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An open-label, randomized phase III study of early switch maintenance vs delayed second-line nivolumab in advanced stage squamous non-small cell lung cancer (NSCLC) patients after standard first-line platinum-based chemotherapy-EDEN trial GOIRC 04–2016

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ABSTRACT

Background: As for squamous (Sq)-NSCLC, Checkmate-017 trial showed a significant overall survival (OS) improvement in favor of Nivolumab (Nivo) over Docetaxel in 2nd-line. We hypothesized that anticipating Nivo use, as early switch maintenance after 1st-line chemotherapy (CHT), might have improved survival as compared to delayed 2nd-line treatment.

Methods: EDEN was an open-label, 2-arm, phase III study which randomized (1:1) stage IIIB/IV Sq-NSCLC pts non-progressive after 1st-line platinum-based CHT, to receive early Nivo as switch maintenance (Arm A) or standard best supportive care followed by 2nd-line Nivo at disease progression (Arm B). In both arms, Nivo was administered at the dose of 240 mg i.v. every 2 weeks until progressive disease, intolerable toxicity, or for a maximum of 2 years. The primary endpoint was OS.

Results: From Sep 2017 to Aug 2020 125 patients (62 Arm A vs 63 Arm B) were randomized from 32 Italian centers. Accrual was stopped early, before the planned sample size (388 pts) was reached, because of registration of ICPIs in 1st-line. Most patients were male (79.2 %), current/former smokers (93.6 %), had stage IV (74.4 %), performance status 0–1 (98.4 %). mOS (95 % CI) was 14.9 (10.4–18.6) months in arm A vs 18.8 (14.4–21.1) months in arm B (HR 1.09, 95 %CI 0.74–1.62, p = 0.659).

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Conclusions: In advanced Sq-NSCLC, the use of Nivo as switch maintenance after 1st-line CHT, does not improve OS compared to its use as 2nd-line. Although the optimal use of ICPIs remains in 1st-line, its role as maintenance has to be better investigated.
ClinicalTrials.gov: registration number: NCT03542461.

1. Introduction

Before the introduction of immune checkpoint inhibitors (ICPIs) in first-line (1L) setting for advanced non-small cell lung cancer (NSCLC) patients without druggable oncogenic drivers, platinum-based chemotherapy (CHT) was the standard of care. The choice of third-generation agent to be combined with platinum was histology-driven. For squamous (Sq) NSCLC patients, cisplatin/carboplatin combined with gemcitabine, vinorelbine or taxanes (paclitaxel or nab-paclitaxel) for up to 4–6 cycles represented the standard of care in 1L setting also for patients with poor Eastern Cooperative Oncology Group Performance status (ECOG PS 2) [1–3]. Unfortunately, overall treatment outcomes in these patients were disappointing with median survival (mOS) of 9–12 months.

Contrary to what happened for non-squamous NSCLC patients [4,5], no randomized study showed a survival benefit from maintenance/consolidation (continuation with the same chemotherapy drug/s or switch to other agent used in 1L) strategy for advanced Sq-NSCLC patients [6–10]. Another phase 3 randomized study compared immediate with delayed docetaxel after front-line platinum-based chemotherapy in advanced NSCLC. The study demonstrated that using immediate docetaxel strategy significantly improved progression free survival (PFS, $p = 0.0001$), with also a positive trend in overall survival (OS, $p = 0.0853$). However, it is noteworthy that less than 20 % of the randomized patients had squamous histology and 37 % of the patients allocated to delayed arm did not receive any systemic treatment, potentially explaining the positive trend in OS improvement [11].

In 2015, the results from Checkmate-017 trial demonstrated the superiority of nivolumab 3 mg/kg every 2 weeks over docetaxel 75 mg/mq every 3 weeks as second line setting for advanced Sq-NSCLC patients, with mOS improvement from 6.0 (95 % CI, 5.1–7.3) months to 9.2 (95 % CI, 7.3–13.3) months (HR 0.59; 95 % CI, 0.44–0.79; $p < 0.001$) [12]. Notably, out of 352 patients assessed for eligibility, only 272 (77 %) of them underwent randomization; for most (70 out of 80) patients excluded, the reason could be reasonably attributed to rapid disease progression, deterioration of clinical conditions and PS (death for 3 patients, no longer met study criteria for 67 patients or adverse event for other 6 patients). Therefore, it had been speculated that early use of nivolumab could lead to a survival improvement by increasing the number of patients benefiting from this treatment.

At the time of the conceptualization and design of the present study, randomized trials were comparing ICPIs against standard platinum-based doublets in 1L setting, but there were no studies assessing their role as switch maintenance/consolidation strategy in advanced Sq-NSCLC patients who had not progressed after the completion of 1L platinum-based CHT. In the case 1L studies had not proved the superiority of ICPIs over standard treatment, their use in the switch maintenance setting could have represented an alternative strategy to anticipate the use of ICPIs and allow more patients to receive, and potentially benefit, from this class of agents.

2. Methods

Study design and endpoints.

EDEN (NCT03542461) was an open-label, two-arm, multicenter, randomized phase III study evaluating the efficacy of using nivolumab as early switch maintenance as compared with itself used as second line at the time of progressive disease (PD) in patients with stage IIIB/IV Sq-NSCLC. After completion of 1L platinum-based CHT (from 4 to up 6 cycles), only patients who had not progressed were randomized (1:1 ratio) into one of the two treatment arms: Nivolumab (arm A, experimental) 240 mg intravenously (i.v.) every 2 weeks or the same treatment as delayed second line (arm B, control) at the time of PD. Nivolumab was continued until PD, unacceptable toxicity, patient's refusal, or investigator's decision, or for a maximum of 2 years. Subjects meeting all eligibility criteria were randomized to arm A or Arm B stratified according to center and response to 1L therapy (complete or partial responses [CR/PR] vs stable disease [SD]), using the minimization method. At the time of progressive disease, for patients randomized to experimental nivolumab, a standard second line chemotherapy could be provided, according to local policy, while for patients randomized control arm nivolumab treatment was provided as second line.

For patients randomized to arm A, nivolumab beyond progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [13] was permitted. Patients enrolled in Arm B could continue nivolumab beyond second PD. This strategy was allowed at the Investigator's discretion if all the following criteria were met: Investigator-assessed clinical benefit, associated with no rapid disease progression; tolerance of study drug; stable ECOG PS; no delay of an imminent intervention preventing serious complications of disease progression. In case of confirmed PD at following tumor assessment, nivolumab had to be discontinued in both arms.

The study was conducted in accordance with the requirements of the Italian regulatory authority and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. The protocol and all amendments were approved by the Italian Medicines Agency (AIFA) and all local ethics committee. All patients provided written informed consent.

The primary objective of the study was to compare the two treatment strategies (switch maintenance vs delayed second line) in terms of survival, measured from the date of randomization to death of any cause. The primary end point was overall survival (OS).

Secondary end points included: progression free survival (PFS), defined as the time from randomization to the date of the first documented tumor progression (per RECIST v1.1) or death due to any cause; progression free survival from induction (PFSind), defined as the time from first chemotherapy cycle until objective tumor progression or death of any cause; time to treatment failure (TTF), measured as the time from randomization to treatment discontinuation from any reason; overall survival from induction (OSind), defined as the time from first chemotherapy cycle to death of any cause. Efficacy analyses included all the patients who underwent randomization (intention-to-treat population) in both treatment arms. The safety analysis was performed in all subjects who received at least one dose of nivolumab.

Patients.

Adult patients (aged $\geq$ 18 years) with pathologically confirmed stage IIIB/IV or recurrent Sq-NSCLC who had not progressed after completion (4 up to 6 cycles) of 1L platinum-based chemotherapy were eligible for participation in the study. Eligible patients had to have ECOG PS 0–2, a life expectancy $\geq$ 12 weeks, and must have completed the last course of platinum-based chemotherapy within 8 weeks from randomization. Patients with treated brain metastases that were stable for at least 4 weeks and off steroids or on a stable dose ($\leq$ 10 mg of prednisone or equivalent) were included in the study. All eligibility criteria are provided in the study protocol (**Supplementary material**).

Assessment.

Tumor radiological assessment was performed at screening (within 28 days prior to first dose), every 8 weeks (±1 week) for the first year

and every 12 weeks (±1 week) thereafter. At the screening, in addition to the chest, abdomen, pelvis and all known sites of disease, a contrast enhanced computed tomography (CT) had to also include brain scans to rule out central nervous system involvement. Changes in tumor measurements and tumor response were assessed by the investigator using the RECIST v1.1. Subjects receiving nivolumab treatment beyond progression underwent regular tumor assessments until permanent treatment discontinuation.

Statistical analysis.

The distribution of OS times was compared between treatment arms using a two-sided unstratified log rank test. HR and its associated two-sided 95 % confidence interval (CI) were estimated using a Cox model with the treatment arm as the only covariate. OS for each treatment arm were estimated and plotted using the Kaplan Meier product-limit method. The estimates of OS medians and two-sided 95 % CIs were calculated by the Brookmeyer and Crowley method. The analyses on the primary endpoint were conducted in accordance with the intention-to-treat (ITT) principle. All secondary time-to-event endpoints were analyzed using the same statistical techniques described for the primary efficacy variable. Demographics and baseline characteristics were summarized by treatment arm using descriptive statistics for all randomized subjects. Safety end points included all adverse events (AEs), drug-related AEs, serious adverse events (SAEs) and drug-related SAEs by treatment arm. They were tabulated using the worst grade according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) v.4.03 by system organ class and preferred term.

According to the original study plan, 388 patients were required to be randomized in a 1:1 ratio to arm A (experimental, nivolumab as early switch maintenance) and arm B (control, delayed nivolumab at the time of PD). Based on the assumption that OS in each arm followed an exponential distribution and the true hazard ratio (HR) for OS was 0.70 in the comparison between arm A versus arm B, 289 events were needed for a two-sided unstratified log-rank test with $\alpha = 0.05$ to have 85 % power. Assuming a mOS from randomization in the control arm of 10 months, a mOS of 14.3 months was expected in the experimental arm. An accrual rate of 100 subjects per year was planned, with a minimum follow-up period of 12 months and an overall rate of 10 % of patients lost to follow-up in both arms.

3. Results

Patients and treatment.

Between September 25, 2017, and August 12, 2020, 125 patients from 32 Italian centers were enrolled into the study and randomized (1:1) to immediate nivolumab (arm A, 62 patients) or delayed nivolumab (arm B, 63 patients) (Fig. 1). Accrual was stopped early because of

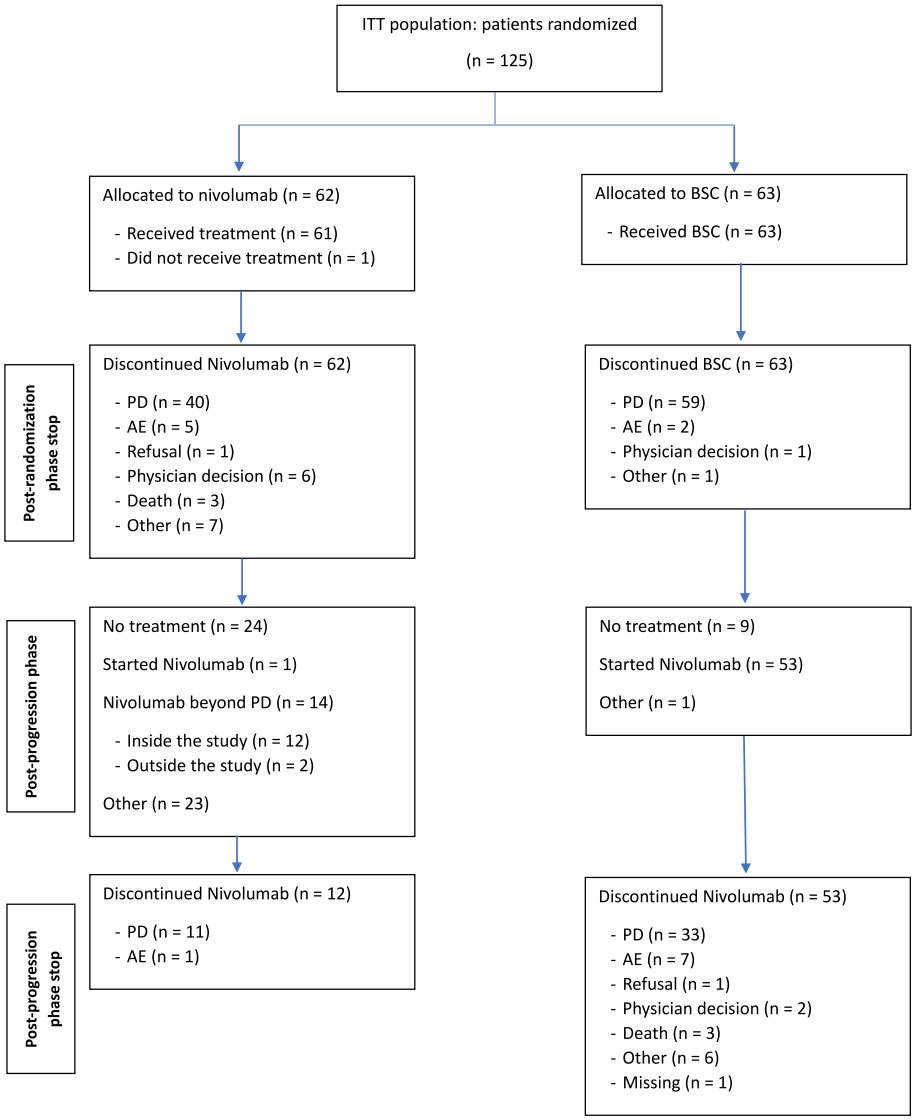

Fig. 1. CONSORT flow diagram. It displays the progress of all participants through the EDEN trial.

registration of ICPIs in first line setting which made the present study ethically unfeasible. At the time of database lock (December 31, 2022), the median follow-up for the overall population was 38.3 months (interquartile range, IQR, 31.0–55.9 months). In the overall patient population, the median age was 71 years (range 41–82). Most of the patients were male (79.2 %), smokers (current/former, 93.6 %), had an ECOG performance status of 0–1 (98.4 %), had stage IV disease (74.4 %) and squamous histology (98.4 %). Except one patient, all had received platinum-based CHT as first line treatment, mostly achieving stable disease (60.0 %) as best response while CR/PR were reported in 2.4 % and 36.8 %, respectively. All demographic and patient characteristics were well balanced between the two arms, except for a slight imbalance in the percentage of stage IV disease (Table 1).

Sixty-one out of 62 patients received immediate nivolumab (experimental, arm A) and were evaluable for safety analyses. No data was available for one patient. A median of 7 doses (range, 1–116) of nivolumab were administered. At least one dose delay occurred in 49.2 % of the patients. Nivolumab was permanently discontinued in 64.5 % and 8.0 % of patients for disease progression and adverse event, respectively.

14 (22.5 %) patients received nivolumab beyond PD, although for 2 patients receiving nivolumab outside protocol no further information was available. Among those 12 patients, 176 courses of nivolumab were administered beyond PD (median 16; range, 1–58). After nivolumab discontinuation, 38.7 % of patients received no other anti-cancer treatment. At the time of database lock, no patient receiving nivolumab in arm A was continuing treatment.

Fifty-three out of 63 patients randomized to delayed treatment (control, arm B) received nivolumab at the time of PD and were evaluable for safety analyses. One patient received other treatment, while 9 (14.3 %) patients did not receive any other therapy. A median of 14 doses (range, 1–98) of nivolumab were administered. At least one dose delay occurred in 50.9 % of the patients. Nivolumab was permanently discontinued in 62.2 % and 13.2 % of patients for disease progression and adverse event, respectively. At the time of database lock, no patient receiving nivolumab in arm B was continuing treatment. After discontinuation of therapy, 69.9 % of patients received no further anti-cancer treatment, and 6.3 % of patients treated with immunotherapy.

Table 1
Baseline patients' characteristics in both immediate Nivo and delayed Nivo arms.

	Arm ANivolumab (n = 62)	Arm BBSC (n = 63)	Overall(n = 125)
Age – yrMedianRange	7041–82	7245–81	7141–82
Sex – no. (%)FemaleMale	13 (21.0)49 (79.0)	13 (20.6) 50 (79.4)	26 (20.8) 99 (79.2)
Histology – no. (%)SquamousOther	61 (98.4)1 (1.6)	62 (98.4)1 (1.6)	123 (98.4) 2 (1.6)
Disease stageIIIBIVOther	16 (25.8)43 (69.4)3 (4.8)	11 (17.5) 50 (79.4)2 (3.2)	27 (21.6) 93 (74.4)5 (4.0)
ECOG performance status score – no. (%)012	35 (56.5)26 (41.9)1 (1.6)	38 (60.3) 24 (38.1)1 (1.6)	73 (58.4) 50 (40.0)2 (1.6)
Smoking status – no. (%)Current/former smokerNever smokerUnknown	58 (93.5)3 (4.8)1 (1.6)	59 (93.7)3 (4.8)1 (1.6)	117 (93.6) 4 (3.2)4 (3.2)
Previous surgery – no. (%)No surgeryCurative	56 (90.3)6 (9.7)	53 (84.1) 10 (15.9)	109 (87.2) 16 (12.8)
Previous radiotherapy – no. (%)No radiotherapyCurativePalliative	48 (77.4)8 (12.9)6 (9.7)	54 (85.7)5 (7.9)4 (6.3)	102 (81.6) 13 (10.4) 10 (8.0)
Prior chemotherapy – no. (%) Platinum-basedOther	61 (98.4)1 (1.6)	63 (100) 0 (0)	124 (98.4) 1 (1.6)
Best response to prior chemotherapy – no. (%)Complete responsePartial responseStable diseaseNot reported	2 (3.2)22 (35.5)38 (61.2)0 (0)	1 (1.6)24 (38.1)37 (58.7)1 (1.6)	3 (2.4)46 (36.8)75 (60.0)1 (0.8)

Efficacy.

The median follow-up for OS was 47.9 months (IQR, 36.3–55.9) for patients enrolled in arm A and 34.9 months (IQR, 28.8–55.7) for patients enrolled in arm B.

The median OS was 14.9 months (95 % CI, 10.4–18.6) in the nivolumab arm as compared with 18.8 months (95 % CI, 14.4–21.1) in the delayed arm (hazard ratio, HR 1.09, 95 % CI, 0.74–1.62; p = 0.659) (Fig. 2). At the time of database lock, 12 (19.4 %) patients enrolled in arm A were alive as compared to 13 (20.6 %) patients enrolled in arm B.

The median PFS was 4.5 months (95 % CI, 2.5–6.7) in the immediate nivolumab group as compared with 1.9 months (95 % CI, 1.7–2.5) in the delayed nivolumab group (Fig. 3**A**). Progression free survival was significantly longer with early nivolumab compared to delayed treatment, with the risk of progression or death 50 % lower with immediate nivolumab (HR 0.50; 95 % CI, 0.35–0.73; p < 0.001). At the time of final analysis, 6 (9.7 %) out of 62 patients enrolled in arm A were alive and progression free as compared to one (1.6 %) patient in arm B.

The median PFS from the start of induction (PFSind) was significantly longer with immediate Nivolumab (8.6 months, 95 % CI, 7.2–12.1) compared to delayed treatment group (7.0 months, 95 % CI, 6.0–7.9; HR 0.55, 95 % CI, 0.38–0.79; p = 0.001) (Fig. 3**B**).

The median TTF was 5.7 months (95 % CI, 3.8–9.1) in the immediate Nivolumab group versus 10.1 months (95 % CI, 7.7–12.2) in the delayed group (Fig. 3**C**). In contrast to the mPFS, the median TTF was not significantly different between the two groups (HR 1.04; 95 % CI, 0.72—1.51; p = 0.825).

Finally, the median OS from the start of induction (OSind) was 19.5 months (95 % CI, 15.9–23.7) in the experimental arm as compared with 22.0 months (95 % CI, 17.8–26.7) in the control arm (HR 1.09; 95 % CI, 0.74–1.62; p = 0.652) (Fig. 3**D**).

Safety.

Sixty-one out of 62 patients randomized to immediate nivolumab (experimental, arm A) were evaluable for safety. Among these patients 963 courses of nivolumab were administered during the post-randomization phase. 72 % of the patients had toxicity events of any grade; 10 % of them had adverse events of grade 3 or 4. No severe hematologic toxicity was reported. The most frequently reported treatment-related adverse events (of any grade) were fatigue (39 %), arthralgia (21 %), appetite loss (20 %), and fever (18 %) (Table 2). Treatment-related serious adverse events (of any grade) involved the following systems: skin (20 %), lung and endocrine (13 % each), liver (8 %), kidney (6 %); lung and liver toxicities of grade 3 or 4 were 3 % each. Infusion-related reactions (of any grade) were reported in 8 % of patients. No event of grade 5 was reported (Table 3). No safety data were available from nivolumab in the post-progression phase in this patients' group.

Fifty-three out of 63 patients randomized to delayed nivolumab (control, arm B) were evaluable for safety. Among these patients 1046 courses were administered. 77 % of the patients had toxicity events of any grade; 15 % of them had adverse events of grade 3 or 4. Hematologic toxicity (of any grade) was reported in 30 % of patients, 4 % had an event of grade 3 or 4. The most frequently reported treatment related adverse events (of any grade) were fatigue (47 %), arthralgia (28 %), fever (24 %), appetite loss (22 %), and diarrhea (11 %) (Table 2). Treatment-related serious adverse events (of any grade) involved the following systems: skin (22 %), lung (19 %), endocrine (11 %), liver (9 %), kidney (7 %); lung and liver toxicities of grade 3 or 4 were 2 % each. Infusion-related reactions (of any grade) were reported in 8 % of patients. No fatal events were reported (Table 3).

Treatment-related adverse events led to treatment discontinuation in 8 % and 13 % of patients treated with nivolumab in arm A and arm B, respectively.

4. Discussion

Conceptualization and design of the present study were conceived

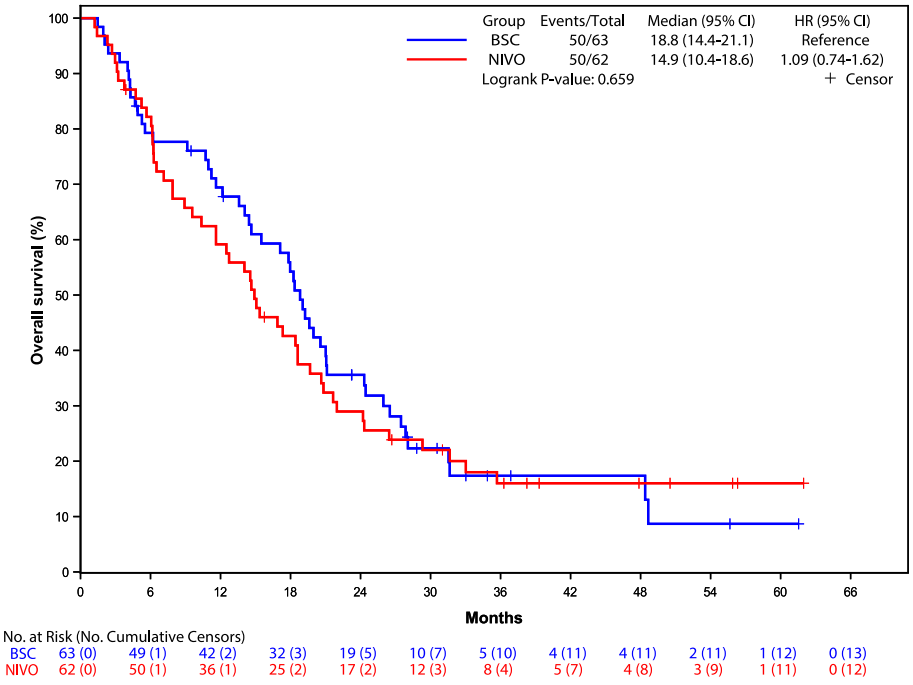

Fig. 2. OS in modified ITT population. Probabilities of OS were calculated according to the Kaplan–Meier product-limit method. Continuous and dashed curves represent survival probabilities in immediate Nivo (red) and delayed Nivo (blue) arms, respectively.

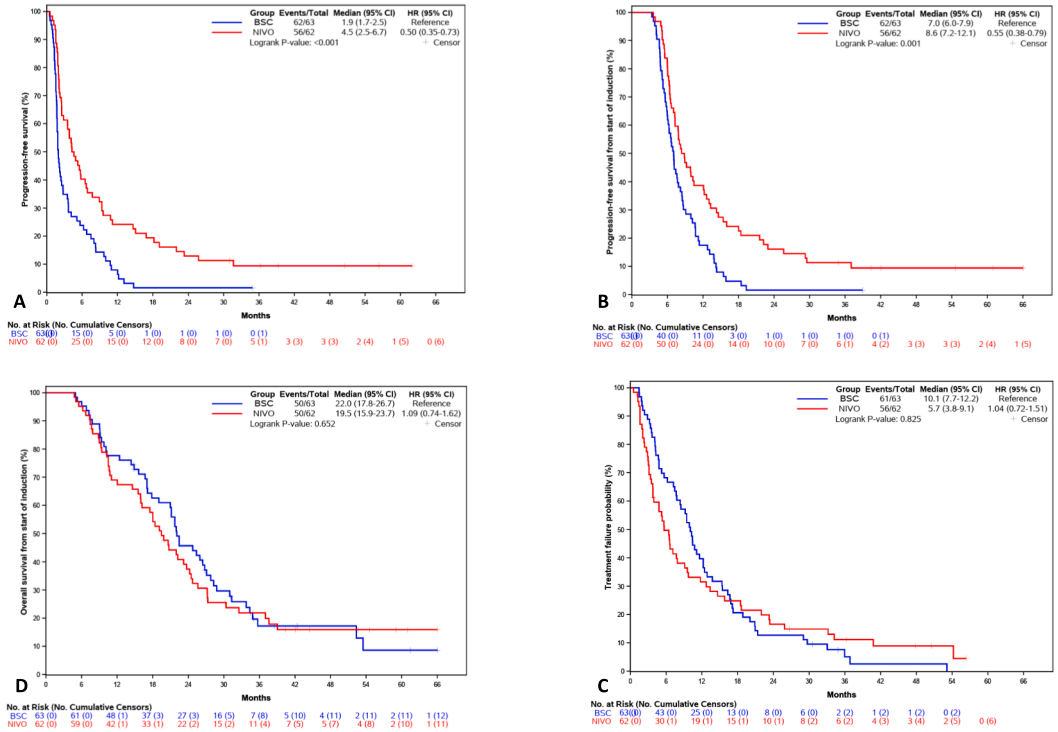

Fig. 3. PFS (A), PFSind (B), TTF (C) and OSind (D) in modified ITT population. Probabilities of PFS, TTF and OS were calculated according to the Kaplan–Meier product-limit method. In all graphs, continuous and dashed curves represent survival probabilities in immediate Nivo (red) and delayed Nivo (blue) arms, respectively.

before the registration of ICPIs, both as single agent and in combination with chemotherapy, for advanced squamous NSCLC in 1L setting. At that time, ICPIs represented the standard of care for patients failing 1L platinum-based chemotherapy [14], while no data were available about the possible role of immunotherapy used earlier as maintenance/consolidation therapy. Therefore, the primary objective of our study was to evaluate whether nivolumab used as switch maintenance, immediately after the completion of 1L chemotherapy, was more effective in terms of survival than its use upon disease progression as second line treatment. Although patients receiving early nivolumab maintenance did have a statistically significant advantage in terms of PFS, compared to those treated with delayed 2nd-line nivolumab at the time of disease

Table 2
Treatment-related adverse events reported in at least 5% of patients in both immediate Nivo and delayed Nivo arms.

	Arm A Nivolumab (n = 61)			Arm B BSC (n = 53)		
Adverse event – No (%)	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any event	44 (72)	4 (6)	2 (3)	41 (77)	6 (11)	2 (4)
Hematological toxicity	17 (28)	0	0	16 (30)	2 (4)	0
Anemia	14 (23)	0	0	13 (24)	2 (4)	0
Leucopenia	4 (6)	0	0	3 (6)	0	0
Neutropenia	1 (2)	0	0	3 (6)	0	0
Thrombocytopenia	3 (5)	0	0	0	0	0
Non hematological toxicity	42 (69)	4 (6)	2 (3)	40 (75)	5 (9)	2 (4)
Nausea	5 (8)	0	0	3 (6)	0	0
Diarrhea	4 (6)	0	0	6 (11)	1 (2)	0
Appetite loss	12 (20)	0	0	12 (22)	1 (2)	0
Mucositis	0	0	0	4 (8)	0	0
Fatigue	24 (39)	0	0	25 (47)	2 (4)	0
Fever	11 (18)	0	0	13 (24)	1 (2)	0
IRR	5 (8)	2 (3)	0	4 (8)	0	0

Table 3
Immune—related serious adverse events in both immediate Nivo and delayed Nivo arms.

	Arm A Nivolumab (n = 61)			Arm B BSC (n = 53)		
Adverse event – No (%)	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Arthralgia	13 (21)	1 (2)	0	15 (28)	1 (2)	1 (2)
Skin toxicity	12 (20)	0	0	12 (22)	0	0
Pulmonary toxicity	8 (13)	1 (2)	1 (2)	10 (19)	0	1 (2)
Liver toxicity	5 (8)	1 (2)	1 (2)	5 (9)	1 (2)	0
Renal toxicity	4 (6)	0	0	4 (8)	0	0
Hyperthyroidism	3 (5)	0	0	2 (4)	0	0
Hypothyroidism	2 (3)	0	0	3 (6)	0	0
Endocrine syndrome	3 (5)	1 (2)	0	1 (2)	0	0
Pancreatic toxicity	1 (2)	0	0	0	0	0

progression (mPFS: 4.5 months [95 %CI, 2.5–6.7] versus 1.9 months [1.7–2.5], HR 0.50 [95 % CI, 0.35–0.73]; $p < 0.001$), our study did not meet its primary objective. In fact, no advantage in terms of OS was shown among patients receiving nivolumab maintenance (mOS: 14.9 months [95 % CI, 10.4–18.6] versus 18.8 months [95 % CI, 14.4–21.1], HR 1.09 [95 %CI, 0.74–1.62]; $p = 0.659$). A plausible reason to explain the lack of OS advantage could be represented by the short interval between randomization and PD in patients assigned to arm B. Nevertheless, 85 % of patients allocated to arm B received a subsequent treatment (nivolumab or other) at the time of PD. This proportion of patients is unlikely to be representative of that receiving a second-line treatment in everyday clinical practice and it may have significantly affected the results of the present study. In fact, the knowledge that patients could have started nivolumab may have affected the Investigators' behavior. Nevertheless, we are aware that a limit of our study is represented by the lack of any information on PD-L1 status in the ITT population, but at the time of the conception of the study no data are available about its role as predictive biomarker of response to ICPIs. Another biological reason to corroborate the lack of OS advantage could be related to the fact that ICPIs retain a good level of efficacy even in second-third line setting [12,15–17], supporting the hypothesis that immunotherapy efficacy is not highly influenced by its timing of use (as it is for chemotherapy). Intriguingly, in our study patients treated with nivolumab as delayed second line had a survival twice as long as compared to the patients treated with second line nivolumab in CheckMate 017 (9.2 months, 95 %CI, 7.3–13.3) [12]. This impressive difference could be explained, at least in part, considering the different clinical characteristics between the two patient populations, particularly ECOG PS and response to prior chemotherapy. Indeed, 60 % of patients treated with early nivolumab in EDEN trial had an ECOG PS of 0 compared to 20 % of patients receiving nivolumab in CheckMate 017. Furthermore, our study included only patients who had not progressed on first line chemotherapy, while 33 % of patients receiving nivolumab in Checkmate 017 have had a progressive disease as best response to prior chemotherapy. Notably, our study population was older than that of CheckMate 017 (median age of 72 [range 45–81] versus 62 [range 39–85]), confirming that age does not affect the probability of deriving a benefit from immunotherapy agents. Another hypothesis leading to design of the present study was that the anticipation of nivolumab from second line to first line maintenance/consolidation would also have had the advantage of providing this agent to a larger proportion of patients, thus increasing the number of patients benefiting from this treatment strategy. Historically, about 30 % of patients progressing after 1L chemotherapy do not have access to second line treatment, because of extensive disease progression and rapid deterioration of clinical conditions and performance status [18]. In CheckMate-017 study [12], about 20 % of eligible patients were excluded from randomization due to this condition. In the present study, fewer (approximately 14 %) eligible patients randomized to delayed second line nivolumab had relentless disease progression and rapid clinical deterioration precluding further anti-cancer treatment. A possible explanation could rely on the planned timing (8 weeks ± 1 week) of tumor assessment of enrolled patients, encouraging the Investigators to treat patients with early and asymptomatic progressive disease, when general clinical conditions were not impaired and more suitable for benefitting from a second line treatment. Indeed, since this was an open-label study and PFS was per Investigator judgment, it cannot be excluded that patients randomized in the control arm were put on second line treatment also in the absence of a clear progressive disease as defined per RECIST 1.1 criteria.

Finally, a plausible biological explanation for the seemingly worse survival of patients in the maintenance/consolidation arm, may reside in the possible immunosuppressive effect of induction chemotherapy, hampering an optimal immune response to ICPIs, if administered immediately after its completion [19–22].

We recognize that the clinical relevance of the results of this study has waned as the data about the ICPIs use in first line setting, alone and combined with chemotherapy, have emerged. Nevertheless, we think that the results of our study present further interesting food for thought. Although potentially under-powered, because of early stopping of accrual, our study showed that nivolumab as maintenance strategy is very unlikely that could improve survival outcome in Sq-NSCLC patients unselected for PD-L1 status. Assuming an additional continuation time of the trial equal to 73 months, required to complete the initially planned accrual (388 patients), we calculated that the conditional power of the two-sided log-rank test for the OS comparison will be equal to 83 %, 9 % and 94 %, assuming that in the remaining part of the trial immediate nivolumab is superior to delayed treatment (HR = 0.70), no significant differences are detected between the two strategies or delayed nivolumab is superior to immediate nivolumab (HR = 1.43) (Fig. 4).

This observation might also be translated into the first line setting where optimal duration and, particularly, the role of maintenance of ICPIs, is not yet completely elucidated and remains one of the most clinically relevant open immunotherapy questions. CheckMate 153 trial was a largely community-based phase IIIb/IV study that enrolled patients with previously treated advanced NSCLC to receive nivolumab 3 mg/kg given intravenously every 2 weeks until progression or

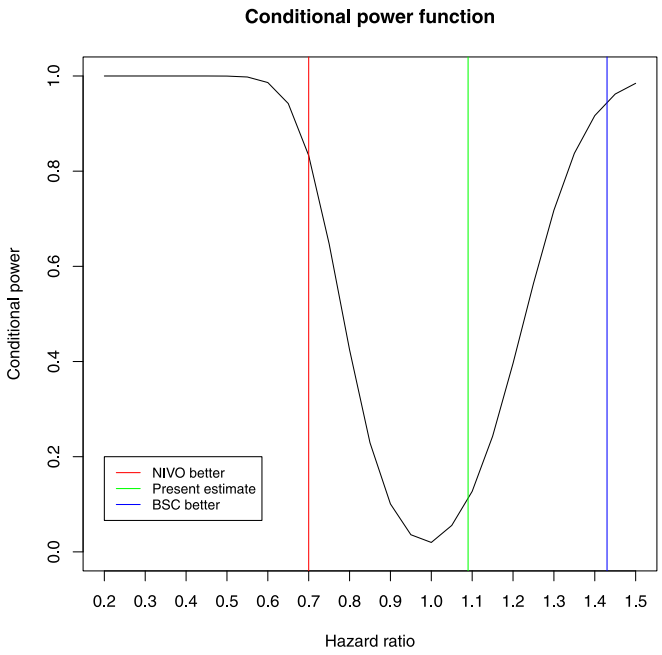

Fig. 4. Conditional power function analysis.

intolerable toxicity [23]. In an exploratory analysis, patients who continued nivolumab at 1 year were randomized to continuous nivolumab versus 1-year fixed duration, with the possibility to restart nivolumab at the time of PD. After a minimum follow-up of 13.5 months, the analysis demonstrated that continuing nivolumab beyond 1-year improved survival outcomes [24]. However, ICPIs duration currently adopted in first-line in clinical practice has been determined in clinical trials with no plausible biological rationale, also considering the impact of the ICPIs over time on both tumor microenvironment and circulating immune cells (myeloid-derived suppressive cells, Treg cells, natural killer, NKT cells and others) on ICPIs resistance and immune response exhaustion [25,26]. The results of our study contribute to highlight the need for appropriate clinical trials in first-line setting comparing standard of care maintenance immunotherapy with immunotherapy interruption and resumed at the time of disease progression.

5. Conclusions

EDEN trial demonstrates that the immediate use of nivolumab as switch maintenance/consolidation after completion of first line chemotherapy does not improve OS compared to delayed use as second line at the time of progressive disease in advanced squamous NSCLC patients. At present time, the optimal use of ICPIs remains in the first line setting, alone or in combination with platinum-based chemotherapy, according to PD-L1 status. Nevertheless, our trial highlights the need to better investigate optimal treatment duration and the role of ICPIs maintenance/consolidation also in this setting.

Ethics approval and consent to participate.

The study protocol was approved by each local institutional ethics committee and conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

No individually identifiable data is presented.

Availability of data and material.

Anonymized dataset may be available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Francesco Gelsomino: Writing – review & editing, Writing – original draft, Validation, Supervision, Investigation, Formal analysis, Data curation, Conceptualization. **Luca Boni:** Writing – review & editing, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marcello Tiseo:** Writing – review & editing, Investigation, Conceptualization. **Serena Ricciardi:** Writing – review & editing, Investigation. **Danilo Rocco:** Writing – review & editing, Investigation. **Diego L Cortinovis:** Writing – review & editing, Investigation. **Manuela Proietto:** Writing – review & editing, Investigation. **Alessio Cogoni:** Writing – review & editing, Investigation. **Giulia Pasello:** Writing – review & editing, Investigation. **Andrea Camerini:** Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Francesca Sperandi:** Writing – review & editing, Investigation. **Ida Colantonio:** Writing – review & editing, Investigation. **Giulio Metro:** Writing – review & editing, Investigation. **Francesca Mazzoni:** Writing – review & editing, Investigation. **Editta Baldini:** Writing – review & editing, Investigation. **Antonello Veccia:** Writing – review & editing, Investigation. **Elisa Bennicelli:** Writing – review & editing, Investigation. **Anna Cecilia Bettini:** Writing – review & editing, Investigation. **Michele Tognetto:** Writing – review & editing, Visualization, Software, Project administration, Data curation, Conceptualization. **Andrea Ardizzoni:** Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Francesco Gelsomino has received honoraria or personal fees for the advisory role or consulting from Eli Lilly, Novartis, AstraZeneca, and Bristol-Myers Squibb. Marcello Tiseo has received institutional research grants from Astra-Zeneca, Boehringer Ingelheim and received speakers' and consultants' fee from Astra-Zeneca, Pfizer, Eli-Lilly, BMS, Novartis, Roche, MSD, Boehringer Ingelheim, Otsuka, Takeda, Pierre Fabre, Amgen, Merck, Sanofi. Diego Cortinovis has received speaker's bureau/scientific advisor activity for BMS, MSD, AstraZeneca, Sanofi Genzyme, Novartis, Amgen, Takeda, Roche, Janssen. Andrea Ardizzoni has received research grants from Celgene, Bristol-Myers Squibb, Ipsen, and Roche; and honoraria for advisory roles from Bristol-Myers Squibb, Merck Sharp & Dohme, ROCHE, AstraZeneca, and Eli Lilly.

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Appendix A. Supplementary data

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