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PD-1 inhibitor and chemotherapy with concurrent irradiation at varied tumor sites in advanced Non-small cell lung cancer: the Prospective Randomized Phase 3 NIRVANA-Lung Trial

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Abstract

Advanced non-small cell lung cancer (NSCLC) remains a high unmet medical need. The first line standard-of-care therapy comprises concurrent chemotherapy-immunotherapy with pembrolizumab. Concurrent irradiation with pembrolizumab has been shown to significantly improve survival benefit compared with immunotherapy alone in a pooled analysis of two randomized phase 2 trials. We present the rationale and study design of the “PD-1 iNhibitor and chemotherapy with concurrent IRradiation at VAried tumor sites in advanced Non-small cell lung cAncer” (NIRVANA-Lung) trial (ClinicalTrials.gov identifier, NCT03774732). This study is a national multicenter 1:1 randomized phase III trial testing in 460 patients, the addition of multisite radiotherapy in advanced non-small-cell lung cancer treated with standard immune checkpoint inhibitors (pembrolizumab)-chemotherapy in first line. The primary objective of the trial is to compare the overall survival between the two arms at year 1 of the study. The secondary objective is to compare the progression-free survival and cancer specific survival at year 1 and 2, as well as to determine quality of life, local and distant control in irradiated and non-irradiated sites at 6 months and year 1.

Keywords: advanced non-small-cell lung cancer; multisite radiotherapy; phase III trial; immune checkpoint inhibitors; chemotherapy

Introduction

In patients without oncogene driver, immune checkpoint inhibitors (ICI) targeting programmed death 1 (PD-1) (e.g. pembrolizumab) or its ligand (anti-PD-L1) have revolutionized the management of advanced non-small cell lung cancer (NSCLC). Increased outcomes rate has been observed in ICI alone (if PD-L1 expression $\geq 50\%$)¹ or with the association of ICI and chemotherapy^{2,3}. Prognosis however still remains poor in advanced NSCLC and 1-year overall survival in first line with chemo-immunotherapy is of 69.2% in non-squamous NSCLC⁴ and of 65.2% months in squamous NSCLC⁵. Novel more effective therapeutic approaches are still needed to improve survival of these patients.

Radiation therapy is a critical component of curative treatment for non-metastatic NSCLC, and has classically been reserved for tumor-related symptom palliation in the metastatic disease setting. Preclinical data showed that that anti-tumor efficacy is increased when anti-PD-1/-L1 are combined with irradiation. Dovedi et al. demonstrated that radiotherapy could durably increase the PD-L1 expression on tumor cells surface and led to better survival in mice when combined with anti PD-L1⁶. Another mechanism that supports the combination of ICI and radiotherapy is that radiotherapy alone can elicit tumor cell death which increases tumor antigen in the blood stream, favoring recognition by the immune system and its activation against tumor cells outside of the radiation field (“abscopal effect”)^{7,8}. Finally, irradiation reverses in vitro/in vivo acquired resistance to PD-1 blockade immunotherapy by limiting T-cell exhaustion⁹. In the clinical setting, Shaverdian et al.¹⁰ reported results in 98 patients from the Keynote-001 trial that tested PD-1 inhibition (pembrolizumab) in progressive stage III or stage IV NSCLC. Very interestingly, median progression-free survival (PFS) was increased by 2.3 months and median overall survival (OS) by 6.3 months. The recent PACIFIC phase III study, among patients with

locally advanced, unresectable NSCLC who had thoracic chemoradiotherapy, PFS was 11 months longer among patients who received consolidative durvalumab than among those who received placebo (hazard ratio for disease progression or death, 0.52; $P < 0.001$)¹¹. Two limited-size randomized phase 2 studies suggested an advantage of combining irradiation and pembrolizumab. The PEMBRO-RT randomized phase 2 study showed a non-significant median PFS increase when stereotactic body radiotherapy (SBRT, 3 times 8 Gy to a single site) was administered 7 days before the anti PD-1 pembrolizumab as compared to a non-irradiated group (median PFS: 6.6 vs 1.9, respectively; $p = 0.2$) in 92 patients with advanced NSCLC¹². In The MDACC phase I/II randomized trial, 100 patients received pembrolizumab +/- radiotherapy (SBRT or hypofractionated radiotherapy). PFS were not different (median of 9.1 months in the combination arm vs. 5.1 months if immunotherapy alone, $p = 0.5$), unless if higher radiotherapy doses were applied (50 Gy in four fractions) leading to a median PFS increase (20.8 months vs 6.8 months, $p = 0.03$)¹³. A subsequent pooled analysis of the PEMBRO-RT and MDACC trials including 148 patients showed significant improvement of both median PFS (Hazard ratio (HR) = 0.67 [0.45-0.99], $p = 0.04$) and median OS (HR=0.67 [0.54-0.84], $p = 0.0004$)¹⁴. Such results needs to be validated in a proper phase II including the first-line standard of care chemo-immunotherapy.

The randomized phase III NIRVANA-Lung study (ClinicalTrials.gov identifier, NCT03774732) will investigate the efficacy and safety of multisite concurrent radiation therapy in first-line advanced NSCLC patients receiving standard chemo-immunotherapy with pembrolizumab. In the present report, we have described the study design.

Materials and Methods

Study Design

NIRVANA-Lung is a phase III, randomized, multicenter, national study in patients with advanced NSCLC. In total, 460 patients will be randomized in ratio 1:1 to the control arm: pembrolizumab/ chemotherapy (which will be administered as per standard of care) or pembrolizumab/chemotherapy + multisite radiotherapy (**Figure 1**).

In both arms, chemo-immunotherapy consists of pembrolizumab every 3 weeks until progression or toxicity and for 1) squamous NSCLC carboplatin AUC6, paclitaxel 200 mg/m² every 3 weeks for 4 cycles; 2) for non-squamous NSCLC carboplatin AUC5 or cisplatin 75 mg/m² every 3 weeks for 4 cycles, and pemetrexed 500 mg/m² every 3 weeks until progression or toxicity.

In the experimental arm, patients will receive the same treatment as the control arm (pembrolizumab and chemotherapy) in addition with conformal 3D radiotherapy (3D-CRT) or stereotactic ablative radiotherapy (SABR) that will be delivered 15 days after the beginning of immunotherapy/chemotherapy using photons/electrons with standard field encompassing tumor. Irradiation techniques (3D-CRT or SABR) will be used at the discretion of the treating physician. In order to take into account potential tumor heterogeneity, one metastasis per tumor site should be irradiated not exceeding 7 treatments. Ideally, oligometastatic patients (defined by the presence of less than 6 metastases) should be treated with SABR and non-oligometastatic patients should be treated with 3D-CRT. Radiotherapy will deliver at least a dose of 18 Gy in 3 x 6 Gy for 3D-CRT¹⁵ while not delivering more than 12 Gy per session¹⁶. Irradiated tumor size will be ≤ 5 cm (GTV < 65mL sphere) ; partial tumor irradiation should be delivered for the treatment of larger tumor size while respecting dose constraints.

Key Eligibility Criteria

Study entry is limited to patients with (**Table 1**) histologically or cytologically confirmed advanced (stage IIIB/IIIC/IV), squamous or non-squamous NSCLC eligible for first line treatment with pembrolizumab according to the European Marketing Authorization. Patients should be ≥ 18 and ≤ 80 years of age with an ECOG performance status 0 – 1 and metastases eligible for 3 dimensional conventional radiotherapy (3D-CRT) or stereotactic ablative radiotherapy (SABR) in terms of organ at risk dose constraints (according to QUANTEC review)¹⁷.

The main exclusion criteria include patients with targetable tumor mutations, activating epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocation not treated before with the appropriate targeted therapy. Clinical need of radiotherapy (e.g.: whole brain irradiation, painful metastasis, bleeding, compressive metastases), irradiation within 2 months before inclusion (because of possible synergic effect with ICI if radiotherapy administration happens almost concomitantly¹⁰), leptomeningeal carcinomatosis, or metastases with indistinct borders, evidence of active central nervous system (CNS) metastases and/or carcinomatous meningitis.

Study Endpoints

The primary objective of this study is to evaluate the efficacy of a combination of multisite radiotherapy with chemotherapy and pembrolizumab for the treatment of patients with advanced (stage IIIB/IIIC/IV) NSCLC treated at the first-line systemic chemotherapy in terms of the overall survival rate (OS) with report of 1 and 2 years rates.

The secondary objective include the cause of death, toxicities, Progression-Free Survival (PFS) with report of 1 and 2 year rates, Cancer Specific Survival (CSS) with report of 1 and 2 year rates, local and distant control in irradiated and non-irradiated sites (at 6 months and 1 year).

Additional secondary endpoints include quality of life using the European Organization for Research and Treatment of Cancer quality-of-life questionnaires (EORTC QLQ-C30). Ancillary studies include immunohistochemical analysis testing several immune markers¹⁸. The present trial is also part of the ONCOBIOME consortium (<https://www.oncobiome.eu/>) which will analyze stool immune markers. All biomarkers will be tested as potential predictors for survival or toxicities.

Study Assessments

Objective tumor assessments will be performed using RECIST v1.1 and iRECIST. The assessments will be conducted at screening and every 6th week (\pm 5 days) until week 24 and then at least every 3 months until disease progression requiring discontinuation of study therapy (or until discontinuation of study therapy in patients receiving Checkpoints inhibitors beyond progression), lost to follow-up, withdrawal of consent, or start of a subsequent anti-cancer therapy. In case of prolonged tumor response, evaluation will be done every 12 weeks for the first year and then every 16 weeks until the end of study. AEs will be graded using the Common Terminology Criteria for Adverse Events, version 5.0.

Statistical Analysis

According to literature, survival at 1 year is 65.2% for squamous cell carcinoma patients and 69.2% for non-squamous cell carcinoma patients with the combo pembrolizumab/chemotherapy^{2,3}. By assuming 20% of patients are included in first line and 80% in second line, survival at 1 year is 50%.

The objective of the study is to increase from 50% to 59.5% (median OS from 12 months to 16 months), the 1 year OS rate in the ICI + radiotherapy arm which corresponds to a hazard ratio HR

of 0.75. The objective of the study is to increase from 67% to 75.5% (median OS from 1.73 years to 2.5 years), the 1-year OS rate in the pembrolizumab/chemotherapy + radiotherapy arm which corresponds to a hazard ratio HR = 0.70.

In total, 460 patients (230 in each arm) will be randomized in order to observe 252 events to obtain a power of 80% to detect a difference between the two treatment arms, with a bilateral test, exponential survival distribution, a period of accrual of 3 years, a minimum follow-up of one year (total duration of the study 4 years) and a significance level of 5%. An interim efficacy analysis will be performed when 126 events are observed.

The randomization will be, minimized by the following stratification factors: (i) patients who had previously received radiotherapy or who had not received, (ii) use of steroids or not (iii), age (≥ 70 years or not) and (iv) presence of brain metastases or not. To test whether the immune-related adverse events (irAE) grade 3-5 rate is not superior to 20% in the radiotherapy arm, a sequential analysis based on the triangular test ($\alpha=10\%$, $\beta=5\%$, $p_0=5\%$) will be used. Four analyses will be driven after the inclusion of 30, 60, 90 and 120 patients in the radiotherapy arm. These analyses will be reviewed by an independent data monitoring committee (IDMC). The irAE grade 3-5 rate will be estimated with its 95% confidence interval but will not be compared to the rate in the pembrolizumab/chemotherapy arm. One interim analysis on OS will be performed after 126 events (50%) corresponding to the inclusion of 386 patients using O'Brien and Fleming boundaries (two-sided) ($p=0.003$ for interim analysis and $p=0.05$ for final analysis).

Ethical Considerations

The study is being conducted in accordance with the protocol and the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines. French ethics committee (CPP Sud-Est V) has approved initially the protocol on 08/2018 and this

amended version on 06/2020 (CPP reference number: 18-UNIC-01). The institutional review board at all participating sites has approved the study protocol. Patient information and informed consent from the patient are handled in accordance with the French regulation. Prior to participation, patient will be informed both verbally and in writing about the objectives of the trial, its methods, anticipated benefits and potential risks and the discomfort to which they may be exposed. The informed consent form for study and ancillary studies, are personally dated and signed by the patient and investigator. It will be possible to obtain data underlying the findings described in the final report for this study in accordance with Unicancer's data sharing policy.

Conclusion

New treatment options are required for patients with advanced NSCLC. The NIRVANA-Lung the first phase III designed to demonstrate a significant improvement in OS when multisite radiotherapy is added to standard first-line pembrolizumab/chemotherapy in advanced NSCLC. The trial started on 09/2020 and recruitment is ongoing in 30 hospitals across France.

Disclosure

J Doyen: consulting/advisory board for AstraZeneca and Bristol-Myers Squibb

Other authors have stated that they have no conflicts of interest.

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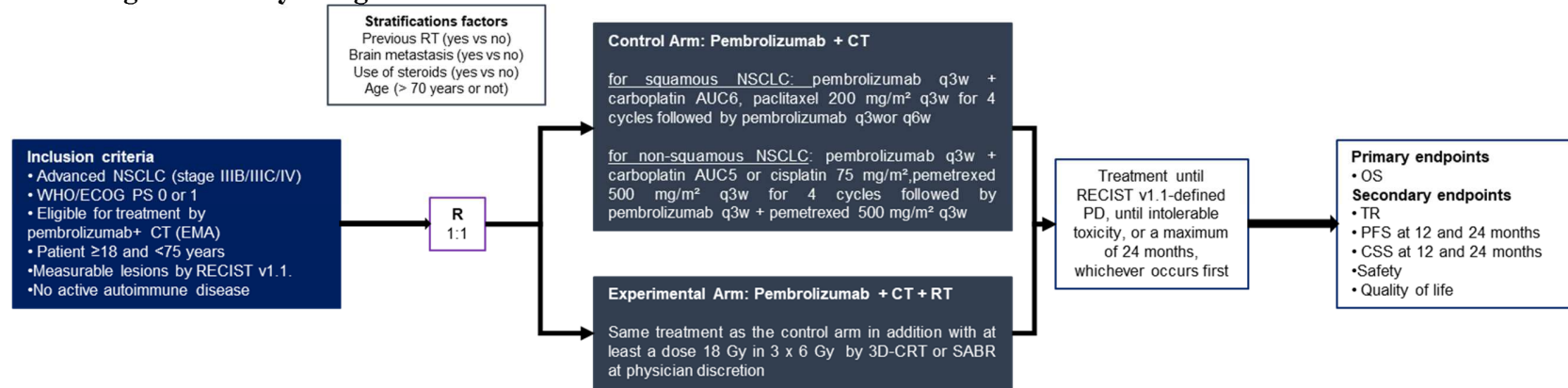
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Figure 1: Study Design



Abbreviations: 3D-CRT = conformal 3D radiotherapy; AUC = area under the curve; CT = Chemotherapy; CSS = cancer specific survival; ECOG = Eastern Cooperative Oncology Group; EMA = European Market Authorization; NSCLC = non small-cell lung cancer; OS =overall survival; PD=progressive disease; PFS =progression-free survival; PS = performance status; q3w =every 3 weeks; q6w = every 6 weeks R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; RT= radiotherapy; SABR = stereotactic ablative radiotherapy; TR = Tumor Response percentage of complete or partial response; WHO=World Health Organization.

Table 1 : Key Eligibility Criteria

INCLUSION CRITERIA:

- Histologically or cytologically confirmed advanced (stage IIIB/IIIC/IV), squamous or non-squamous NSCLC
- NSCLC patients eligible for treatment with pembrolizumab and chemotherapy according to the European Marketing Authorization:
 - squamous: in combination with carboplatin and either paclitaxel or nab-paclitaxel
 - non squamous with no EGFR or ALK positive mutations: in combination with pemetrexed and a platinum based chemotherapy
- Patient ≥ 18 and < 75 years of age.
- ECOG performance status 0 – 1
- Life expectancy > 3 months
- Measurable lesion as assessed by RECIST version 1.1.
- Metastases and/or primary tumour eligible for 3 dimensional conventional radiotherapy (3D-CRT) or stereotactic ablative radiotherapy (SABR) in terms of dose constraints at organ at risk (according to QUANTEC review)

EXCLUSION CRITERIA:

- Non-squamous NSCLC with targetable tumor mutations, activating *EGFR* mutations or *ALK* translocation.
- Stage IIIB/IIIC NSCLC patient eligible to curative (thoracic radiotherapy or surgery) treatments in first line treatment.
- Prior therapy with T-cell costimulation or checkpoint-targeted agents
- Clinical need of radiotherapy (e.g.: whole brain irradiation, painful metastasis, bleeding, compressive metastases)
- Irradiation within 2 months before inclusion.
- Leptomeningeal carcinomatosis, or metastases with indistinct borders making targeting not feasible. Patient with evidence of active (presence of symptoms or requiring steroid treatment) central nervous system (CNS) metastases and/or carcinomatous meningitis. Patient with brain metastasis can be included if asymptomatic and not requiring steroids
- Metastases located within 3 cm of the previously irradiated structures (EQD2doses):
 - o Spinal cord previously irradiated to > 40 Gy;
 - o Brachial plexus previously irradiated to > 50 Gy;
 - o Small intestine, large intestine, or stomach previously irradiated to > 45 Gy;
 - o Brainstem previously irradiated to > 50 Gy;
 - o Lung previously irradiated with prior V20Gy $> 30\%$
- Active autoimmune disease except vitiligo, type-1 diabetes, hypothyroid stabilized with hormonal substitution, psoriasis
- Symptomatic interstitial lung disease
- Systemic immunosuppression or systemic immunosuppressive medicinal products within 2 weeks prior to study entry.
- Concomitant treatment with steroids > 10 mg.
- *Note 1: higher dose of steroids can be prescribed in case of occurrence of toxicities during radiotherapy; prophylactic dose of maximum 1 mg per kg during 2 weeks are authorized during the delivery of more than 6 Gy per fraction.*
- *Note 2: temporary use of steroid (less than 4 weeks) at a dose of 1 mg/kg is accepted*
- Prior invasive malignancy within the past 2 years (except non-melanomatous skin cancer non-invasive carcinoma in-situ of the breast, oral cavity, bladder or cervix)
- Active or uncontrolled co-morbidity
- Investigational medicinal product or have used an investigational device within 30 days of inclusion
- Pregnant or breast feeding woman