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ORIGINAL ARTICLE

Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy — results from the randomised phase II ETOP/IFCT 4-12 STIMULI trial

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Background: Concurrent chemotherapy and thoracic radiotherapy followed by prophylactic cranial irradiation (PCI) is the standard treatment in limited-disease small-cell lung cancer (LD-SCLC), with 5-year overall survival (OS) of only 25% to 33%.

Patients and methods: STIMULI is a 1:1 randomised phase II trial aiming to demonstrate superiority of consolidation combination immunotherapy versus observation after chemo-radiotherapy plus PCI (protocol amendment-1). Consolidation immunotherapy consisted of four cycles of nivolumab [1 mg/kg, every three weeks (Q3W)] plus ipilimumab (3 mg/kg, Q3W), followed by nivolumab monotherapy (240 mg, Q2W) for up to 12 months. Patient recruitment closed prematurely due to slow accrual and the statistical analyses plan was updated to address progression-free survival (PFS) as the only primary endpoint.

Results: Of the 222 patients enrolled, 153 were randomised (78: experimental; 75: observation). Among the randomised patients, median age was 62 years, 60% males, 34%/65% current/former smokers, 31%/66% performance status (PS) 0/1. Up to 25 May 2020 (median follow-up 22.4 months), 40 PFS events were observed in the experimental arm, with median PFS 10.7 months [95% confidence interval (CI) 7.0-not estimable (NE)] versus 42 events and median 14.5 months (8.2-NE) in the observation, hazard ratio (HR) = 1.02 (0.66-1.58), two-sided $P = 0.93$. With updated follow-up (03 June 2021; median: 35 months), median OS was not reached in the experimental arm, while it was 32.1 months (26.1-NE) in observation, with HR = 0.95 (0.59-1.52), $P = 0.82$. In the experimental arm, median time-to-treatment-discontinuation was only 1.7 months. CTCAE v4 grade $\geq$3 adverse events were experienced by 62% of patients in the experimental and 25% in the observation arm, with 4 and 1 fatal, respectively.

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Conclusions: The STIMULI trial did not meet its primary endpoint of improving PFS with nivolumab-ipilimumab consolidation after chemo-radiotherapy in LD-SCLC. A short period on active treatment related to toxicity and treatment discontinuation likely affected the efficacy results.

Key words: nivolumab, ipilimumab, small-cell lung cancer, SCLC, limited disease, randomised clinical trial

INTRODUCTION

Immune-checkpoint inhibitors have proven to provide clinical benefits in patients with small-cell lung cancer (SCLC). In the extensive disease (ED) setting, the programmed death-ligand 1 (PD-L1) inhibitors atezolizumab and durvalumab, in combination with etoposide and platinum-based chemotherapy, improved survival in treatment-naive patients.[1,2] Clinical activity was also observed in later line treatment with pembrolizumab or nivolumab, with or without ipilimumab.[3-5] In contrast, nivolumab with or without ipilimumab as maintenance treatment after frontline chemotherapy or as second-line treatment, did not demonstrate a clinical benefit over established standards of care.[6,7]

At diagnosis, 30% of SCLC patients present with limited-disease (LD), defined as stage I-IIIB (7th edition of the IASLC TNM classification). Despite a curative-intent treatment strategy, the outcome of LD-SCLC remains poor, with a median survival of 16-24 months and only 25% to 33% 5-year survival.

Chemotherapy consisting of cisplatin or carboplatin plus etoposide and thoracic radiotherapy remains the standard treatment approach in LD-SCLC. Concurrent chemo-radiotherapy is superior to sequential treatment and thoracic irradiation starting with the first or second chemotherapy cycle appears beneficial.[8] Survival outcomes did not significantly differ between lower dose, twice-daily and high dose once-daily concurrent chemo-radiotherapy and toxicity was similar to historical series with both regimens.[9] Availability and routine use of hyper-fractionated radiotherapy, however, remains a matter of debate. Prophylactic cranial irradiation (PCI) remains a standard of care in LD-SCLC, allowing for a long-term survival improvement of 5.4% at 3 years.[10]

CheckMate-032, a randomised open-label phase I/II trial, tested in a 3:2 manner, four cycles of nivolumab monotherapy (3 mg/kg, every 2 weeks) versus four cycles of nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) every 3 weeks, followed by nivolumab maintenance (3 mg/kg, every 2 weeks). In the cohort of 147 pretreated patients with ED-SCLC, a response rate of 21.9%, disease stabilisation in 16.7% and overall survival (OS) of 4.7 months were observed for the nivolumab plus ipilimumab combination, compared to 11.6%, 17% and 5.7 months for nivolumab monotherapy.[11] Both treatment regimens were tolerable and the safety profile comparable to nivolumab with or without ipilimumab in other disease settings. These results led to the design of CheckMate-451, examining nivolumab plus ipilimumab consolidation therapy in ED-SCLC and the randomised phase II STIMULI trial in LD-SCLC (NCT02046733), which results are presented here.

METHODS

Patients

Eligible patients were adults with stage I-IIIB histologically or cytologically confirmed LD-SCLC, based on the 7th tumour-node-metastasis (TNM) classification,[12] an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and adequate haematological, renal, lung and pulmonary function. Baseline assessments consisted of either whole-body fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) with contrast-enhanced computed tomography (CT) or contrast-enhanced CT of thorax and upper abdomen and bone scan, brain imaging by magnetic resonance imaging (MRI) or high-resolution CT and a pulmonary function test. Prior anti-cancer systemic therapy (except for one single chemotherapy cycle) and thoracic radiotherapy was excluded. Post-enrolment, patients were eligible for randomisation only if they had received (i) four cycles of chemotherapy, (ii) at least 85% of the planning target volume (PTV) dose of thoracic radiotherapy and PCI and (iii) were progression-free (as per radiological tumour assessment).

Trial design and study oversight

STIMULI, an open-label, randomised, multicenter, phase II trial, compared the efficacy of adding consolidation nivolumab with ipilimumab to standard chemo-radiotherapy and PCI, versus standard chemo-radiotherapy and PCI alone, in patients with LD-SCLC.

The trial was activated in December 2013, initially with only ipilimumab in the experimental arm. The low accrual rate and reports showing significant clinical activity of nivolumab with or without ipilimumab,[13] led to a protocol amendment (AM1; activated September 2015). The study remained open to accrual until 30 April 2019, when an external decision by the funding company was implemented in agreement with the STIMULI steering committee to close accrual due to a relatively high attrition rate between enrolment and randomisation, an expected protracted accrual duration for sample size completion, and emerging data with nivolumab plus ipilimumab showing no statistically significant survival benefit in the maintenance setting of first-line ED-SCLC.[6] Patients already enrolled in the chemo-radiotherapy phase meeting the criteria, were allowed to be randomised. Reported results are based on all patients randomised under AM1.

Interim safety data were reviewed by the European Thoracic Oncology Platform (ETOP) independent data monitoring committee (IDMC) every 3 months.

Treatment schedule

Patients received standard platinum chemotherapy (four cycles cisplatin, 25 mg/m^2 intravenously [i.v.] on days 1-3 or 75 mg/m^2 on day 1 or carboplatin, AUC 5-6, as per Calvert formula, i.v. on day 1), plus etoposide, 100 mg/m^2 i.v. days 1-3, every 3 weeks. Concomitant thoracic radiotherapy (45 Gy in 30 twice-daily fractions of 1.5 Gy or 56 Gy in 28 once-daily fractions of 2 Gy) could start either on day one of chemotherapy cycle one or two (exceptionally of cycle three, for patients enrolled after one chemotherapy cycle). PCI (25 Gy in 10 fractions) was administered between days 8 and 15 of chemotherapy cycle four.

After completion of chemo-radiotherapy and PCI, patients who had not progressed were randomised to either the experimental arm or to observation. Patients in the experimental arm first received four cycles of induction nivolumab (1 mg/kg i.v.) plus ipilimumab (3 mg/kg i.v.) every 3 weeks, followed by nivolumab maintenance (240 mg i.v. every 2 weeks) for a maximum of 12 months.

Randomisation and masking

Blocked stratified randomisation (1:1) with two stratification factors, radiotherapy fractions per day (1 versus 2) and FDG-PET-CT at baseline (done versus not) was used.

Endpoints and assessments

The primary endpoint was progression-free-survival (PFS), locally assessed, defined as time from randomisation until documented progression (PD) according to RECIST v1.1 or death from any cause (whichever occurred first), in the intention-to-treat population (ITT). Patients alive, without PD were censored at the time of their last tumour assessment. Secondary endpoints included, overall survival (OS; time from randomisation to death from any cause), objective response rate (ORR) according to RECIST v1.1, time-to-treatment failure (TTF; time from randomisation to treatment failure for any reason) and safety. Safety profile was assessed on the basis of the nature, frequency, and severity of adverse events (AEs), according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0). Exploratory endpoints included time-to-treatment discontinuation (TTD; time from randomisation to treatment discontinuation for any reason; patients completing protocol treatment were censored) and duration of response (DoR; time from documented objective response to PD or death from any cause).

Regular tumour assessments for all patients were carried out by CT-scan of the thorax and upper abdomen at baseline before enrolment and before randomisation and then every 9 weeks up to 18 months follow-up, every 12 weeks up to 2 years, every 26 weeks at years 3 and 4 and at week 260 at 5 years until disease progression determined according to RECIST v1.1.

Statistical analysis

Under AM1, PFS and OS were co-primary endpoints tested at an overall one-sided significance level alpha of 0.05, split to 0.01 and 0.04, respectively. According to the latest design modification due to the premature accrual termination, PFS was defined as the only primary endpoint to be tested at the one-sided significance level of 0.05. The aim remained the same, i.e. to detect a hazard ratio (HR) of 0.57, translating to an improvement in median PFS from 13.1 months in the observation arm to 22.8 months in the experimental arm. A total of 81 PFS events were needed to provide 80% power using a stratified log-rank test.

Balance of baseline characteristics between the two treatment arms was tested by Fisher's exact and Mann-Whitney test. For the primary efficacy analysis, PFS was compared between the two arms with the log-rank test, stratified by the number of radiotherapy fractions per day and FDG-PET-CT.

All time-to-event endpoints were estimated by the Kaplan-Meier method and HRs with associated 95% confidence intervals (CIs) were calculated with the use of stratified Cox proportional-hazards models with Breslow's method of tie handling.[14] The Cox models were adjusted for clinicopathological variables: sex, smoking history, PS at randomisation, stage, age, response to chemo-radiotherapy before randomisation and the two stratification factors. The backward elimination method, with removal criterion $P \geq 10\%$, was applied for the selection of the statistically significant predictors. The proportional hazards assumption was tested, using the Schoenfeld residuals[15] as well as the interaction of treatment effect with time. In case of violation of the proportionality assumption, exploratory piecewise HRs and restricted mean survival time (RMST) at the minimum of the longest observed survival time, were also calculated.[16,17] In order to explore the consistency of the treatment effect in prespecified subgroups, preplanned PFS analyses were carried out.

Analyses of secondary time-to-event efficacy endpoints (OS, TTF, TTD, DoR) were analogous to PFS analysis. AEs were analysed descriptively. No interim efficacy analysis was planned, while a pre-planned early safety evaluation was carried out 12 weeks after the first 30 patients had been randomised to the experimental arm (raising no safety concerns).

All statistical results were produced using SAS version 9.4 and all reported *P* values are two-sided.

Analysis population

All efficacy data were summarised and analysed in the ITT cohort, which included all randomised patients under protocol AM1, evaluated in the treatment arm to which they were randomly assigned, regardless of the treatment actually received, including patients who were randomised but did not receive any trial treatment. Safety was assessed in the as treated (AT) cohort, including all patients who have received at least one dose of protocol treatment as well as all patients randomised to the observation arm (under protocol AM1).

The trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the institutional review board at each

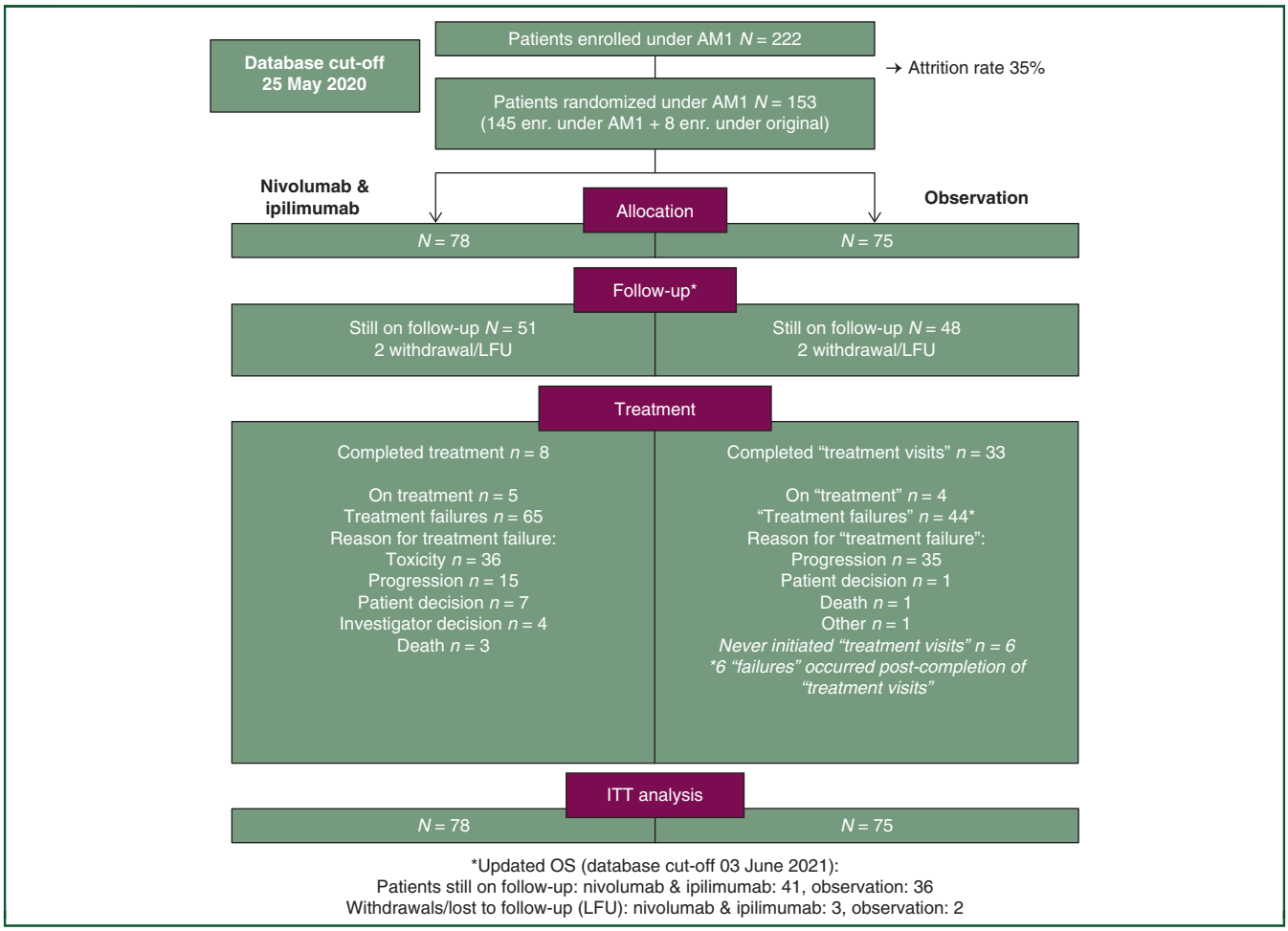

Figure 1. Trial design and flow chart. Note: Eight patients enrolled under the original protocol, reached the time for randomisation when the protocol amendment (AM1) was already approved and implemented, and were analysed in the ITT population.
AM1, protocol amendment; ITT, intention-to-treat; LFU, lost to follow-up; OS, overall survival.

participating centre. All the patients provided written informed consent.

RESULTS

Patient characteristics

From December 2015 to April 2019, a total of 222 patients were enrolled under protocol AM1. Baseline characteristics for these patients are presented in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.09.011. Among the enrolled patients, an attrition rate of 35% was observed, with 77 patients not meeting the criteria for randomisation at the end of the chemo-radiotherapy phase. Detailed information on the corresponding reasons are summarised in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.09.011. A total of 153 patients, (including 8 patients enrolled under the original protocol who completed chemo-radiotherapy after AM1 was activated), were randomised to the experimental arm (78 patients) and to observation (75 patients) (Figure 1).

Patient characteristics at randomisation were well balanced between the two treatment arms (Table 1). Median age was 62 years, with the majority being male (60.1%), of EGOG PS 1 (66.0%), almost all either former (65.4%) or current smokers (34.0%), and often with stage IIIB (7th edition of the IASLC TNM classification) disease (49.7%). Twice-daily radiotherapy and FDG-PET-CT at baseline were each administered in approximately one-third of patients (36.6% and 33.3%, respectively). Among randomised patients, objective response to chemo-radiotherapy was achieved in 94.8% (complete response (CR): $N = 20$, 13.1%, partial response (PR): $N = 125$, 81.7%), with 4.5% reaching only stable disease (SD).

Treatment

From the 153 randomised patients, 99 were still on study (51 in the experimental, 48 in the observation arm), at the data cut-off date of 25 May 2020, with median follow-up of 22.4 [interquartile range (IQR): 13.2-35.5] months. In the experimental arm, the median time from completion of radiotherapy to initiation of nivolumab-ipilimumab treatment was 52.5 days (min-max: 28-86 days) for patients having received once-daily radiotherapy ($n = 48$) and 76 days (min-max: 42-109 days) for patients with twice-daily radiotherapy ($n = 30$). Median time from completion of PCI, the last treatment before randomisation, until nivolumab-ipilimumab start was 22 days (min-max: 7-56 days).

Table 1. Baseline characteristics by treatment arm and overall (ITT cohort)

Characteristic	Nivo + Ipi (n = 78)	Observation (n = 75)	All patients (N = 153)	P value*
Age (years at enrolment)				
Median (Min-Max)	61.1 (37.7-83.2)	61.9 (38.6-77.3)	61.5 (37.7-83.2)	0.13
Mean (95% CI)	60.3 (58.6-62.1)	62.6 (60.7-64.5)	61.4 (60.1-62.7)	
Sex — n (%)				
Male	50 (64.1)	42 (56.0)	92 (60.1)	0.33
Female	28 (35.9)	33 (44.0)	61 (39.9)	
Smoking history — n (%)				
Current	27 (34.6)	25 (33.3)	52 (34.0)	0.86
Former (≥100 cigarettes in the past during the whole life)	51 (65.4)	49 (65.3)	100 (65.4)	>0.99[a]
Never (0-99 cigarettes during the whole life)	—	1 (1.3)	1 (0.7)	
ECOG performance status (at randomization) — n (%)[b]				
0	25 (32.1)	23 (30.7)	48 (31.4)	0.70
1	50 (64.1)	51 (68.0)	101 (66.0)	0.86[c]
2	3 (3.8)	1 (1.3)	4 (2.6)	
Stage — n (%)				
IA	—	2 (2.7)	2 (1.3)	0.57
IB	2 (2.6)	1 (1.3)	3 (2.0)	0.48[d]
IIA	3 (3.8)	5 (6.7)	8 (5.2)	0.81[d,e]
IIB	6 (7.7)	2 (2.7)	8 (5.2)	
IIIA	26 (33.3)	27 (36.0)	53 (34.6)	
IIIB	40 (51.3)	36 (48.0)	76 (49.7)	
Missing	1 (1.3)	2 (2.7)	3 (2.0)	
Response to CRT (before randomization) — n (%)				
CR	9 (11.5)	11 (14.7)	20 (13.1)	0.77
PR	65 (83.3)	60 (80.0)	125 (81.7)	0.80[f]
SD	4 (5.2)	3 (4.0)	7 (4.5)	
NE	—	1 (1.3)	1 (0.7)	
Stratification factors				
Number of RT fractions per day — n (%)				
1	48 (61.5)	49 (65.3)	97 (63.4)	0.74
2	30 (38.5)	26 (34.7)	56 (36.6)	
PET-CT — n (%)				
Done	25 (32.1)	26 (34.7)	51 (33.3)	0.74
Not done	53 (67.9)	49 (65.3)	102 (66.7)	

The date of data cut-off was 25 May 2020.
CI, confidence interval; CR, complete response; CRT, chemotherapy-radiotherapy; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; NE, not-evaluable; PET-CT, positron emission tomography-computed tomography; PR, partial response; RT, radiotherapy; SD, stable disease.
[a] Category 'Never' excluded.
[b] Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with higher scores reflecting greater disability.
[c] Category '2' excluded.
[d] Category 'Missing' excluded.
[e] Categories 'IA' & 'IB', 'IIA' & 'IIB' and 'IIIA' & 'IIIB' combined.
[f] Category 'NE' excluded.
* Fisher's exact test for categorical variables, Mann-Whitney U test for continuous variables.

Median number of nivolumab and ipilimumab cycles during induction phase was two, while 29 patients received all induction treatment cycles according to protocol. In the maintenance phase, 25 patients continued nivolumab with a median of 13 cycles.

In the experimental arm, 65 patients discontinued treatment, 36 (55%) due to toxicities. The most frequent AE leading to discontinuation was pneumonitis, experienced by 10 out of 36 patients (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.09.011). Eight patients (10.3%) completed treatment as per the protocol and five (6.4%) were still on treatment (Figure 1). Median time to nivolumab and ipilimumab discontinuation was 1.7 (95% CI: 1.2-2.5) months with 15.6% of patients still on treatment by 12 months. In the observation arm, 33 patients completed all visits according to the protocol, while 44 patients discontinued, in 80% this was due to PD.

Efficacy

Primary endpoint: Progression-free survival. At the time of the data cut-off, 82 patients (53.6%) had PD or died [40 patients (51.3%) in the experimental arm and 42 patients (56.0%) in the observation arm]. Median PFS was 10.7 [95% CI: 7.0-not evaluable (NE)] months in the experimental and 14.5 (95% CI: 8.2-NE) months in the observation arm, a non-significant difference (HR = 1.02; 95% CI: 0.66-1.58; stratified log-rank P = 0.93; Figure 2A). At 12 months of follow-up, PFS rate was 48.1% (95% CI: 36.1% to 59.0%) in the experimental and 52.8% (95% CI: 40.9% to 63.5%) in the observation arm, while at 24 months the trend was reversed with PFS rates of 43.2% (30.9% to 55.0%) and 40.3% (28.3% to 51.9%), respectively. The proportionality assumption was not violated (P = 0.36). Nevertheless, differences in PFS were also explored through RMST analysis, not revealing statistically significant difference [RMST at the

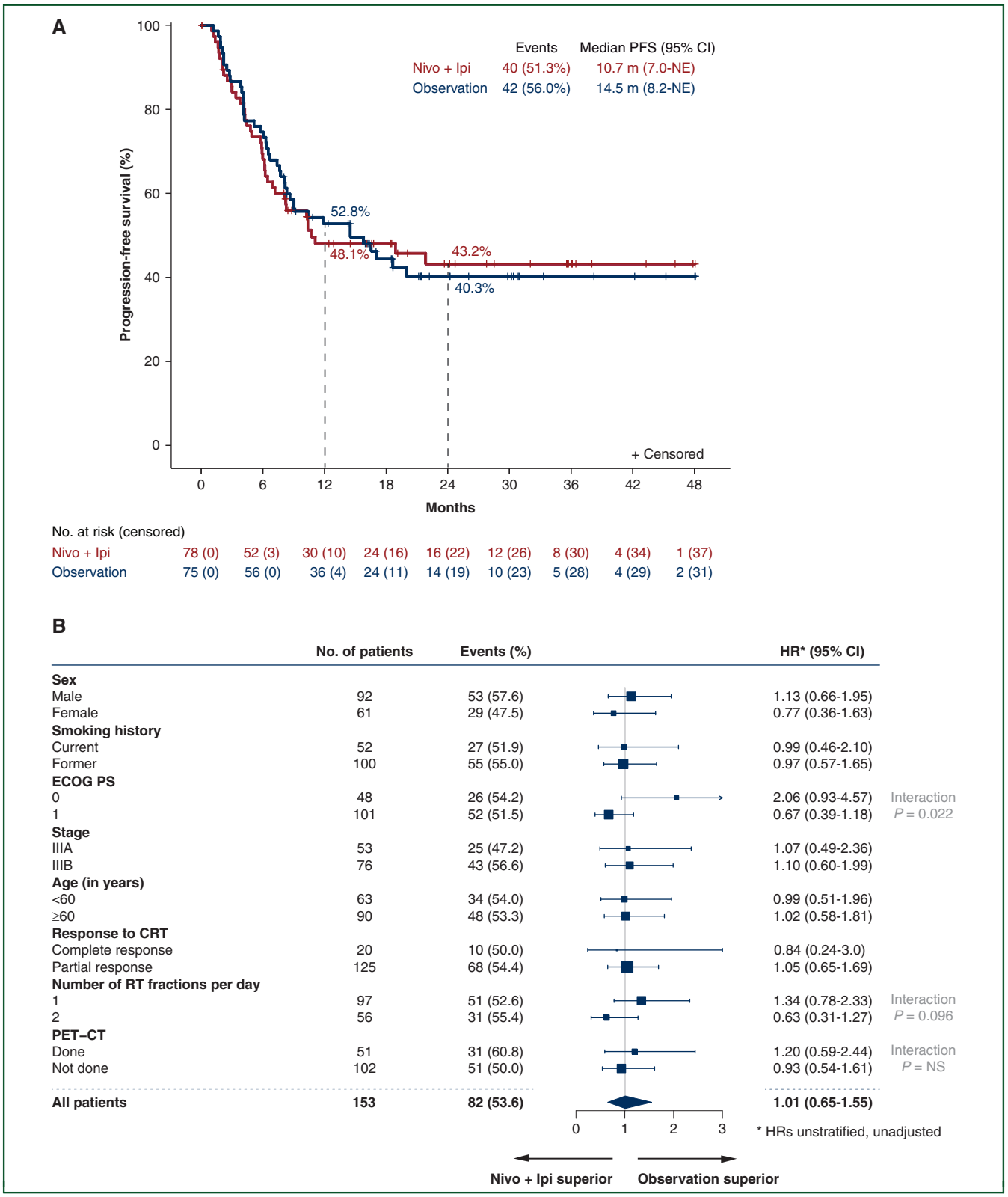

Figure 2. Progression-free survival (ITT cohort). (A) Kaplan-Meier plot for PFS by treatment arm. (B) Exploration of treatment effect within levels of clinicopathological variables of interest. Note: Only HRs (95% CI) for subgroups with $n \geq 10$ and number of events ≥ 5 are presented.
CI, confidence interval; CRT, chemotherapy-radiotherapy; ECOG, Eastern Co-operative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; m, months; NE, not evaluable; NS, not significant; PET-CT, positron emission tomography-computed tomography; PFS, progression-free survival; PS, performance status; RT, radiotherapy.

minimum of the longest observed survival time 0.49 (95% CI: -6.4 to 7.4)]. In all subgroups, no PFS difference was found between the two arms, while a significant differentiation of the treatment effect was observed for PS and for radiotherapy (RT) schedule, with higher treatment benefit for patients with PS 1 and patients who received

two RT fractions per day (interaction $P = 0.022$ and 0.096, respectively) (Figure 2B).

Overall survival. OS was updated per 03 June 2021, with median follow-up of 35.0 months (IQR: 25.5-48.1) and 77 patients still on follow-up. Median OS was not reached (NR) (95% CI: 24.1 months -NE) in the experimental arm, while it was 32.1 (95% CI: 26.1-NE) months in the observation arm. In total 71 deaths (46.4%) were observed (34 in the experimental and 37 in the observation arm). OS was not found to be significantly longer in the experimental arm (HR = 0.95; 95% CI: 0.59-1.52; stratified log-rank $P = 0.82$; Figure 3A). OS rate at 24 months was 62.9% (95% CI: 50.9% to 72.7%) and 66.4% (95% CI: 54.4% to 75.9%), in the experimental and observation arms respectively. Due to the observed survival crossing, non-proportionality was examined and not found statistically significant by this follow-up time ($P = 0.070$). Piecewise HRs show a trend towards more benefit attributed to the experimental arm [from HR = 1.60 (95% CI: 0.73-3.54) at <12 months to HR = 0.84 (95% CI: 0.39-1.81) for 12-24 months and HR = 0.51 (95% CI: 0.19-1.40) at >24 months], but RMST at the end of follow-up (minimum of the longest observed survival time) is non-significant (1.57 months, 95% CI: −1.57-8.9 months; $P = 0.67$).

In the pre-planned subgroup analysis on the two stratification factors, a differential OS benefit was detected between different RT schedules, with higher benefit of nivolumab plus ipilimumab in patients receiving twice daily RT (interaction $P = 0.010$, Figure 3B; Supplementary Figure S1A and B, available at https://doi.org/10.1016/j.annonc.2021.09.011), while no such effect was observed on the FDG-PET-CT categories. Exploratory analysis, showed a differential effect based on PS (0 versus 1), with higher apparent benefit in patients with PS 1 (interaction $P < 0.001$; Figure 3B; Supplementary Figure S2A and B, available at https://doi.org/10.1016/j.annonc.2021.09.011).

When estimated from date of enrolment of all 230 patients (153 randomised and 77 not eligible for randomisation), median OS becomes 34.6 (95% CI: 28.5-53.1) months; with 38.7 (95% CI 32.0-NE) months for randomised and 23.9 (95% CI: 17.0-34.5) months for non-randomised patients (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2021.09.011).

Objective response rate. Among the 153 randomised patients, 133 were assessable for OR with residual disease at randomisation, since 20 patients had already achieved complete response (CR) after chemo-radiotherapy (9 patients in the experimental and 11 in the observation arm, Table 1). ORR in the experimental arm was 38% (95% CI: 26% to 50%; 26 patients), taking into account, tumour assessments from randomisation until end of treatment, and 47% (95% CI: 34% to 60%; 30 patients) in the observation arm, while median DoR was NR in both arms and 12-month DoR of 63.0% (95% CI: 40.5-79.0%) and 73.2% (95% CI: 53.4% to 86.0%) in the observation and experimental arm respectively (Supplementary Figure S4A, B and C, available at https://doi.org/10.1016/j.annonc.2021.09.011). No significant difference in ORR was observed between the two arms (Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2021.09.011). Additional details including best relative tumour size change (waterfall plots) and tumour size changes over time (spider plots) per arm are summarised in Supplementary Figures S5A and B and S6A and B, available at https://doi.org/10.1016/j.annonc.2021.09.011. Taking into account also tumour assessments after treatment discontinuation, ORR in the experimental arm increased to 45% (95% CI: 33% to 57%) (Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2021.09.011, Supplementary Figure S7A and B, available at https://doi.org/10.1016/j.annonc.2021.09.011).

Sites of progression. Thirty-four (85%) and 39 (93%) recorded PFS events were documented progressions in the experimental and observation arm, respectively. The majority involved metastases with appearance of new lesions: 31 (91%) in the experimental and 30 (77%) in the observation arm, while in 5 (15%) and 7 (18%) also locoregional progression occurred (Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2021.09.011).

Metastases in only one site were detected for 25 (81%) and 21 (70%) patients and two sites in 5 (16%) and 8 (27%) patients, in the experimental and observation arms, respectively, while three metastatic sites were detected in one (3%) patient per arm. Most frequent new metastatic sites in both arms were liver [8 (26%); 8 (27%)], lymph-nodes [7 (23%); 8 (27%)] and lung [5 (16%); 8 (27%)], while brain progression was observed in three patients (10%) per arm (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2021.09.011).

Safety

The safety cohort consists of all 153 randomised patients (identical to ITT cohort), since all patients randomised to the experimental arm received at least one dose of experimental treatment. AEs of any grade, irrespective of relation to treatment were experienced by 98.7% of patients in the experimental arm and 86.7% in the observation arm, while 96.2% of patients in the experimental arm experienced at least one treatment-related AE. The percentage of patients with a grade ≥3 any-cause AE was 61.5% in the experimental (51.3% patients in particular with treatment-related AE) and 25.3% in the observation arm. Over half (55.1%) of patients in the experimental arm had AEs resulting in treatment discontinuation. Treatment-related deaths occurred in four patients (5.1%) (ileus: 1, lung infection: 1 and pneumonitis: 2), while one patient (1.3%) died in the observation arm (unspecified death). Most common AEs were fatigue and anorexia, experienced by 38.6% and 24.2% of patients (Table 2). The frequency of all (serious) AEs by grade, arm and system organ class is presented in Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2021.09.011.

DISCUSSION

STIMULI aimed at evaluating the impact of dual immune-checkpoint inhibition consolidation in LD-SCLC. The

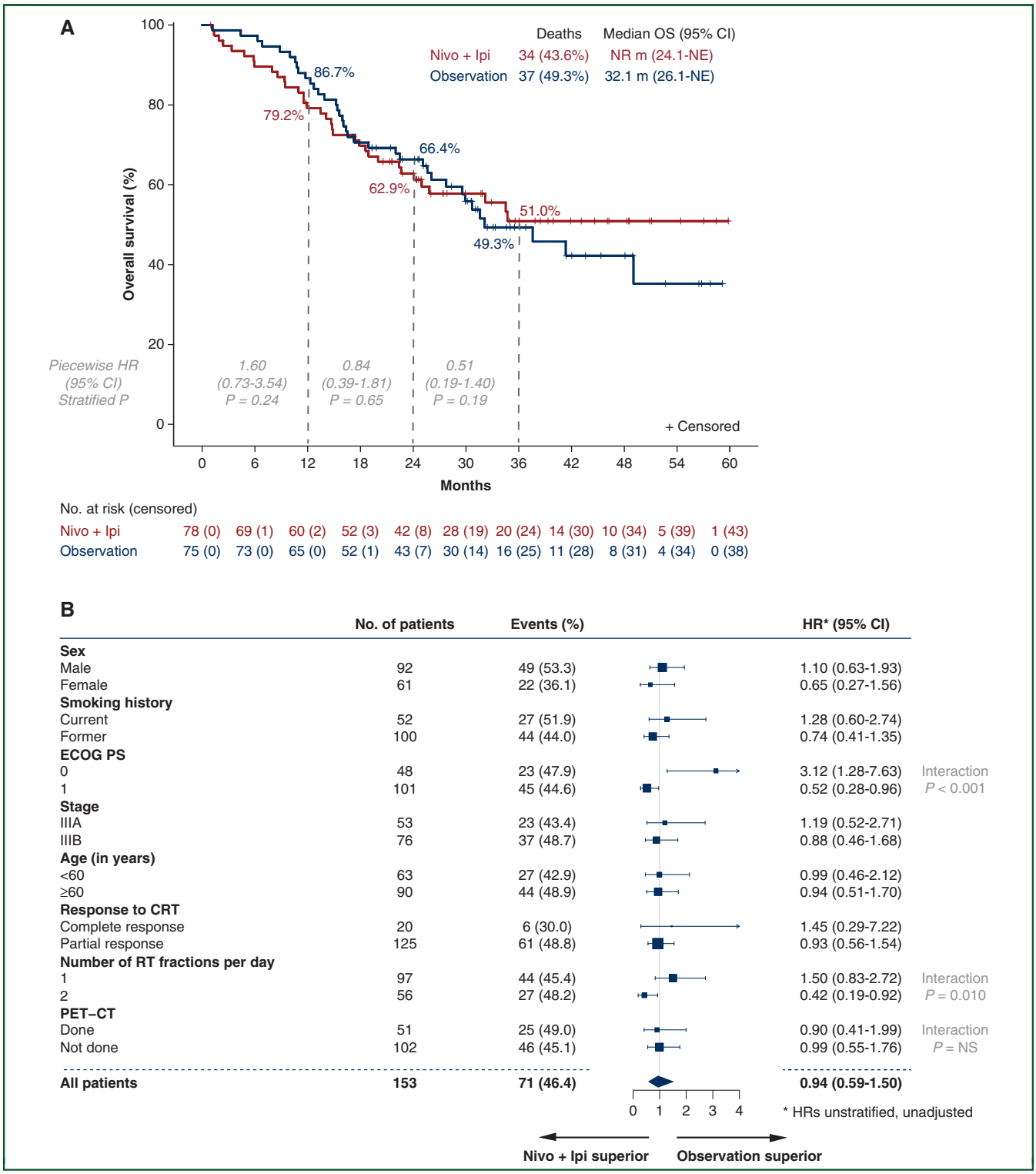

Figure 3. Overall survival (ITT cohort). (A) Kaplan-Meier plot for OS by treatment arm. (B) Exploration of treatment effect within levels of clinicopathological variables of interest. Note: Only HRs (95% CI) for subgroups with $n \geq 10$ and number of events ≥ 5 are presented.
CI, confidence interval; CRT, chemotherapy-radiotherapy; ECOG, Eastern Co-operative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; m, months; NE, not evaluable; NR, not reached; NS, not significant; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PS, performance status; RT, radiotherapy.

concept was developed based on the suggestion that the ipilimumab-nivolumab combination, followed by nivolumab maintenance might be an active treatment regimen for SCLC.[3,11] The trial enrolled treatment-naive patients intended for curative treatment consisting of concurrent chemo-radiotherapy and PCI. Randomisation was conditional on completion of the standard multimodality treatment and absence of evidence of PD. We hypothesised this minimal residual disease setting to be the optimal scenario for consolidation immunotherapy.

Table 2. Safety information of the as-treated cohort

	Nivo + Ipi (n = 78)		Observation (n = 75)	
	Number of patients (%)			
Any adverse event	77 (98.7)		65 (86.7)	
Treatment related adverse events	75 (96.2)		—	
Adverse events of grade ≥3	48 (61.5)		19 (25.3)	
Adverse events leading to treatment discontinuation	43 (55.1)		—	
Adverse events leading to death	4[a] (5.1)		1[b] (1.3)	
AEs occurring in ≥15% of the patients in either arm	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Fatigue	38 (48.7)	7 (9.0)	21 (28.0)	—
Anorexia	25 (32.1)	5 (6.4)	12 (16.0)	—
Diarrhoea	22 (28.2)	7 (9.0)	6 (8.0)	—
Vomiting	21(26.9)	1 (1.3)	5 (6.7)	—
Pneumonitis	22 (28.2)	7 (9.0)	4 (5.3)	1 (1.3)
Nausea	19 (24.4)	2 (2.6)	6 (8.0)	—
Cough	20 (25.6)	—	5 (6.7)	—
Hyperthyroidism	22 (28.2)	2 (2.6)	1 (1.3)	1 (1.3)
Anaemia	7 (9.0)	1 (1.3)	13 (17.3)	1 (1.3)
Dyspnoea	13 (16.7)	1 (1.3)	6 (8.0)	1 (1.3)
Pruritus	19 (24.4)	1 (1.3)	—	—
Constipation	15 (19.2)	1 (1.3)	3 (4.0)	—
Hypothyroidism	13 (16.7)	—	—	—

The date of data cut-off was 25 May 2020.

Multiple occurrences of the same adverse event in one patient were counted only once at the highest grade for the preferred term. The adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

[a] Ileus (1), lung infection (1), pneumonitis (2).

[b] Death (not otherwise specified).

STIMULI accrual was behind schedule, prompting the Steering Committee to close recruitment after 222 patients. The slow accrual was attributed to a lower than expected prevalence of LD-SCLC, accentuated by more accurate radiological staging methods, including FDG-PET-CT and brain MRI. In addition the strict randomisation criteria led to an unexpectedly high proportion of registered patients that were not amenable for the intended full curative treatment strategy, leading to an attrition rate of 35%. The STIMULI trial did not meet its primary endpoint of improving PFS with nivolumab-ipilimumab consolidation after standard chemo-radiotherapy, in LD-SCLC.

The short period on active treatment, with a median time to nivolumab and ipilimumab discontinuation of 1.7 months has certainly affected the efficacy. Similar observations were made in the Checkmate-451 trial, with ipilimumab-nivolumab maintenance at the same schedule, where only a median of two treatment cycles could be delivered.[6] In the CASPIAN trial that tested a tremelimumab-durvalumab-chemotherapy combination, only 60% of patients could receive the planned five doses of tremelimumab and median cycle number of durvalumab was also lower than in the durvalumab-chemotherapy arm. In 21% of patients AEs led to treatment discontinuation.[18]

Alternative schedules of nivolumab-ipilimumab combinations, used in non-small-cell lung cancer (NSCLC), led to better tolerability. The CheckMate-012 phase I trial evaluated nivolumab-ipilimumab combination at different doses and schedules and established the regimen with 3 mg/kg nivolumab every 2 weeks plus 1 mg/kg ipilimumab every 6 weeks as most tolerable and suitable for final phase II/III development in NSCLC, leading to new registered evidence-based treatment options.[19-21]

Taking into account the significant limitations in drug exposure, the updated analysis of the STIMULI trial at longer follow-up with a median of 35 months, failed to demonstrate a significant late effect of immunotherapy consolidation on survival. Median OS was not reached (95% CI: 24.1-NE) in the experimental arm, while it was 32.1 (95% CI: 26.1-NE) months in the observation arm. Most probably, even longer follow-up will not lead to statistical significance in OS.

When we defined the radiotherapy in the STIMULI trial, neither the CONVERT[9] nor the Cancer and Leukaemia Group B (CALGB) 30 610 (Alliance)/Radiation Therapy Oncology Group (RTOG) 0538[22] results were available. In STIMULI we allowed the 56 Gy dose, once daily, as it was still used in many centres that were reluctant to deliver the new standard schedule of 45 Gy twice daily.[9] The protocol explicitly recommended the 45 Gy twice daily, however, over the 56 Gy once daily schedule.

Our finding of a differential OS benefit between the RT schedules, with statistically significant benefit for the nivolumab-ipilimumab combination in patients on a twice-daily RT schedule, underlines the need to further investigate the optimal RT schedule for the combination with immunotherapy, in order to promote potential synergistic effects.[23] Alternatively, the statistically significant treatment effect on OS found for the twice daily schedule could be an effect of other confounding factors, such as treatment strategy of individual institutions or socioeconomic differences. PS was not found to be a confounding factor, since exploratory analyses did neither show an association of PS with RT dosing nor a three-way interaction in the multivariable Cox model (data not shown).

Translational analysis on tumour and plasma samples from trials establishing immune-checkpoint inhibition in

ED-SCLC failed to define any predictive biomarker.[1,2] While PD-L1 expression did not correlate with outcome across all available datasets, higher tissue tumour mutational burden (TMB) correlated with improved outcomes under nivolumab-ipilimumab and to a lesser extent nivolumab monotherapy in the pooled data of the non-randomised and randomised cohorts of CheckMate-032.[24] Exploratory translational work in STIMULI is ongoing to identify biomarker-defined subgroups that could benefit from immune-checkpoint consolidation treatment.

While two studies have shown modest but significant efficacy of first-line platinum-etoposide combined with anti-PD-L1 therapy, followed by a median of three maintenance immunotherapy cycles in patients with ED-SCLC, the focus now turns to patients with LD-SCLC. The concept of consolidation immune-checkpoint inhibition after chemo-radiotherapy is investigated in a phase III trial of durvalumab with or without tremelimumab (NCT03703297) as well as in a randomised phase II trial of atezolizumab (NCT03540420). Another randomised phase II trial is evaluating chemo-radiotherapy combined with atezolizumab followed by maintenance atezolizumab compared to standard of care (NCT03811002). In all these trials, the feasibility of immune-checkpoint inhibition consolidation has been proven to be safe.

New immunological treatment paradigms are needed in SCLC. In the future, such clinical attempts will hopefully rely on strong translational research data obtained from current trials, reflecting the unique biology and natural history of SCLC and offer acceptable tolerability in these fragile and comorbid patients.

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REFERENCES

1. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379(23):2220-2229.
2. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394(10212):1929-1939.
3. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17(7):883-895.
4. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results from the KEYNOTE-028 and KEYNOTE-158 Studies. *J Thorac Oncol*. 2020;15(4):618-627.
5. Ready N, Farago AF, de Braud F, et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. *J Thorac Oncol*. 2019;14(2):237-244.
6. Owonikoko TK, Park K, Govindan R, et al. Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: CheckMate 451. *J Clin Oncol*. 2021;39(12):1349-1359.
7. Spigel DR, Vicente D, Ciuleanu TE, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331*. *Ann Oncol*. 2021;32(5):631-641.
8. Spiro SG, James LE, Rudd RM, et al. Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis. *J Clin Oncol*. 2006;24(24):3823-3830.
9. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol*. 2017;18(8):1116-1125.
10. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999;341(7):476-484.
11. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the CheckMate 032 randomized cohort. *J Thorac Oncol*. 2020;15(3):426-435.
12. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*. 2010;17(6):1471-1474.
13. Antonia SJ, Bendell JC, Taylor MH, et al. Phase I/II study of nivolumab with or without ipilimumab for treatment of recurrent small cell lung cancer (SCLC): CA209-032. *J Clin Oncol*. 2015;33(suppl 15):7503.
14. Breslow N. Covariance analysis of censored survival data. *Biometrics*. 1974;30(1):89-99.
15. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69(1):239-241.
16. Tian L, Zhao L, Wei LJ. Predicting the restricted mean event time with the subject's baseline covariates in survival analysis. *Biostatistics (Oxford, England)*. 2014;15(2):222-233.
17. Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. *J Clin Oncol*. 2014;32(22):2380-2385.
18. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(1):51-65.
19. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N Engl J Med*. 2017;376(25):2415-2426.
20. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol*. 2017;18(1):31-41.
21. Paz-Ares L, Ciuleanu T-E, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):198-211.
22. Bogart JA, Wang XF, Masters GA, et al. Phase 3 comparison of high-dose once-daily (QD) thoracic radiotherapy (TRT) with standard twice-daily (BID) TRT in limited stage small cell lung cancer (LSCLC): CALGB 30610 (Alliance)/RTOG 0538. *J Clin Oncol*. 2021;39(suppl 15):8505.
23. Sharabi AB, Lim M, DeWeese TL, Drake CG. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol*. 2015;16(13):e498-e509.
24. Hellmann MD, Callahan MK, Awad MM, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. *Cancer Cell*. 2018;33(5):853-861.e4.

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