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Original Research Article

Anti PD-L1 DUrvalumab combined with Cetuximab and RadiOtherapy in locally advanced squamous cell carcinoma of the head and neck: A phase I/II study (DUCRO)

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ABSTRACT

Introduction and background: Head and neck squamous cell carcinoma (HNSCC) has been increasingly recognized as an immune suppressive malignancy. The efficacy of immune checkpoint inhibitors (ICI's) in the context of recurrent/metastatic (R/M) setting anticipates the possible integration of immunotherapy into the therapeutic armamentarium of locally advanced disease. Durvalumab (DUR) is a humanized monoclonal IgG1, anti-PD-L1 antibody with promising data in R/M HNSCC. The aim of our study is to test the antitumor activity of a combined regimen incorporating an immune checkpoint inhibitor into a conventional bio-radiation strategy for the cure of unfavorable locally advanced HNSCC.
Methods/design: In this open label, multi-center, single-arm, phase I/II study, enrolled patients will receive Radiotherapy (RT) (69.9 Gy/2.12 Gy in 33 fractions) with concurrent Cetuximab (CTX) (400 mg/m^2 1 week before RT start followed by 250 mg/m^2 weekly) and DUR (fixed dose of 1500 mg every 4 weeks starting from RT-CTX week 1) followed by adjuvant DUR (to a maximum of 6 months after completion of RT-CTX). Primary endpoint of the study is 2-year progression-free survival (PFS). A safety run-in is planned after the enrollment of first 12, 24 and 36 patients. Patients affected by high-risk (≥N2a or ≥T3, any N) larynx, hypopharynx and HPV negative oropharynx or HPV-positive oropharynx (≥T2, ≥N2b, ≥10 pack/years) will be eligible.
Discussion: Conventional intensification strategies failed to provide any benefit for the cure of locally advanced HNSCC. For the still prevalent HPV-negative population and the high risk-HPV positive disease, there is an unmet need for alternative treatment paradigms. Potentially, the inhibition of the PD-1/PD-L1 checkpoint may synergize with both CTX and RT through immunologic interplay, ultimately aiming to reverse the HNSCC-induced immune suppression. The DUCRO study will seek to demonstrate if such a strategy may be safe and active.
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Trial registration: Eudract number: 2016-004668-20

Introduction

Loco-regionally advanced head and neck squamous cell carcinoma (HNSCC) is amenable to curative treatment but its management poses a significant challenge to the multidisciplinary team. In both primary [1,2] and high-risk post-operative settings [3,4], the combination of radiotherapy (RT) with cisplatin (100 mg/m^2 every 3 weeks) is the standard non-surgical approach. However, this treatment is associated with poor compliance and high rates of acute and late side effects [5].

In 2006, the landmark IMCL 9815 phase 3 trial [6] demonstrated that the combination of RT with Cetuximab (CTX), a chimeric mouse IgG1 monoclonal anti-EGFR antibody, led to improved survival compared with RT alone without an increased rate of ≥G3 acute toxicity or a detrimental effect on compliance and quality of life [7,8]. In current practice, this effective regimen is an option for patients with locally advanced HNSCC who are deemed ineligible to cisplatin, still pending the results of RTOG 1016

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(NCT01302834), the only large phase 3 randomized trial ever designed to directly compare RT-CTX with chemo-radiation with overall survival (OS) as primary endpoint. A series of clinical trials conducted in last 10 years exploring other anti-EGFR targeted strategies consistently failed [9–12] to replicate the magnitude of benefit observed with CTX, both in the locally advanced and recurrent/metastatic (R/M) setting. The hallmark of an unsuccessful intensification approach in biomarker-unselected patients is represented by the phase III RTOG 0522 study [13], which did not show any benefit by adding CTX to cisplatin-based chemoradiation, but only led to more ≥G3 toxicity and RT interruptions. The negative results of the trial generated the hypothesis [14] that platin-compounds and CTX may exert overlapping, but not supra-additive, effects of radiosensitization, therefore resulting in no additional benefit when administered together. The observation that the efficacy of anti-EGFR treatment in HNSCC is mainly restricted to CTX can justify the hypothesis that other factors play a role in favoring its anticancer effect, namely immunologic mechanisms. Other than inducing pro-apoptotic signals and inhibiting DNA double strand break repair mechanisms, the interplay of CTX with both innate and adaptive immunity has been described by several investigators [15–18]. In light of its chimeric antibody composition and IgG1 isotype, it has been shown that CTX can rapidly elicit a process of antibody-dependent-cellular cytoxicity (ADCC) by natural killer (NK) cells. In addition, CTX is able to enhance the antigenic cross-talk between dendritic and NK cells, which in turn may favor a sustained recruitment of EGFR-specific T cells [19,20].

Despite the fact that multimodality treatment is standard of care in locally-advanced HNSCC, the overall prognosis has not changed appreciably in last decades, with the only notable exception represented by the 60% reduction in risk of death observed in the growing population with Human Papilloma Virus (HPV) – driven oropharyngeal cancer.

It is growingly recognized that HNSCC is an immune suppressive malignancy [21,22]. Among other mechanisms of immune evasion, both HPV negative and positive tumors are able to induce a marked anergy in tumor-infiltrating lymphocytes (TIL's) by upregulating co-inhibitory signals at the tumor cell – T cell interface. In particular, as one of main immune system's mechanisms involved in preventing excessive inflammatory responses, the programmed death ligand 1 (PD-L1)/PD-1 axis is commonly exploited in HNSCC to promote immune escape. Over 60% of both HPV positive and negative tumors overexpress PD-L1, thereby exhausting PD-1 positive T cells and preventing immune elimination. Given these observations, it has been postulated that HNSCC may benefit from immunotherapeutic strategies, primarily aimed at PD-L1/PD1 checkpoint blockade. In analogy with two other anti-PD1 antibodies [23,24], Durvalumab (DUR) was the first humanized monoclonal IgG1 anti PD-L1 agent to yield promising anti-tumor response in heavily pre-treated, PD-L1 positive HNSCC patients with R/M disease [25]. The efficacy of immune checkpoint inhibitors (ICI's) in the context of R/M setting anticipates the potential implications of integrating immunotherapy into the therapeutic armamentarium of locally advanced disease.

For the still predominant patients' population with HPV – negative disease, disease-free survival has not improved beyond the historical 50% rate notwithstanding intensification approaches. In light of the unacceptable toxicity observed with conventional strategies, an unmet clinical need is to look for alternative therapeutic paradigms.

For HPV-positive, low-risk oropharyngeal cancer, ongoing de-escalation trials will seek to demonstrate if a reduction of treatment intensity can be safely employed, both in terms of non-inferior outcome and reduced morbidity compared with standard concurrent chemo-radiation. However, novel treatments have to be explored for the high-risk HPV-positive subgroup, where advanced disease and significant tobacco exposure are associated with suboptimal long-term disease control, particularly due to distant failure [26].

With this background in mind, the aim of our study is to test the antitumor activity of a combined regimen incorporating an immune checkpoint inhibitor into a conventional bio-radiation strategy for the cure of unfavorable locally advanced HNSCC.

Materials and methods

Study design and patient population

In this open label, multi-center, single-arm, phase I/II study, enrolled patients will receive RT (69.9 Gy/2.12 Gy fx in 33 fractions over 7 weeks) with concurrent CTX (400 mg/m^2 1 week before RT start followed by 250 mg/m^2 weekly) and DUR (fixed dose of 1500 mg delivered every 4 weeks starting from RT-CTX week 1) followed by adjuvant DUR with the same schedule to a maximum of 6 months after completion of RT-CTX (flow chart shown in Fig. 1). The total treatment time will be of 8 months. After the last administration of DUR, the follow-up time will consist of 36 months of observation.

Patients will undergo a centralized assessment of their tumor tissue sample to determine PD-L1 status through Ventana SP263 assay. A pre-specified cut-off level of ≥25% of tumoral PD-L1 expression will categorize the samples into PD-L1 positive or negative.

Patients eligible for curative treatment not considered for primary surgery based on multidisciplinary decision will be enrolled. The main inclusion criteria are as follows:

- histologically proven diagnosis of squamous cell carcinoma of the oropharynx, hypopharynx and larynx
- for patients with oropharyngeal cancer: confirmed HPV status by HPV-DNA in-situ hybridization prior to registration
- clinical stage of HPV-negative oropharynx and all hypopharynx and larynx: T1-2, N2a-N3 or T3-4, any N (AJCC, 7th ed.)
- clinical stage of HPV-positive oropharynx: T2-4, N2b-N3 (AJCC, 7th ed), with smoking history of ≥10 pack/years
- adequate normal organ and marrow function
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

- head and neck cancer of any other primary anatomic location not specified in the inclusion criteria including patients with HNSCC of unknown primary

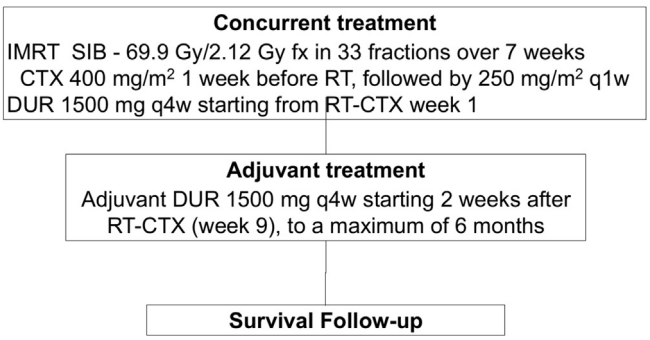

Fig. 1. Study schema.