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Phase I/II trial of Durvalumab plus Tremelimumab and stereotactic body radiotherapy for metastatic head and neck carcinoma

Houda Bahig[1,3], Francine Aubin[2,3], John Stagg[3], Olguta Gologan[3,4], Olivier Ballivy[1,3], Eric Bissada[3,5], Felix-Phuc Nguyen-Tan[1,3], Denis Soulières[2,3], Louis Guertin[3,5], Edith Filion[1,3], Apostolos Christopoulos[3,5], Louise Lambert[1,3], Mustapha Tehfe[2,3], Tareck Ayad[3,5], Danielle Charpentier[2,3], Rahima Jamal[2,3] and Philip Wong[1,3*]

Abstract

Background: The efficacy of immunotherapy targeting the PD-1/PD-L1 pathway has previously been demonstrated in metastatic head and neck squamous cell carcinoma (HNSCC). Stereotactic Body Radiotherapy (SBRT) aims at ablating metastatic lesions and may play a synergistic role with immunotherapy. The purpose of this study is to assess the safety and efficacy of triple treatment combination (TTC) consisting of the administration of durvalumab and tremelimumab in combination with SBRT in metastatic HNSCC.

Method: This is a phase I/II single arm study that will include 35 patients with 2–10 extracranial metastatic lesions. Patients will receive durvalumab (1500 mg IV every 4 weeks (Q4W)) and tremelimumab (75 mg IV Q4W for a total of 4 doses) until progression, unacceptable toxicity or patient withdrawal. SBRT to 2–5 metastases will be administered between cycles 2 and 3 of immunotherapy. The safety of the treatment combination will be evaluated through assessment of TTC-related toxicities, defined as grade 3–5 toxicities based on Common Terminology Criteria for Adverse Events (v 4.03), occurring within 6 weeks from SBRT start, and that are definitely, probably or possibly related to the combination of all treatments. We hypothesize that dual targeting of PD-L1 and CTLA-4 pathways combined with SBRT will lead to < 35% grade 3–5 acute toxicities related to TTC. Progression free survival (PFS) will be the primary endpoint of the phase II portion of this study and will be assessed with radiological exams every 8 weeks using the RECIST version 1.1 criteria.

Discussion: The combination of synergistic dual checkpoints inhibition along with ablative radiation may significantly potentiate the local and systemic disease control. This study constitutes the first clinical trial combining effects of SBRT with dual checkpoint blockade with durvalumab and tremelimumab in the treatment of metastatic HNSCC. If positive, this study would lead to a phase III trial testing this treatment combination against standard of care in metastatic HNSCC.

Trial registration: NCT03283605. Registration date: September 14, 2017; version 1.

Keywords: Head and neck cancer, Metastatic, Immunotherapy, SBRT, Durvalumab, Tremelimumab

* Correspondence: philip.wong.chum@ssss.gouv.qc.ca
[1]Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal, 1051 Sanguinet Street, Montreal, QC H2X 3E4, Canada
[3]Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada
Full list of author information is available at the end of the article

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Background

Metastatic head and neck cancer

Each year, up to 60,000 new cases of head and neck squamous cell cancer (HNSCC) are diagnosed in the United States [1]. The prevalence of distant metastasis at diagnosis varies between 4 and 26% [2–5]. Among patients without metastasis at diagnosis, up to 30% will develop distant failure [6, 7]. The prognosis of patients with distant metastasis is poor, and standard of care remains palliative chemotherapy. Palliative chemotherapy includes combinations of cetuximab, platinum and fluorouracil-based combinations associated with a median overall survival of 10 months and a response rate of 30% [8]. Alternatively, doublet platinum chemotherapy is associated with a median overall survival (OS) of 6–8 months [9]. Patients that are refractory or progress on first-line chemotherapy have limited treatment options as response rates to second-line therapies are between 3 and 13% [10].

Local ablative therapy for oligometastatic HNSCC

Local ablation (by surgical resection or radiotherapy) of oligometastasis (defined broadly as metastatic cancer with limited burden of disease) [11], aims at achieving prolonged progression free survival (PFS), and sometimes cure [12, 13]. This model is supported by results of the phase II randomized trial by Gomez et al. [14] showing that local ablation of non-small cell lung cancer oligometastasis was associated with 3 folds increase in median PFS compared to systemic maintenance treatment (12 vs. 4 months). A meta-analysis of 13 studies including 403 patients with HNSCC that underwent surgical resection of metachronous lung metastases showed 5-year OS of 29% [15]. SBRT is a highly conformal imaged-guided radiotherapy technique allowing for delivery of an ablative dose of radiotherapy in a small number of fractions [16]. The use of SBRT as a radical approach in oligometastatic disease is attractive given its non-invasive nature, its excellent local control (above 80%) [17, 18], and its safety with < 5–10% risk of grade ≥ 3 toxicities [19–22].

Immunotherapy in HNSCC

HNSCC tumors are highly immunogenic, with PD-L1 expression found in up to 60% of HNSCC along with elevated levels of intra-tumoral regulatory T cells infiltration [23, 24], thus making immunotherapy particularly attractive in HNSCC. Pembrolizumab and nivolumab are human IgG4 anti-PD-1 monoclonal antibodies approved as second line therapy for metastatic HNSCC by the US FDA, which respectively showed 3 months OS benefit over standard chemotherapy in platinum-refractory recurrent and metastatic HNSCC [25], and 18% response rate in recurrent or metastatic HNSCC [26, 27]. Results from Keynote 048, a randomized phase 3 study of pembrolizumab vs. cetuximab combined with platinum chemotherapy plus fluorouracil as first-line systemic therapy recurrent/metastatic HNSCC, were presented at the European Society for Medical Oncology 2018 meeting and showed that pembrolizumab was associated with significantly improved OS compared to the standard arm. Similarly, Keynote 040, a phase 3 randomized trial of pembrolizumab vs. investigator's choice of methotrexate, docetaxel, or cetuximab, showed improved OS with pembrolizumab (8.4 vs. 6.9 months) and reduced grade 3 or worse toxicities in the treatment of recurrent or metastatic HNSCC [28].

Durvalumab (MEDI4736) is a selective human anti-PD-L1 IgG1 monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80. Durvalumab induced overall response rates of 11% in metastatic or recurrent HNSCC and 18% in patients with high PD-L1 expression [29]. Tremelimumab is a selective human anti-CTLA-4 IgG2 monoclonal antibody [30]. The mechanisms of action of CTLA-4 and PD-L1 pathways are non-redundant as preclinical data indicate that inhibiting both pathways have synergistic antitumor activity [31]. While anti-PD-1/PD-L1 monotherapy seems associated with a greater clinical benefit in tumors expressing PD-L1, combination with anti-CTLA-4 therapy has the potential to enhance antitumor activity of anti-PD-1/PD-L1 agents in both PD-L1 positive and PD-L1 negative tumors [32]. The combination of anti-PD-1 and anti-CTLA-4 was shown to improve PFS vs. anti-PD-1 alone in melanoma (12 months vs. 7 months) [33]. This benefit came however at the price of increased grade 3–4 toxicities (55% vs. 27%, respectively.) A multicenter phase IB study assessing the combination of durvalumab and tremelimumab in non-small cell lung cancer reported 23% objective responses, irrespective of PD-L1 status; treatment related grade 3–4 toxicities were observed in 22% of patients [34]. In HNSCC, several trials are on-going to assess the safety and efficacy durvalumab and tremelimumab vs. monotherapy in recurrent or metastatic HNSCC [35] or as first line approach in advanced HNSCC (KESTREL (NCT02551159) and EAGLE [36]).

Combining immunotherapy and radiotherapy in head and neck cancers

Radiotherapy has been shown to induce anti-tumor immune effect in addition to cytotoxic effect [37, 38]. In fact, radiotherapy plays a role in the recruitment of T cells in the tumor microenvironment [39], secretion of cytokines, enhanced tumor antigen presentation [40, 41], and increased expression of PD-L1 in irradiated tumors [42]. In addition, induction of abscopal effect, which consists in anti-tumor response outside the radiotherapy field [42–45], has been suggested in both pre-clinical and clinical data. In mice, concomitant radiotherapy and anti-CTLA-4 antibodies induced abscopal effect [46, 47]; in addition, PD-1 blockade after completion of

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radiotherapy was shown to induce elimination of persistent tumors [42]. Dual checkpoint blockade (anti-CTLA-4 and anti-PD-L1) in combination with radiation has been shown to activate non-redundant immune mechanisms [38]. Single fraction radiation doses between 15 Gy and 25 Gy were shown to promote T-cell-mediated anti-tumor response at both the primary and distant metastases sites in mice model [48]. Similarly, hypofractionated regimen of 15 Gy in 1 fraction were associated with a greater tumor infiltration by immune cells compared to 15 Gy in 5 fractions regimen [49]. SBRT fractionation may therefore be advantageous for immune-stimulation and may work synergistically with immunotherapy [50]. Abscopal effect is reported in an increasing number of clinical reports, in particular in the context of the combination of immune checkpoint inhibitors and radiation [51–53].

Dual checkpoint blockade in combination with SBRT has not yet been reported in human clinical trials. Although the addition of SBRT to immunotherapy may generate higher response rates, it may increase the frequency and/or severity of toxicities. In this study, we will assess the safety and efficacy of a triple treatment combination (TTC) consisting of durvalumab, tremelilumab and SBRT in the treatment of patients with 2–10 metastasis from HNSCC.

Methods and design

Study design

This is a phase I/II single arm study evaluating the safety and efficacy of durvalumab, tremelimumab and SBRT combination in metastatic HNSCC. The study will include 35 patients with ≥2 extracranial measurable metastatic lesions and a maximum of 10 metastatic lesions in total, at the time of enrolment. Patients will be treated with durvalumab (1500 mg IV every 4 weeks (Q4W)) and tremelimumab (75 mg IV Q4W for a total of 4 doses) until progression, unacceptable toxicity or patient withdrawal. SBRT to 2–5 metastases will be administered between cycles 2 and 3 of immunotherapy (Fig. 1). This study is approved by the Centre de Recherche du Centre Hospitalier de l'Université de Montréal Institutional Review Board and is registered on clinicaltrials.gov (NCT03283605). Other participating academic institutions can be found on clinicaltrials.gov.

Primary objectives

Phase I

To determine the safety of durvalumab and tremelimumab in combination with SBRT to 2–5 metastatic lesions by assessing rates of TTC-related serious adverse events (SAE) within 6 weeks from the start of SBRT treatments.

Primary endpoint TTC-related SAE, defined as grade 3–5 toxicities based on Common Terminology Criteria for Adverse Events (CTCAE), are defined as definitely, probably, or possibly related to the combination of all 3 treatments, beyond what is expected by either treatment alone.

Phase II

To provide an estimate of PFS at 6-months in patients treated with durvalumab and tremelimumab in combination and SBRT.

Primary endpoint PFS will be measured from the start of treatment with durvalumab and tremelimumab until the documentation of regional or distant disease progression or death due to any cause, whichever occurs first.

Secondary objectives

1. To assess the rate and proportion of SAE at each time point (at 3, 6, 12 and 28 weeks post-radiotherapy).
2. To estimate local control (LC) of the treatment combination.
3. To estimate median OS of the treatment combination.
4. To estimate the rate of abscopal events from the combination therapy.
5. To measure patient quality of life.
6. To correlate LC and PFS with biopsy and serum biomarkers (exploratory).
7. To correlate OS and treatment toxicity with activity tracker metrics (exploratory).

Secondary endpoints LC of treated lesions will be measured from the end of SBRT treatment to date of local failure. OS will be measured from the start of treatment with durvalumab and tremelimumab to time of death. In subset of patients where at least 1 measurable lesion will not have been addressed by SBRT, abscopal effect will be estimated by comparing response rate of untreated lesion to historical response rate expected from durvalumab and tremelimumab combination alone. Quality of life will be measured in evaluable patients using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30; version 3.0) and the head and neck cancer specific module EORTC QLQ-H&N35.

Conditions for patient eligibility

1. Patient willing and able to give written informed consent
2. Patient willing and able to comply with the protocol for the duration of the study
3. ≥ 18 years of age at time of study entry
4. Body weight > 30 kg
5. Life expectancy > 24 weeks, as estimated by the treating team

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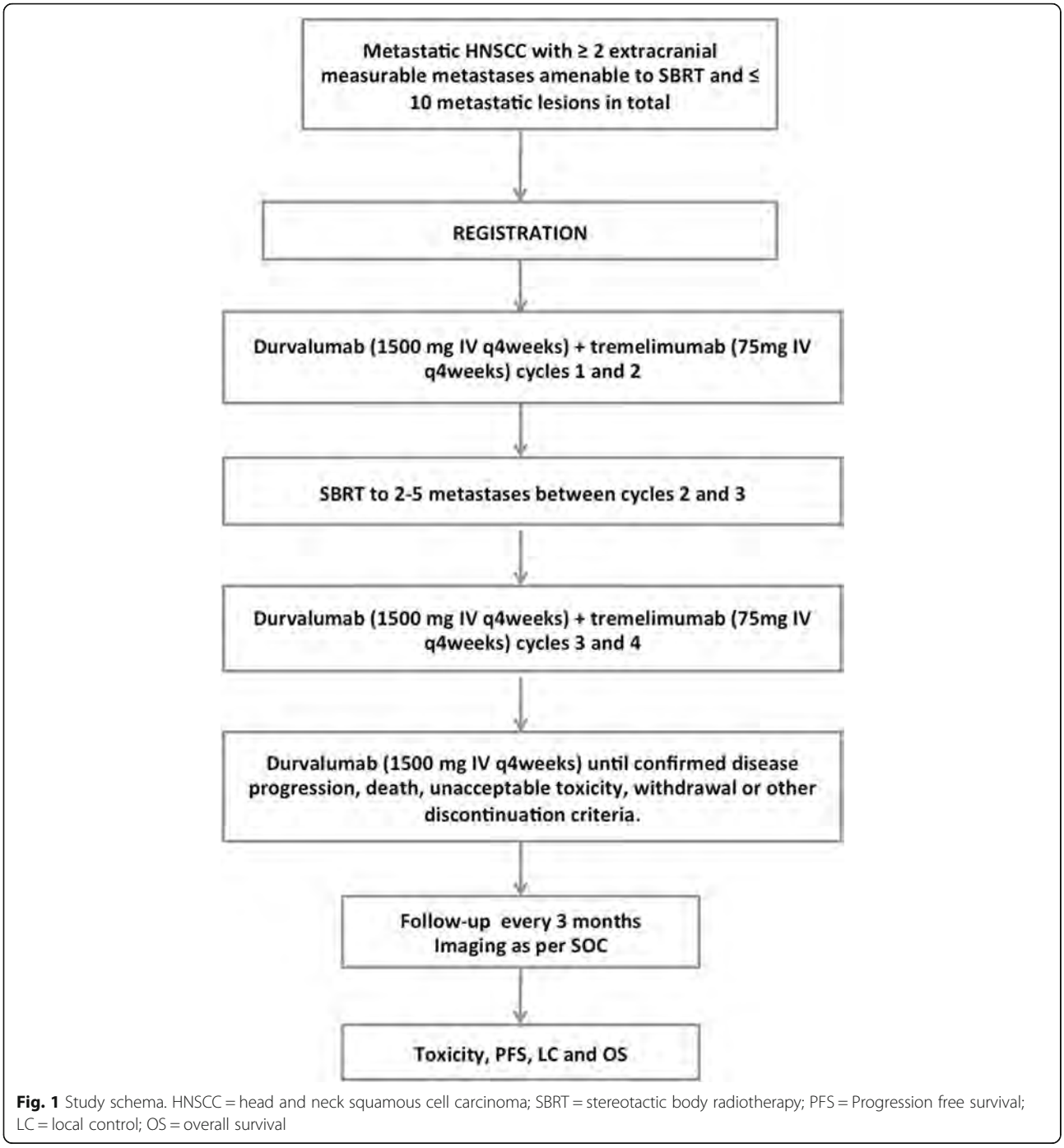

Fig. 1 Study schema. HNSCC = head and neck squamous cell carcinoma; SBRT = stereotactic body radiotherapy; PFS = Progression free survival; LC = local control; OS = overall survival

6. All standard tumor-staging procedures necessary to define the baseline disease burden must be completed within 28 days to registration
7. Pathologically (histologically or cytologically) confirmed diagnosis HNSCC at a metastatic site
8. ≥ 2 extracranial measurable metastatic lesions (no brain metastases) as per RECIST v1.1, or lesions < 1 cm showing at least a 1 mm increase in size 2 consecutive imaging that amenable to SBRT.
9. ≤ 10 metastatic lesions
10. Eastern Cooperative Oncology Group/World Health Organisation (ECOG/WHO) performance status score of ≤1
11. Adequate normal organ and marrow function as defined below:
    - Haemoglobin ≥9.0 g/dL
    - Absolute neutrophil count (ANC ≥ 1.5 x (> 1500 per mm3)

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- Platelet count ≥100 × 109/L (> 75,000 per mm3)
- Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN).
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5x ULN
- Serum creatinine CL > 40 mL/min by the Cockcroft-Gault formula

12. The following imaging workup to document metastases within 45 days prior to study registration:
    a. Computed tomography of the chest, abdomen and pelvis OR whole body Positron Emission Tomography/Computed Tomography
        - Patients with locoregional recurrence(s) are included only if they have evidence of distant metastasis; patients with locoregional recurrences which are symptomatic and/or potentially affect quality of life may undergo palliative radiation therapy to this region prior to enrolment on the protocol at the discretion of the treating physician. The dose and technique (conventional vs. SBRT) is at the discretion of the treating physician, with a dosimetric planning prioritization on organs at risk over tumor target coverage when in conflict. However, a minimum of 28 days must elapse before receiving protocol treatment.
13. Serum pregnancy test for female pre-menopausal patients
14. Patients who have received prior anti-PD-1, anti PD-L1 or anti CTLA-4, including durvalumab and tremelimumab if the following are fulfilled:
    - Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy.
    - All adverse events (AE) of prior immunotherapy must have completely resolved or returned to baseline prior to screening for this study.
    - Must not have experienced a ≥ Grade 3 immune related AE or an immune-related neurologic or ocular AE of any grade while receiving prior immunotherapy.
    - Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE and not have experienced recurrence of an AE if re-challenged.

Conditions for patient ineligibility

1. Nasopharyngeal carcinoma
2. Concurrent enrolment in another clinical study, unless it is an observational clinical study or during the follow-up period of an interventional study
3. > 4 prior treatment lines with systemic therapy
4. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolization, monoclonal antibodies) ≤ 30 days prior to the first dose of study drug
5. Any unresolved toxicity CTCAE Grade ≥ 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    - ○ Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician
    - ○ Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician
6. Any concurrent chemotherapy, investigational product (IP), biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions is acceptable
7. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug
8. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable
9. History of allogenic organ transplantation
10. Active or prior documented autoimmune or inflammatory disorders including diverticulitis, systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome are excluded. However, patients without active disease in the last 5 years may enter the trial after consultation with the study physician.
11. Uncontrolled undercurrent illness that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent
12. History of another primary malignancy except for
    - ○ Malignancy treated with curative intent and with no known active disease ≥5 years and of low potential risk for recurrence
    - ○ Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - ○ Adequately treated carcinoma in situ without evidence of disease
13. Presence of brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each preferably with IV contrast of the brain prior to study entry

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