Comprehensive Genome Profiling in Patients With Metastatic Non–Small Cell Lung Cancer: The Precision Medicine Phase II Randomized SAFIR02-Lung Trial

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ABSTRACT

Purpose: Targeted therapies (TT) and immune checkpoint blockers (ICB) have revolutionized the approach to non–small cell lung cancer (NSCLC) treatment in the era of precision medicine. Their impact as switch maintenance therapy based on molecular characterization is unknown.

Patients and Methods: SAFIR02-Lung was an open-label, randomized, phase II trial, involving 33 centers in France. We investigated eight TT (substudy-1) and one ICB (substudy-2), compared with standard-of-care as a maintenance strategy in patients with advanced *EGFR*, *ALK* wild-type (wt) NSCLC without progression after first-line chemotherapy, based on high-throughput genome analysis. The primary outcome was progression-free survival (PFS).

Results: Among the 175 patients randomized in substudy-1, 116 received TT (selumetinib, vistusertib, capivasertib, AZD4547, AZD8931, vandetanib, olaparib, savolitinib) and 59 standard-of-care. Median PFS was 2.7 months [95% confidence interval (CI), 1.6–2.9] with TT versus 2.7 months (1.6–4.1) with standard-of-care (HR, 0.97; 95% CI, 0.7–1.36; $P = 0.87$). There were no significant differences in PFS within any molecular subgroup. In substudy-2, 183 patients were randomized, 121 received durvalumab and 62 standard-of-care. Median PFS was 3.0 months (2.3–4.4) with durvalumab versus 3.0 months (2.0–5.1) with standard-of-care (HR, 0.86; 95% CI, 0.62–1.20; $P = 0.38$). Preplanned subgroup analysis showed an enhanced benefit with durvalumab in patients with PD-L1 tumor proportion score (TPS) ≥1%, ($n = 29$; HR, 0.29; 95% CI, 0.11–0.75) as compared with PD-L1 <1% ($n = 31$; HR, 0.71; 95% CI, 0.31–1.60; $P_{\text{interaction}} = 0.036$).

Conclusions: Molecular profiling can feasibly be implemented to guide treatment choice for the maintenance strategy in EGFR/ALK wt NSCLC; in this study it did not lead to substantial treatment benefits beyond durvalumab for PD-L1 ≥ 1 patients.

Introduction

The advent of precision medicine has dramatically revolutionized the landscape of cancer treatment (1). With an increasing number of molecular alterations susceptible to targeted treatment, next-generation sequencing (NGS) is progressively replacing sequential strategies in several cancer types, including non–small cell lung cancer (NSCLC), as it allows sequencing of a high number of nucleotides in a short timeframe at an affordable cost (2).

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Translational Relevance

To our knowledge, the UNICANCER SAFIR02-Lung/IFCT 1301 study is the first randomized phase II trial to evaluate the use of next-generation sequencing (NGS)–based molecular profiling to guide treatment selection for switch maintenance therapy in metastatic non–small cell lung cancer. The SAFIR 02-Lung study demonstrated that serial collection of tissue biopsies and blood samples followed by NGS analysis is feasible in a large number of centers, including both large university hospitals as well as smaller community hospitals. This study highlighted that non-EGFR, non-ALK NGS-guided maintenance therapy is feasible, albeit it did not lead to a substantial clinical benefit beyond durvalumab for PD-L1–positive patients.

Several studies have confirmed the feasibility of implementing NGS in therapeutic decision-making in patients with advanced cancer. In the SAFIR01 trial (3), a targetable abnormality was identified in 69% of 251 patients with breast cancer for whom high throughput genome analysis was performed. In the MOSCATO trial, a molecular portrait with NGS found an actionable alteration in 411 of 843 patients with various advanced cancers, and 199 of them received a targeted therapy matched to a genomic alteration. Although the objective response rate (ORR) of 11% reported in the MOSCATO study does not reach the impressive antitumor results seen with EGFR tyrosine kinase inhibitors and ALK and ROS1 inhibitors, nonetheless improved outcomes were reported in a subset of patients (4).

Maintenance therapy either with the same agent used during induction phase (continuation maintenance) or with different agent (switch maintenance) is an option for patients with unselected advanced NSCLC, after four cycles of first-line platinum-based chemotherapy. Pemetrexed (5), gemcitabine (6), or targeted therapy such as erlotinib (7) has been shown to delay recurrence in this setting. To date, the role of targeted agents and immune checkpoint blockers (ICB) in molecularly selected patients with NSCLC as maintenance treatment based on a broad NGS panel, has not been addressed. We performed a prospective phase II randomized study to evaluate the use of NGS-based molecular profiling to guide treatment selection for maintenance therapy in this metastatic NSCLC.

Patients and Methods

Trial design and molecular profiling

SAFIR02-Lung is a French phase II interventional randomized open-label trial comparing several targeted therapies in NSCLC patients with a corresponding actionable genomic alteration and immunotherapy in patients who do not present an actionable genomic alteration found with centralized molecular analysis or have contra-indication to targeted agents as decided by the molecular tumor board based on the clinical, versus standard of care, following first-line chemotherapy. The first patient was randomized in substudy 1 on July 10, 2014, and the last patient on May 7, 2019, and in substudy 2, the first patient was randomized on the January 26, 2016, and the last on April 3, 2019. The SAFIR02-Lung trial is summarized in **Fig. 1**.

Eligible patients have *EGFR* and *ALK* wild-type chemonaïve NSCLC with metastatic relapse or stage IV disease at diagnosis or stage IIIb disease not amenable to surgery or radiotherapy. For substudy 1, patients had to have a targetable alteration, as identified by the molecular tumor board, and stable or responding disease after four cycles of chemotherapy. Patients not eligible for substudy 1, including those without a targetable alteration, who had stable or responding disease after four cycles of platinum-based chemotherapy were eligible for substudy 2. To identify patient with a targetable alteration, a fresh biopsy prior to the initiation of first-line platinum-based chemotherapy or at least before the third cycle was required. If the biopsy was unusable, an archived formalin-fixed paraffin-embedded (FFPE) biopsy or FFPE cytoblock or frozen biopsy was acceptable. When neither fresh or archived tissue was suitable for the study (<30% tumor cells for frozen and <10% for FFPE or insufficient size) and the patient could not undergo a new biopsy (e.g., inaccessible location, bone disease as the sole site, or safety concerns), circulating tumor DNA (ctDNA) on blood samples obtained before third cycle was a tertiary option.

Array comparative genomic hybridization (CGH) was performed using five platforms either with Affymetrix CytoScan assays for fresh tumor DNA or Affymetrix OncoScan assays for FFPE or ctDNA samples. NGS was performed with Ion Torrent PGM, or Illumina MiSeq/MiniSeq, or AmpliSeq technology, using a panel of approximately 70 genes (Supplementary Materials and Methods; Study protocol – Appendix 4).

Copy-number variations (CNV) from CytoScan and OncoScan were defined using the R package rCGH (v1.16.0 under R v3.6.3). Log2 relative ratios were calculated before centralization of the profile to set the baseline from which copy-number alterations were estimated (two copies being the neutral level). Break points in the log2 relative ratio continuity were identified by profile segmentation. These segments were used to determine a potential gain or loss [scale in copy-number (CN) CN = 0: homozygous deletion – CN = 1: loss – CN = 2: copy neutral – CN = 3–4: gain – CN = 5 or more: amplification].

All cases were discussed during a bi-monthly national molecular tumor board meeting. Eligible patients were allocated to substudy 1 according to the protocol (Supplementary Materials and Methods; Study protocol – Appendices 5 and 6).

Randomization

In substudy 1, patients with an actionable alteration corresponding to categories A to D were randomized in a 2:1 ratio using minimization to the corresponding targeted treatment or standard of care. All other patients were randomized in a 2:1 ratio to substudy 2, to receive durvalumab or standard of care, irrespective of their PD-L1 status, using minimization.

For substudy 1, randomization was stratified by histologic subtype (squamous vs. nonsquamous), by chemotherapy tumor response (stable disease vs. tumor response), by smoker/nonsmoker, and by molecular alteration category (defined as Category A: *HER2* or *RET* aberration or *FGFR1* amplification OR *FGFR2* mutation OR *FGFR3* mutation or any other aberration that is not in B, C, D; Category B: no *HER2, RET, FGFR1-2-3, LKB1* aberration but *KRAS* OR *BRAF* mutation; Category C: no *HER2, RET, FGFR1-2-3, LKB1, KRAS, BRAF* aberration but *PIK3CA* mutation OR *PIK3CA* amplification OR *PTEN* loss OR *PTEN* mutation OR *AKT1* mutation; Category D: no *HER2, RET, FGFR1-2-3, KRAS, BRAF, PIK3CA, PTEN, AKT1*, aberration but *LKB1* mutation. For substudy 2, randomization was stratified by histologic subtype (squamous vs. nonsquamous), by tumor response (stable disease vs. tumor response), and by smoker/nonsmoker status.

The trial was approved by the local ethics committee (CPP Ile de France 2 on November 9, 2013; 2013-08-04) and the French health authorities (October 17, 2013; 130975A-12), and was conducted in accordance with the Declaration of Helsinki, current International Conference on Harmonization guidelines and all applicable regulatory

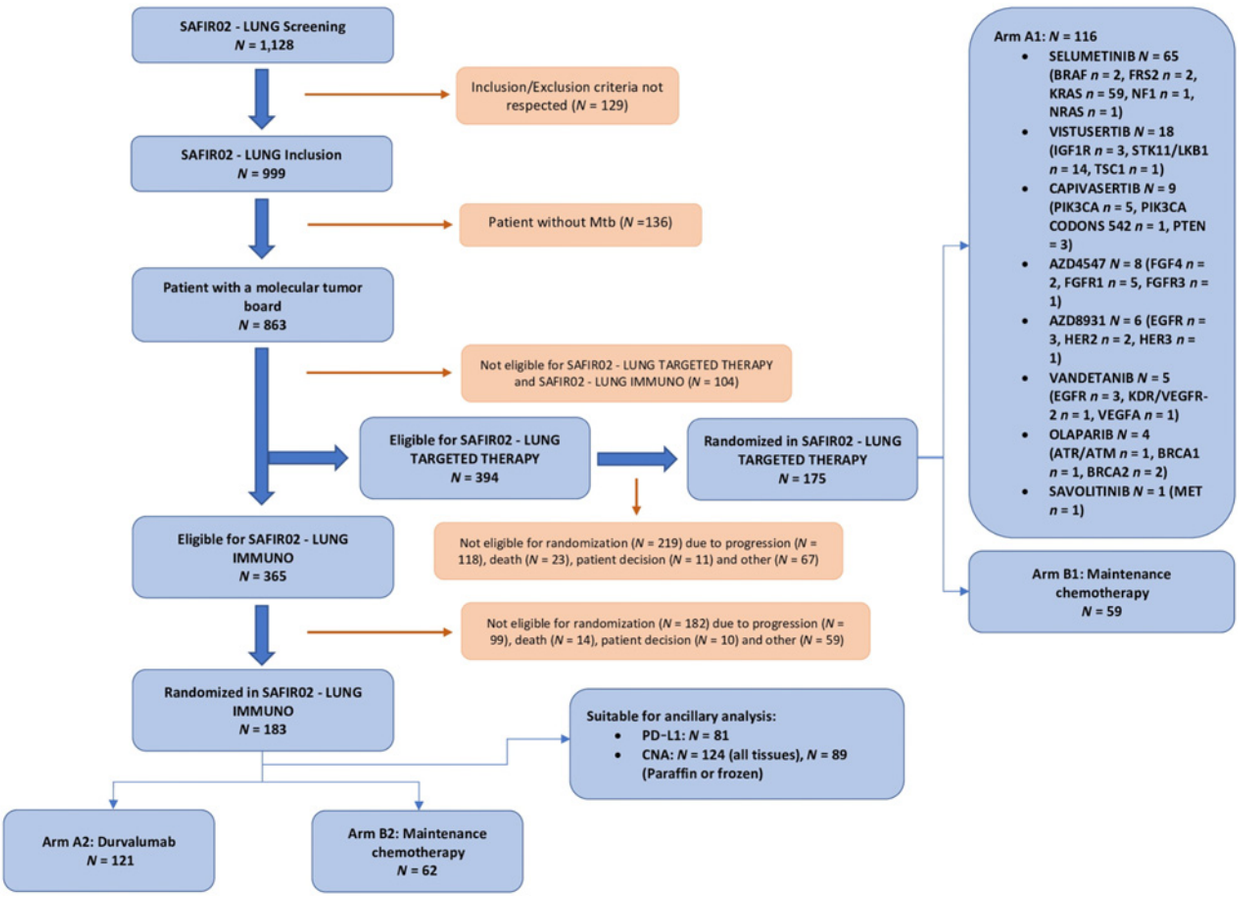

Figure 1.
CONSORT diagram for the SAFIR 02-Lung trial.

and ethical requirements. All patients provided written informed consent for biopsies, randomization, and use of their biological samples for research purposes. The study protocol and statistical analysis plan are available as Supplementary Information.

Treatment and follow-up

Eligible patients received four cycles of platinum-based chemotherapy according to local standard practice. In the interventional part of the study, patients without disease progression were randomized and treated either with matched targeted therapy, durvalumab or standard maintenance therapy until disease progression or unacceptable toxicity. The following targeted therapies were administered in substudy 1: selumetinib 75 mg twice every day, vistusertib 50 mg twice every day, capivasertib 480 mg twice every day, AZD4547 80 mg twice every day, AZD8931 40 mg twice every day, vandetanib 300 mg once every day, olaparib 300 mg twice every day, savolitinib 600 mg every day (or 400 mg every day for patients with body weight less than 50 kg) or vemurafenib 960 mg twice every day plus cobimetinib 60 mg every day; in substudy 2, durvalumab (10 mg/kg every 2 weeks) was used.

Treatment efficacy was monitored by a computed tomography scan every 6 weeks during the initial 6 months after randomization to maintenance, and every 9 weeks thereafter.

Outcomes

In both substudies, the primary endpoint was progression-free survival (PFS), defined as the time from randomization until the date of objective radiologic disease progression (assessed via RECIST v1.1; ref. 8), clinical progression or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to disease progression. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable efficacy assessment. However, if the patient progressed or died after two or more missing visits, the patient was censored at the time of the latest evaluable assessment. The secondary endpoints were overall survival (OS) and overall response rate (ORR). OS was defined as the time from randomization to death due to any cause. Patients still alive at the time of analysis (including lost to follow-up) were censored at the last known alive date and patients without post-baseline survival information were censored at day 1. ORR was defined as the percentage of patients with at least one tumor assessment demonstrating a complete response (CR) or partial response (PR) using RECIST v1.1 criteria. Safety data were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (v4.03).

Statistical analysis

For substudy 1, the primary objective was to demonstrate that a targeted therapeutic approach guided by genomic analysis (arm A1) improves PFS compared with nontargeted maintenance therapy (arm B1). Assuming exponential survival, to detect an increase in median PFS from 4 months (arm B1) to 6 months (arm A1; HR, 0.66) with 80% power at a two-sided significance level of 0.05 using the log-rank test and a 2:1 randomization (arm A1: arm B1), 205 events were required. Assuming a 72-month enrollment period with uniform accrual, and 12 months additional follow-up, a total of 230 patients were planned to be randomized.

For substudy 2, the primary objective was to demonstrate that maintenance with immunotherapy (durvalumab, arm A2) improves PFS compared with standard maintenance therapy (arm B2). Assuming exponential survival, to detect an increase in median PFS from 4 months (Arm B2) to 6.5 months (Arm A2), corresponding to a HR of 0.62, with 80% power at a two-sided significance level of 0.05 using the log-rank test and a 2:1 randomization (arm A2: arm B2), 155 events were required. Assuming a 54-month enrolment period with uniform accrual, and an additional 5.5 months follow-up, a total of 180 patients were planned to be randomized.

Efficacy endpoints were analyzed in the intention-to-treat population, defined as all randomized patients analyzed in the treatment group they were assigned to. Safety results were to be summarized by the treatment patients actually received.

For each substudy, baseline characteristics (age at randomization, gender, ECOG performance status, histologic subtype, stage, number of metastatic sites at screening, liver metastasis status, bone metastasis status) were summarized by treatment arm using descriptive statistics. Continuous variables were summarized using median and QR (first; third quartiles). Qualitative variables were summarized using counts and percents.

For each substudy and for PFS and OS, a Cox regression model was used to compare the PFS and OS between the two treatment arms, adjusted for the stratification factors from the randomization. An adjusted HR between the two treatment arms (i.e., the magnitude of treatment effect) was estimated by this model and its 95% confidence interval (CI). The Kaplan–Meier approach was used to estimate survival rates for each treatment arm. For substudy 1, each individual experimental drug was compared separately with standard maintenance therapy using Kaplan–Meier approach and log-rank test including only those patients that were oriented to that particular drug.

Preplanned subgroups were PDL1≥1% versus PDL1<1% (only for substudy 2), histologic subtype (squamous vs. nonsquamous), smoking status (smoker/nonsmoker), initial tumor response after chemotherapy (stable disease vs. tumor response), molecular alterations (categories A, B, C, D from randomization), age (<65, 65–74, and ≥75 years old), gender, performance status (ECOG score 0 vs. ≥1), presence of brain metastasis, number of metastases (≤3 vs. >3), and presence of KRAS mutation (only for substudy 2). Forest plots were used for visual representation, and test for interactions. One unplanned subgroup analysis was performed in substudy 2 according to the presence of copy-number alterations.

ORR was assessed by treatment arm and the comparison between arms was performed using Chi-square or Fisher exact test. A two-sided significance level of 0.05 was applied separately for each substudy. All statistical analyses were performed using SAS.

Role of the funding source

The study funders did not play any role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. They provided usual information regarding the adequate use of their products and patients' selection in the study.

Data sharing statement

The data generated in this study are available upon request from the sponsor (Unicancer). Please email the corresponding author and safirlung-data@unicancer.fr with requests.

Results

Overall, 999 patients were included in SAFIR02-Lung in 33 centers across France between July 2014 and May 2019, and molecular profiling was successful in 863. All 863 cases were discussed in the study's molecular tumor board, while 138 were excluded ($n = 48$: no biopsy performed or procedure failure; $n = 88$: non usable sample as <30% tumor cells or fragment too small). Out of 394 patients with a molecular alteration eligible for inclusion in substudy 1, 219 resulted not eligible to randomization due to progression ($n = 118$), death ($n = 23$), patient decision ($n = 11$) and other ($n = 67$), while out of the 365 patients included in substudy 2, 182 were not eligible for randomization due to progression ($n = 99$), death ($n = 14$), patient decision ($n = 10$) and other reasons ($n = 59$). **Figure 1** presents a Consolidated Standards of Reporting Trials (CONSORT) diagram according to the two substudies. Substudy 1 was prematurely closed due to slow recruitment.

Impact on survival of matched targeted therapy as maintenance therapy

A total of 175 patients were randomized in substudy 1 following chemotherapy (Category A, $n = 48$; Category B, $n = 99$; Category C, $n = 12$; Category D, $n = 16$). **Table 1** presents baseline characteristics of the randomized patients; 59% were male, 44% had an ECOG performance status of 0, and the majority (87%) had an adenocarcinoma histology. Response to first-line induction chemotherapy was reported in 47 patients (27%). Overall, 116 patients were randomized to targeted treatment (65 selumetinib, 18 vistusertib, 9 capivasertib, 8 AZD4547, 6 AZD8931, 5 vandetanib, 4 olaparib, 1 savolitinib) and 59 to standard of care (54 pemetrexed, 4 gemcitabine, and 1 erlotinib). A median of seven cycles of targeted treatment (IQR 5; 14) was administered and four cycles (IQR 2;8) of standard of care.

In total, 112 of the 113 (99.1%) patients who received targeted treatment and 56 of 57 (98.2%) treated with standard of care permanently discontinued treatment, with the main reason for discontinuation being disease progression (132 radiologic and 5 clinical progression) in 137 patients (81.6%). Representativeness of study participants is summarized in Supplementary Table S1. Adverse events are described in Supplementary Materials and Methods (section 1 of substudy 1 statistical report), and are consistent with previous reports.

The median follow-up for PFS was 42.0 months (95% CI, 18.8–42.0). At the cut-off date (October 12, 2020), 168 (96%) patients had progressive disease or had died. The median PFS was 2.7 months (95% CI, 1.6–2.9) in patients who received targeted treatment and 2.7 months (95% CI, 1.6–4.1) with standard of care (adjusted HR, 0.97; 95% CI, 0.7–1.36; $P = 0.87$; **Fig. 2**).

Median follow-up for overall survival (OS) was 27.1 months (95% CI, 26.0–29.6). Overall, 115 (66%) patients had died at the cut-off date. Median OS was 14.3 months for targeted treatment (95% CI, 11.0–18.3) and 14.1 months (95% CI, 8.0–30.9) for standard of care (adjusted HR, 1.03; 95% CI, 0.69–1.55; $P = 0.87$; **Fig. 2**).

Planned exploratory analyses by study drug for selumetinib, vistusertib, and capivasertib did not reveal significant differences between

Table 1. Baseline characteristics of patients randomized in substudy 1 (targeted therapy).

Variable		Total $N = 175$	Arm A $N = 116$ (targeted treatment)	Arm B $N = 59$ (standard of care)
Age at randomization	<65 years	131 (74.9%)	91 (78.4%)	40 (67.8%)
	65–74 years	39 (22.3%)	21 (18.1%)	18 (30.5%)
	>74 years	5 (2.9%)	4 (3.4%)	1 (1.7%)
Gender	Male	104 (59.4%)	70 (60.3%)	34 (57.6%)
	Female	71 (40.6%)	46 (39.7%)	25 (42.4%)
Smoking habits	Current	92 (52.6%)	64 (55.2%)	28 (47.5%)
	Former	75 (42.9%)	47 (40.5%)	28 (47.5%)
	Never	8 (4.6%)	5 (4.3%)	3 (5.1%)
ECOG performance status	0	77 (44.0%)	45 (38.8%)	32 (54.2%)
	1	98 (56.0%)	71 (61.2%)	27 (45.8%)
Histological subtype	Adenocarcinoma	153 (87.4%)	102 (87.9%)	51 (86.4%)
	Large cell carcinoma	1 (0.6%)	0	1 (1.7%)
	Squamous cell carcinoma	20 (11.4%)	14 (12.1%)	6 (10.2%)
	Other	1 (0.6%)	0	1 (1.7%)
Stage	IB	3 (1.7%)	2 (1.7%)	1 (1.7%)
	IIIB	8 (4.6%)	7 (6.0%)	1 (1.7%)
	IV	162 (92.6%)	106 (91.4%)	56 (94.9%)
	Unknown	2 (1.1%)	1 (0.9%)	1 (1.7%)
Number of metastatic sites at screening	Mean (sd)	2.9 (1.4)	2.9 (1.3)	3.0 (1.6)
	Median (Q1; Q3)	3 (2; 4)	3 (2; 4)	3 (2; 4)
	Min; Max	0; 8	0; 8	1; 7
Liver metastasis	0 lesions	148 (84.6%)	100 (86.2%)	48 (81.4%)
	1 lesion	12 (6.9%)	8 (6.9%)	4 (6.8%)
	≥2 lesions	15 (8.6%)	8 (6.9%)	7 (11.9%)
Bone metastasis	0 lesions	109 (62.3%)	72 (62.1%)	37 (62.7%)
	1 lesion	20 (11.4%)	14 (12.1%)	6 (10.2%)
	≥ 2 lesions	43 (24.6%)	28 (24.1%)	15 (25.4%)
	Effusion	3 (1.7%)	2 (1.7%)	1 (1.7%)

targeted treatment and standard of care in terms of PFS or OS (Supplementary Fig. S1). Survival curves for AZD8931, AZD4547, olaparib, savolitinib, and vandetanib were not estimated due to the small number of patients treated with these drugs. Other planned subgroup analyses for PFS and OS are detailed in the Supplementary Materials and Methods—Section 2 of substudy 1 statistical report and Supplementary Figs. S2 and S3.

ORRs were not statistically significantly different between targeted treatment (5.3%) and standard of care (10.5%; $P = 0.22$).

Impact on survival of durvalumab as maintenance treatment

A total of 183 patients were randomized in substudy 2, 49 of whom had an response to induction chemotherapy, 62% were male, 37% had a performance ECOG status of 0, and the majority (89%) had an adenocarcinoma histology (**Table 2**). A total of 121 patients were randomized to durvalumab and 62 to standard of care (57 received treatment, 51 pemetrexed, 5 gemcitabine, and 1 other). A median of eight cycles of durvalumab were administered (IQR 3; 19), versus a median of four cycles (IQR 2; 8) of standard of care.

In total, 109 of the 121 (92%) patients who received durvalumab and all 57 (100%) treated with standard of care permanently discontinued treatment, with the main reason being disease progression, which was reported in 126 patients (75.9%, 122 radiological and four clinical progression). Adverse events are described in Supplementary Materials and Methods (section 1 of substudy 2 statistical report), and are consistent with previous reports.

The median follow-up time for PFS was 23.8 months (95% CI, 19.6– 28.8). At the cut-off date (February 5, 2020), 162 (89%) patients had progressive disease or had died. Median PFS was 3.0 months (95% CI, 2.3–4.4) in patients randomized to durvalumab and 3.0 months (95% CI, 2.0–5.1) in patients randomized to standard of care (HR adjusted for stratification factors = 0.86; 95% CI, 0.62–1.20; $P = 0.38$).

Planned subgroup analyses for PFS are provide in the Supplementary Fig. S4. Of 81 patients for whom PD-L1 expression tested, 29 had positive PD-L1 (≥1%), 31 negative (<1%), and 21 patients missing measurement. An enhanced benefit with durvalumab versus standard-of-care was observed in patients with PD-L1 ≥ 1% ($n = 29$, HR = 0.29; 0.11–0.75) as compared with PD-L1 <1% ($n = 31$; HR, 0.71; 95% CI, 0.31–1.60; $P_{\text{interaction}} = 0.036$; **Fig. 3**; Supplementary Fig. S4).

Unplanned exploratory analyses for the presence of copy-number alterations or a *KRAS* mutation did not identify enhanced treatment effects (Supplementary Materials and Section—Section 2 in substudy 2 statistical report).

Median follow-up for OS was months 21.6 months (95% CI, 19.6–24.3). A total of 107 patients had died at the cut-off time (58.5%). Median OS was 17.0 months in patients randomized to durvalumab (95% CI, 12.1–19.5) and 14.9 months (95% CI, 10.5–22.0) with standard of care (HR adjusted for stratification factors, 0.93; 95% CI, 0.61–1.40; $P = 0.73$). Planned subgroup analyses for OS are provide in the Supplementary Fig. S5.

Exploratory subgroup analysis in terms of OS found a stronger benefit for durvalumab compared with standard of care arm in PD-L1 ≥ 1% patients HR = 0.32 (95% CI, 0.12–0.83) as compared with PD-L1 ≤ 1 patients HR = 1.20 (95% CI, 0.48–2.99; $P_{\text{interaction}} = 0.039$; **Fig. 3**; Supplementary Fig. S5). No significant difference was identified

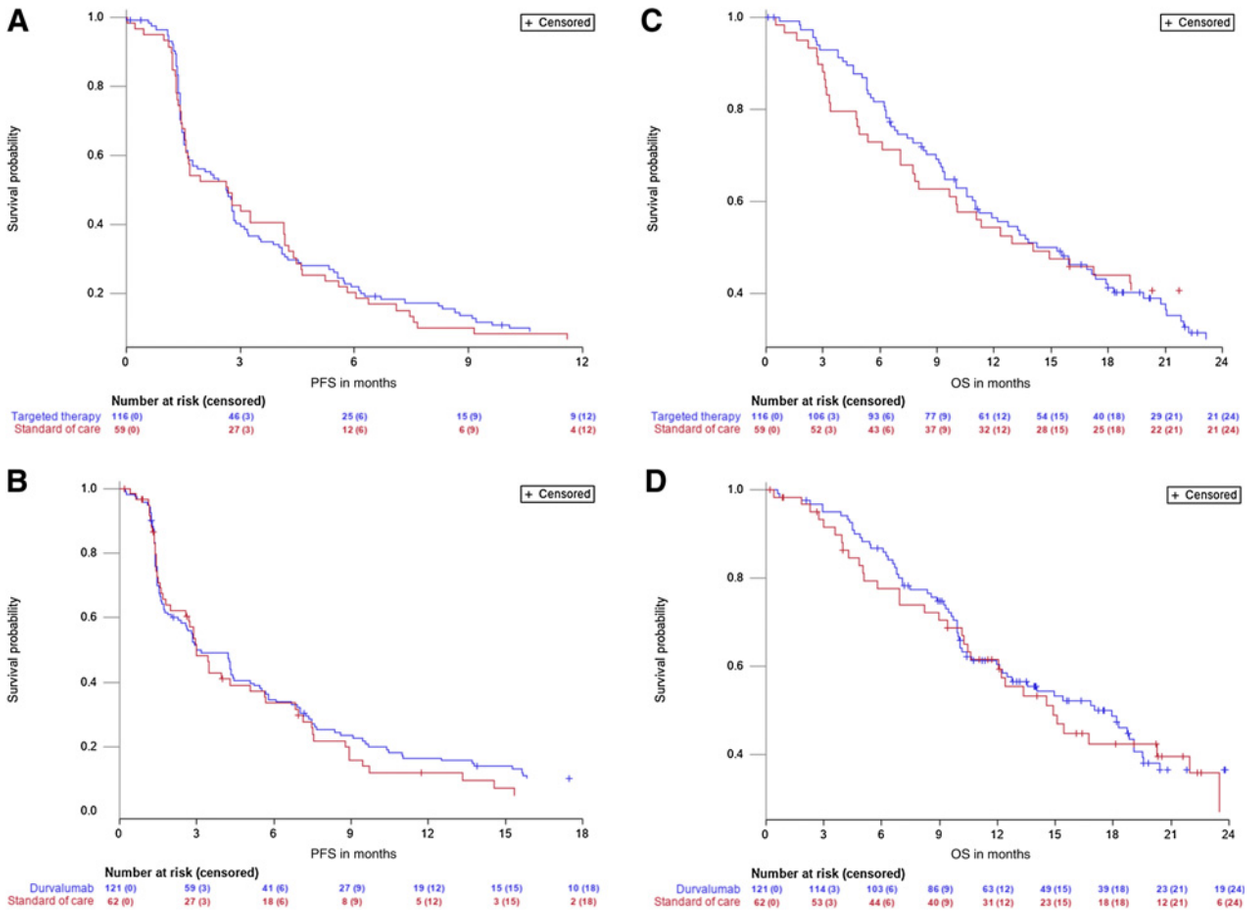

Figure 2.

PFS and OS in substudy 1 and 2. **A,** PFS for targeted therapy versus standard of care in substudy 1. **B,** OS for targeted therapy versus standard of care in substudy 1. **C,** PFS for durvalumab versus standard of care in substudy 2. **D,** OS for durvalumab versus standard of care in substudy 2.

in terms of ORR (14.3% for durvalumab vs. 3.6% for standard of care, $P = 0.10$).

Discussion

Until recently, platinum-based chemotherapy administered for four cycles followed by maintenance treatment has been considered as the standard frontline treatment for advanced NSCLC. This evolved with the advent of chemo-immunotherapy combinations, however to date the use of targeted agents or ICB selected on the basis of a broad NGS panel to guide the maintenance therapy for advanced NSCLC has not been reported. Our study showed that maintenance treatment selected this way, either targeted therapy or immune-checkpoint blockade, did not result in any improvement over standard of care, albeit a signal of immune checkpoint blockade activity was seen in patients with PD-L1 ≥1% tumors. It is important to highlight that overall, this study demonstrated that serial collection of tissue biopsies and blood samples followed by NGS analysis is feasible in a large number of centers, including both large university hospitals as well as smaller community hospitals.

Other studies have evaluated the efficacy of multigene molecular abnormality screening approaches to personalized therapy in later lines of therapy. In the SAFIR01 trial (3), only 30% of the treated patients with breast cancer presented an objective response or stable disease. The MOSCATO trial reached its primary objective of evaluating clinical benefit as measured by the percentage of patients presenting PFS on matched therapy that was 1.3-fold longer than PFS on prior therapy (4). In the SHIVA randomized trial (9), no significant improvement in PFS was observed in the precision medicine arm compared with the standard of care arm.

Substudy 1 evaluating targeted therapies supports the feasibility of NGS for decision-making on a large scale, albeit it did not reach its original planned number of patients or events and did not identify an important benefit of the approach on clinical outcome. Anyway it should be also considered that we excluded *EGFR* and *ALK* positive patients and not all the molecular alterations considered are true oncogenes or are targeted by a selective inhibitor. Finally, current knowledge has progressed since the SAFIR02-Lung study was initiated, and available drugs are more active and could be more promising for further evaluation in this setting. For example, we used vandetanib for *RET* translocation, savolitinib in *MET* exon 14 splice site mutation, and selumetinib in *KRAS* mutation positive patients, which are no longer considered the treatments of choice in these cancers, and new agents with higher activity are or will soon be available, such as selpercatinib (10), capmatinib (11), and

Table 2. Baseline characteristics of patients randomized in substudy 2 (immunotherapy).

		Overall $N = 183$	Arm A $N = 121$ (durvalumab)	Arm B $N = 62$ (standard of care)
Age at randomization	<65 years	113 (61.7%)	78 (64.5%)	35 (56.5%)
	65–74 years	58 (31.7%)	35 (28.9%)	23 (37.1%)
	≥75 years	12 (6.6%)	8 (6.6%)	4 (6.5%)
Gender	Male	114 (62.3%)	73 (60.3%)	41 (66.1%)
	Female	69 (37.7%)	48 (39.7%)	21 (33.9%)
Smoking habits	Current	92 (52.6%)	64 (55.2%)	28 (47.5%)
	Former	75 (42.9%)	47 (40.5%)	28 (47.5%)
	Never	8 (4.6%)	5 (4.3%)	3 (5.1%)
ECOG performance status	0	67 (36.6%)	48 (39.7%)	19 (30.6%)
	1	116 (63.4%)	73 (60.3%)	43 (69.4%)
Histological subtype	Adenocarcinoma	162 (88.5%)	107 (88.4%)	55 (88.7%)
	Large cell carcinoma	6 (3.3%)	5 (4.1%)	1 (1.6%)
	Other	2 (1.1%)	1 (0.8%)	1 (1.6%)
	Squamous cell carcinoma	13 (7.1%)	8 (6.6%)	5 (8.1%)
Stage	IA	1 (0.5%)		1 (1.6%)
	IIB	1 (0.5%)	1 (0.8%)	
	IIIA	1 (0.5%)	1 (0.8%)	
	IIIB	10 (5.5%)	7 (5.8%)	3 (4.8%)
	IV	170 (92.9%)	112 (92.6%)	58 (93.5%)
Number of metastatic sites at screening	Mean	2.7	2.8	2.6
	SD	1.32	1.41	1.10
	Median	3.0	3.0	3.0
	Q1–Q3	2–3	2–4	2–3
	Min–Max	1–7	1–7	1–6
Bone	0 Lesions	109 (59.6%)	69 (57.0%)	40 (64.5%)
	1 Lesion	23 (12.6%)	18 (14.9%)	5 (8.1%)
	≥2 Lesions	50 (27.3%)	33 (27.3%)	17 (27.4%)
	Effusion	1 (0.5%)	1 (0.8%)	
Liver	0 lesions	161 (88.0%)	103 (85.1%)	58 (93.5%)
	1 lesion	11 (6.0%)	9 (7.4%)	2 (3.2%)
	≥2 lesions	11 (6.0%)	9 (7.4%)	2 (3.2%)
Tumor cell PD-L1 ($n = 81$)	<1%	31	20	11
	≥1%	29	22	7
	Missing	21	14	7

sotorasib (12). In particular, sotorasib has recently shown promising activity in a phase I trial including pretreated patients with NSCLC with a *KRAS* p.G12C mutation, although the ORR and PFS (32.2% and 6.3 months, respectively) are not comparable with those seen with EGFR inhibitors in patients with *EGFR* mutations, or with ALK inhibitors in patients with *ALK* rearrangements. A similar rationale could lead to consideration of new agents that could be not enough promising to replace chemoimmunotherapy in the first-line, whereas the maintenance setting could be an interesting strategy to explore.

Our immunotherapy substudy also highlighted that the therapeutic landscape has evolved relative to the time of the study design, with immune checkpoint blockade moving from the second-line to the first-line treatment following the results of the KEYNOTE-024 study with pembrolizumab monotherapy in patients with PD-L1 ≥50% (13) and KEYNOTE-189 (14) and KEYNOTE-407 (15) for pembrolizumab in combination with platinum-based chemotherapy for nonsquamous and squamous NSCLC.

Moreover, due to the study design such that only those patients who are not suitable for substudy 1 are able to enroll in substudy 2, our population treated with durvalumab vs. standard of care is highly selected and different subpopulations were excluded from enrollment. For example, patients with *KRAS* mutation positive cancer were only included in substudy 2 if they met the exclusion criteria for substudy 1, and a recent analysis showed that these patients particularly benefit from ICI (16).

An interesting finding comes from the preplanned subgroup analysis of PD-L1 ≥1% patients, in which durvalumab resulted in a significantly larger benefit on PFS and OS compared with standard of care. This is consistent with the available evidences from clinical trials, where the magnitude of benefit obtained with ICB increased proportionally with the increase in PD-L1 TPS (13, 17, 18). This finding also highlights how precision medicine and biomarker analysis is an important step in selecting the right patients to be treated with new agents.

This strategy could be of interest in patients who are candidates for combination chemo-immunotherapy, however there are safety concerns or other reasons for excluding a combination regimen (e.g., preexisting autoimmune disease) for which it could be difficult to attribute a toxicity to chemotherapy or immunotherapy.

Few patients, including in the United States and the majority of European countries, receive the results of frontline NGS testing before starting any treatment, including in the case of all-comer patients receiving combined chemotherapy and immunotherapy. In this context, the SAFIR02-Lung trial illustrates how it could be both feasible and also potentially important, to identify actionable targets, especially

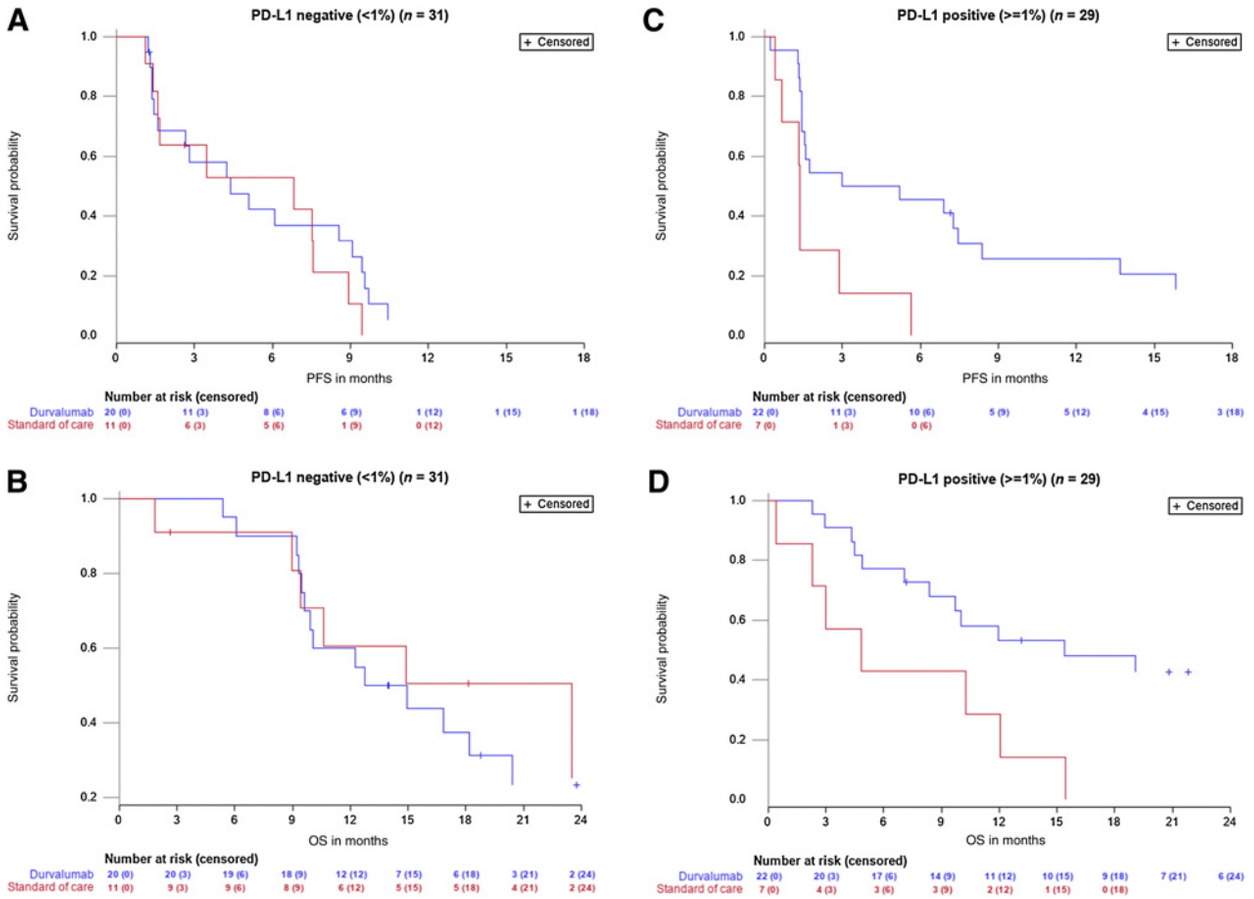

Figure 3.

PFS and OS for durvalumab versus standard of care in substudy 2 according to PD-L1 expression. **A,** PFS for durvalumab versus standard of care in PD-L1 negative patients. **B,** OS for durvalumab versus standard of care in PD-L1 negative patients. **C,** PFS for durvalumab versus standard of care in PD-L1 positive patients. **D,** OS for durvalumab versus standard of care in PD-L1 positive patients.

as highly active drugs for *MET, RET, NTRK, KRAS*, and other alterations are now available.

In conclusion, our study showed the feasibility of using NGS for decision-making within the maintenance strategy in NSCLC, albeit it did not translate into an increased clinical outcome as compared with standard of care. Further studies should evaluate new targeted agents in molecularly-selected patients and restrict the use of anti-PD-1/PD-L1 to PD-L1 ≥ 1% patients.

Authors' Disclosures

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Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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