

## ESMO Research Research Fellowship (January 2021 – January 2022)

**Francesco Cortiula**

### FINAL REPORT

Host Institute: **Maastricht University Medical Center +**

Mentor: **Lizza E.L. Hendriks, MD, PhD**

Project title: **Concurrent chemotherapy and proton therapy compared to photon therapy, followed by durvalumab maintenance in stage III non-small cell lung cancer (PROMETHEUS study): immunological and hematological effects.**

Home Institute: **University of Udine, Italy (IT)**

#### **Introduction**

Based on the PACIFIC trial, standard of care (SoC) for patients with unresectable stage III NSCLC is concurrent chemoradiation (cCRT), with a radiation dose of 60 Gy in 2 Gy daily fractions<sup>1,2</sup>, followed by durvalumab<sup>3,4</sup>. Adjuvant durvalumab treatment increases 3 year OS from 43.5% to 57%<sup>5</sup>. Larger irradiated volumes can result in more toxicity: a higher bone marrow RT dose results in more hematological toxicity<sup>6</sup>, causing neutropenia (associated with development of acute radiation-induced dysphagia)<sup>7</sup> and lymphopenia, which is a known negative prognostic factor<sup>8</sup>. Time needed to recover from acute CCRT toxicity can delay the start of, or limit the eligibility of patients to receive durvalumab: as according to the PACIFIC trial, durvalumab should only be given within 42 days from the end of radiotherapy to patients in a good clinical condition, that have recovered from acute CCRT toxicities<sup>9</sup>. Furthermore, bone marrow toxicity, and radiation scattering to lymph nodes can result in an immunosuppressed status. An effective strategy to minimize organs at risk (OARs) toxicity is reducing unnecessary radiation exposure<sup>10</sup>.

#### **Rationale and Aim**

Proton radiation has unique depth-dose characteristics which can limit the OARs exposure compared to photon therapy<sup>11</sup>. On the other hand, proton-related costs are significantly higher than for the best photon therapy. Retrospective studies and a single institution observational study (N-51) have demonstrated a more favourable toxicity profile with proton versus photon therapy used in cCRT<sup>12–16</sup>. In contrast, in a randomized trial, 12-month local failure and 12 month-radiation pneumonitis incidence did not differ between the proton vs photon arm<sup>17</sup>. So far, little is known on the effect of protons on the immune environment and body composition in stage III NSCLC patients treated with cCRT, and whether this affects durvalumab efficacy. An in vitro study showed that proton radiation upregulates immune-stimulatory molecules but in mice models protons lead to shorter survivals compared to photons, possibly due to induced immune suppression<sup>18,19</sup>. Furthermore, no solid data about bone marrow toxicity in NSCLC and proton therapy are reported. In esophageal cancer, protons resulted in less lymphopenia compared with photon therapy<sup>20</sup>. Therefore, proton therapy, reducing the off target radiation dose, could theoretically lower the incidence of neutropenia, infections and immune suppression during cCRT, providing a faster recover from cCRT and increased eligibility of patients to receive adjuvant durvalumab and improving the immune response with durvalumab. The present study will evaluate the effects of proton versus photon therapy in stage III NSCLC patients treated with cCRT. Focus will be on hematological toxicity in relation to the irradiated bone marrow and on the effects of both radiation types on the immune system. Eligibility for

durvalumab and effects on body composition (cachexia/sarcopenia) will also be evaluated for proton versus photon treated patients.

### **Experimental design**

The PROMETHEUS study is an observational prospective study (prospectively collected list, retrospectively added data) including unresectable stage III NSCLC patients eligible for CCRT, treated with proton (IMPT) or photon (IMRT) radiation therapy, with or without adjuvant durvalumab.

Main inclusion criteria: AJCC 8th edition stage III, unresectable NSCLC; histo- or cytological diagnosis; staged with FDG-PET, contrast enhanced CT of thorax and upper abdomen, and brain imaging (MRI/CT) within 42 days before chemoradiation; participating in the afore-mentioned phase II trial; no prior lung radiotherapy.

Aims and endpoints: The primary question the PROMETHEUS study aims to answer is whether proton therapy can reduce the hematological toxicity in patients treated with CCRT for stage III NSCLC. Accordingly, the primary endpoint of the study is the incidence of lymphopenia grade  $\geq 3$  in proton treated vs photon treated patients.

Secondary aims are to investigate whether proton therapy can reduce other hematological and non-hematological toxicity. Accordingly, secondary endpoints are: incidence of neutropenia, febrile neutropenia, anemia thrombocytopenia, dyspnea, dysphagia, anorexia, cough, infection and pneumonitis in proton vs photon treated patients. We assessed the incidence of toxicities not only during treatment but also at day 21 and at day 42 after the end of CCRT, in order to evaluate whether the radiotherapy treatment type influences the eligibility to durvalumab treatment. We described also the incidence of immune related adverse events during durvalumab treatment and the PFS and OS of Durvalumab treated patients stratified according to IMPT vs IMRT. Subsequently, we explored whether the hematological toxicities (neutropenia, febrile neutropenia and lymphopenia) are correlated with the radiation volumes delivered to the bone marrow or to the heart and lungs, which are rich in circulating white blood cells that could be affected by radiation. Finally, we explored whether the radiation volumes to bone marrow and other OARs were different between IMPT treatment plans and IMRT treatment plans. This evaluation was possible because for proton treated patients also a photon treatment plan is made in clinical practice; therefore we run an intra-patient comparison to assess differences in the dose volumes parameters between photon and proton plans. Progression Free Survival and Overall Survival of the patients' cohort, stratified according to the radiotherapy treatment received (IMPT vs IMRT) are also described.

Statistical considerations: We expected that 210 patients (160 patients in the photon arm and 50 patients in the proton arm) would have been eligible for the main cohort of the present study. We anticipated a dropout of 20% due to missing clinical data or due unanticipated exclusion criteria, and therefore 132 patients in photon arm and 40 patients in the proton arm would be eligible. Assuming a reduction of Grade  $\geq 3$  lymphopenia from 25% in the photon therapy arm to 7% in the proton therapy the present study was expected to have at an alpha error of 0.10 and a power of 80% (type II error of 0.20).

### **Results, Conclusions and Future Perspectives**

Results (this section has to be considered confidential, since data has been submitted to international conferences – ESTRO 2022 and ELCC 2022 - and data are still under embargo)

210 consecutive patients were screened and 169 patients were included (IMPT: n = 35, IMRT: n = 134). Median age was 66 years, 53.3% were male, 40.8% had a squamous NSCLC and 41% of patients had a WHO Performance Status (PS) = 0. Median Gross Tumor volume (GTV) was 70.4 cm<sup>3</sup>. No differences in age, gender, baseline PS, GTV and tumor histology were noted between IMPT and IMRT. 98.2% of the patients

received a RT dose of 60-66Gy. 46.2% of IMPT treated patients and 75% IMRT treated patients developed lymphopenia  $G \geq 3$  (Odds Ratio [OR]: 3.5, 95% CI 1.1-12.1,  $p=0.042$ ). Including age, comorbidities, chemotherapy regimen, gender, disease stage (IIIA vs. IIIB/IIIC) and GTV in the multivariate analysis, IMPT confirmed to be associated with less lymphopenia (OR: 0.07, 95% CI: 0.01-0.54,  $p=0.01$ ). Neutropenia  $G \geq 3$  occurred in 62% and 68% in IMPT and IMRT treated patients respectively ( $p=0.51$ ). This was 31% and 29% respectively for febrile neutropenia ( $p=0.74$ ). Bone marrow RVs were associated with a higher risk of lymphopenia  $G \geq 3$  (V4, V5, V10 and V20, with a significance level of 0.05, 0.034, 0.023, and 0.026 respectively). IMPT was also associated with a lower rate of  $PS \geq 2$  at day 21 (OR: 0.3, 95% CI 0.1-0.95,  $p=0.042$ ). Overall, sixty-seven patients received adjuvant durvalumab (IMPT:  $n=28$ , IMRT:  $n=39$ ). All patients treated with adjuvant Durvalumab, received 60-64 Gy of RT. Programmed death-ligand 1 (PDL-1) level was available for 76% of pts and 39% had a PDL-1  $\geq 50\%$  (no significant differences between IMPT and IMRT). At day 21 after CCRT, 93% (IMPT) vs 72% (IMRT) treated patients had a  $PS \leq 1$  (Odds Ratio 0.8, 95% CI: 0.67-0.95,  $p=0.03$ ). The median time from the end of CCRT and start of D was 32 vs 38 days respectively (Not Significant (NS)). IRAEs of any grade were reported in 21% versus 31% of patients treated with IMPT versus IMRT, respectively (NS). Hypothyroidism accounted for 44% of IRAEs. Pneumonitis during durvalumab was reported in 25% of IMPT and 23% of IMRT (NS). Grade 3 pneumonitis during durvalumab occurred in 6% of patients overall (NS differences between IMPT and IMRT). Within the durvalumab cohort, median follow-up was 19.5 months and 9.5 months for IMRT and IMPT respectively. 90% of patients were still alive and 73% were disease free.

**Conclusions:** (this section has to be considered confidential, since data has been submitted to international conferences – ESTRO 2022 and ELCC 2022 - and data are still under embargo) IMPT reduces the incidence of lymphopenia  $G \geq 3$  in patients with stage III NSCLC treated with CCRT, due to lower bone marrow RVs. In addition, IMPT led to a faster PS recovery after CCRT, thus potentially increasing the number of patients eligible for adjuvant durvalumab. Proton therapy appears to be as safe as photon therapy regarding IRAEs.

**Future Perspectives:** We are working on several strategy to implement the PROMETHEUS project. First, we will update our dataset in the first half of the 2022 with late toxicities outcomes (particularly collecting cardiac and pulmonary late toxicities data) to investigate possible protective effects of proton-therapy. The survival analyses will be also updated with a new data cut-off set at 06/2022.

At the same time, we will validate the above presented results on a cohort of patients treated with CCRT at the proton-therapy facility of the University Hospital of Groningen (The Netherlands) and at my home institution, the University Hospital of Udine. Ethics approval is under way for both centers.

We are already investigating whether proton-therapy could affect the development of cachexia compared to photon therapy in patients treated with adjuvant durvalumab, and whether cachexia would affect the survival of these patients.

We are also implementing a deep-learning model with all the CT-scans that we manually delineated for this project, to automatically delineate the bone marrow structures in future studies and possibly in the clinical practice.

The future development of the project will be possible since my researcher position and privileges at the Maastricht University Hospital+ (and the MAASTRO clinic) has been extended and I can work on the projects remotely from Italy. I will also meet regularly with my mentors, dr. Hendriks and prof. De Ruyscher, to ensure a timely development of the project.

#### **List of Publications and Presentations Resulting from the Translational Research Project “PROMETHEUS”**

The abstract “Proton-therapy and concurrent chemotherapy in stage III NSCLC: effects on hematological toxicity” has been accepted for presentation as a Proffered Paper at the ESTRO 2022 congress

The abstract “**Proton-therapy and concurrent chemotherapy in stage III NSCLC: Effects on Durvalumab eligibility and safety profile**” has been submitted to the ELCC 2022 congress.

We will ultimate the full paper when the data from the validation cohort will be collected (estimated mid 2022). One to four full paper publications are expected from the PROMETHEUS project in the 2022-2023 period.

**List of Publications and Presentations resulting from other projects during the fellowship period (if applicable)**

Physical exercise at the crossroad between muscle wasting and the immune system: implications for lung cancer cachexia. *Journal of Cachexia, Sarcopenia and Muscle*

**Cortiula F**, Hendriks LEL, van de Worp WRPH, Schols AMWJ, Vaes RDW, Langen RCJ and De Ruyscher D.  
<https://onlinelibrary.wiley.com/doi/abs/10.1002/jcsm>.

Narrative review on immunotherapy in unresectable stage III NSCLC – in writing

**Selection of Courses and Workshops Attended During the Fellowship**

EORTC Lung Cancer Group Young Investigators Webinar – February 2021

EORTC Lung Cancer Group Spring Meeting – March 2021

ESMO congress 2021 –September 2021

ESMO Virtual Advanced Course on KRAS Targeting in NSCLC- October 2021

EORTC Lung Cancer Group Autumn Meeting – October 2021

Thoracic academy –November 2021

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I wish to thank Prof. Fabio Puglisi, the head of the School of Medical Oncology at my home Institution, the University of Udine, for enthusiastically supporting my ESMO research fellowship.

**Personal Statement**

I believe that the ESMO Fellowship represents a terrific opportunity for young medical oncologists; it is the ideal launch pad for young oncologists willing to improve their research skills. I could develop my own research projects with the guidance of brilliant and supportive mentors, learning how to face research challenges. Working and living abroad, outside of my comfort zone, represented a tremendous gain form me, personally and professionally. For me, one of the most exciting thing about the ESMO fellowship is that even after the fellowship year, I got the opportunity to keep working with my mentors and with the professional network that I have developed in Maastricht, and that represents an incredible boost for my professional growth.

Finally, I have been working in a motivating environment, I have met nice colleagues and researchers and I have been living in a beautiful and international city.

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<b>SIGNATURES</b>	
<b>Award Recipient full name</b>	<b>Signature and Date</b>
Francesco Cortiula	12.01.2022
<b>Research Mentor full name</b>	<b>Signature and Date</b>
Lizza Elizabeth Lucia Hendriks	12.01.2022



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