Phase II study of concomitant radiotherapy with atezolizumab in oligometastatic soft tissue sarcomas: STEREOSARC trial protocol

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ABSTRACT

Introduction Up to 50% of soft tissue sarcoma (STS) patients develop metastases in the course of their disease. Cytotoxic therapy is a standard treatment in this setting but yields average tumour response rates of 25% at first line and ≤10% at later lines. In oligometastatic stage, stereotactic body radiation therapy (SBRT) allows reaching high control rates at treated sites (≥80%) and is potentially equally effective to surgery in term of overall survival. In order to shift the balance towards antitumour immunity by multisite irradiation, radiation could be combined with inhibitors of the immunosuppressive pathways.

Methods and analysis STEREOSARC is a prospective, multicentric, randomised phase II, designed to evaluate the efficacy of SBRT associated with immunotherapy versus SBRT only. Randomisation is performed with a 2:1 ratio within two arms. The primary objective is to evaluate the efficacy, in term of progression-free survival rate at 6 months of atezolizumab with or without stereotactic body radiation therapy in oligometastatic sarcoma. The secondary objectives include PFS by immune response criteria, overall survival, quality-of-life evaluation and developing mathematical models of tumour growth and dissemination predictive of oligometastatic versus polymetastatic evolution. Patients will be randomised in two groups: SBRT with atezolizumab and SBRT alone. The total number of included patients should be 103.

Trial registration The trial is registered on ClinicalTrials.gov (ID: NCT03548428).

Ethics and dissemination This study has been approved by Comité de Protection des Personnes du sud-ouest et outre-mer 4 on 18 October 2019 (Reference CPP2019-09-076-PP) and from National Agency for Medical and Health products Safety (Reference: MEDAECONAT-2019-08-00004_2017-004239-35) on 18 September 2019.

The results will be disseminated to patients upon individual request or through media release from scientific meetings. The results will be communicated through scientific meetings and publications.

Strengths and limitations of this study

► This multicentric and prospective study is the first trial in oligometastatic sarcomas, evaluating the efficacy, in term of progression-free survival rate at 6 months of atezolizumab with or without stereotactic body radiation therapy in oligometastatic sarcoma.

► The oligometastatic state is defined as a state with up to five metastases that are all irradiated.

► The purpose of the ancillary study is to determine predictive markers of response to immunotherapy.

INTRODUCTION

Up to 50% of soft tissue sarcoma (STS) patients will develop metastases in the course of their disease. Cytotoxic therapy is a standard treatment in this setting but yields average tumour response rates of 25% at first line and ≤10% at later lines.

The concept of oligometastatic stage includes a variety of very specific clinical situations, be it oligoprogression, oligorecurrent or oligoconsolidation. Oligoprogression is defined as the progression of a few metastases (<5), in an otherwise stable polymetastatic context. Oligoconsolidation describes a situation in which an initially polymetastatic disease responds globally to systemic treatment except for a few metastases. Here, we choose to treat oligorecurrents, defined as a recurrence in the form of a limited number of metastases, while the primary one is controlled. Oligorecurrence is an intermediate stage between a disseminated metastatic disease and a purely local stage. It is usually defined as a cancer patient with 1–5 metastatic lesions. It has been theorised for several years now that a local treatment,
in this particular state of the disease could lead to better long-term survival. Recent trials suggest that consolidative ablation of residual oligometastases refractory to chemotherapy is used in ~20% of patients in clinical trials, suggesting that integration of local metastatic treatments should be taken into account in the overall strategy of metastatic (oligo)sarcomas. Historically, surgical strategies to treat patients with oligometastases from sarcomas enabled to yield prolonged survival times. Alternatively and increasingly performed, stereotactic body radiation therapy (SBRT) allows reaching high control rates at treated sites (>80%) and is potentially equally effective to surgery in term of overall survival. Moreover, SBRT gives the possibility to deliver an effective treatment to anatomic sites that may not be amenable to surgery.

Several potent immunomodulators that skew the tumour immune microenvironment toward antitumor immunity context are being investigated in sarcomas. The PD-1 receptor is present within the tumour microenvironment, and limits the activity of infiltrating cytotoxic T lymphocytes, thus blocking effective immune responses. PD-1 can stimulate antitumour immune responses. Significant responses have been obtained in several sarcomas (NCT01343043; NCT02107963; NCT01953900) with acceptable tolerance. Preliminary clinical experience also suggests that immunotherapy can be efficient in refractory leiomyosarcomas.

The rationale for this study is to assess the efficacy of immunotherapy in a situation where the macroscopic bulk of the metastatic disease is eradicated by the high dose hypofractionated stereotactic body radiotherapy. The hypothesis behind is that the situation to obtain full potential from immunotherapy due to tumour bulk and stimulation of immune responses further to tumour destruction by SBRT. Indeed, as sarcomas are known to have a high propensity to metastasise, the combination of a treatment for macrometastasis with a treatment for micrometastatic disease could lead to a higher rate of control of the disease. This study does not specifically address the efficacy of multisite irradiation and delayed occurrence or absence of new metastases after multisite stereotactic irradiation performed under the mediation of the immune system: indeed, immunotherapy in the setting of eradicated macrometastatic bulk is expected to delay the need for further therapies (systemic or local). The systemic effect of radiation therapy seems more pronounced in the case of hypofractionated high-dose irradiation such as SBRT, compared with the normal fractionation. The combination of SBRT with inhibitors of the immunosuppressive pathways could also shift the balance towards antitumour immunity and enhance the abscopal effects of radiation but this is expected to prevent the occurrence of new macroscopic (detectable on imaging) metastases.

Assuming that the immunotargeting of the PD1–PDL1 axis after SBRT could improve progression-free survival (PFS), we here propose a prospective, multicentric, randomised study to evaluate the combination of SBRT and immunotherapy in oligometastatic STS patients.

**STRENGTHS AND LIMITATIONS OF THIS STUDY**

**Method and analysis**

The SPIRIT reporting guidelines were used for the drafting of this protocol.

**Study design**

STEREOSARC (protocol V.1.1) is a prospective, multicentric, randomised phase II, designed to evaluate the efficacy of a SBRT associated with immunotherapy versus SBRT only. Randomisation is performed with a 2:1 ratio within two arms.

SBRT can be proposed as first/second lines owing to the excellent local control rates (>80%) SBRT is delivered as described in paragraph 6.1 (dose regimen, dose constraints to healthy tissues and quality assurance process, full protocol and guidelines and quality assurance process provided on request).

Randomisation 2:1 will be realised with strata:

- Leiomyosarcomas versus liposarcomas versus undifferentiated sarcomas: these STSs were chosen because there show high mutational load. Because there are also the most frequent STSs, it ensures accrual feasibility and also will be easier to interpret with respect to benefit of immunotherapy in comparison with a multihistology trial.
- First versus second metastatic line.

**Primary objective**

The primary objective is to evaluate the efficacy, in term of PFS according to RECIST V.1.1 rate at 6 months, of immunomodulated stereotactic irradiation in oligometastatic sarcoma patients. RECIST was chosen to also evaluate response after SBRT. iRECIST will be assessed separately.

**Secondary objectives**

The secondary objectives are:

- PFS by immune response criteria, defined as the time between initiation of treatment and progression.
- Ratio PFS after radiotherapy/PFS during the previous line of treatment.
- Objective response rate, defined as the rate of patients with at least a partial response after treatment, out of the total number of patients included in the study.
- Rate of PFS at 6 months, defined as the number of patients with at least a partial response according to RECIST 1.1 criteria out of the total number of patients in the study, at 6 months, by line of treatment and histology.
- Evaluation of the toxicity of the treatment, according to CTCAE V.4.0.
- Overall survival, defined as the time from diagnosis of STS to death.
Quality-of-life evaluation, assessed with quality of life QLQ C30 Questionnaire (until progression, optional thereafter per ethical recommendations).

Evaluation of the cost of treatment, calculated on the basis of the length of hospitalisation in days.

Rate of PET-CT at inclusion.

Impact of biomarkers (PD1/PDL1 immunostaining in tumour and microenvironment, C reactive protein (CRP), albumin, neutrophils/lymphocytes, mutational load at baseline and Circulating tumour (ct) DNA at baseline, 6 months and relapse) on PFS as previously described.

Impact of biomarkers (PD1/PDL1 immunostaining in tumour and microenvironment, CRP, albumin, neutrophils/lymphocytes, mutational load at baseline and ctDNA at baseline, 6 months and relapse) on response rate as previously described.

Developing mathematical models of tumour growth and dissemination, predictive of oligometastatic versus polymetastatic evolution.

Eligibility criteria
Patients have to fulfil the following main inclusion criteria:

- Histologically proven STS (leiomyosarcomas uterine/extrauterine, liposarcomas, undifferentiated sarcomas), any grade.
- First or second metastatic line.
- Greater than or equal to 18 years of age on day of signing informed consent.
- Performance status 0 or 1 on the ECOG Performance Scale.
- Metastatic disease (1–5 synchronous macroscopic metastases by chest and abdominopelvic CT, maximal cumulated diameter 6 cm) at any anatomic site.
- Demonstrate adequate organ function: absolute neutrophil count ≥1500/mL; platelets ≥100 000; haemoglobin ≥9 g/dL or ≥5.6 mmol/L; serum creatinine ≤1.5 times the upper limit of normal (ULN) OR measured or calculated creatinine clearance with MDRD equation ≥50 mL/min for subject with creatinine levels >1.5 times the institutional ULN; serum total bilirubin ≤1.5 times the ULN OR direct bilirubin ≤1.5 times the ULN OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 ULN; AST (SGOT) and ALT (SGPT) ≤2.5 times the ULN OR ≤5 times the ULN for subjects with liver metastases.
- Surgery for one of the oligometastases remains possible, if performed at least 4 weeks prior to randomisation, and as long as at least one target lesion remains to be treated with SBRT.
- Diagnosis of immunodeficiency, or is receiving systemic steroid therapy, or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Diagnosis of active autoimmune disease requiring systemic treatment within the past 3 months prior randomisation, or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.
- Has had prior chemotherapy or targeted small molecule therapy within 4 weeks prior to randomisation or who has not recovered (ie, ≤grade 1 or at baseline) from adverse events due to a previously administered agent.
- If subjects received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- Have had previous radical radiation to any tumour site within 4 weeks prior to randomisation.
- Have had previous ablative treatment within 4 weeks prior to randomisation (radiofrequency, surgery).
- Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anticytotoxic T lymphocyte-associated antigen-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways).

Study sites
The list of study sites is available on https://clinicaltrials.gov/ct2/show/record/NCT03548428?term=stereosar&rank=1. on the website of the National Cancer Institute.

Atezolizumab
Subjects randomised in the experimental arm will receive atezolizumab 1200mg in combination with SBRT, every 3 weeks, (six cycles) for 4 months until progression/completion.

Atezolizumab will be discontinued in case of progression, unacceptable toxicity or withdrawal of patient consent to receive study treatment.

There will be no dose reduction for atezolizumab in this study. Any toxicity observed during the study treatment phase could be managed by interruption of the dose of atezolizumab if deemed appropriate by the investigator. Treatment must be temporarily or permanently interrupted if any National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC AE
V.5.0 grade 3 or 4 adverse event occurs. Atezolizumab must be interrupted until the patient recovers completely or the toxicity reverts to grade 1 or less.

There will be no double-blind placebo administration.

**Drug supply**

Atezolizumab will be provided by the Sponsor (Centre Antoine Lacassagne).

**Radiation therapy**

SBRT can be performed with different equipments (CyberKnife, Truebeam, etc) using dose prescription and organ at risk constraints guidelines. Adequate tumour tracking and patient set-up/repositioning as well as online image-guided radiation therapy must be performed at each fraction. The maximal cumulative tumour diameter is 6cm to maintain an advantageous risk–benefit ratio with SBRT. Two types of fractionation are proposed to account for tumour size and proximity of the tumour to sensitive organs at risk. Three fractions are proposed in favourable cases, five in more delicate cases.Fractions can be performed on consecutive days. The whole SBRT duration should not exceed 3 weeks. A quality assurance of radiation therapy will be performed by expert with post hoc analysis of all the files dosimetry with DICOM RT data to quote SBRT quality and account for it in the analyses.

SBRT and atezolizumab will start the same day on day 1, with SBRT first followed by atezolizumab. The study scheme is described in [Figure 1](#).

**Calculation of the number of patients**

The sample size is calculated using the single-stage Fleming phase II 2:1 design, with an \( \alpha \) value of 0.05 and a \( \beta \) value of 0.05, one sided. The 6-month PFS rate should be around 50% for the arm SBRT alone and 70% (6.1) with SBRT and atezolizumab combination. Sixty-two evaluable patients in the experimental group and thirty-one patients in the control group are needed. A 10% loss to follow-up is accepted; the total number of included patients will be 103.

**Statistical analysis plan**

Qualitative data will be presented as absolute frequency, relative frequency, 95% CI and percentage of missing data. These data will be compared according to the \( \chi^2 \) test or...
Independent of the trial, a methodologist statistician, and results. This committee will be composed of two clinicians trial and to ensure an independent review of the scientific conducted ethically, to assess the benefit/risk ratio of the protection of the patients, to ensure that the trial is considered primary.

The inclusion period will last 30 months, the estimated study completion date will be August 2026.

**Patient-specific quality assurance in radiotherapy**

Inclusion/exclusion criteria and tumour and organs at risk prescription rules are checked and related minor or major deviations or treatments per protocols used as discretised parameters to assess overall treatment quality. Conservative guidelines are given regarding dose to organs at risk considering that patients are treated for metastatic diseases. Quality of SBRT plans is evaluated in routine practice using dose distribution and dose volume histograms. Further plan quality metrics are integrated in our analyses to more objectively measure the quality of SBRT plans and to correlate those with tumour control and toxicity. Retrospective review of DICOM RT using plan quality metrics data will be performed in all patients with indexes and will conform to ICRU-91 recommendations: The Conformity Index indicates whether irradiated volume is greater than target volume or if the target volume is only partially irradiated. The quality of coverage evaluates the minimum dose in the target with respect to the prescription dose. The Homogeneity Index evaluates hot spots in the target and can be very significantly between SBRT techniques in the macroscopic tumour volume. Other indexes will be used for organs at risk.

**Independent Data Monitoring Committee (IDMC) is planned**

A monitoring committee will be set-up to guarantee the protection of the patients, to ensure that the trial is conducted ethically, to assess the benefit/risk ratio of the trial and to ensure an independent review of the scientific results. This committee will be composed of two clinicians independent of the trial, a methodologist statistician, and a pharmacovigilance specialist. The IDMC can propose early discontinuation of the trial if one of the following conditions is met:

- The results of the intermediate analysis (after inclusion of the 25th patient) clearly show (10% or more grade 4 non-haematological toxicities) that the trial treatment is indicated or contraindicated.
- Unacceptable toxicity (describe the method used for the discontinuation rule).
- All the available data (including tumour failures/progression) acquired from the trial or from other sources are sufficiently convincing to influence the therapeutic practices of the majority of physicians.

The committee has a consultative role under the sponsor and coordinator, who will be responsible for making the final decision to implement recommendations and to draft an amendment, if necessary.

An audit can be conducted at any stage of the study, from the development of the protocol to the publication of the results and the filing of the data or the products used during the study.

**Biological ancillary study**

In sarcomas, current data do not permit to select patients who will benefit from immune therapies. The rapid introduction of complementary tests seems essential. Though an insufficient positive predictive value, the immunohistochemically evaluation of PDL1 appears to be the most universally usable predictive biomarker for anticipating response to anti-PD1 or anti-PDL1 treatment.14

Recently, a high tumour mutational burden (TMB) has been identified as a genetic signature that is associated with a favourable outcome for immune checkpoint inhibitor therapy. The TMB is defined as the total number of non-synonymous mutations per coding area of a tumour genome. Initially, it was determined using whole exome sequencing, but due to the high costs and long turn-around time of this method, targeted panel sequencing is currently being explored to measure TMB. Tumour samples will be collected and TMB evaluation will be performed at baseline. The objective of TMB evaluation is to correlate between mutational load and response to immunotherapy.

A panel of eight proteins involved in immune response will thus be tested on primary sarcoma tissue or metastatic material. Several immunostainings of the tissue sample will be performed for immune cells lymphocytes B, T regulator and histiocytes (CD3, CD20, CD4, CD8, CD45, CD68, CD163 and FOXP3) and PDL1 status. Immunohisto-architectural features including PD-L1 expression, patterns of immune cell infiltration, and lymphocyte subpopulations (immunological scores such as CPS…), will be assessed for interrelation ships and potential correlations with clinical outcomes.

ctDNA quantification will be performed at baseline, at 6 months and relapse. The mutational load will be assessed from baseline tissue, only for the first 25th patients, for correlation with ctDNA quantification and the impact on the clinical endpoint. Specific funding may be searched for the identification of specific mutations (P53 and MDM2). The study also includes an analysis of biomarkers specific to inflammation, as it seems that neutrophils, a common marker of infection, could also be considered as a novel and simple biomarker for cancer. Neutrophils or neutrophils to lymphocyte ratio (NLR) count is described as a prognosis factor for many cancers.15 In case of patients with metastatic STS, Jiang et al found that NLR and monocytes counts seem to be a prognosis factor for both overall and PFS.16 Neutrophils count is described as a prognosis factor for local progression-free, disease-free and overall survival in

le Guevelou J, et al. BMJ Open 2020;10:e038391. doi:10.1136/bmjopen-2020-038391
Moreover, since many years effects of radiotherapy toward the immune system are described and it has been reported that high dose irradiation promotes immunomodulator and increases the release of tumour antigen leading to indirect tumour cell death. Here, it could be useful to study the evolution of blood count kinetic, because radiotherapy could deplete neutrophils blood count, distant neutropaenia could be both a predictor of non-evolution, but at contrary it could also be a reflect of immune system failure and in this case leading to disease relapse. We propose to study blood cell count: leucocyte blood count and their subtypes and C reactive protein, albumin, to find a simple and efficient blood biomarker.

No additional consent is required for the ancillary study.

Patient and public involvement

Cancer Research Patients Committee of the French League Against Cancer was involved in the validation of the patient information consent form. Patients were not involved in the design of the study. They were recruited in the study based on their eligibility and agreement to participate (signed informed consent form).

Ethics and dissemination

This study was approved by Comité de Protection des Personnes du sud-ouest et outre-mer 4 on 18 October 2019 (Reference CPP2019-09-076-PP) and by the National Agency for Medical and Health products Safety (Reference: MEDAECNAT-2019-08-00004_2017-004239-35) on 18 September 2019. The results will be disseminated to patients on individual request or through media release from scientific meetings. The results will be communicated through scientific meetings and publications.

DISCUSSION

The rationale behind combining multisite SBRT and immunotherapy is the synergistic stimulation of the immune system, with enhanced tumour antigen expression and facilitated priming and activating of T cells with antitumour effects. Immunomodulation by the addition of concurrent systemic immunotherapy can help to promote the so-called abscopal effect to prevent the growth of microscopic yet undetectable distant tumour foci into macroscopic metastases, or to promote the regression of millimetric metastases (<5 mm). In this protocol, multisite irradiation is required, it is not expected that the abscopal effect be efficient on macroscopic tumors as these are treated with SBRT, but rather on microscopic subclinical disease. This protocol differs from previously published immunotherapy reports in that it uses a synergy between a highly effective well tolerated form of radiotherapy even in radiosensitive tumours in a subgroup of tumours with high mutational load. Another innovation is the reliance on immunomodulated SBRT to target circulating/disseminated tumour cells to delay metastatic relapse and possibly those in dormancy and those reversed from dormancy to active cell cycle phase by SBRT. The first centre has been opened for patient inclusions in Nice on 4 June 2020.

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Acknowledgements

We thank the Cancer Research Patients Committee of the French League Against Cancer for their re-readings of the Patient Information Form.

Contributors

JG, CD, ES-B, JV, DT, NP, MPS, LM-Z, MB, OV, AD, CIP, MJ, CB, DV, AE, RS, CL, JT and NK: substantial contributions to the conception of the work, drafting the work or revising it critically for important intellectual content, final approval of the version to be published, agreement to be 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.

Funding

The trial (NCT03548428) is granted by the Institut National du Cancer (PHRC-K-16-072). Roche SAS provide the atezolizumab and the funding for the companion test analysis.

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

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REFERENCES

1 Anna A, Gutinotov SI, Weichselbaum RR. Radiotherapy and Immunotherapy for Cancer: From “Systemic” to “Multisite”. Clin Cancer Res 2020;26:2777–82.
2 Ratam R, Patel SR. Chemotherapy for soft tissue sarcoma. Cancer 2016;122:2392–60.
3 Olivier T, Pop D, Chouiter Djebaili A, et al. Treating metastatic sarcomas locally: a paradox, a rationale, an evidence? Crit Rev Oncol Hematol 2015;95:62–77.
4 Blay J-Y, Leahy MG, Nguyen BB, et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. *Eur J Cancer* 2014;50:1137–47.
5 Shultz DB, Filippi AR, Thariat J, et al. Stereotactic ablative radiotherapy for pulmonary oligometastases and oligometastatic lung cancer. *J Thorac Oncol* 2014;9:1426–33.
6 Grilley-Olson JE, Webber NP, Demos DS, et al. Multidisciplinary management of oligometastatic soft tissue sarcoma. *Am Soc Clin Oncol Educ Book* 2018;38:939–48.
7 Lee A, Huang P, DeMatteo RP, et al. Immunotherapy for soft tissue sarcoma: tomorrow is only a day away. *Am Soc Clin Oncol Educ Book* 2016;35:281–90.
8 Heine A, Kristiansen G, Schild HH, et al. Successful treatment of refractory leiomyosarcoma with the PD-1 inhibitor nivolumab. *Ann Oncol* 2016;27:1813–4.
9 Formenti SC, Demaria S. Systemic effects of local radiotherapy. *Lancet Oncol* 2009;10:718–26.
10 Kim M-S, Kim W, Park IH, et al. Radiobiological mechanisms of stereotactic body radiation therapy and stereotactic radiation surgery. *Radiat Oncol J* 2015;33:265–75.
11 Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. *Nature* 2015;520:373–7.
12 Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res* 2009;15:5379–88.
13 Chan A-W, Tetzlaff JM, Altman DG, et al. Spirit 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
14 Bertucci F, Finetti P, Perrot D, et al. PDL1 expression is a poor-prognosis factor in soft-tissue sarcomas. *Oncoimmunology* 2017;6:e1278100.
15 Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst* 2014;106:dju124.
16 Jiang L, Jiang S, Situ D, et al. Prognostic value of monocyte and neutrophils to lymphocytes ratio in patients with metastatic soft tissue sarcoma. *Oncotarget* 2016;8:9542–50.
17 Escande A, Haie-Meder C, Maroun P, et al. Neutrophilia in locally advanced cervical cancer: a novel biomarker for image-guided adaptive brachytherapy? *Oncotarget* 2016;7:74886–94.
18 Falk AT, Thyss A, Thariat J. Metastatic ablation for sarcomas: methodological and ethical dilemmas for prospective studies. *Clin Oncol* 2015;27:429–30.
19 Falk AT, Moureau-Zabotto L, Ouali M, et al. Effect on survival of local ablative treatment of metastases from sarcomas: a study of the French sarcoma group. *Clin Oncol* 2015;27:48–55.
20 Demicheli R, Retsky MW, Hrushesky WJM, et al. Tumor dormancy and surgery-driven interruption of dormancy in breast cancer: learning from failures. *Nat Clin Pract Oncol* 2007;4:699–710.
21 Romero I, Garrido F, García-Lora AM. Metastases in immune-mediated dormancy: a new opportunity for targeting cancer. *Cancer Res* 2014;74:6750–7.