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Trial in progress

Predictive role of functional respiratory tests in LUng toxicity in stage III NSCLC treated with chemo-, raDIO- and immuno-therapy: PRELUDIO TRIAL

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ABSTRACT

Introduction: Stage III unresectable non-small cell lung cancer (NSCLC) represents a heterogeneous group, for which consolidation immunotherapy with durvalumab, after chemo-radiotherapy, is currently considered the standard of treatment by all national and international guidelines, based on data from the PACIFIC trial. Regarding adverse reactions, pulmonary toxicities represent the most difficult to diagnose and manage.
Methods: It is planned to include 123 patients at 28 sites in Southern Italy experiencing lung cancer in this observational study. The recruitment phase is scheduled to last 24 months (from October 1, 2024, to October 1, 2026) and the followup phase is scheduled to last 24–36 months after durvalumab discontinuation. Retrospective data collection can be considered from 09/01/2023. The duration of the study will be 60 months. We propose to estimate the incidence and grading of pulmonary toxicity from radiation therapy and immunotherapy, according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and to investigate the correlation of

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pulmonary toxicity with pulmonary function tests (PFTs), with a particular focus on forced expiratory volume in one second (%FEV1) and forced vital capacity (%FVC) based on spirometry, diffusing capacity of the lung for carbon monoxide (%DLCO), partial pressure of arterial oxygen (PaO2) based on arterial blood gas (ABG) sampling and maximal distance that patients can walk at their own pace in 6 min and minimal oxygen saturation (SpO2) during the 6-minute walking test (6MWT). Pulmonary function tests (basal spirometry, DLCO, 6MWT, ABG) are evaluated at Time 0 (baseline), at Time 1 (post- RT), at Time 2 (after 6 cycles of immunotherapy) and at Time 3 (end of treatment). At data cut-off (31 mar 2025), 45 patients were enrolled and 10 patients were screened failure. Among the 45 patients enrolled, there were 7 cases of pulmonary toxicity (15.5 %). All of the cases showed post-actinic pneumonia (4 cases of grade 2, 2 cases of grade 3 and one case of grade 4 pneumonia). *Twitteable abstract:* PRELUDIO trial is a study in stage III NSCLC undergoing consolidation immunotherapy with durvalumab, after chemo-radiotherapy, with the aim to estimate the incidence and grading of pulmonary toxicity according to CTCAE and to investigate the correlation of pulmonary toxicity with pulmonary function tests (PFTs), performed per clinical practice.

1. Background

Non-small cell lung cancer (NSCLC) accounts for 85 % of lung cancer cases and one-third of these patients have stage III (locally advanced not resectable) disease at the time of their diagnosis [1]. According to PACIFIC trial, the consolidation with the PD-L1 inhibitor durvalumab after completion of concurrent platinum-based chemoradiotherapy has been shown to provide a clinically and statistically significant benefit in both overall survival (OS) and progression-free survival (PFS), becoming the standard of care worldwide [2,3]. Among the toxicities observed, the most frequent adverse events were pneumonitis or radiation pneumonitis (incidence rates of 6.3 % and 4.3 %, respectively). In patients who received durvalumab, pneumonitis or radiation pneumonitis of any grade occurred in 33.9 % and 24.8 % of patients, respectively. Pneumonitis or radiation pneumonitis of grade 3 or 4 occurred in 3.4 % and 2.6 % of patients [5]. Pneumonitis poses a significant challenge in the management of patients with locally advanced NSCLC undergoing chemoradiation therapy (CRT) as it is associated with a high rate of morbidity [6]. Consequently, we proposed this observational clinical trial investigating the analysis of lung function tests as predictors of pulmonary toxicities.

2. Primary endpoints

– To estimate the incidence of pulmonary toxicity and grading, classified according guidelines following the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [8,9].

– To investigate the correlation of pulmonary toxicity $\geq$ G3 with changes in pulmonary function tests (PFTs), as described below.

3. Secondary endpoints

– to collect real world data on 1-year, 2-year, and 3-year progression-free survival (PFS) and Overall survival (OS) rates following the conclusion of durvalumab therapy.

4. Inclusion Criteria

- Stage III NSCLC with PD-L1 TPS $\geq$ 1 patient receiving chemo and radiotherapy (with sequentially or concurrently definitive-dose) followed by durvalumab consolidation
- Age $\geq$ 18 years old
- ECOG Performance Status 0–2

Patient socio-demographic characteristics	Age, year of birth, SEX	Height (cm), weight (Kg), BMI	Smoking history	ECOG PS Score (basal)	Comorbidities (respiratory and cardiovascular diseases)
Clinical and treatment characteristics	Date of diagnosis	Histology subtype and biomarkers	Cancer stage	Chemotherapy treatment (regimen, duration and cycles)	Thoracic Radiotherapy (timing, duration and total dose)
Outcome variables	Best response after Chemotherapy or chemoradiation	Lung toxicity: ILD/pneumonitis during radiation treatment	Lung toxicity: ILD/pneumonitis at the end of radiation treatment	Lung toxicity: ILD/pneumonitis during durvalumab therapy	Lung toxicity: ILD/pneumonitis at the end durvalumab therapy
Pulmonary function tests (PFRs)	Spirometry: - FEV1 (percentage of predicted value) - FEV1/FVC (absolute value) - VC (percentage of predicted value)	Spirometry: - FVC (percentage of predicted value) - MEF25 (L/s), MEF 50 (L/s), MEF 75 (L/s)	Diffusing capacity of the lung for carbon monoxide: DLCO, KCO (DLCO/VA)	Arterial blood gas analysis: -pH -pCO2 (mmHg) -pO2 (mmHg) -Bicarbonate (mmol/L) -Lactates (mmol/L) -P/F ratio -% Oxygen Saturation (%SpO2)	Six minute walking test (6MWT) -distance (m) -baseline Borg (dyspnea) -final Borg (dyspnea) -baseline modified Borg (fatigue) -final modified Borg (fatigue) -baseline %SpO2 -final %SpO2 -minimum %SpO2 -maximal %SpO2 -baseline Heart Rate (HR) -final Heart Rate (HR)

Fig. 1. Schedule of assesment.

5. Methods

5.1. Study design and treatment

An Italian, prospective and retrospective, observational and multicentre trial on pulmonary function tests (PFRs) as predictors of pulmonary toxicities as showed in Fig. 1.

5.2. Statistical analysis

Functional variables employed in statistical analysis (Fig. 1) will be recorded as follows in three severity levels.

Logistic regression model will evaluate pulmonary function tests (PFRs) as predictors of pneumonitis as primary outcome. Kaplan-Meyer curves will be employed for PFS and OS. The association of functional variables with these outcomes will be evaluated using Cox regression models.

5.3. Accrual goal

It is planned to include 123 patients at 28 sites in Southern Italy experiencing lung cancer in this observational study. The recruitment phase is 24 months (10/2024–2026) and follow-up phase 24–36 months after durvalumab, with retrospective data from 09/01/2023.

At cut-off (31(03/2025), 45 patients were enrolled and 10 patients were screened failure. Of 45 patients evaluated at baseline, 19 patients were evaluated also after thoraco-mediastinal RT, 7 patients after 6 administrations of durvalumab. Among the 45 patients enrolled, there were 7 cases of pulmonary toxicity (15.5 %). All the cases showed post-actinic pneumonia (4 cases of grade 2, 2 cases of grade 3 and one case of grade 4 pneumonia).

CRediT authorship contribution statement

P.M. Medusa: Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **N. Carro:** Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **F. Morgillo:** Writing – review & editing, Supervision, Methodology, Investigation. **G.Di Guida:** Project administration, Methodology, Investigation, Data curation. **V. Nardone:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Investigation, Data curation, Conceptualization. **M. Gilli:** Writing – review & editing, Methodology, Investigation, Conceptualization. **G. Viscardi:** Investigation, Formal analysis, Data curation, Conceptualization. **C. Borrelli:** Investigation. **G. Totaro:** Methodology, Investigation. **R. Costanzo:** Methodology, Investigation. **V. Sforza:** Investigation. **A. Manzo:** Investigation. **G. Esposito:** Investigation. **A. Montanino:** Investigation. **A. Servetto:** Validation, Supervision, Methodology, Data curation, Conceptualization. **F. Salomone:** Methodology, Investigation, Data curation. **A. Viggiano:** Investigation. **F. Ambrosio:** Investigation. **R.Di Liello:** Writing – review & editing, Investigation, Data curation. **T. Fabozzi:** Investigation. **S. Feliciano:** Investigation. **R. Ronga:** Investigation. **L. Notizia:** Investigation. **A. Russo:** Methodology, Investigation, Conceptualization. **G. Motta:** Investigation. **V. Gristina:** Methodology, Investigation. **F. Spinnato:** Investigation. **C. Sergi:** Investigation. **F. Buzzacchino:** Investigation. **A. Ungaro:** Investigation. **T.Del Giudice:** Investigation. **L. Montella:** Investigation. **A.C. Tralongo:** Methodology, Investigation, Data curation. **Vittorio Simeon:** . **C.M. Della Corte:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **F. Vitiello:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Further Reading

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