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LETTER TO THE EDITOR

Precision radiation of immune checkpoint therapy resistant melanoma metastases (PROMMEL study): study protocol for a phase II open-label multicenter trial

Ellen Backlund[a,b], Muyi Yang[b], Vitali Grozman[c,d], Giuseppe Masucci[b], Johan Falkenius[b], Hanna Eriksson[a,b], Braslav Jovanovic[b], Katarina Hammarlund[a], Ulf Isacsson[e,f], Calin Radu[f], Edvard Abel[g], Kristin Karlsson[b,h], Ricardo Palanco Zamora[b,h], Peter Wersäll[a,b], Ulrika Edbäck[b], Stina Wickström[b], Eva Darai Ramqvist[i], Suzanne Egyhazi Brage[b], Rolf Kiessling[b], Kristina Viktorsson[b], Bo Franzén[b], Rolf Lewensohn[b], Roger Olofsson Bagge[j], Gustav J. Ullenhag[f,k], Lars Ny[g], Karin Lindberg[a,b] and Hildur Helgadottir[a,b]

[a]Department of Oncology, Karolinska University Hospital, Stockholm, Sweden; [b]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [c]Department of Diagnostic Radiology, Karolinska University Hospital, Sweden; [d]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [e]Medical Radiation Physics, Uppsala University Hospital, Uppsala, Sweden; [f]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden; [g]Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden; [h]Department of Medical Radiation Physics and Nuclear Medicine, Karolinska University Hospital, Stockholm, Sweden; [i]Department of Clinical Pathology and Cytology, Karolinska University Hospital, Stockholm, Sweden; [j]Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [k]Department of Oncology, Uppsala University Hospital, Uppsala, Sweden

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Background

The world-wide incidence rate of cutaneous melanoma has been rising continuously with annual increases as high as 4–6% in high-risk fair-skinned populations, and in 2020 nearly 325,000 new patients and 57,000 deaths were reported globally [1]. In Sweden, cutaneous melanoma is the fifth most common malignancy and the incidence is showing an alarming increase with a doubling the last two decades [2]. If detected in an early stage, the disease is curable with surgical resection, while, in the event of advanced disease the prognosis is poor. Until recently the only available systemic treatment was chemotherapy with limited clinical efficacy and a median overall survival (OS) less than one year [3].

Fortunately, the development of immune checkpoint inhibitors (ICI) and targeted therapies with BRAF and MEK inhibitors have vastly improved the outcome of patients with metastatic melanoma [4–9]. Several clinical studies have demonstrated that programmed death receptor 1 (PD-1) inhibitors, as monotherapy or in combination with the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor ipilimumab, are efficient in treating metastatic melanoma [5,7,10]. There is also evidence supporting ICIs as the first line of treatment in patients with *BRAF* mutated melanoma [11]. Treatments with PD-1 inhibitors generates a response in more than 40% of melanoma patients regardless of their *BRAF* mutation status. For patients who respond, the median duration of the response is several years, and some patients are potentially cured [12]. However, within the first year nearly 50% of the patients suffer from progressive disease [5,13,14]. Progressing patients with *BRAF* mutated melanoma are candidates for treatment with BRAF and MEK inhibitors, to which the majority respond, but the duration of response is limited to a median of approximately 1.5 years [15]. Patients with primary or secondary resistance to ICIs are hence left with inadequate treatment options and further research is of essence [5,13].

Radiotherapy (RT) is currently mainly used as a symptom-relieving palliative measure in metastatic melanoma patients. Based on early *in vitro* and retrospective studies, melanoma was considered a RT resilient tumor [16,17]. This resistance to RT is believed to stem from different features often present in melanoma cells, including resistance to apoptosis, high DNA repair capacity, high proliferation capacity and poor cell differentiation, in addition to a hypoxic tumor microenvironment [17].

Stereotactic body radiation therapy (SBRT) is today a recognized RT-technique in which the RT is delivered with inhomogeneous dose distribution in a few fractions and with high absorbed doses per fraction (usually 10–20 Gy) with resultant high biological effectiveness. SBRT has been successful thanks to the high rate of local control of the treated lesions and the limited side effects for the patients [18]. Even melanoma tumors with their relative resistance to RT have a local control rate with SBRT that is over 80% [19]. Retrospective studies in metastatic melanoma patients have

CONTACT Ellen Backlund ellenbacklund@gmail.com Department of Oncology-Pathology, Karolinska Institutet, K7 Oncology-Pathology 171 64, Stockholm 171 76, Sweden

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shown that RT, conventional and hypo-fractionated RT as well as SBRT, in combination with ICIs, is well tolerated and the type and grade of side effects are in a range that could be expected for each of the modalities separately [17,19–25].

Radiation of tumors can evoke an immune response through various processes, including apoptosis, DNA damage, tumor lysis, release of tumor antigens and cytokines, inflammation, and infiltration of immune cells, including tumor-specific cytotoxic CD8+ T-cells which enhances the diversity of the T-cell receptor (TCR) repertoire of intertumoral T-cells [26–28]. RT induced immune activation in the target area can potentially result in a systemic activation and an immune mediated shrinkage also of tumors distant to the irradiated area – a phenomenon known as an 'abscopal effect' [29,30]. An abscopal effect is, however, an event rarely seen when RT is given solely [31].

An attractive approach would thus be to use the radiation induced immune response to potentiate the clinical effect of ICI and further enhance tumor shrinkage outside of the irradiation field. In retrospective reports of melanoma patients receiving RT on progressing metastases while continuing treatment with PD-1 inhibitors, an abscopal shrinkage has been observed in 15–35% of the non-irradiated tumor lesions [21,23]. However, prospective studies are lacking [21,23,32]. There is moreover no definite consensus on the optimal dose per fraction nor the total absorbed tumor dose for triggering an abscopal effect [33]. Some experts argue in favor of a conventional fractionated dosage [34] whereas others believe that a high-dose-hypofractionated radiation dose shows improved response [35,36]. The PROMMEL phase II trial aims to study the hypothesis that an abscopal effect can be generated when adding SBRT to ICI resistant melanoma metastases while continuing treatment with ICIs. If our hypothesis is supported, it will be a highly anticipated treatment method for this patient group where efficient treatment options are lacking. Additionally, biomarkers in blood and tumors samples will be assessed to study the biologic processes and mechanisms behind abscopal effect.

Methods

Aim

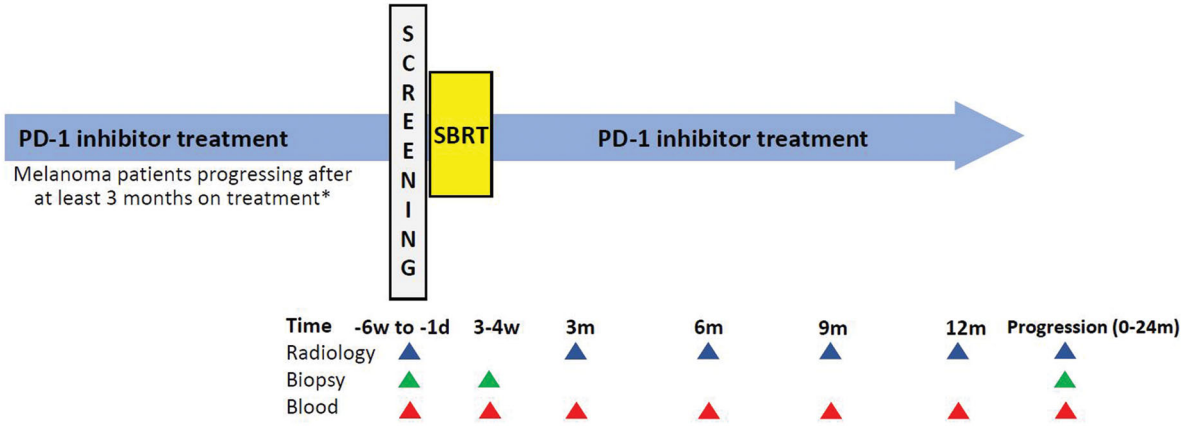
This is to our knowledge the first prospective trial focusing on melanoma patients and the occurrence of abscopal effect when ICI resistant metastases are treated with SBRT technique. The PROMMEL study is a phase II open-label multicenter trial supported by the Swedish Melanoma Study Group (SMSG). See Figure 1 for overall study design.

Study population

The study population includes metastatic melanoma patients progressing on PD-1 inhibitor treatment, meeting all the inclusion and exclusion criteria (see below). Patients in this study will be recruited from melanoma oncology clinics at three Swedish University Hospitals: Karolinska University Hospital in Stockholm, Sahlgrenska University Hospital in Gothenburg and Uppsala University Hospital.

Inclusion criteria

1. Age $\geq$ 18.
2. ECOG performance status of 0–1.
3. Signed and dated written informed consent.
4. Verified disease progression after at least 3 months of PD-1 inhibitor treatment (alone or in combination with CTLA-4 inhibitor) as the first line of therapy for unresectable metastatic cutaneous melanoma. Patients with primary or secondary resistance to the PD-1 inhibitor treatment will be included.
5. At least one progressing metastasis that is judged to be safely amenable to SBRT in the opinion of treating



*At least one progressing lesion amenable for stereotactic body radiotherapy (SBRT) AND at least one, not-to-be-irradiated progressing lesion, measurable by CT or MRI per RECIST 1.1 criteria.

Figure 1. Trial design.

radiation oncologist. A fine-needle aspiration (FNA) biopsy from a progressing lesion or a new lesion is recommended to confirm the presence of viable tumor cells.
6. At least one, not-to-be-irradiated new or progressing lesion measurable as assessed by CT or MRI per RECIST 1.1 criteria where up to four radiation target fields are allowed.
7. No contraindication for continuing PD-1 inhibitor 12 months after radiation.

Exclusion criteria

1. Inability to understand given information or undergo study procedure according to protocol.
2. Pregnant or breast-feeding. Patients must agree to safe contraception.
3. Systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medication.
4. Have an active infection requiring systemic therapy.
5. Concomitant therapy with any anti-tumor medication other than ICI.
6. Prior RT preventing the study intervention with SBRT.
7. Location, size, or number of metastases deemed too large or not appropriate for SBRT.
8. Active brain metastases.
9. Prior malignancy within five years.

Endpoints

The primary endpoint is to evaluate overall response rate (ORR) in non-irradiated lesions according to RECIST 1.1 (37). The secondary endpoints are ORR in irradiated lesions, median progression-free survival (PFS) and OS, PFS and OS rate at 6 and 12 months and adverse events. Tumor biopsies, primarily from non-irradiated lesions, will be secured for translational research, including genomic (DNA and RNA) and proteomic analysis exploring tumor heterogeneity and mechanisms of ICI resistance. Blood samples for biomarker analysis, including FACS analyses of peripheral leukocytes, analyses of plasma cytokines, extracellular vesicles/exosomes and circulating tumor DNA (ctDNA), will be taken at both screening and at follow-up visits. Secondary and exploratory endpoints can be found specified in detail in the Study protocol attached in the Supplementary Material.

Study design

The study participant will undergo SBRT and continue the same regimen of anti PD-1 inhibitor therapy (nivolumab or pembrolizumab) until progression, discontinue due to side effects or up to 12 months of treatment. Assessment whether at least one metastasis is suitable for SBRT is made by the treating radiation oncologist. Overview of fractionation schedules for different target locations are shown in Table 1. Target areas are extracranial metastases, such as (but not limited to) lungs, lymph nodes, liver, and bone. A CT or PET-CT scan will be performed every three months to evaluate clinical response according to RECIST 1.1 criteria [38]. The subjects will be followed until study discontinuation, death, disease progression or up to a maximum of 24 months.

The study will be conducted according to Simon's two stage minimax design [39]. Patients will be enrolled in two stages, the first consisting of 13 patients. If no objective responses are reported in any of the patients in this step, the study is interrupted early for futility. If objective response in non-irradiated lesions has been achieved in at least one patient when the 13th patient has been evaluated, the recruitment can proceed into the second step. Fourteen more patients will then be included up to a total of 27 patients to determine ORR in non-irradiated lesions along with the 95% confidence interval. The sample size and power estimation are based on the primary endpoint ORR. Power is required to be 80%. We consider ORR of 15% to be sufficient to conclude that the treatment combination is useful. A low number is motivated by the fact that patients who have experienced disease progression, are unlikely to respond if continuing with the same treatment only.

'Pseudo-progression' is a phenomenon that has been described in association with ICI treatment, where an increase in tumor size or occurrence of a new lesion is related to inflammation and infiltration of immune cells, and not to progression of tumor cells. In melanoma, pseudo-progression is expected to occur in around 5% of ICI treated patients [40,41]. In the PROMMEL study, the following steps are taken to decrease the likelihood of including pseudo-progressing patients:

Table 1. Overview of fractionation schedules, target volume definition and dosage for different target locations possible to use in the study.

	Lung lesions	Liver lesions	Abdominal lesions	Lymph nodes	Subcutan. lesions	Spine lesions	Non-spine bony lesions
Fractionation schedule							
15 Gy × 3	x	x	–	–	–	–	–
10 Gy × 5	x	x	x	x	x	–	–
8 Gy × 5	–	–	x	x	x	x	x
Gross tumor volume (GTV), definition	NA	NA	NA	NA	NA	Tumor	NA
Clinical target volume (CTV), definition	Tumor[a]	Tumor[a]	Tumor[a,b]	Entire lymph node	Tumor[a]	Vertebra [37]	Tumor[a]
CTV-PTV margins	Individual	Individual	Individual	Individual	Individual	[c]	Individual
Isodose prescription (encompassing the PTV)[d]	65–70%	65–70%	65–83%	65–83%	65–83%	[c]	70–83%
Maximum target dose[e]	150%	150%	120–150%	120–150%	120–150%	[c]	120–140%[f]

GTV: gross tumor volume. CTV: clinical target volume. PTV: planning target volume.
[a]Including the diffuse growth at the borders. [b]The entire adrenal gland comprises the CTV when treating adrenal lesions. [c]See the study protocol for details. [d]As a percentage of the maximum dose value in the center of the CTV. [e]Percent of prescribed dose. [f]Even homogeneous dosage may be considered in selected cases.

1. The lesion(s) should increase with at least 30% in size, which is larger than the RECIST 1.1. criteria of 20% increase for progressive disease
2. Biopsy is recommended from target lesions to confirm if tumors are dominated by viable melanoma cells.
3. Radiologic evaluation is performed by radiologists with expertise in evaluating response in ICI treated melanoma patients and familiar with the specific patterns associated with pseudo-progression, including mixed responses.

Ethical consideration

Both ICI and SBRT are well-established treatments that have shown to be effective in melanoma patients, and data from retrospective studies when the treatments have been combined have not shown more side-effects, than what could be expected from each of these therapies separately. The treatment combination with SBRT and ICI in the PROMMEL study is hence considered ethically justified and potential side effects will be closely monitored and reported. The investigators will ensure that all subjects are given oral and written information regarding risks of participating and the opportunity to discontinue from the study at any time. All subjects are required to give signed and dated informed consent for participation. The study will be performed according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. The trial protocol is reported in accordance with the SPIRIT guidelines [42] for clinical trials please see Supplementary Material. The study has been approved by Swedish Ethical Review Authority (Dnr 2020-05584) and by the Swedish Biobank Authority. ClinicalTrials.gov identifier NCT04793737, registered on March 11th, 2021.

Perspectives

In the PROMMEL trial, metastatic melanoma patients progressing on ICI, will be treated with SBRT of their tumors and continue treatment with PD-1 inhibitors. We aim to study the hypothesis that this treatment strategy will create an abscopal effect in nonirradiated tumor(s). Since this study is the first prospective trial focusing on melanoma patients and abscopal effect, we anticipate that the result will be of high interest whether the study outcome supports or disproves the hypothesis.

Trial status

As of September 13th, 2021, the PROMMEL study is open at the three participating sites, in Stockholm, Gothenburg and Uppsala. On February 25th, 2022, six patients have been included and all of them have received the SBRT intervention and thereafter continued with the PD-1 inhibitor treatment.

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Authors contributions

HH is the principal investigator and contributed with the design of the study and writing of the study protocol. VG, RL, GM, KK, RPZ, KV, ROB, GU, KL, and LN contributed to the study design and protocol. HH, EB, LN, GU, JF, HE, BJ and KH are responsible for recruitment and follow-up of the patients. VG, UI, CR, EA, KK, RPZ, PW, and KL are responsible for radiologic evaluation and planning of SBRT. HH, MY, UE, SW, SEB, RK, KV, BF, and EDR are responsible for collection and analyses of the patients' biological samples. EB and HH drafted the manuscript that all authors have read, participated in revisions, and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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ORCID

Giuseppe Masucci http://orcid.org/0000-0002-9583-2306
Stina Wickström http://orcid.org/0000-0003-0349-4918
Rolf Kiessling http://orcid.org/0000-0003-0663-5763
Roger Olofsson Bagge http://orcid.org/0000-0001-5795-0355
Lars Ny http://orcid.org/0000-0003-3864-5958

Data availability

Data sharing is not applicable to this study protocol since no data were generated or analyzed. Results from the PROMMEL study will be published and specific data will be available on reasonable request.

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