G.O.N.O.

GRUPPO ONCOLOGICO DEL NORD OVEST

TITLE:

The CONFRONT Phase I – II Trial: A*C*tivati*ON* o*F* immune *R*esp*ON*se in pa*T*ients with R-M Head and Neck Cancer. Multimodality immunotherapy with Avelumab, short course radiotherapy and Cyclophosphamide in Head and Neck cancer.

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1. **PI** Marco Carlo Merlano
2. **Institution** G.O.N.O Gruppo Oncologico Nord Ovest
3. **Contact Info:**

Principal Investigator

MERLANO MARCO CARLO
mcmerlano@gmail.com, merlano.m@ospedale.cuneo.it
Oncology Department AO Santa Croce E Carle
Via Michele Coppino 26
12100 Cuneo Italy
+390171616739
Fax +390171616737

Coinvestigators

NERINA DENARO nerinadenaro@gmail.com Oncology Department AO Santa Croce e Carle Via Michele Coppino 26 12100 Cuneo Italy +390171616350 Fax +390171616737
ELVIO GRAZIOSO RUSSI elviorussi@gmail.com Oncology Department AO Santa Croce e Carle Via Michele Coppino 26 12100 Cuneo Italy +390171616739 Fax +390171616737
ELENA FEA fea.e@ospedale.cuneo.it Oncology Department AO Santa Croce e Carle Via Michele Coppino 26 12100 Cuneo Italy +390171616350 Fax +390171616737
ANNAMARIA MERLOTTI merlotti.a@ospedale.cuneo.it Radiotherapy Department AO Santa Croce e Carle Via Michele Coppino 26 12100 Cuneo Italy +390171616739 Fax +390171616737

INVESTIGATOR AGREEMENT

I have read the Protocol entitled **The CONFRONT Phase I – II Trial: A*C*tivati*ON* o*F* immune *R*esp*ON*se in pa*T*ients with R-M Head and Neck Cancer. Multimodality immunotherapy with Avelumab, short course radiotherapy and Cyclophosphamide in Head and Neck cancer** and I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for good clinical Practice and applicable regulatory requirements.

Principal Investigator's Signature

Dr. Marco Carlo Merlano

May 7th, 2018

Date

PARTICIPATING SITE PRINCIPAL INVESTIGATOR

Dr. _____

Signature _____

1.0 TRIAL SUMMARY

Phase I - II trial of the combination of cyclophosphamide, RT, and Avelumab in relapsed/metastatic HNSCC (R/M-HNC).

Patients pretreated with at least one line therapy containing platinum, fluorouracil, and Cetuximab. Treatment consists of metronomic cyclophosphamide 50 mg daily without drug free break, avelumab 10 mg/kg d1 and 15 q 29, and radiotherapy in one or three daily fractions up to 8 Gy maximum dose, starting at day 8.

The aim of the study is to reverse tumor immune-escape by:

1. Provide a self-vaccination with radiotherapy
2. Inhibit the immunosuppressive CD4+ CD25+ FoxP3+ Treg cells with metronomic cyclophosphamide
3. Reactivate the effector T cell by the inhibition of PD-1 – PD-L1 axis with avelumab.

Due to the supposed biological effects of the present trial, an ancillary translational study is needed and will be extended to all the patients' population enrolled.

2.0 BACKGROUND & RATIONAL

2.1 Unmet medical need and trial rational

2.1.1 Unmet clinical need

Platinum resistant relapsed/metastatic HNC (RM-HNC) shows a dismal prognosis. No approved second line are yet available.

Methotrexate is sometimes used following platinum failure or in patients not fit enough for platinum therapy, but this agent has not demonstrated any Overall Survival (OS) improvement.

Second line treatment with methotrexate was recently compared to afatinib in a randomized trial. Response rate was low in both arms (6.5% vs 10% respectively). Progression free survival favoured significantly afatinib, but the difference was clinically irrelevant[1].

The EGFR-targeting monoclonal antibody cetuximab (plus platinum-based chemotherapy) was approved in the US and Europe (NCCN. Clinical Practice Guidelines in Oncology. Head and Neck Cancer) [2] in first line therapy of relapsed metastatic disease.

However, only FDA approved cetuximab in second-line but not EMA, due to the limited benefit observed.

Taxanes have also been used. However, no study has been able to show that these agents improve OS.

The new insight in immunology as well as the understanding of the immunologic effects both of chemotherapy and radiotherapy, paves the way to a novel approach to cancer treatment based on the strengthening of host natural defence rather than to the direct tumor aggression.
Phase II and III trials showed improvement in OS and quality of life in patients treated with anti-PD-1 regardless the number of prior chemotherapy lines. Results showed also a limited but significant number of long-term survivors. However, most patients do not achieve an objective response or relapse within one year from treatment start. This outcome reflects the limit of targeting a single pathway in the achievement of major results in this setting of patients[3-4].

2.1.2 Rational of the trial

Hereby we propose a phase I - II trial in RM-HNC based on pharmacologic and physic interventions related to each other facing immunology as a system rather than a single pathway, theoretically able to restore immune competence toward the tumor. The immune suppressive mechanisms that could be affected by this study and how the experimental approach could inhibit them, are listed below:

- PD-1 - PD-L1 axis is widespread among immune cell family including CTL, Treg, NK, NKT, APC and others[5] showing, for example, opposite effect in CD8+ CTL (inhibitory signal)[6] or in CD4+ CD25+ Foxp3+ (activating signal)[7].

- Depletion of Treg results in tumor regression, in experimental models[8-9]. The effect seems to be dependent on the extent of Treg suppression[10].

- Avelumab is a fully human anti-PD-L1 IgG1 monoclonal antibody. It enables the activation of T-cells and the adaptive immune system by inhibiting PD-1 - PD-L1 axis, induces antibody-dependent cell-mediated cytotoxicity (ADCC) and engages the innate immune system[11].

- Low dose cyclophosphamide (metronomic cyclophosphamide), selectively reduce Treg population both in experimental models and in humans, but it does not affect effector T cells[12]

- PD-1 – PD-L1 axis enhances and sustains Foxp3 expression and the suppressive function of inducible Tregs (iTrge)[7]. The blockade of the PD1 – PDL1 axis by Avelumab may have an opposite effect.

- The contemporary use of two, independent, mechanisms of Treg control (Avelumab inhibiting Treg clonal expansion and functions, and cyclophosphamide reducing Treg population) may result in a profound inhibition of Treg population.

- If the suppressive mechanisms of the immune system are weakened, the release of high quantity of tumor specific antigens or stress related antigens (epcam, HSPs, HMBG-1, Calreticulin, ATP), obtained by the induction of immunogenic cell death[13] may induce a sort of "self vaccination" resulting into an effective immune response.

- Radiation may induce immunogenic cell death[14] even in heavily pretreated patients in whom the use of cytotoxic chemotherapy may not, due to the previous exposure to drugs and the development of resistance mechanisms. More precisely, this effect is considered the basis of the Abscopal effect, i.e. the regression of tumor deposits outside the irradiated field. This effect is more frequently observed with low-dose, non ablative, hypofractionated radiation therapy (described at point 2.3.2) and represent a proof of concept that in particular situations, radiotherapy act as an inducer of "self vaccination".

- IgG1 mAbs, such as Avelumab, triggers ADCC; PD-L1 is widely express in many tumors and so ADCC may represent an additional mechanism of tumor control.

2.2 Pharmaceutical and Therapeutic Background

2.2.1 Avelumab

Avelumab is anti-PD-L1 monoclonal antibody (MSB0010718C). Avelumab selectively binds to PD-L1 and competitively blocks its interaction with PD-1. Compared with anti-PD-1 antibodies that target T-cells, avelumab targets tumor cells, and therefore is expected to have fewer side effects, including a lower risk of autoimmune-related safety issues, as blockade of PD-L1 leaves the PD-L2 – PD-1 pathway intact to promote peripheral self-tolerance.
For complete details of the in vitro and nonclinical studies, please refer to the Investigator's Brochure.

Avelumab, as a MoAb, is not expected to have a direct drug-drug interaction (DDI) effect on other small molecule drugs. In addition, like other checkpoint inhibitors in the class, avelumab is not considered to be a cytokine modulator, which was confirmed by cytokine data collected from EMR 1000700-001. Several major circulating cytokines were measured in EMR 1000700-001 over 6

weeks including IL-1b, IL-2, IL-4, IL-6, IL-10, IFNγ, and TNFα which have been reported to be involved in cytochrome P (CYP) 450 expression [15] .After repeated administration of avelumab at 10 mg/kg, only a transient and mild change (< 2-fold) in cytokine was observed, which is consistent with published results from another anti-PD-L1 antibody [16] .

Based on the acquired information, avelumab is unlikely to have an effect on drug metabolizing enzymes or transporters in terms of inhibition or induction.

In summary, Avelumab is not expected to have DDI with other drugs because it is primarily metabolized through catabolic pathways and is not expected to affect the expression of CYP450 enzymes.

2.2.1.1 Pre-clinical Studies

Avelumab has been investigated in 14 nonclinical trials.

The nonclinical pharmacology investigations have shown that avelumab functionally enhances T cell activation in vitro and significantly inhibits the growth of PD-L1 expressing tumors in vivo. In agreement with the hypothesis that PD-L1 neutralization acts to release anti-tumor T cells from immune suppression, the anti-tumor effects of avelumab in vivo were found to be primarily mediated by CD8+ T cells, as highlighted by the observation that the in vivo depletion of this cell type was sufficient to completely abrogate anti-tumor activity. Depletion of CD8+ T cells also eliminated the synergistic efficacy of avelumab when given in combination with radiotherapy, suggesting that this combination synergizes through cooperative immune-enhancing mechanisms. As a second mode of action, avelumab is capable of stimulating ADCC activity against PD-L1+ tumor cells in vitro and elimination of ADCC potential in vivo significantly reduced anti-tumor activity. Of the combination approaches that have currently been explored for avelumab, chemotherapy with FOLFOX and radiation therapy showed the better tumor growth inhibition. In particular, radiation therapy was found to be a highly synergistic combination capable of causing complete regression of established tumors with the potential to generate anti-tumor immune memory.

2.2.1.2 Phase I study

Recently, Heery C.R. et al. published a phase Ia on avelumab in a multicohort population. 53 patients were enrolled and avelumab was tested at 1 mg/kg, 3 mg/kg, 10 mg/kg and 20 mg/kg. No dose limiting toxicity (DLT) was observed and no maximum tolerated dose (MTD) was determined. On the basis of target occupancy, immunological analysis and pharmacokinetics, the dose of 10 mg/kg was chosen for further development.[17]

2.2.1.3 Ongoing Clinical Trials

Avelumab is currently in clinical development in 12 phase III trials.

As of 05 November 2015, 1353 subjects have received at least 1 dose of Avelumab at doses ranging from 1.0 to 20 mg/kg in Trial EMR 100070-001. Overall, 1300 subjects have received the proposed dose of 10 mg/kg in the pooled expansion cohort. No new safety signals were identified upon preliminary review of data from these subjects.

The safety profile of avelumab has so far been evaluated from data in more than 1400 subjects in 4 ongoing trials in subjects with various solid tumors: Trial EMR 100070-001, Japan local Trial EMR 100070-002 , Trial EMR 100070-003, and Trial EMR 100070-004 . These safety data from subjects with different tumor types treated with avelumab suggest an acceptable safety profile of the compound. Most of the observed events were either in line with those expected in subjects with advanced solid tumors or with similar class effects of MoAb blocking the PD-1/PD-L1 axis.

Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions have been identified as important risks for avelumab. Respective risk mitigation measures have been implemented in all ongoing clinical studies with Avelumab.

2.3 Information on Other Trial-Related Therapy

2.3.1 Cyclophosphamide

Cyclophosphamide, a nitrogen mustard, is an alkylating agent from the oxazophosphorine group.

The former undergoes spontaneous degradation whereas the latter is excreted into the urine. These compounds crosslink DNA by adding an alkyl group (CnH2n+1) to the guanine base of DNA, at the number seven nitrogen atom of the imidazole ring. This induces inhibition of DNA replication, leading to cell death. In addition, CYC adds methyl or other alkyl groups onto molecules where they do not belong which in turn inhibits their correct utilization by base pairing and causes a miscoding of DNA. Alkylating agents are cell cycle-nonspecific. CYC damages DNA via the formation of cross-links (bonds between atoms in the DNA which prevents DNA from being separated for synthesis or transcription, and via the induction of mispairing of the nucleotides leading to mutations. CYC exerts its cytotoxic effect on both resting and dividing lymphocytes. It undergoes extensive metabolism via the cytochrome-P450 enzymatic system with phosphoramide mustard and acrolein as the main active and inactive metabolites, respectively.[12]

2.3.1.1 Metronomic Cyclophosphamide

Cyclophosphamide was used at dosages far below the maximum tolerated doses (MTD) against many tumor types in a scheduling called "metronomic".

Metronomic chemotherapy refers to the administration of cytotoxic drugs at doses significantly less than the MTD and with short or no drug-free breaks. When metronomic cyclophosphamide (mCTX) is given, a daily scheduling and the oral route of administration are usually preferred. Penel N et al recently reviewed this topic[18].

Most dosages of oral mCTX vary between daily 50 mg to 100 mg total dose or per square meter of body surface.

mCTX was also combined with other drugs including chemotherapy, anti-angiogenetic drugs and monoclonal antibodies directed against the PD-1 – PD-L1 axis.

Mechanism of action and toxicity of mCTX

Initially, the mechanism of action of mCTX was believed to depend on its antiangiogenic activity demonstrated in experimental models. More recently, additional effects of mCTX were identified both in experimental models and in humans. They include the selective elimination of immunosuppressive cells and the stimulation of the antitumor immune responses. Hao Y-B et al have recently reviewed this topic[19].

mCTX showed activity against a numebr of different solid tumors, including some who do not respond to standard dose of cyclophosphamide, such as prostate cancer, colon cancer and sarcoma[20].

In the next paragraphs we describe the toxicity profile of mCTX at different scheduling and dosages given either alone or in combination with other drugs, including immune checkpoints inhibitors, in retrospective and prospective clinical studies.

Metronomic cyclophosphamide: Doses, schedulings and toxicity

Cyclophosphamide 50 mg daily without drug-free break

In 2010, Nelius t et al reported a pilot prospective study with cylophosphamide, 50mg daily given to 17 patients with metastatic prostate cancer all pre-treated with docetaxel. No grade III or IV toxicity was recorded and no one patient required treatment breaks due to side effects. Less than 13% of the patients experienced grade I-II toxicity[21].

Ladoire S et al reported a second prospectic study in 23 prostate cancer pts with cyclophosphamide 50mg daily. All these patients were symptomatic, 3 had ECOG performance status of 3 and 13 were ECOG 2. Median age was 74 (range 55 - 88).

All patients were preatreated with docetaxel, and 13 received 2 ore more lines of chemotherapy before cyclophosphamide. One patient with extensive bone metastases and heavy pre-treatment,

required treatment stop due to non-febrile grade IV neutropenia. Two patients developed Grade III anemia, while the remaining did not developed grade III-IV toxicity[22].

Cyclophosphamide 50 mg/m^2 daily without drug-free break

Lord R et al reported a phase II study on 58 patients with hormone refractory prostate cancer. Median age was 69 (range 51 – 86). No one patient required to stop treatment due to side effects. Three patients required a break (anemia, diarrhea and neutropenia) of 2 weeks before recommencing treatment. Grade III anemia was observed in 1 patient, and 1 other patient developed grade III non febrile neutropenia. No grade IV toxicity was observed[23].

Cyclophosphamide 50 mg b.i.d. daily (100 mg daily) every other week

Penel N et al randomly assigned 88 pts heavily pretreated to megestrol acetate or mCTX (100 mg daily). Patients with different cancer types were enrolled. Most of them suffered from colon and rectum cancer, lung cancer, sarcoma and melanoma.

Almost 80% of them received 2 or more previous lines of therapy and almost 50% of the patient population had ECOG performance status of 1 or 2. Median age was 66 (range 57 - 71).

Among 44 patients enrolled to metronomic cyclophosphamide, no one developed grade IV toxicity. Two developed grade III vomiting, and grade I-II toxicity was observed in 10 and 4 patients respectively. There was neither dose reduction nor transient treatment break[20].

Overall, prospective clinical trials based on mCTX at 50 mg daily, 50 mg/m^2 or 100 mg daily, show that the treatment is remarkably well tolerated even in elderly and heavily pretreated patients.

Metronomic cyclophosphamide in elderly and frail patients

Fontana A et al reported a retrospective series of 29 consecutive elderly patients (median age 83, range 78 - 92) with prostatic cancers. The median number of comorbidities was 2 and 19 patients were deemed frail. Ten patients received one or more previous chemotherapy line. Patients where treated with the combination of cyclophosphamide (50 mg daily without drug-free break) and celecoxib. No Grade III-IV toxicity was observed. Four patients developed grade II anaemia and 2 grade II thrombocytopenia. One of the two patients with thrombocytopenia discontinued the treatment[24].

This experience confirms that mCTX can be administered to aged patients and that the treatment can be extended even to frail patients.

Metronomic cyclophosphamide: combination

Many clinical trials investigated mCTX in combination with other metronomic chemotherapeutic drugs and/or with target agents or immunotherapy (inhibitors of PD-L1 –PD-1 axis).

Phase I combination trials are rarely reported and in most of them, due to the low anticipated toxicity, cyclophosphamide is maintained at constant dose (mainly 50 mg daily without breaks) and the dose escalation is limited to the companion drug[25,26].

Orlando L et al, investigated the combination of cyclophosphamide 50 mg daily without drug free break and methotrexate, 5 mg twice a week on 153 breast cancer patients, 70% of whom preatreated with at least one course of chemotherapy. The Authors updated the results of their study, and described the outcome of the 26 patients who achieved a prolonged clinical benefit, i.e. remained on treatment for a minimum of 12 months. No grade IV side effect was observed. Grade III neutropenia occurred in 2 patients and thrombocytopenia in 1. One additional patients developed a grade III clinically silent increase in transaminases. No one of these patients required stop the treatment due to side effect[27].

This study suggests that even combined with low dose methotrexate and delivered for 1 year or more, mCTX is an exceptionally well tolerated treatment with no significant side effects.

Garcia A et al reported a phase II study of bevacizumab, 10 mg/kg every two weeks and mCTX 50 mg daily. The study showed that mCTX did not exacerbate bevacizumab toxicity[28].

Metronomic cyclophosphamide: combination with immune check point inhibitors

Toulmonde M et al recently reported a phase II study combining the anti PD-1 pembrolizumab at the standard dose of 200 mg and mCTX at 100 mg daily for 7 days every other week. Authors treated 57 patients with advanced soft tissue sarcomas. Most of them were heavily pretreated (74% received 2 or more prior lines of chemotherapy). Median age was 59.5 (range 18,5 - 84) and median ECOG performance status was 1. In the toxicity report, grade I and II were cumulated as well as grade III and IV. The most common side effects were grade I-II fatigue, anemia and diarrhea. Ten patients experienced grade III-IV toxicity (fatigue in 2, oral mucositis in 2, anaemia in 4 and lymphocyte count decrease in 2). Overall, 4 patients discontinued the treatment due to toxicity as per protocol definition. No grade V or hospitalization were reported[29].

2.3.2 Radiotherapy

Beyond its well know antitumor cytotoxic effect, radiation induces changes to tumor immunogenicity. These changes are both immune stimulatory and immunosuppressive. The prevailing effect is dose and fractionation dependent. This topic has been recently reviewed by S.J. Haikerwal et al30.

Low single dose (< 2 Gy) tends to promote anti-inflammatory (immune suppressive) responses, leading to reduced release of nitric oxide and IL-1β, and to increased release of IL-10 and TGF-β.
High single dose (> 5 – 10 Gy) results in induction of MHC class I expression, favouring recognition of tumor cells by Effector CD4+ and CD8+ T cells, and releases markers of immunogenic cell death (calreticulin, HMGB1, ATP) able to trigger the immune system through the activation of immature dendritic cells. In support of these experimental data, Chi HK e al delivered a single dose of 8 Gy of external-beam radiation therapy to 14 patients with hepatocellular carcinoma. After the treatment, patients received an intratumoral administration of immature dendritic cells. Twelve patients achieved a partial response and no treatment related grade III-IV toxicity was observed31.
Chandra et al reported a second interesting experience. He reviewed 47 cases with metastatic melanoma treated at his institution with ipilimumab and radiotherapy and found a significant correlation between Abscopal effect and multiple fraction radiotherapy. Median age of patients was 57 (50 - 65); median total dose of RT was 30 (8 - 66); radiation fraction size (Gy) was 3 (2 - 25); median time between radiotherapy and ipilimumab (months) < 1. Median survival was 28 months and the estimated 5-year survival was 20%32.
More useful for the present project, the Toulose University Institute of Cancer in France reported a series of 59 melanoma patients treated with PD-1 –PD-L1 axis inhibitors (either pembrolizumab or nivolumab). Clinical outcome and acute and delayed toxicity were compared between patients receiving concurrent hypofractionated, non ablative radiotherapy or no irradiation.
After a 10-month median follow-up, the objective response rate was significantly higher in those receiving radiotherapy. More important, this study showed that PD-1 –PD-L1 axis inhibitors can be safely combined with hypofractionated non ablative radiotherapy.
Indeed overall immune related adverse event were 29% in patients receiving concomitant radiotherapy and 34% in those who did not. Grade III-IV adverse event were 7% in those receiving radiotherapy and 12% in those who did not. Even delayed toxcity did not differ between the two groups. In particular the only two case of grade III-IV delayed toxicities occurred in the non irradiated patients33.

These data suggest that hypo-fractionated radiation regimen and/or low dose, non-ablative radiation, are more effective at modulating the immune stimulatory status of cancer. Consistent with this theory, most clinical cases reporting an Abscopal effect in response to localized radiation therapy, employed hypo-fractionated radiotherapy (reviewed in De la Cruz-Merino L et al34).
Based on these preclinical and clinical data, many ongoing trials testing the combination of immunotherapy and low total dose, hypofractionated radiotherapy are presently recruiting.

Among them, many trials are evaluating inhibitors of the PD-1 – PD-L1 axis (pembrolizumab, durvalumab and nivolumab, always given at standard dose) with radiotherapy delivered at different fractionations and total doses: single fraction of 20 Gy or 17 Gy (NCT 02499367, NCT 02303566, NCT 02639026) or multiple fractions, such as 6 Gy x 5 (NCT 02730130) or 8 Gy x 3 (NCT 02639026).

Moreover, recently published data reported above, reassure about the toxicity of radiotherapy concurrent with PD-1 –PD-L1 axis inhibitors: no additional toxicity was observed by the combination of these two treatments in the daily clinical practice.

2.4 Rational for dose selection in the present study

On the basis of the data reported in the literature, we choose the following drug and radiation dose in our experimental study:

Published experiences of mCTX (100 mg/daily every other week) in combination with an inhibitor of the PD-1 –PD-L1 axis at its standard dose showed no increased toxicity over that expected from the immune check point inhibitor alone.

We chose to deliver mCTX at 50 mg/daily without drug free breaks because of its excellent toxicity profile and in particular the lack of G III vomiting, compared to the every other week scheduling.

Moreover, this dose level does not affect effector T cells as showed by Ghiringhelli et al 12.

Avelumab is delivered at the standard dose of 10mg/kg determined only on the basis of target occupacy, immunological analysis and pharmacokinetics, because neither MTD nor DLT was observed in the published phase I study (Heery CR).

Moreover, data with other inhibitors of the PD-1 –PD-L1 axis shows that these drugs can be safely added to metronomic cyclophosphamide or hypofractionated, non ablative radiotherapy.

Radiotherapy is delivered at a maximum dose of 8 Gy either in a single fraction or up to 3 daily fractions. There is no agreement whether single fraction or multiple fractions is to be preferred, as clearly demonstrated by the heterogeneity of radiotherapy schedulings choosen by ongoing clinical trials in combination with immune check point inhibitors. There is however consensus that a non ablative (low) dose is to be preferred when radiotherapy is used for its immunologic properties. The dose we selected is in the range of those accepted on the basis of preclinical and clinical experience31, 32.

2.5 Risk/Benefit profile

There are two levels of potential risks in this study:

- risks related to an excess of toxicity
- risks related to reduced benefit compared to the benefit expected with the standard treatment.

Risk related to an excess of toxicity.

There is no such a risk with any of the drugs/procedures used in this study: both chemotherapy (metronomic cyclophosphamide) and radiotherapy (non ablative dose) are well tolerated with anecdotal cases of grade III toxicities. The inhibitor of PD-L1 – PD-1 axis avelumab did not show any DLT at doses double of that selected for clinical use.

Data published in the last few months did not show any increased toxicity by the combination of inhibitors of PD-L1 – PD-1 axis with either non ablative radiotherapy or metronomic cyclophosphamide. Therefore it seems unlikely that the combination of all these drugs and non ablative radiotherapy may induce an unacceptable toxicity profile. However, considering that the combination under investigation has not been previously tested, this study is designed as a phase I – II trial. Phase II will be performed only after the demonstration of tolerability of the schedule within the phase I study.

Risks related to reduced benefit.

PD-L1 – PD-1 axis inhibitors are the new standard treatment for second line relapsed metastatic head and neck cancer. There is no credible alternative to PD-L1 – PD-1 axis in second line. Since avelumab is a PD-L1 – PD-1 axis inhibitors and till now no differences among the drugs of this family have been observed when tested in head and neck cancer, we presume that the patients enrolled in the present study will receive at least the same benefit of the patients treated in the daily clinical practice.

Expected benefit

The immune response theoretically inducible by the proposed combined treatment, could strongly improve the activity of avelumab without increasing its toxic profile.

3.0 STUDY OBJECTIVES

3.1 Primary study Objectives

a. Assessment of the safety of the combination of avelumab, mCTX and non ablative radiotherapy (phase I).

b. Assessment of activity of avelumab, mCTX and non ablative radiotherapy in a population of heavily pre-treated RM-HNSCC patients (phase II).

3.2 Secondary study Objectives

c. Assessment of the safety of the combination of avelumab, mCTX and non ablative radiotherapy.
d. Description of progression free survival (PFS) and overall survival (OS)
e. Exploratory description of Health-related Quality of Life

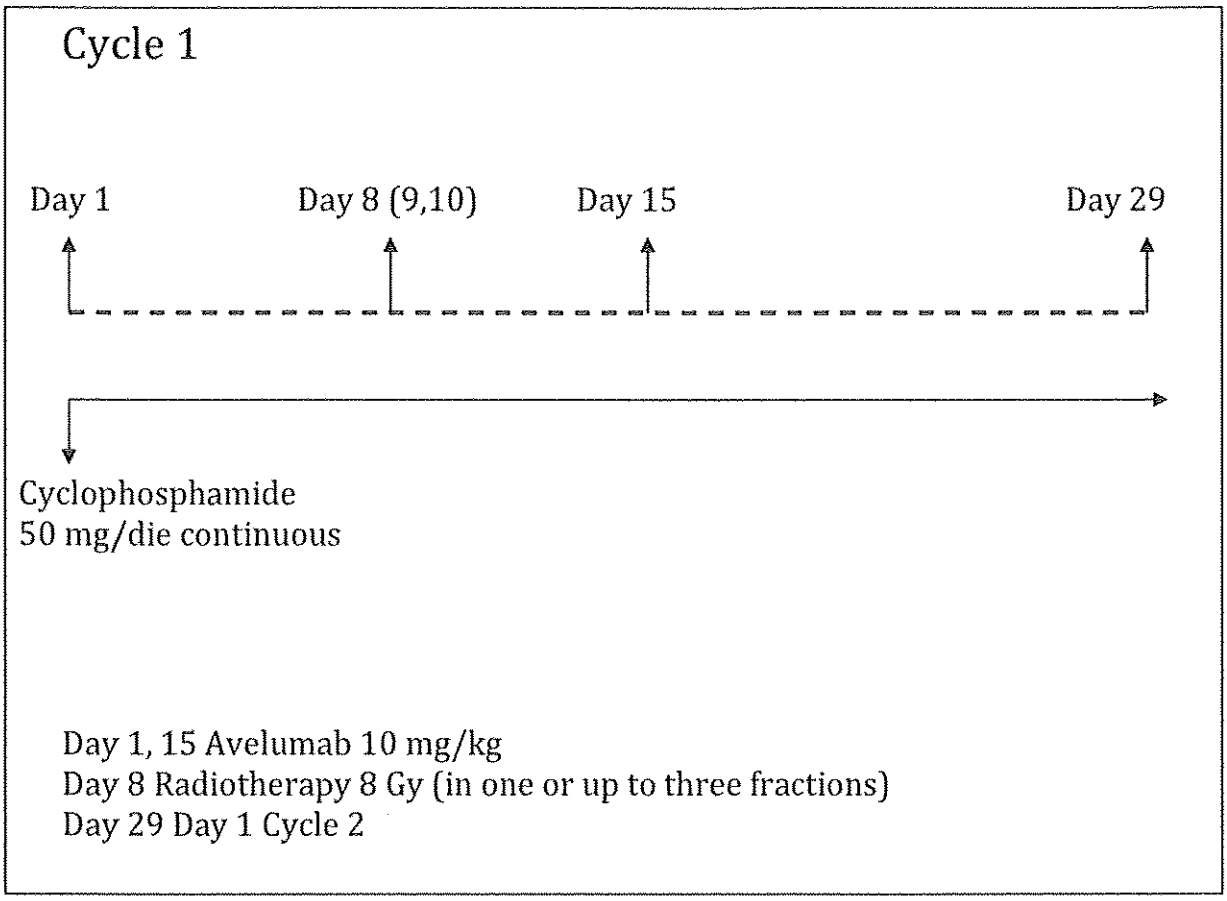
4.0 STUDY DESIGN

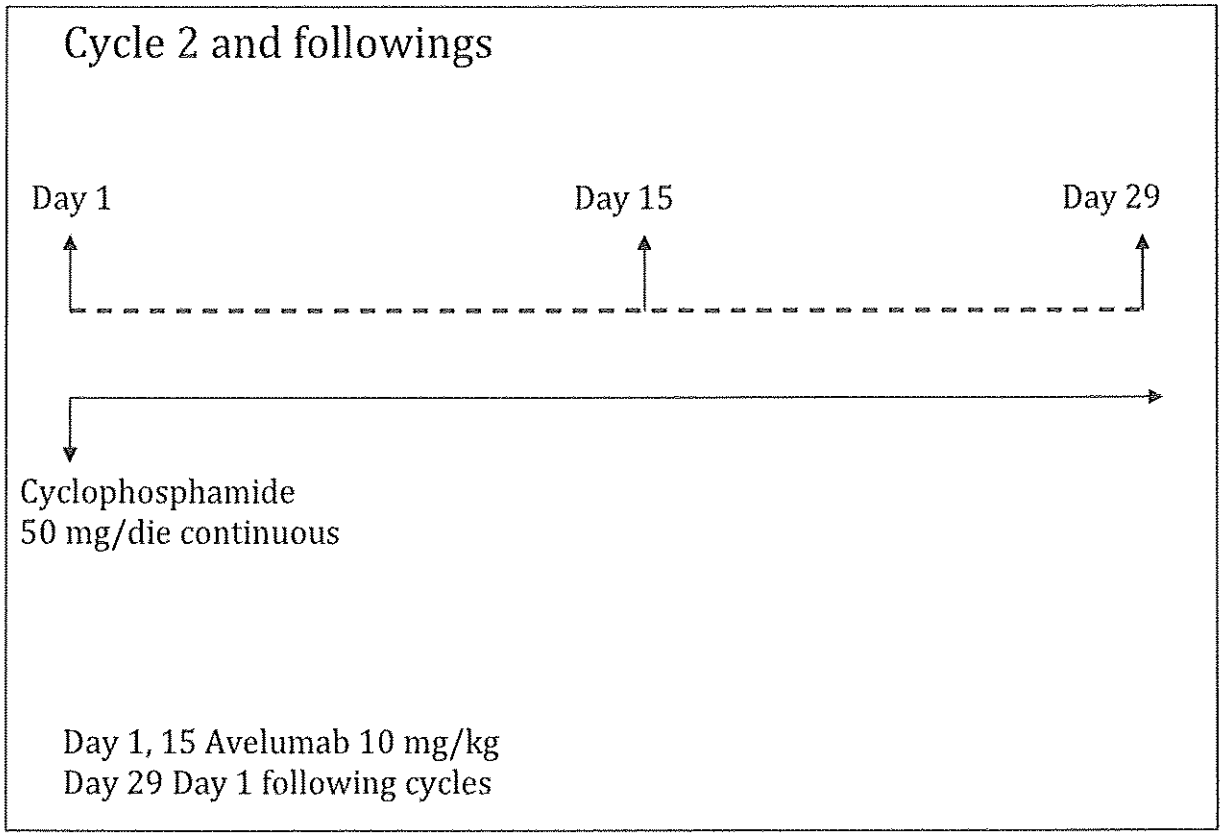
The "CONFRONT" trial is a phase I - II study in patients with head and neck cancer who received at least one prior line of systemic therapy for relapsed or metastatic disease

4.1 Treatment

- Avelumab 10 mg/Kg i.v. day 1 repeated every 14 days until progression, unacceptable toxicity or informed consent withdrawal
- Cyclophosphamide 50/mg tab daily continuously until progression or unacceptable toxicity
- Radiotherapy day 7: targeting 1 macroscopic lesion with highly conformal hypofractionated RT with maximum doses of 8 Gy, in 1 – 3 fractions, depending on constraints of healthy tissues and toxicity risk.

4.2 Trial Diagram





5.0 SELECTION CRITERIA

5.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for the translational study.

2. Be ≥ 18 years of age on day of signing informed consent.

3. ECOG Performance Status 0-2.

4. Have histologically or cytologically-confirmed recurrent or metastatic (disseminated) head and neck squamous cell carcinoma

5. Have a disease progression after treatment with at least one line of therapy including at least Cisplatin, Fluorouracil and Cetuximab for recurrent (disease not amenable to curative treatment)/metastatic disease.

6. Measurable disease by RECIST criteria.

7. At least one metastatic site suitable for irradiation

8. Life expectancy > 3 months.

9. Adequate bone marrow function: neutrophils $\geq$ 1.5 x 10^9/L, platelets $\geq$ 100 x 10^9/L, hemoglobin $\geq$9 g/dL.

10. Adequate liver function: AST and ALT levels $\leq$ 2.5 × ULN; bilirubin $\leq$ 1.5 x ULN.

11. Adequate renal function: creatinine clearance $\geq$ 30 mL/min (Cockroft-Gault).

12. Fertil men must be using adequate contraceptive measures throughout the study period if their partner are women of childbearing potential.

13. If of childbearing potential, women must use effective contraceptive method (Pearl Index < 1; e.g. oral contraceptive (pill), hormone spiral, hormone implant, transdermal patch, a combination of two barrier methods (condom and diaphragm), sterilisation, sexual abstinence) for the study duration and for at least 6 months after last avelumab treatment administration if the risk of conception exists.

5.2 Exclusion Criteria

1. History of malignant disease (with the exception of non-melanoma skin tumours and/or in situ cervical cancer) in the preceding five years.

2. Brain metastases.

3. Autoimmune disorders. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible.

4. Allergic disorders.

5. Cyclophosphamide treatment contraindications:
   a. Cystitis.
   b. Urinary Obstruction.

c. Inadequate bone marrow function: WBC <2900 mm3 and/or HCT <30% and/or platelets count <90000 mm3.
d. Active infections.
e. Pregnancy or breast feeding.

6. Prior treatment with inhibitors of the PD-L1 – PD – 1 axis or inhibitors of CTLA-4 (immune check point inhibitors)

7. Previous HBV or HCV infections.

8. Current use of immunosuppressive medication, EXCEPT for the following: a. intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

9. Any active infection requiring specific treatment (Antibiotics, antimicotic, antiviral).

10. Radiotherapy within 6 weeks before enrolment

11. Other non-malignant uncontrolled systemic diseases or social conditions that would preclude trial entry in the opinion of the investigator.

12. Prior organ transplantation including allogenic stem-cell transplantation.

13. Vaccination within 4 weeks of the first dose of avelumab and while on trials is prohibited except for administration of inactivated vaccines.

14. Persisting toxicity related to prior therapy (NCI CTCAE v. 4.03 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.

15. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behaviour; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or

may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

16. Avelumab treatment contraindications:
    a. Hypersensitivity to the active ingredient or to any excipient.
    b. Inadequate bone marrow function: WBC <2900 mm3 and/or HCT <30% and/or platelets count <90000 mm3.
    c. Uncontrolled serous effusions (pleural, pericardic or peritoneal)
    d. Blood Pressure <60 mmHg.
    e. Pregnancy or breast feeding.
    f. Active infections.
       Known history of testing positive for HIV or known acquired immunodeficiency syndrome.
    g. Brain metastases.
    h. Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
17. Participation to other concomitant experimental study.

6.0 PROTOCOL PROCEDURES

6.1 Drug administration

Patients will be treated with therapy courses of 28 days.

Course number 1 will be different from the followings because it will harbor radiotherapy to induce self-vaccination through immunologic cell death.

- Cyclophosphamide 50 mg tab will be given by the pharmacy to patients on day 1 each course . Treatment will be self-administered every day, 50 mg/day, from day 1 to day 28.
- Avelumab 10 mg/kg will be administered in day hospital every other week.
    - Premedication: In order to mitigate infusion-related reactions, a premedication with an antihistamine and with paracetamol (acetaminophen) 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650

mg paracetamol IV or oral). Premedication should be administered for subsequent avelumab infusions based upon clinical judgement and presence/severity of prior infusion reactions. This may be modified based on local treatment standards and guidelines, as appropriate.

- Setting: Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

- Observation period: Following avelumab infusions, patients must be observed for 30 minutes post-infusion for potential infusion-related reactions.

6.2 Study procedures and Safety assessments

6.2.1 BEFORE TREATMENT (baseline)

- Complete medical history, ECOG PS, physical examination (including height, weight), vital signs
- Electrocardiogram
- Within 14 days before treatment start complete blood count and differential, blood chemistry: bilirubin, AST, ALT, Alkaline phosphatase, LDH, clearance creatinine (Cockroft-Gault), electrolytes (Na, K, Mg, Ca), GGT, pregnancy test if clinically indicated, Protrombine Time, Activated Partial Thromboplastin Time (APTT), C Reactive Protein (CRP), Erythrocyte Sedimentation rate (ESR), B and C hepatitis markers (if not yet known)
- Free T4 and TSH
- Neck CT scan or MRI within 28 days
- Chest and abdomen CT scan within 28 days
- Soft tissue ultrasound, bone scan, brain MRI or CT scan if clinically indicated, within 28 days from enrollment.
- EORTC QLQ-C30 and QLQ-H&N35 questionnaires
- Written informed consent

6.2.2 Informed consent procedures

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks and other critical issues participating the study. The informed consent form will adhere to the ethical principles in the Declaration of Helsinki and Good Clinical Practice Guidelines. Coordinator and Participating Ethical Committees must evaluate and approve the informed consent form.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which the subject volunteers to participate.

Investigators must:

- Provide the patient with a copy of the EC approved consent form and written information about the study in Italian. Patients not familiar with Italian language will receive the informations about the study and the informed consent form with the support of an interpreter.
- Allow time necessary for subject, or subject's legally acceptable representative, to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

6.2.2.1 PROTECTION OF CHILDBEARING WOMEN AND/OR OF THE PARTNER

Information to the women.

In case of childbearing patient, she must commit to avoid pregnancy, while under experimental treatment because of possible side effects on the embryo or foetus. Otherwise she will not be accrued into the study.

The use of adequate contraceptive is mandatory during the study and up to six months after treatment end, for all childbearing women. The principal investigator or the co-investigators will

help the women for the choice, and will carefully explain the use, of the most adequate contraceptive.

If the pregnancy will occur, the woman must promptly inform the principal investigator or a co-investigator. The treatment will be stopped and the patient will be excluded from the study.

Moreover she must inform her gynaecologist.

Information to the men.

Patients under experimental treatment must commit to prevent his partner' pregnancy, because of possible side effects on the embryo or foetus.

The use of adequate contraceptive is mandatory during the study and up to six months after treatment end.

If the partner is planning a pregnancy, the patient will not be accrued into the study.

6.2.3 BEFORE EACH COURSE (every 28 days)

- Complete blood count and differential, blood chemistry: bilirubin, AST, ALT, LDH, clearance creatinine, urine pregnancy test.
- Adverse events and toxicity evaluation with NCI CTC AC (version 4.0).
- ECOG PS, physical examination (including weight), vital signs
- EORTC QLQ-C30 and QLQ-H&N35 questionnaires

6.2.4 EVERY 8 WEEKS

- Free T4 and TSH

6.2.5 EVERY 12 WEEKS UNTIL PROGRESSION OR GENERAL CONDITION DETERIORATION

- Complete blood count and differential, blood chemistry: bilirubin, AST, ALT, LDH, clearance creatinine, CRP, ESR, Electrolytes (Na, Mg, K, Ca)
- ECOG PS, physical examination (including weight), vital signs
- EORTC QLQ-C30 and QLQ-H&N35 questionnaires.
- Instrumental Tumor evaluation (using the same examinations as baseline)

6.2.6 OFF-PROTOCOL EVALUATION (Extended safety Follow-up)

Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of avelumab administration.
The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

All patients progressed during treatment or requiring treatment interruption due to adverse events will undergo to:

- End of treatment physical examination (within 14 days from the end of treatment)
- Follow-up of any unresolved adverse event
- Follow up: physical and instrumental examinations if clinically indicated every 12 weeks until death.

6.2.7 TOXICITY-RELATED DOSE ADJUSTAMENT

Toxicity will be graded according to the NCI-CTC AE version 4.0 25.
Modifications of dose/scheduling are not allowed except for treatment modification for symptoms of infusion-related reactions to avelumab (point 6.2.8)

Any Grade 4 Adverse Drug Reactions (ADRs) require treatment discontinuation with avelumab except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management

Any Grade 3 ADRs require treatment discontinuation with avelumab except for any of the following:

- Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management
- Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1

- Single laboratory values out of normal range (excluding Grade ≥ 3 liver function test increase) that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor
- Change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration)

Any Grade 2 ADR should be managed as follows:

- If a Grade 2 ADR resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue.
- If a Grade 2 ADR does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the subject should permanently discontinue treatment with a avelumab ADR (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted).
- Upon the second occurrence of the same Grade 2 ADR (except for hormone insufficiencies that can be managed by replacement therapy) in the same subject, treatment with avelumab has to be permanently discontinued.

6.2.8 TREATMENT MODIFICATION FOR SYMPTOMS OF INFUSION-RELATED REACTIONS

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Temporarily discontinue avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study avelumab and must not receive any further avelumab treatment.
- If avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment.- If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

6.2.9 MANAGEMENT OF IMMUNE-MEDIATED ADVERSE REACIOTN

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.

Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).

Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1	Continue avelumab therapy	Continue renal function

Creatinine increased > ULN to 1.5 x ULN		monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	If returns to Grade ≤1: Taper steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	Initial Management	Follow-up Management
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral

	Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		
Endocrine irAEs		
Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

	(for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone

	as appropriate • Perform pituitary MRI and visual field examination as indicated If hypophysitis confirmed: • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.

	Specialty consult as appropriate	
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	Permanently discontinue avelumab therapy Specialty consult	

6.3 Safety reporting

The following reportable events must be submitted to the Chief Investigator (CI) within 24 hours (or immediately for death or life-threatening events) using the applicable safety report form provided (see Appendix 1). CI will assume responsibility for submitting the reportable event to Merck as well as ensuring that any local reporting requirements are completed in parallel.

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury: these events are considered important medical events and should be reported as SAEs.

Contact information for submission of reportable events to Chief Investigator:

Fax: 0039 0171 616737

OR

E-mail: mcmerlano@gmail.com, merlano.m@ospedale.cuneo.it, denaro.n@ospedale.cuneo.it, trials@ospedale.cuneo.it

Specifying:

- PROTOCOL Number
- SUBJECT Number
- SITE Number/PI Name
- SAE/ONSET DATE

6.4 Sample collection, handling, shipping and analysis

Sample collection, handling, shipping and analysis are described in the translational study, section 11.3.

7.0 STUDY ENDPOINTS

7.1 Primary endpoint

The primary endpoint of the phase I trial is the absence of unacceptable toxicity. Assessment of the safety profile of the association of avelumab and metronomic cyclophosphamide will be graded using the common toxicity criteria and adverse events (NCI CTC-AE v 4.0).

The primary activity endpoint is the achievement of an objective response.
Objective response is defined as complete response or partial response as defined as per RECIST evaluation criteria v1.1 (RECIST 1.1).
The rates of objective response will be reported.

7.2 Secondary endpoints

- Assessment of the safety profile of the association of avelumab and metronomic cyclophosphamide will be graded using the common toxicity criteria and adverse events (NCI CTC-AE v 4.0).
- Progression free survival is defined as the time from study treatment initiation to the first occurrence of disease progression or death of any cause, whichever occurs first; Overall survival is defined as the time from treatment initiation to death for any cause.
- Quality of Life will be assessed using the EORTC QLQ -30 and EORTC QLQ – H&N35

8.0 STATISTICAL CONSIDERATIONS

8.1 Hypothesis

Objective response rate can be recognized activity endpoint for second line treatment of relapsed/metastatic head and neck cancer. Indeed, the historical response rate with chemotherapy was about 6 % and 10% with target therapy. These unsatisfactory results anticipated a poor median progression free survival (around 2 – 3 months) and median overall survival (6 months).
Immunotherapy with PD-L1 – PD-1 axis inhibitors increased response rate up to about 20%, without any amelioration of progression free survival (albeit a small proportion of patients remained free of progression more than 1 year in 3 different studies). Moreover, the higher response rate correlated with a slight improvement of overall survival (median overall survival of about 8 months), which reached the statistical significance in one study.
On the basis of the weak relationship observed between the gain in response rate and the changes in progression free survival and overall survival, we considered a strong level of interest (40% response rate) as the level to justify further investigations of the proposed experimental approach.

8.2 Statistical considerations, study design and sample size

8.2.1 Preliminary considerations

This is a proof of concept trial combining two low toxic treatments (metronomic cyclophosphamide and low dose, non ablative, radiotherapy) with an inhibitor of the PD-1 – PD-L1 axis (avelumab). Each one of these treatments drives positive immunological effects and their combination could, in theory, favours a reversal of immune suppression in the tumor microenvironment.

Whether this happens and whether the effect is clinically relevant cannot be directly demonstrated. It is necessary to observe the clinical effect of the treatment. In our opinion, response rate will offer the faster way to support the hypothesis.

It is supposed that the major risk of highly effective immune-therapy may be immune related toxicity.

However, data published very recently, added new insight on this topic as reported at 2.2.1.2 (avelumab, phase I study), at 2.3.1 (Metronomic cyclophosphamide: combination with immune check point inhibitors) and at 2.4 (concurrent delivery of PD-1 –PD-L1 axis inhibitors and hypofractionated non ablative radiotherapy) suggesting that the proposed combination should not add toxicity to that anticipated for avelumab alone.

However, of course, safety analysis, including quality of life analysis, remains an important objective of the present trial.

In addition a correlative trial is necessary to understand the effect on immunosystem induced by this multitarget approach.

8.2.2 Statistical considerations

Despite the fact that, in light of the most recent reported data on the safety of PD-L1 – PD-1 axis inhibitors in combination with metronomic cyclophosphamide and in line with published and ongoing studies of immunotherapy and non ablative hypofractionated radiotherapy, a low toxicity profile can be anticipated for the study combination, the study is designed as a phase I – II trial. The phase II trial will be conducted only after the demonstration of tolerability in patients enrolled in the phase I part.

8.2.3 Study design and sample size

Multicenter, phase I - II trial "two stage design".

The phase I study will be only conducted at the Istituto Nazionale Tumori in Milan (Prof. Lisa Licitra) and will be followed by a multicenter, phase II trial "two stage design".

8.2.3.1 Phase I:

In order to verify the tolerability of the study combination, study will start with a phase I part.

First 6 patients will be treated at dose level I (CTX 50 mg daily without drug free interval, Avelumab 10 mg/kg every two weeks and radiotherapy, 8 Gy in one ore up to 3 daily fractions).

The maximum follow-up for evaluation of unacceptable toxicity for patients enrolled in phase I study will be 120 days.

If more than 1 unacceptable toxicity will be observed, the study will be closed (unacceptable toxicities are detailed in appendix III)

If no more than 1 unacceptable toxicity will be observed in the first 6 patients, the study will continue with the enrollment of 14 patients at dose level I up to the completion of stage I of the Simon's two stage design (in other words, patients enrolled in phase I will be evaluated also for activity and will concur to the number of subjects planned for the first stage of the phase II).

8.2.3.2 Phase II study

Simon's two-stage optimal design (Simon, 1989) will be used. The null hypothesis that the true response rate is 25% (according with published results of other PD1 inhibitors) will be tested against a one-sided alternative. In the first stage, 20 patients will be accrued. If there are 5 or fewer objective response in these 20 patients, the study will be stopped. Otherwise, 51 additional patients will be accrued for a total of 71. The null hypothesis will be rejected if 24 or more responses are observed in 71 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 40%.

8.3 Response evaluation

All patients who will be enrolled into the study and who started the treatment will be considered for toxicity evaluation.

All patients who completed at least one course of treatment will be considered evaluable for response.

All patients recruited into the study will be considered evaluable for progression free survival and overall survival.

All patients recruited into the study who will complete at least two QoL questionnaires, will be considered for QoL analysis.

Response will be evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.

Objective response rate is defined as the proportion of patients with measurable disease at baseline who have an investigator-assessed complete response (CR) or partial response (PR). Clinical benefit rate (CBR) encompasses the proportion of patients who have an objective response at any time during the study and who maintain stable disease for six months or longer from the first treatment dose.

8.4 Study Duration

The total study duration will be approximately 54 months, including 42 months of active enrolment.
Planned start date (first patient on study): may 2018.
The planned study termination (clinical cutoff) will be 12 months after the last patient is included.

9.0 FEASIBILITY OF ENROLLING PROPOSED POPULATION, INCLUDING PROJECTIONS

This study will be a multicenter study, participants centres will include Santa Croce e Carle General Hospital Cuneo, Policlinico San Martino Hospital Genoa, IRCCS Candiolo Turin and Istituto nazionale Tumori in Milan.
The phase I will be conducted at the Istituto Nazionale Tumori in Milan which is an autocertified centre for phase I studies. Accrual of phase I will be completed in 3 months from the first enrolled patient. Safety analysis of the phase I will be completed within 7 months from the first patient enrolled. Stage I (20 patients enrolled) will be completed within 17 months from the first enrolled patient. Stage II (51 additional patients enrolled) will be completed within 42 months from the first enrolled patient.

10. QUALITY ASSURANCE AND TRIAL MONITORING

10.1 Monitoring of the trial

10.1.1 Steering Committee

The study will be supervised and monitored by a Steering Committee comprising members participating in the study:
Dr. M. C. Merlano, chairman of the committee and co-ordinating investigator
Prof. L. Licitra, investigator and Medical Oncologist
Dr. F. Montemurro, Investigator and Medical Oncologist
Prof. M. Di Maio, Medical Oncologist and biostatistician
Dr. E. Russi, Investigator and Radiation Oncologist
Dr C. Fruttero, Pharmacist

Prof. R. Corvò, Investigator and Radiation Oncologist

Dr. P. Curcio, Co-ordinating clinical research Assistant

Dr. N. Denaro, Investigator, Medical Oncologist, scientific secretariat Steering Committee

Dr. S. Vecchio, Investigator, Medical Oncologist, scientific secretariat Steering Committee

The Steering Committee ensures:

- Implementation and regular follow-up of the study
- Review of the safety following the inclusion of the first 6 treated patients (section 8.2.2.1)
- Patient protection
- That the trial is conducted ethically, in accordance with the protocol
- That the trial benefit/risk ratio is evaluated and the scientific results are checked during or at the end of the trial.

It decides on any protocol amendment that is required in order to continue the study, prior to submission to the Ethical Committee. Decisions on whether to open or close research sites, discussion on results and strategies for their publication.

10.1.2 Independent Data Monitoring Committee (IDMC)

10.1.2.1 Composition of the IDMC

The Committee comprise one qualified Oncologist, one qualified Radiation Oncologist and one Statistician:

- Qualified Oncologist (Dr. M. Benasso)
- Radiation Oncologist (Dr. G. Sanguineti)
- Statistician (Prof. V. Torri)

All the IDMC members have experience in the monitoring and analysis of clinical trials. One of them will be appointed as Trial Rapporteur.

All the IDMC members are not connected with the trial and therefore are not trial investigators.

These members are appointed by the Sponsor in consultation with the trial co-ordinator and the Steering Committee.

10.1.2.2 Responsabilities of the IDMC

The IDMC is responsible for:

- Analyzing preliminary efficacy and data safety
- Making recommendations on the continuation, early discontinuation (in the case of toxicity or lack of benefit) or publication of the trial results

- Drafting the minutes after each meeting and monitoring their confidentiality

Recommendations from the IDMC will be announced to the steering committee and to the Sponsor. The Sponsor is responsible for sending IDMC recommendations to the Regulatoy Authorities.

10.2 Quality Assurance

10.2.1 Data collection

Data record and data collection are centralised by Ufficio sperimentazioni cliniche, A.O. S. Croce e Carle in Cuneo. Registration form and clinical data will be collected through a specific electronic case report form (e-CRF).

10.2.2 Data Protection

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to Italian regulatory requirements. All patients will be identified only by code number generated during the registration process. Registration form and clinical data will be collected through electronic case report forms (e-CRFs).

Data record and data collection are centralised by Ufficio sperimentazioni cliniche, A.O. S. Croce e Carle in Cuneo.

10.2.3 Monitoring

In order to guarantee the authenticity and credibility of the data in accordance with the principles of GCP (good clinical practice), the sponsor shall implement a quality assurance system comprising:

- check compliance with the protocol, GCP and current legislation and regulations,
- check the consent and eligibility of each patient taking part in the trial,
- check the consistency and coherence of case report form date against the source documents.
- check that each serious adverse event is reported,
- monitor the traceability of the study medication (dispensation, storage and drug accountability),
- check, where applicable, that the persons likely to take part in the trial are not already participating in another trial that could prevent them from being included in the clinical trial proposed.

10.2.4 Handling of missing data

The monitoring of data for adverse events will be carried out regularly in order to effectively limit the amount of missing data likely to prevent or hamper trial implementation and analysis

10.2.5 Audits

The Sponsor, the local Authorities to which information about this study has been submitted can decide to have an audit. All documents relating to this study must be available for such an inspection after prior notification.

11.0 TRANSLATIONAL study

Immunoescape is the last step in the process that leads to tumor growth imbalance in favour of the system of inhibitory activity including changes in cancer cells and microenviroment[35].

However, there is scientific evidence from studies in animal models that the immune escape is not an irreversible process. Indeed changes in inducible suppressive can make back to immunosurveillance or even elimination of the disease[36].

Most of the knowledge on "immunoediting" derived from experimental models and little has been demonstrated in humans.

We propose to analyze the effects of this immunological treatment (RT+ Avelumab + Cyclophosphamide) both on cell homeostasis and humoral homeostasis developed by the tumor to survive and growth.

11.1 Translational objectives

- To identify variations among the major circulating immunological factors during the study CONFRONT.
- To identify the impact of the observed changes (if any) on outcome of the patient.
- To identify the immune status to disease progression.

11.2 Translational Scheduling

- Baseline assessment (Day 0: signature day)

  1. Evaluation of the main circulating T cells, MDSC and of circulating dendritic cells (DCs)

  2. Evaluation of cell subpopulations-specific interleukins

  3. Evaluation of the major cytokines (such as VEGF, TGF-beta, TNF-alpha, IFN-□ and IDO).

4. Evaluation of the main tumor associated antigens (TAA) inducible immunogenic cell death (such as HSP70, HSP90, HMBG1, EpCAM)

- The day after radiotherapy repeat the same determinations as baseline
- At the beginning of cycle 2, repeat the tests at points_1, 2 and 3 of the baseline
- At disease progression repeat the tests at points 1, 2 and 3 of the baseline

11.3 Translational materials and methods

11.3.1 Sample Collection, handling and shipment

15 ml blood samples collected at baseline, the day after RT, at the beginning of cycle 2, at disease progression.

Plasma samples will obtained by centrifugating one vacutainer at 1500 g for 10'. Aliquotes of 600 µl in 2 ml cryovials should be kept at -80°C.

PBMCs will be obtained through Ficoll separation, following standard procedures, from the remaining two vacutainers. Cells have to be frozen as vital by planer instrument or by slow freezing (2h at 4°C, 2h at -20°C, then -80°C) in aliquotes of 3x10^6 cells.

All cryovials, both plasma and PBMCs, should be kept at -80°C until shipping by courier to the coordinating center in dry ice. After biological sample collection shipment will be scheduled with each center. Samples will be shipped to Medical Oncology, Translational Oncology Lab, S. Croce e Carle Hospital, Cuneo

11.3.2 Analysis

The following cell population will be studied by flow cytometry:

CD3+ CD4+ CD25+ Foxp3+ T-lymphocytes

CD3+ CD8+ T-lymphocytes

NK cells: CD3- CD56+

MDSC: CD33+ CD11b+ CD14- HLA-DR(low)

myeloid DC HLA-DR+lindim/negative/CD11c+ and plasmacytoid DC HLA-DR+lindim/negative/CD123+

- VEGF, TGF-beta and the other cytokines and interleukins will be studied using commercial available kit:

  - Th1: IL-2, IL-12, IL-15, IL-21, IFN-γ and TNF-α

  - Th2: IL-4 (B cell stimulating factor BSF-1), IL-5, IL-6, IL-10, IL-13 HSP70, HSP90, EpCAM e and HMBG1 will be measured with ELISA Kit commercial available.

11.4 Statistical Analysis of translational data

We shall evaluate circulating factors that are significantly changing during treatment period, by means of the Wilcoxon's test, and in particular variation between:

- baseline to the day after radiotherapy
- baseline to the start of cycle 2
- baseline to disease progression.

Considering the large number of comparisons planned, we will adjust for multiple testing using the "false discovery rate method" which is the adequate standard procedure of adjustment for multiple testing.

The correlation between the level pattern of circulating immunological factors at baseline and during treatment on and clinical objective response (responders vs non-responders) will be essentially descriptive and do not applied formal statistical texts.

The interpretation of the data collected will be conducted in collaboration with the Institute of Candiolo tumors by Prof. M. Aglietta and Prof. D. Sangiolo. The statistical analysis will be conducted by University of Turin (Prof. M. Di Maio).

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13.0 SUPPORTING DOCUMENTATION

Appendix I SAE Form – FAC-SIMILE

G.O.N.O.
Gruppo Oncologico Nord Ovest
PI Marco Carlo Merlano

Serious Adverse Event Report Form

(Investigator Sponsored Study)

Version N°1.0 - Date:18/12/2017

N° EudraCT: 2017-000353-39

CONFRONT Trial

COMPANY USE ONLY
Receipt date of this report (stamp or date)

TYPE OF REPORT	
☐ Initial	☐ Follow-up

A. REPORTER INFORMATION

Reporter's First Name	Reporter's Last Name
Investigator's First Name (if different from Reporter)	Investigator's Last Name (if different from Reporter)
Address	City
Country	Phone Number
E-Mail:	Fax Number

B. SUBJECT INFORMATION

Subject ID Center No. Subject No.			
Subject Initials NA	Sex ☐ Female ☐ Male	Height cm	Weight kg
Date of Birth (dd/mmm/yyyy) OR Age at Time of Adverse Event (Specify unit, e.g. years months, etc.) / /			
Ethnicity/Race ☐ American Indian/Alaska native ☐ Asian ☐ Black or African American ☐ Caucasian/White ☐ Hispanic or Latino ☐ Native Hawaiian or other Pacific islander ☐ other _____			

C. RELEVANT MEDICAL HISTORY

Condition/Disorder	Start Date (dd/mmm/yyyy)	End Date (dd/mmm/yyyy)	Ongoing
	/ /	/ /	☐
	/ /	/ /	☐
	/ /	/ /	☐
	/ /	/ /	☐
	/ /	/ /	☐

D. CONCOMITANT MEDICATIONS

Drug Trade Name	Single Dose	Frequency of Administration	Route	Start Date (dd/mmm/yyyy)	Stop Date (dd/mmm/yyyy)	Indication
				/ /	/ /	
				/ /	/ /	
				/ /	/ /	

				/ /	/ /	

E. INVESTIGATIONAL MEDICINAL PRODUCT(S)

Indication of Investigational Medicinal Product(s)

R-M Head and Neck Cancer

1	Investigational Medicinal Product Name / Route of Administration: **Avelumab (MSB0010718C) / Infusion**	Kit/Batch/Lot Number
Not yet administered:		
Date and Time of first administration: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Date and Time of most recent administration prior to SAE: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Number of administrations prior to SAE:		

ACTIONS TAKEN REGARDING THIS INVESTIGATIONAL MEDICINAL PRODUCT

☐ Temporary discontinued on: ____/____/____	Event subsided?	☐ Yes	☐ No	☐ Unknown
.....	If "yes", how long after cessation of treatment? _____			
☐ If temporary discontinued, restarted on: ____/____/____.	At previous dose?	☐ Yes	☐ No	☐ Unknown
.....	Event subsequently reappeared?	☐ Yes	☐ No	☐ Unknown
☐Permanently discontinued on: ____/____/____.....				
☐ Dose Reduced on: ____/____/____	Event subsided?	☐ Yes	☐ No	☐ Unknown
☐ Treatment Continued without Change				
☐ Not Applicable				
☐ Unknown				

2	Investigational Medicinal Product Name / Route of Administration Cyclophosphamide	
Not yet administered:		
Date and Time of first administration: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Date and Time of most recent administration prior to SAE: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Number of administrations prior to SAE:		

ACTIONS TAKEN REGARDING THIS INVESTIGATIONAL MEDICINAL PRODUCT

☐ Temporary discontinued on: ____/____/____	Event subsided?	☐ Yes	☐ No	☐ Unknown
.....	If "yes", how long after cessation of treatment? _____			
☐ If temporary discontinued, restarted on: ____/____/____	At previous dose?	☐ Yes	☐ No	☐ Unknown
.....	Event subsequently reappeared?	☐ Yes	☐ No	☐ Unknown
☐Permanently discontinued on: ____/____/____.....				

☐ Dose Reduced on: ___/___/___ ..... Event subsided? ..... ☐ Yes ☐ No ☐ Unknown		
☐ Treatment Continued without Change		
☐ Not Applicable		
☐ Unknown		
3	Other Study Treatment (e.g. Non-IMP/Radiotherapy) Radiotherapy	Kit/Batch/Lot Number
Not yet administered:		
Date and Time of first administration: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Date and Time of most recent administration prior to SAE: (dd/mmm/yyyy) / / (hh:mm) /		Dose/Unit:
Number of administrations prior to SAE:		

ACTIONS TAKEN REGARDING OTHER STUDY TREATMENT				
☐ Temporary discontinued on: ____/____/____	Event subsided?	☐ Yes	☐ No	☐ Unknown
.....	If "yes", how long after cessation of treatment?			
☐ If temporary discontinued, restarted on: ____/____/____.	At previous dose?	☐ Yes	☐ No	☐ Unknown
.....	Event subsequently reappeared?	☐ Yes	☐ No	☐ Unknown
☐Permanently discontinued on: ____/____/____				
☐ Dose Reduced on: ____/____/____	Event subsided?	☐ Yes	☐ No	☐ Unknown
☐ Treatment Continued without Change				
☐ Not Applicable				
☐ Unknown				

F. ADVERSE EVENT(S) *(If there are more than three adverse events, reprint this page as many times as is necessary.)*						
*Report adverse event **diagnosis (ses)**, if not available provide sign(s) and symptom(s)*	AE ____:		AE ____:		AE ____:	
Onset Date and Time (dd/mmm/yyyy hh:mm)	____/____/____ __:__		____/____/____ __:__		____/____/____ __:__	
Resolution Date (dd/mmm/yyyy)	____/____/____		____/____/____		____/____/____	
Duration, if less than 24h	____ ☐ hr ☐ min		____ ☐ hr ☐ min		____ ☐ hr ☐ min	
SEVERITY						
Severity Grade *Use either NCI-CTC grading **OR** Qualitative Scale*	☐ 1	☐ Mild	☐ 1	☐ Mild	☐ 1	☐ Mild
	☐ 2	☐ Moderate	☐ 2	☐ Moderate	☐ 2	☐ Moderate
	☐ 3	☐ Severe	☐ 3	☐ Severe	☐ 3	☐ Severe
	☐ 4	☐ Life-threatening	☐ 4	☐ Life-threatening	☐ 4	☐ Life-threatening
	☐ 5	☐ Death	☐ 5	☐ Death	☐ 5	☐ Death
SERIOUSNESS						
Resulted in Death	☐		☐		☐	
Is Life-Threatening	☐		☐		☐	
Requires/Prolongs Hospitalization	☐		☐		☐	
Persistent/Significant Disability/Incapacity	☐		☐		☐	
Medically Significant	☐		☐		☐	
Is Congenital Anomaly/Birth Defect	*Parent-Child/Foetus Report Form must be completed*		*Parent-Child/Foetus Report Form must be completed*		*Parent-Child/Foetus Report Form must be completed*	
OUTCOME						
Unknown (only applicable if subject is lost to follow-up)	☐		☐		☐	
Fatal (AE resulted in death)	☐		☐		☐	
Ongoing	☐		☐		☐	
Resolved without Sequelae	☐		☐		☐	
Resolved with Sequelae	☐ Specify:		☐ Specify:		☐ Specify:	

RELATION TO THE INVESTIGATIONAL MEDICINAL PRODUCT(S) / STUDY TREATMENT *If an event is unrelated, please indicate any other causality factors in the appropriate section and/or provide further details in the narrative (Description of Adverse Event(s)).*

	Related	Unrelated	Related	Unrelated	Related	Unrelated
Avelumab (MSB0010718C)	☐	☐	☐	☐	☐	☐
Cyclophosphamide	☐	☐	☐	☐	☐	☐
Other Study Drug (Non-IMP)	☐	☐	☐	☐	☐	☐
Radiotherapy	☐	☐	☐	☐	☐	☐

G. DESCRIPTION OF ADVERSE EVENT(S)

Provide a detailed description of AE, i.e. clinical course of event(s), signs, symptoms, laboratory results, treatment of AE, etc.

1) In Case of Death

Cause of Death: ☐ AE ☐ Other If "other", specify: _____

Date of Death*: ____/____/____ Autopsy performed? ☐ Yes ☐ No If "yes", please attach autopsy report if available.

2) In Case of Hospitalization or Prolonged Hospitalization

Admission Date*: ____/____/____ Discharge Date*: ____/____/____ ☐ Not Discharged

H. RELEVANT TESTS/PROCEDURES/LABORATORY TESTS TO CONFIRM ADVERSE EVENT

I. OTHER RELEVANT RISK FACTORS

☐ Alcohol Use	☐ Physical Therapy	☐ Contraceptive	☐ Smoking
☐ Pace Maker	☐ Drug Dependence	☐ Radiation Therapy	☐ Diet
☐ Metabolic Disorders	☐ Drug Abuse	☐ Obesity	☐ Allergy
☐ Implants	☐ Other, specify: _____		

J. CAUSALITY FACTORS OTHER THAN TRIAL TREATMENT

☐ Concomitant Medication, please specify suspected drug:_____(record details in section D)

☐ Medical History, please specify disease:_____(record details in section C)

☐ Disease Under Study ☐ Disease Progression; specify:_____

☐ Trial Procedure ☐ Other; specify:_____

K. INVESTIGATOR SIGNATURE

Investigator's Signature _____ Date of Report*: _____

TYPE OF REPORT – Please indicate if this is an initial report or a follow-up report.

A. REPORTER INFORMATION
Adequate contact information is requested as further clarification might be required.

B. SUBJECT INFORMATION
- **Subject ID** – Composed of Trial, Center and Subject numbers, it is only applicable for those subjects receiving the drug in the framework of a trial.
- **Trial** – Provide the Clinical Trial Protocol number for the trial.
- **Center No.** – Since most trials are multi-center, provide the center/site number (including leading zeros).
- **Subject No.** – This should be a four digit number (including leading zeros).
- **Randomization Number** – Consult the Clinical Trial Protocol. This is not necessarily the same as the Subject ID.
- **Subject Initials** – Provide the first letter of the first/given name, the second/middle name and the last/family name in the order stated here, but give no more than three letters, or indicate if they are unknown. Please consult local legislation concerning privacy and protection of personal data before collecting initials as it may be forbidden.
- **Sex** - please provide gender of the subject.
- **Height** should be given in centimeters and **Weight** in kilograms. If these are unfamiliar to the reporter, other standard units, e.g. feet, pounds, can be used, but the unit used must be clearly indicated on the form.
- **Date of Birth or Age at time of AE** – Provide the birth date or the estimated age at time of AE.
- **Ethnicity/Race** – Select appropriate ethnicity/race
- **Assignment to treatment group or dose cohort** - please describe treatment group or dose cohort.
- **If blinded, unblinded by investigator?** – If the subject was unblinded, select "yes" and provide date. Otherwise select "no".

C. RELEVANT MEDICAL HISTORY
Detail relevant medical/drug history which contributes to a better understanding of the clinical course of the AE(s). Medical/drug history which has no link to the AE(s) should not be reported.

D. CONCOMITANT MEDICATIONS
Report only those medications relevant to the assessment of the reported adverse events.
- **Drug Trade Name** – Provide the trade name or generic name (active ingredient). In the case of a multi-ingredient drug, the trade name is preferred.
- **Single Dose** – Provide dose and unit, e.g. 44 mcg, 0.8 mg/kg. If the dosage form is a tablet, vial, etc., specify the mass/volume of the dosage form. Do not give the dose as a percentage, e.g. 50%, unless it is clear of what it is a percentage, e.g. 50% of 44 mcg. Do not confuse dose with strength.
- **Frequency of Administration** – Provide the number of times the given dosage (see above) is administered in a specific period of time, e.g. 3 times per week, 2 times per day. Standard abbreviations (TIW, BID, BIS, QD, etc.) or easily understandable shorthand (3x/week) can be used.
- **Route (of drug administration)** – Specify how the drug was administered. Use standard abbreviations, e.g. PO, SC, IM, IV, etc.
- **Start Date/Stop Date** – The dates corresponding to the first time and the last time the drug was administered. If exact dates are not available, provide appropriate estimates, e.g. month and year for short duration, or only the year for long duration. *Always* include the year.
- **Indication** – Provide the name of the condition for which the drug is administered.

E. INVESTIGATIONAL MEDICINAL PRODUCT(S) / STUDY TREATMENT(S)
Space has been provided to enter the investigational medicinal products. Other medicinal products should be listed as concomitant medication. If more than two IMPs are to be reported, this page should be copied, filled out accordingly and attached to the report.
- **Indication of Investigational Medicinal Product** – Provide the name of the condition for which the drug is administered.

- **Investigational Medicinal Product(s)** / Study Treatment(s)– Provide the trade name or generic name (active ingredient). In the case of a multi-ingredient drug, the trade name is preferred. Also describe "Other Study Treatment" with Non-IMP / Radiotherapy.
- **Route of Administration** – Specify how the drug was administered. Use standard abbreviations, e.g. PO, SC, IM, IV, etc.
- **Kit/Batch/Lot Number** – Where available, provide relevant tracking information.
- **Not yet administered** – please provide information if drug was not yet administered.
- **Date and Time of first and most recent administration/intake** – Provide the exact date and time of the first and most recent dose the subject received prior to the AE. If not possible, provide the closest approximation.
- **Dose of the first/most recent administration/intake** – Provide dose and unit, e.g. 44 mcg, 0.8 mg/kg. If the dosage form is a tablet, vial, etc., specify the mass/volume of the dosage form. Do not give the dose as a percentage, e.g. 50%, unless it is clear of what it is a percentage, e.g. 50% of 44 mcg. Do not confuse dose with strength.
- **Number of administrations/cycles/doses** – Provide the number of times the given dosage (see above) is administered in a specific period of time, e.g. 3 times per week, 2 times per day. Standard abbreviations (TIW, BID, BIS, QD, etc.) or easily understandable shorthand (3x/week) can be used.

ACTIONS TAKEN REGARDING THIS INVESTIGATIONAL MEDICINAL PRODUCT

Select any and all actions that are relevant, providing corresponding dates and outcomes.

- **Temporary Discontinued** – Select if the suspected IMP was temporary discontinued due to AE for any period of time.
  - **Event subsided?** – Indicate if the event subsided following the discontinuation of the suspected IMP.
  - **If "yes", how long after cessation of treatment?** – If the event did subside after discontinuing the suspected IMP, indicate how long following the discontinuation, being sure to give the unit of time as well (minutes, hours, etc.).
- **If "temporary discontinued, restarted on"** – please enter the date when IMP administration was restarted.
  - **At previous dose?** –If the dose given upon restarting the suspected IMP was the same as at the time of the discontinuation of the IMP, select "yes".
  - **Event subsequently reappeared?** – Indicate if the event reappeared after restarting the suspected IMP.
- **Permanently Discontinued** – Select if the suspected IMP was permanently discontinued due to AE for any period of time.
- **Dose Reduced** – Select if the dose of the suspected IMP was reduced due to AE for any period of time.
  - **Event subsided?** – Indicate if the event subsided following the reduction of the dose of the suspected IMP.
- **Treatment Continued without Change** – Select if nothing was done with respect to the suspected IMP. If this is selected then no others can be selected.
- **Not Applicable** – Select if actions were not possible, e.g. the course of treatment had already ended when the subject presented with event.
- **Unknown** – Select if actions taken regarding the suspected IMP are unknown.

F. ADVERSE EVENT(S)

This applies to AEs experienced by the subject only. Provide the diagnosis at the time of reporting. If no diagnosis has yet been made, provide the most relevant sign(s) and/or symptom(s). When a final diagnosis is made, it should be provided in this same field on a subsequent follow-up report along with corresponding signs/symptoms/additional findings specified below in the AE description. The terms used should be *factual* and *concise*; any relevant details can be included in the AE description. If more than three events are to be reported, this page should be copied, filled out accordingly and attached to the report.

- **Onset Date and Time** – Provide the date and time of the first sign or symptom and not the date when the diagnosis was confirmed. In the case of the worsening of a pre-existing condition, this date should correspond to the date of the first sign or symptom of the worsening.
- **Resolution Date** – Enter only if the AE has resolved.
- **Duration, if less than 24h** – Provide only when the type of event makes it meaningful, i.e. those of a short duration like anaphylactic shock or cardiac arrhythmia. Specify the unit of time.

- **Severity** – Provide an appropriate grade for the AE following the Common Terminology Criteria for Adverse Events or the Qualitative Scale as described in Clinical Trial Protocol.

- **Seriousness** – The reporter is asked not to assess the seriousness of the event but rather to provide the factual information on the basis of which, the seriousness of the event will be determined. ***Check all that apply to the AE.***
  - **Resulted in Death** – Select if the subject died due to this event. Selecting this does not imply that the event was also immediately life threatening. If selected complete corresponding item in section G: "In Case of Death".
  - **Is Life-Threatening** – The subject was at *immediate* risk of dying at the time of the event.
  - **Requires/Prolongs Hospitalization** – Select, if the subject was admitted to the hospital **over night** in order to treat the AE or as a result of the AE sustained by the subject.. If selected, complete corresponding item in section G: "In Case of Hospitalization".
  - **Persistent/Significant Disability/Incapacity** – Select, if AE resulted in a substantial disruption of the subject's ability to conduct their life. An example would be hepatitis that results in the subject not being able to take certain drugs. If selected, the disability should be adequately described in the AE description.
  - **Medically Significant** – If the event is assessed by a medical professional to be medically significant, but it does not match any of the criteria above, select this.
  - **Congenital Anomaly/Birth Defect** – If this is the only AE then the Parent-Child/Foetus Report Form should be completed instead of this one. If the subject also experienced an AE then continue with this form as well as the Parent-Child/Foetus Report Form.

- **Outcome** – Due to the importance of this information, every attempt should be made in order to determine the outcome.
  - **Unknown** – Select, if the current status of the subject is unknown to the reporter, only to be used if the subject is lost to follow-up.
  - **Fatal** – Select, if the subject died as a result of the AE. In this case, the date and cause of death should be provided in the corresponding item in section G: "In Case of Death".
  - **Ongoing** – Select, if the AE has not resolved or has worsened.
  - **Resolved without Sequelae** – Select if the subject has fully recovered from the AE.
  - **Resolved with Sequelae** – Sequelae are any significant lesions or medical conditions which persist after resolution of the AE or stabilization of the subject's condition, e.g. scarring following skin necrosis. Sequelae are not substantial disruptions of the subject's ability to conduct their life. Provide a description if known.

- **Relation to the Investigational Medicinal Product(s) / Study Treatment** – For each IMP, indicate if it is related/suspected or unrelated/not suspected with respect to this particular AE. Additional lines have been provided for adding items other than the IMPs, e.g. other medicinal products, other study treatment, etc.

G. DESCRIPTION OF ADVERSE EVENT (S)
Describe the clinical course of the AE(s), including occurrence of signs and symptoms in chronological order, temporal relationship to the administration of suspected drug's, and any other relevant observations (diagnostic procedures, treatment of AE, laboratory tests, autopsy findings in the event of death, etc.). The clinical course of the AE(s) should be described so that the temporal sequence of events is clear, concise and factual. Attach additional pages where necessary.
- **Cause of Death** – If AE did not directly cause the death of the subject (e.g. hyperkalemia), but instead led to another event which caused the death, select "other" and provide details.
- **Date of Death** – Provide the date the subject died.
- **Autopsy Performed** – If 'yes', provide the entire autopsy report or relevant details when the autopsy report is not available.
- **Admission from...to...** – Provide the dates of the subject's hospitalization. If the subject has not yet been discharged at the time of reporting, also check the corresponding box marked "Not discharged" rather than simply leaving the discharge date blank.

H. RELEVANT TESTS/PROCEDURES/LABORATORY TESTS TO CONFIRM ADVERSE EVENT
Provided any further details concerning methods used to confirm the event.

I. OTHER RELEVANT RISK FACTORS
Select any of the items that apply, providing details where indicated.

J. CAUSALITY FACTORS OTHER THAN TRIAL TREATMENT Select any of the items below that apply, providing details where indicated.

K. INVESTIGATOR SIGNATURE
- **Investigator's Signature** – The Investigator/Co-Investigator has to review and sign the SAE report.
- **Date of Report** – This corresponds to the date the Investigator/Co-Investigator signs the report. If the report is not signed, it need not be dated.

Please send the completed SAE report form to the email address or fax number given on top

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

UNACCEPTABLE TOXICITIES:

Unacceptable toxicities are defined as it follows:

- grade 4 neutropenia persisting $\geq$ 7 days or requiring treatment with granulocyte colony-stimulating factor,
- febbrile neutropenia,
- grade IV thrombocytopenia
- grade III decreased platelet count requiring platelet transfusion
- grade IV anemia requiring a red blood cell transfusion
- grade $\geq$ 3 non emathological toxicity, excluding controllable grade III nausea, vomiting, or diarrhea that recovered to grade $\leq$ 1 as a redsult of treatment prior to infusion in the next cycle