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Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-radiotherapy regimen in stage III non-small cell lung cancer—The ETOP NICOLAS trial

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ABSTRACT

Objectives: Chemo-radiotherapy (CRT) and concurrent PD-1 inhibition has shown promising results in pre-clinical models. So far, the feasibility of delivering concurrent CRT and PD-1/PD-L1 inhibition has never been assessed in a clinical trial.

Material and methods: NICOLAS is a phase-II trial evaluating the safety and efficacy of nivolumab combined with CRT in stage III NSCLC. Patients received 3 cycles of platinum-based chemotherapy and concurrent RT (66 Gy/33fractions). Nivolumab started concurrently with RT. The primary endpoint was 6-month post-RT rate of grade-≥3-pneumonitis. A formal interim safety analysis (IA) was scheduled when the first 21 patients reached 3 months follow-up post-RT. An early positive safety conclusion would be reached at IA if there were no grade ≥3-pneumonitis in those patients. Efficacy evaluation was planned provided the safety conclusion was reached.

Results and conclusion: As of 13 December 2018, 82 patients were recruited with median follow-up of 13.4 months. The most frequent adverse events (AEs) were anaemia, fatigue and pneumonitis. No unexpected AEs or increased toxicities were observed. For the first 21 patients, no grade-≥3-pneumonitis was observed by the end of the 3-month post-RT follow-up period.

The early safety IA provides evidence that the addition of nivolumab to concurrent CRT is safe and tolerable regarding the 6-month rate of pneumonitis grade ≥3 at the one-sided significance level of 5%. Following that, the 1-year progression-free survival will be evaluated in an expanded patient cohort. NICOLAS trial creates the opportunity for assessing the activity of the combination of checkpoint with concurrent CRT in larger prospective trials for locally advanced NSCLC.

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1. Introduction

Clinical efficacy of ionizing radiation is usually attributed to induced DNA damage, resulting in direct tumour cell death. The existence of radiation-induced immune mechanisms of tumour control have been described in preclinical models [1]. In the clinical setting, it has been postulated that local radiotherapy could promote local and systemic anti-cancer immune response inducing a phenomenon called "immunogenic cell death" amongst other mechanisms and suggesting that mobilization of antitumour immunity might be a determinant of the overall clinical efficacy of radiotherapy on targeted and distant tumours [2].

Supporting this hypothesis, a retrospective analysis of the phase-I pembrolizumab KEYNOTE-001 trial in advanced non-small cell lung cancer (NSCLC) demonstrated that previous treatment with radiotherapy could result in longer progression-free survival (PFS) and overall survival (OS), irrespective of radiotherapy for cranial or extracranial sites, with an acceptable safety profile [3].

More recently, the maintenance administration of the anti-PD-L1 agent durvalumab after completion of radical chemo-radiotherapy (CRT) for non-progressive stage III unresectable NSCLC in the placebo-controlled phase-III PACIFIC trial demonstrated significant PFS and OS improvement [4,5]. Incidence of pneumonitis under durvalumab was 33.9% (overall) and 3.4% (grade ≥3).

Of interest, in mice models, the concurrent administration of a PD-1 inhibitor and radiotherapy has been shown to optimize immune activation over the sequential administration [6]. However, the feasibility of combining concurrent immune-checkpoint inhibition and radical CRT has never been prospectively assessed in stage III NSCLC, and is of high scientific and clinical interest.

NICOLAS (NCT02434081) is a single-arm phase-II trial evaluating the safety and efficacy of the addition of concurrent anti-PD-1 nivolumab to standard first-line CRT in locally advanced stage III NSCLC. Here we present the safety evaluation of the NICOLAS patients, enrolled under protocol versions 2.0/3.0.

2. Methods

Patients with histologically or cytologically confirmed locally advanced stage IIIA/B NSCLC (7th-TNM-classification) and ECOG-PS 0–1 were eligible. Patients with prior chemo-, radio- or molecular targeted therapy were excluded.

The protocol originally allowed either sequential or concurrent CRT, followed by nivolumab consolidation. Since the first protocol-amendment, nivolumab was to start concurrently with radiotherapy (v2.0) while in the second amendment, calling for an expansion cohort to evaluate efficacy, only concurrent CRT (v3.0) was allowed (Supplementary Fig. 1).

The sequential question of protocol v1.0 was answered in the large PACIFIC trial [4,5]. Protocol v2.0 was designed to build the opportunity for a concurrent treatment in order to pave new ways beyond the safe sequential approach.

In protocol versions v2.0 and v3.0, nivolumab was administered at 360 mg every three weeks for the first four doses (eight doses in the case of sequential CRT of protocol v2.0), followed by 480 mg every four weeks, for up to one year or until disease progression or unacceptable toxicities. Due to the different safety profile for patients under v1.0, they are not included in the formal safety analysis.

Chemotherapy consisted of three cycles cis- or carboplatin combined with vinorelbine, etoposide or pemetrexed (non-squamous histology). In the concurrent CRT regimen, radiotherapy was delivered at 66 Gy in 33 daily fractions, while for the sequential CRT regimen, radiotherapy was given in 24 daily fractions of 2.75 Gy, both using standard dose-constraints and specifications (Supplementary Fig. 1). The mean lung dose was restricted to 20 Gy.

Radiotherapy techniques, target volume definitions and specifications were done according to the European Organisation for Research and Treatment of Cancer (EORTC) recommendations [7]. In brief, the gross tumour volume (GTV) of the primary tumour and the lymph nodes was defined on the fluorodeoxyglucose-positron emission tomography–computed tomography (FDG-PET-CT) scan taking into account the findings on bronchoscopy, endobronchial ultrasound (EBUS), endoscopic ultrasound (EUS) and mediastinoscopy (if applicable), with an expansion of 5 mm for the clinical target volume (CTV), for which edition, e.g., for bony structures, was allowed. The planning target volume (PTV) margins had to be calculated according to established formulas. Motion had to be taken into account with established techniques (e.g., mid-ventilation or internal target volume (ITV) approach) using 4D-CT scans. Pencil beam algorithms were not allowed for dose calculation. Dose constraints were defined according to EORTC standards and dose specifications according to the International Commission on Radiation Units and Measurements (ICRU). All techniques (e.g., intensity-modulated radiotherapy (IMRT), 3D-conformal radiation therapy, volumetric modulated arc therapy (VMAT), tomotherapy) and energies (e.g. 6 MV, 10 MV) were allowed as long as the dose and volume criteria were met.

The primary endpoint was safety, defined by an adequate 6-month post-radiotherapy (post-RT) pneumonitis-free rate (grade ≥3; CTCAE-

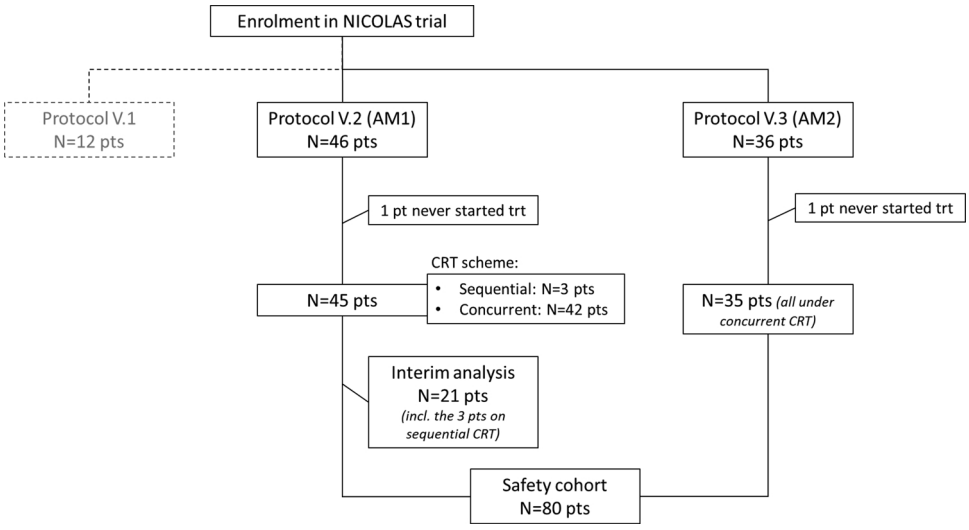

Fig. 1. Consort diagram.

v4.0). Forty-one patients, evaluable for pneumonitis at 6 months post-RT, were needed for testing the null hypothesis that the 6-month pneumonitis-free rate of grade ≥3, was less or equal to 67% versus the alternative of at least 85% (exact-group-sequential test; one-sided alpha = 0.05; power = 83%). Assuming 70% of pneumonitis events occur within 3 months post-RT, one interim look for treatment safety (O'Brien-Fleming boundaries), was planned to be performed on the 21 first patients evaluable for pneumonitis at 3months post-RT. If none of the 21 patients experienced grade-≥3-pneumonitis, an early positive conclusion on safety could be reached. Otherwise, the trial would continue to final safety analysis, with at least 33 of the 41 patients needed to reach 6 months post-RT pneumonitis-free, to reject the null hypothesis.

In protocol-v3.0, the 1-year PFS is planned to be hierarchically tested in an expanded cohort of 74 patients, conditional on proven acceptable safety.

The protocol was approved by institutional review boards at each site and was conducted in accordance with the Declaration of Helsinki, the Guideline for Good Clinical Practice, and the International Conference on Harmonization Tripartite Guideline. Safety was reviewed every 3 months by the ETOP Independent Data Monitoring Committee (IDMC).

3. Results

The current report includes 82 patients under protocol-v2.0/v3.0, recruited between 23/08/2016 and 06/08/2018, with follow-up up to 13/12/2018. Two patients died before starting treatment, thus the safety cohort consists of 80 patients receiving at least one dose of trial treatment, with only three (3.75%) of them treated with sequential CRT (Fig. 1). The 12 patients enrolled under protocol-v1.0 are not part of this analysis.

The majority of patients are male (65.9%), former smokers (68.3%) with tumour stage IIIB (62.2%), and median age of 62 years (interquartile range, IQR: 41–78). Median follow-up is 13.4 months (IQR: 9.0–18.4), and 61 (74.4%) patients are still on follow-up. So far, 16 patients have completed the per-protocol treatment successfully, remaining on nivolumab for one year, while 44 patients (53.7%) discontinued treatment.

3.1. Safety evaluation

3.1.1. Formal interim safety analysis (IA)

The IA of the first 21 patients reaching 3 months follow-up post-RT, was completed in September 2017. Among the 21 patients (non-squamous:12; squamous:9), 18 were on concurrent and three on sequential CRT regimen. Combination of cisplatin with either pemetrexed/etoposide/vinorelbine was administered in six patients each, while carboplatin was combined with etoposide or vinorelbine in two and one patient, respectively.

No grade-≥3-pneumonitis was observed, leading to the rejection of the null hypothesis. The conclusion that safety is adequate was reached.

3.1.2. Informal verification in 41 patients

In August 2018, among the first 47 enrolled patients, 41 evaluable patients reached 6 months follow-up post-RT, with 36 not having experienced grade-≥3-pneumonitis, above the boundary for null hypothesis rejection of ≥33 patients event-free. Thus, this result provided informal verification of the IA conclusion, which is also confirmed if only patients with concurrent CRT are included in the analysis. Six non-evaluable patients included three deaths (one before starting treatment), two discontinuations due to toxicity (other than pneumonitis), one patient withdrawal.

3.1.3. Incidence of pneumonitis grade ≥3 in the safety cohort

Among the 80 patients in the safety cohort, eight grade-3-

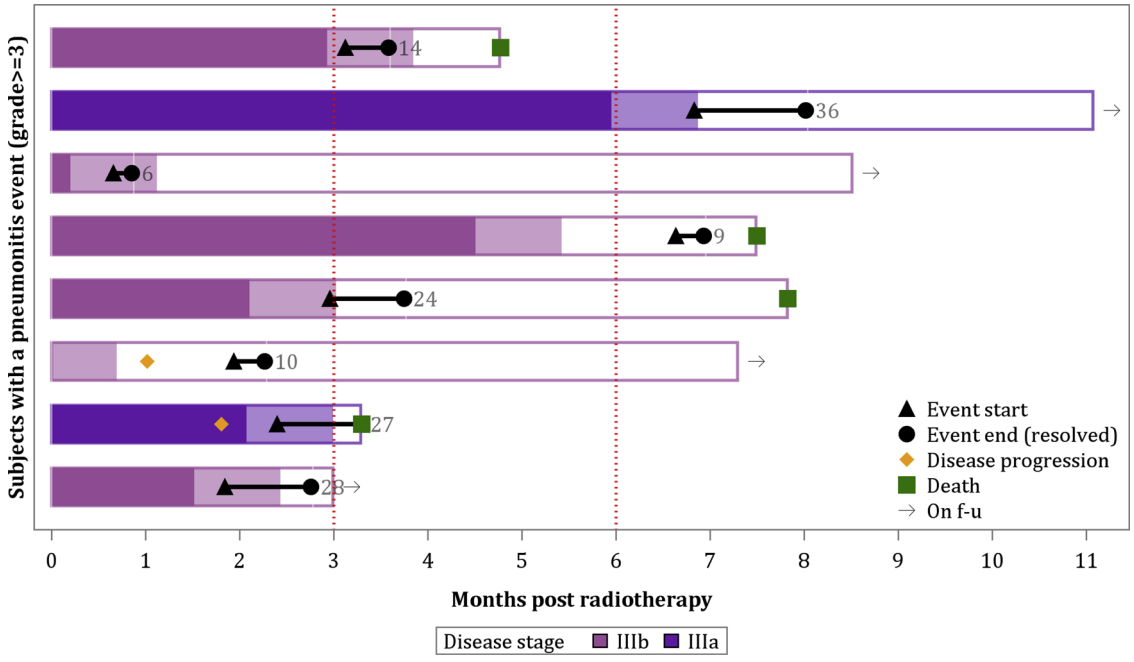

Fig. 2. Timing of grade-≥3-pneumonitis any time post-radiotherapy in safety cohort.
Each bar represents one patient with grade-≥3-pneumonitis during follow-up.
Time 0 represents date of end of radiotherapy.
Coloured part of bar: period from end of radiotherapy until last nivolumab administration.
Coloured transparent part of bar: period from last to next scheduled nivolumab administration (21–28 days).
Bar extends to latest available follow-up.
Next to each event-line, the duration of the pneumonitis event (in days) is shown.
Vertical dotted reference lines at 3 months and 6 months post-RT.

pneumonitis events were observed (none among the three patients under the sequential CRT), with no higher grade event. The post-RT timing of these events, along with treatment-discontinuation/progression/death information is presented in Fig. 2.

3.1.4. Adverse events and toxicity

In the safety cohort, adverse events (AEs) per patient ranged from one to 22. In total, 709 AEs, irrespective of relation to treatment, were recorded in 77 of the 80 patients (Supplementary Table1). The most frequent AEs were anaemia in 38 (47.5%), fatigue in 36 (45.0%) and pneumonitis in 34 (42.5%) patients. For pneumonitis, seven AEs were grade 1, 19 grade 2 and 8 grade 3 (Fig. 2). Mean lung dose and V20 lung dose were not significantly associated to pneumonitis incidence of any grade (Wilcoxon p-value > 10%).

Overall, 55.0% of the AEs were mild, 30.3% moderate, 10.9% severe. Twenty life-threatening events (2.8%) were observed in 15 patients, while fatal events were observed in seven patients (two strokes; colitis, oesophageal-fistula, autoimmune-disorder, bronchopulmonary-haemorrhage, pulmonary fibrosis). Among these seven fatal events, only one (autoimmune-disorder) could be potentially attributed to nivolumab, while bronchopulmonary haemorrhage, related to tumour disease, was possibly related to radiotherapy. After central medical review, the isolated oesophageal fistula was attributed to standard CRT.

Among AEs of grade 4–5, eight life-threatening and five fatal events were serious adverse events (SAEs). Furthermore, 37 patients experienced 1–4 SAEs, in a total of 60 SAEs (Supplementary Table1).

4. Discussion

Locally advanced NSCLC accounts for approximately 25% of all new lung cancer cases and represents a heterogeneous disease with concurrent CRT as standard treatment for patients with unresectable disease, without significant progress in the systemic therapy during the last decades [8–11].

The PACIFIC trial, a randomized, double-blinded, placebo-controlled multicentre trial of 713 patients showed that consolidation durvalumab significantly improved PFS and OS after CRT [5]. Results of PACIFIC provide compelling evidence for sequential addition of durvalumab after completion of standard of care CRT in this patient population, which proves the immunotherapy concept for locally advanced NSCLC and suggests a synergistic role between CRT and immune-checkpoint inhibitors. PACIFIC trial paves the way for a new generation of trials combining immunotherapy to the radical treatment of unresectable stage III disease.

Very few data are available regarding toxicity of immunotherapy in the context of the radical treatment strategy of CRT for stage III NSCLC. In the phase-II trial of concurrent CRT with consolidation pembrolizumab in patients with unresectable stage III NSCLC Hoosier Cancer Research Network (LUN 14–179), 93 patients were evaluable for toxicity. Pneumonitis grade > 2 was observed in 17.2% of patients, with 10.8% grade 2, 4.3% grade 3 and 1.1% grade 4 and 5 respectively [12]. In the PACIFIC phase-III trial, durvalumab, as compared with placebo, resulted in pneumonitis or radiation pneumonitis of any grade in 33.9% and 24.8% and pneumonitis or radiation pneumonitis of grade 3 or 4 in 3.4% and 2.6%; pneumonia of any grade occurred in 13.1% and 7.7%, and pneumonia of grade 3 or 4 occurred in 4.4% and 3.8% [5].

The main point of NICOLAS was to assess the debated suspicion of potentially increased lung toxicities by using concurrent immunotherapy and CRT. This question is timely framed ahead of many large trials opening based on this strategy. Sample size is sufficient to evaluate this parameter of great importance, but not to capture patients' prognostic factors diversity in stage III in general, and particularly as compared to larger previous series. Of note, concerning distant organs and systemic toxicities of nivolumab and chemotherapy, the safety of this combination was previously demonstrated in Checkmate 012 and Checkmate 227 (PD-L1 negative subgroup), as well as many large phase III trials using other anti-PD(L)-1 (Keynote 189, Keynote 407, IMPOWER 130, 131, 132).

The pre-specified, formal NICOLAS IA was successful in rejecting the null hypothesis on the primary endpoint, providing evidence that the addition of nivolumab to CRT, is safe and tolerable regarding the 6-month rate of pneumonitis grade ≥3 at the one-sided significance level of 5%. In the IA cohort of the 21 patients evaluable at 3 months post-RT, no grade ≥3 pneumonitis was observed, while one late event occurred 6 months post-RT. Patients in this analysis received either concurrent or sequential CRT.

Our underlying study design assumption for the interim analysis was that the expected occurrence of pneumonitis by 3 months post-RT would represent 70% of the events occurring by 6 months post-RT. So far, five events occurred within the first three months post-RT, corresponding to 83% of the six observed events by 6 months. Thus, our assumption was, if anything, more conservative, rendering the conclusion of the interim analysis even safer than originally designed.

If we were to explore 6-month rate of pneumonitis grade ≥3 at the final analysis of the 41 first evaluable patients, the conclusion of achieving safety, would again have been reached. In addition, the same conclusion would again have been reached, if the three patients who received sequential CRT were excluded from consideration.

In the expanded cohort of 80 patients, eight grade-≥3-pneumonitis are observed so far, with two events after 6 months post-RT. This is the expanded cohort for evaluating PFS, and safety information is presented here only for completeness since available.

We acknowledge that the mortality rate observed in this clinical trial was higher than in other series (not too high, though, e.g., treatment-related death was more than 5% in the PACIFIC trial [4,5]), pointing to the fact that a larger number of patients treated with this regimen is needed, in order to evaluate in a multivariate analysis the potential factors contributing to patients' outcome beyond lung toxicity.

In conclusion, NICOLAS demonstrates the feasibility of CRT combination with concurrent and maintenance nivolumab in unresectable stage III NSCLC, with no unexpected adverse events or increased severe pneumonitis risk observed. The 1-year PFS will be evaluated according to the hierarchical design in the expanded cohort of all patients enrolled.

Conflict of interest

Author's name	Affiliation
Dr. Peters	Personal fees from: Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Boehringer-Ingelheim, Bistrol-Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, F. Hoffmann-La Roche, Foundation Medicine, Illumina, Janssen, Merck Sharp & Dohme, Merck Serono, Merrimack, Novartis, Pharma Mar, Pfizer, Regeneron, Sanofi, Seattle Genetics and Takeda. Non-financial support from: Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Meyers Squibb, Clovis, F. Hoffmann-La Roche, Illumina, Merck Sharp and Dohme, Merck Serono, Novartis, Pfizer outside the submitted work.
Dr. Felip	Personal fees from: ABBVIE, AstraZeneca, Blue Print Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Guardant Health, Merck KGaA, Merck Sharp & Dohme, Novartis, Pfizer, Roche, TAKEDA, Janssen outside the submitted work
Dr. Guckenberger	Support from: AstraZeneca during the conduct of the study
Dr. Nadal	Personal fees from: BMS, MSD, Astra Zeneca Grants and personal fees from Roche outside the submitted work

Dr. Pless	Personal fees from: BMS, MSD, Astra Zeneca, Roche outside the submitted work
Dr. Martinez-Marti	Personal fees from: Bristol-Myers Squibb, F. Hoffmann-La Roche, Merck Sharp & Dohme, Pfizer, Boehringer Ingelheim outside the submitted work
Dr. Tufman	Personal fees from: Celgene, Takeda, BMS, Roche, AstraZeneca outside the submitted work
Dr. Lambrecht	Personal fees: Astra Zeneca, non-financial support from Roche, outside the submitted work
Dr. Stahel	Grants from ETOP during the conduct of the study Personal fees from: Abbvie, AstraZeneca, Boehringer Ingelheim, MSD, Pfizer, Roche, Takeda, grants from AstraZeneca, BMS, Boehringer Ingelheim, Genentech, MSD, Roche, and Pfizer outside the submitted work
Dr. De Ruysscher	Grants and other from: BMS, Astra Zeneca, Roche/Genentech, Merck/Pfizer, Celgene during the conduct of the study

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.05.001.

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