mentioned studies.[12,13,14] However, the definition of AR is not well established, and some authors do not distinguish between AR and ORR.[35] Moreover, these studies present a considerable amount of heterogeneity in terms of design, inclusion criteria, and treatment variables.[12,13,14] Local control was considerably high (84%), comparable with other studies with higher doses of SABR.[15] We only found 6% grade 3 adverse effects, and none of these were related to SABR, as they occurred outside the irradiation field and several months after RT. These results are comparable with the 7% to 16% grade ≥3 toxicity reported in the anti-PD-1/PD-L1 monotherapy trials[2,36] and better than those in PEMBRO-RT (20% grade ≥3).[12]

Being that I-SABR is a considerably recent approach in the clinical setting, the optimal treatment setup is still under debate.[35,37,38] When considering RT fractionation, we prioritized safety over definitive doses. Given that most treatment sites were thoracic, 35 Gy in 5 fx better allowed us to not surpass dose-limiting constraints while delivering slightly higher doses than those in previous studies.[12,24] This fractionation would also allow us to reirradiate during follow-up. Moreover, this and similar fractionation schemes had previously shown more immunogenic responses than lower or higher doses in preclinical studies[39,40] and have also been tested in recent phase 2 trials by Theleen et al[12] and Formenti et al.[24] In contrast, the phase 2 trial conducted by Welsh et al[13] delivered higher doses, although the ORR was comparable to the one in our cohort. Doses were also higher in the Concurrent or Sequential Ipilimumab, Nivolumab, and stereotactic body Radiotherapy in patients with stage IV non-small cell lung cancer (COSINR) study, but its RECIST best response of 11% CR and 47% PR, while impressive, cannot be directly compared with our primary endpoint of ORR at the end of follow-up.[27] The influence of target location remains unclear. Nodal radiation has been suggested as detrimental owing to induced lymphopenia,[41] although nodal sites represented 34% of treatments in our study and responses were still high, as they were in other studies.[32] Although the ideal sequence is also unknown, we opted for a concurrent treatment given that the safety of this approach had already been established in various trials.[13,24,42] The effect of concomitant versus sequential treatment is still not clear. Recently, the COSINR study reported no significant differences in PFS or OS, but ongoing studies including

concurrent and sequential arms may shed some light on this matter (NCT02400814, NCT03307759). As for the number of treated locations, although the study was designed with the possibility of treating up to 5 metastases, evidence for multisite SABR was scarce at the time. Therefore, 31/50 patients received SABR to just 1 site. As data in favor of the safety of multisite SABR emerged, later patients received treatment to more than 1 site. Although there is a growing trend toward treating more than 1 lesion,[43] single- versus multisite SABR has not been assessed in a randomized setting yet, and we found no significant differences in our study.

Limitations

Our study has several limitations that must be noted. First, because of its observational nature, selection bias and confounding factors are issues that can limit the validity of our results. Even though we tried to account for possible biases and confounding factors during the study design and the statistical interpretation, recruitment depended on which patients were referred to our department during the active period of the study. We acknowledge that this is a source of selection bias. However, considering that there were no published data regarding rates of response to I-SABR in the oligoprogressive setting at the time, we were unable to estimate an adequate sample size. Although patients were treated with 2 different ICI agents (pembrolizumab and nivolumab), both are anti-PD-1 with similar profiles. We included metastatic melanoma and NSCLC because these are the histologies with more evidence for benefit with I-SABR. Although a single tumor type would have better controlled confounding, we thought that this would lead to insufficient patient recruitment. We are aware that evidence for melanoma with anti-PD-1 is more lacking. However, several prospective studies have been published with anti −cytotoxic T-lymphocyte antigen 4, which shares a similar mechanism and, when combined with SABR, seems to achieve comparable rates of response.[44-46] Furthermore, at the time of the study design, iRECIST criteria were not validated and all participating centers only used RECIST to define response for the duration of follow-up. Therefore, we were unable to evaluate possible discrepancies between the 2 criteria.

The lack of consensus on the definition of the most adequate endpoints for I-SABR studies is also a relevant limitation. This is particularly critical for the AR. The classical definition for AR as an out-of-field response after RT becomes considerably more complex when this RT is administered concomitantly with systemic immunotherapy agents. Although preclinical data have suggested several molecules that may have an influence on response[47-49] and might explain the AR, we were unable to obtain tumor or blood samples during the study to evaluate biomarkers. In the absence of molecular criteria, we are left with clinical definitions of AR. In that sense, the benefit in PFS that we observed in those patients with AR must be interpreted with caution. When designing this study, we decided that it was important to distinguish between ORR and AR. Even if a patient presents AR in certain lesions, this immune response might not be sufficient to elicit a global response of the disease. Given that our intention was to extend the clinical benefit of anti-PD-1, we concluded that ORR including all lesions was the most adequate primary endpoint. This difference might explain why, even though our AR is higher than other previously reported data, our results in terms of ORR are quite comparable with other studies that might not have characterized AR as a separate endpoint from ORR.

As mentioned before, we could not detect possible differences in response between the PD-L1 positive and negative subgroups because of missing data from several patients. Further studies are warranted to find predictors of response to I-SABR.

In conclusion, the results of this study suggest that I-SABR in metastatic NSCLC and melanoma is associated with high rates of local and systemic response after oligoprogression to anti-PD-1. This improved response can delay further progression, allowing for the continuation of the same line of systemic therapy while maintaining a safe toxicity profile. This approach should be evaluated in larger phase 2 to 3 studies that confirm this benefit and give rise to studies that explore possible stratification strategies.

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