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ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

PET/CT-guided management of immune checkpoint blockade and multi-modal profiling following treatment in long-term responders with metastatic lung cancer in the National Network Genomic Medicine Lung Cancer Germany (nNGM)

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Background: The optimal duration of immune checkpoint blockade (ICB) in lung cancer remains undefined. Indefinite treatment in long-term responders increases health care burden, exposes patients to avoidable toxicities, and is not supported by any clinical or biological rationale or translational data. Prospective strategies to determine the optimal duration of immunotherapy in lung cancer are urgently needed.

Patients and methods: In this retrospective cohort study, 455 patients from 21 National Network Genomic Medicine Lung Cancer Germany (nNGM) centers with $\geq$2 years of disease control on first-line ICB-based therapy were grouped into PET/CT-guided discontinuation (cohort A, $n = 126$) or continued ICB without PET/CT (cohort B, $n = 329$), and assessed for overall survival (OS). Matched pre- and post-ICB tumor samples from cohort A patients with persistent or progressive disease were analyzed by comprehensive genomic profiling, histological tumor-infiltrating lymphocyte quantification, and spatial transcriptomics to explore mechanisms of late resistance.

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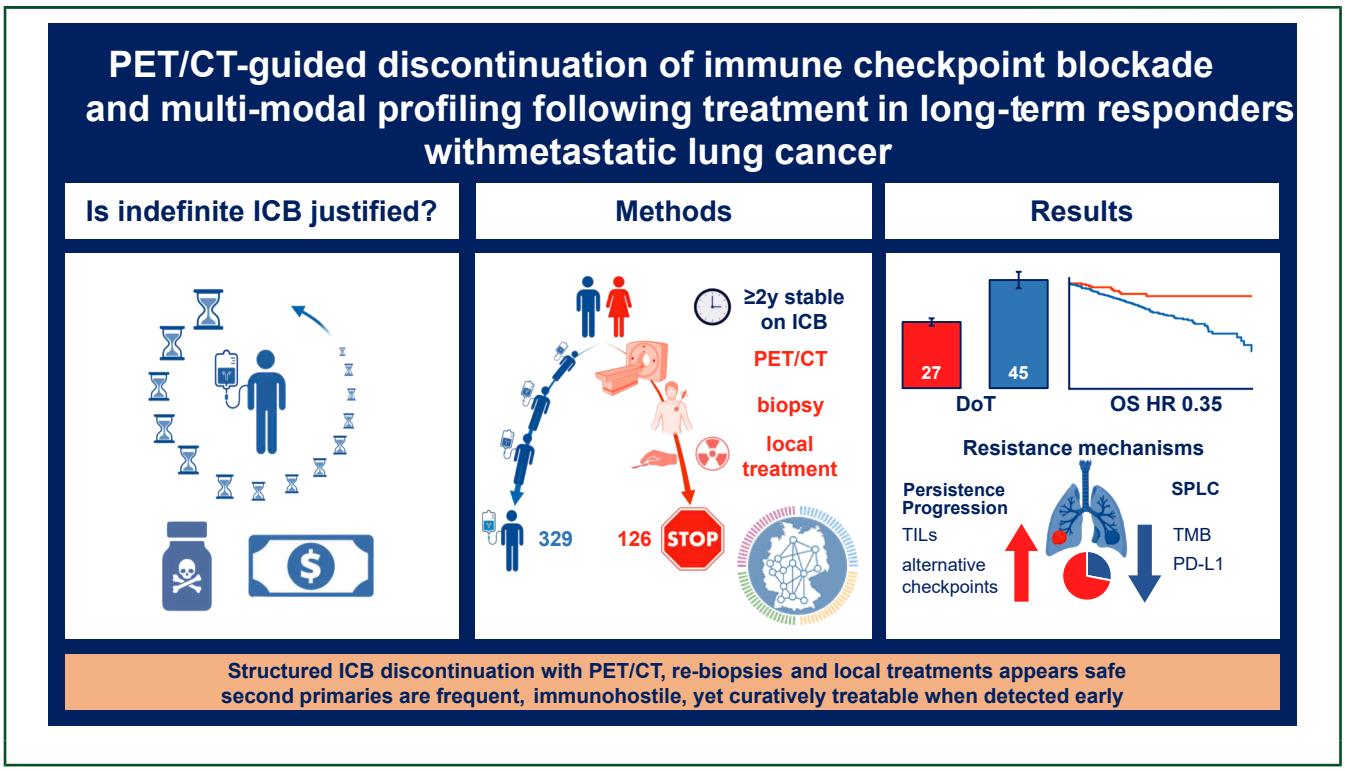
Results: After a median follow-up of 55 months, cohort A showed significantly longer OS [median not reached versus 82 months, hazard ratio 0.35 (95% confidence interval 0.18-0.67), $P = 0.002$], despite substantially shorter treatment duration (27 versus 45 months, $P < 0.001$). Discontinuation was either PET-driven (A) or resulted from immune-related toxicity, progression, or patients' choice (B). Systematic re-biopsies in cohort A revealed a high incidence of second primary lung cancers (SPLC, 28%). All progression events were managed exclusively with local (ablative) treatments in 53% (A) versus 17% (B). Tumors that occurred after treatment exhibited features of acquired resistance, whereas SPLC displayed characteristics of primary resistance, including low programmed death ligand 1 expression, low tumor mutational burden, and immunologically cold tumor microenvironments.

Conclusions: A structured discontinuation strategy appears to provide a safe approach for long-term ICB responders, enabling earlier detection of resistance before generalized progression. A confirmatory prospective non-inferiority randomized trial within the nNGM is underway.

Key words: lung cancer, immune checkpoint blockade, long-term response, discontinuation, resistance mechanisms, second primary lung cancer

GRAPHICAL ABSTRACT



DoT, duration of treatment; HR, hazard ratio; ICB, immune checkpoint blockade; OS, overall survival; PD-L1, programmed death ligand 1; PET/CT, 18F-fluorodeoxyglucose positron emission tomography; SPLC, second primary lung cancer; TIL, tumor-infiltrating lymphocyte; TMB, tumor mutational burden.

INTRODUCTION

Immune checkpoint blockade (ICB) has significantly improved survival in patients with non-oncogenic-addicted metastatic lung cancer.[1] However, the optimal treatment duration remains undetermined. In key registrational trials, ICB was either administered for a maximum of 2 years[2-9] or continued until progression or unacceptable toxicity without a set endpoint.[10-15] Due to open-ended regulatory approvals and the observation of inferior survival with time-limited treatments in the second-line setting, indefinite treatment continuation has become standard practice in clinical routine.[16-18] However, this practice largely lacks supporting evidence and, more importantly, there is no biological rationale or clinical confirmation to justify indefinite continuation. A clinical response to ICB typically emerges early after treatment initiation, whereas prolonged therapy rarely yields further clinical benefit or significant immunological changes.[19,20] Notably, both

clinical trials in treatment-naïve patients with programmed death ligand 1 (PD-L1)—high non-small-cell lung cancer [NSCLC; ≥50% tumor proportion score (TPS)] and real-world data in PD-L1 all-comers have demonstrated comparable overall survival (OS) outcomes, regardless of whether ICB was administered for a fixed duration or continued beyond 2 years.[4,17,21,22]

Thus, many patients could likely discontinue ICB without compromising outcomes, reducing both individual toxicity and the financial burden on the health care system, particularly given the high costs associated with thoracic malignancies.[23] However, a subset remains at risk for disease progression even after completing a 2-year course of treatment during follow-up.[24-26] This dual challenge underscores the urgent need for individualized, safe discontinuation strategies that balance treatment efficacy while minimizing unnecessary exposure. In this context, 18F-fluorodeoxyglucose positron emission tomography (PET/CT) may aid in differentiating viable residual tumor from post-therapeutic changes such as fibrosis or scarring, by providing metabolic information beyond anatomical imaging.[27-29]

In this study, we analyzed survival outcomes in ICB long-term responders from the National Network Genomic Medicine Lung Cancer Germany (nNGM), comparing patients who underwent PET/CT, typically followed by treatment discontinuation, with those who continued therapy. The primary aim was to determine whether a more in-depth, imaging-based tumor assessment could help individualize treatment strategies without compromising survival. In parallel, we investigated mechanisms of late-onset resistance. Residual tumors after prolonged ICB are presumed to have undergone adaptive molecular and cellular changes mediating acquired resistance,[30] yet mechanistic insights in this specific clinical context remain limited. To address this, we carried out a comprehensive analysis of tumor samples after treatment, integrating histopathology, genomic profiling, and spatial transcriptomics to uncover putative drivers of ICB resistance.

PATIENTS AND METHODS

Patient population

This cohort included data from 21 nNGM centers (NCT05934032), a nationwide consortium of certified oncology centers and partner institutions implementing standardized molecular diagnostics and interdisciplinary evaluation (see Supplementary Material, available at https://doi.org/10.1016/j.annonc.2025.12.011 for a detailed description). All consecutive patients starting first-line ICB between January 2017 and December 2022 with ≥2 years of disease control were included. Patients with oligo-progression <2 years were eligible if ICB was continued for 2 additional years after local therapy. Patients were assigned to two cohorts by management strategy. Cohort A patients once underwent PET/CT after ≥2 years of treatment following discussion in a multidisciplinary tumor board (MDT), without a predefined time point. Patients with oligo-progression on ICB after ≥2 years were eligible for cohort A if PET/CT was carried out to assess local ablative treatment (LAT) suitability as well as potential treatment discontinuation, serving the same decision-making purpose. Although PET/CT use was standardized in some centers, it was applied case by case in others. Estimation of a complete metabolic response (CMR) followed PET Response Criteria in Solid Tumors (PERCIST) and was investigator-assessed.[31,32] If PET/CT did not show CMR, biopsies of PET-avid lesions were offered. Vital tumors prompted LAT of oligo-persistent disease (OPD). For this study, we pragmatically defined oligo-progression and oligo-persistence as any focal progression or residual disease deemed amenable to LAT, in line with consensus recommendations.[33,34] A treatment pause was considered after CMR, negative biopsy, or successful LAT, whereas cohort B continued ICB beyond 2 years without PET/CT per guidelines.[33,35] Out of 582 potentially eligible patients, 455 met the pre-specified inclusion criteria and were analyzed (Figure 1, CONSORT diagram). Radiological assessments in both cohorts during treatment and follow-up followed guideline recommendations and did not include routine PET/CT surveillance. Additional PET/CT examinations could be carried out in cases of suspected oligo-progression but did not affect cohort assignment, as they were not intended to guide ICB discontinuation.

Evaluated endpoints

OS was selected as the primary and clinically meaningful endpoint. Non-inferiority of the structured approach in cohort A was assumed if the 3-year OS was no more than 5% lower than that observed in cohort B. Secondary endpoints included PET/CT outcomes (cohort A only), objective response rates (ORR), index cancer-specific progression-free survival {PFS, excluding second primary (lung) cancers [SP(L)C]}, duration of treatment (DoT), post-progression (OS2) and lung cancer-specific survival. Responses were physician-assessed per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, without central review.[36]

Outcome assessment was calculated in months from the first ICB dose until the last administration (DoT), until disease progression (PD), either radiographically defined or due to death from any cause, whichever occurred first (PFS), or until death from any cause (OS), respectively. In patients undergoing LAT for OPD, PFS was measured from the last LAT session until PD or death, whichever occurred first. Post-progression survival (OS2) was defined as the time from PD until death from any cause. The database was locked on 15 February 2025.

Tissue analysis

Since re-biopsies were systematically carried out only in cohort A, histological analyses were restricted to this cohort. Biopsies were categorized according to the timing of tissue acquisition: either as tumor persistence, defined by PET-avid lesions at the ≥2-year assessment, or as progression, defined by newly emerging or progressive lesions during extended follow-up. In total, 39 patients had re-biopsies confirming viable tumor tissue ('persistence', $n = 19$; 'progression', $n = 20$). Translational analyses were feasible in 32 cases (13 with persistence, 5 with progression on ICB, 14

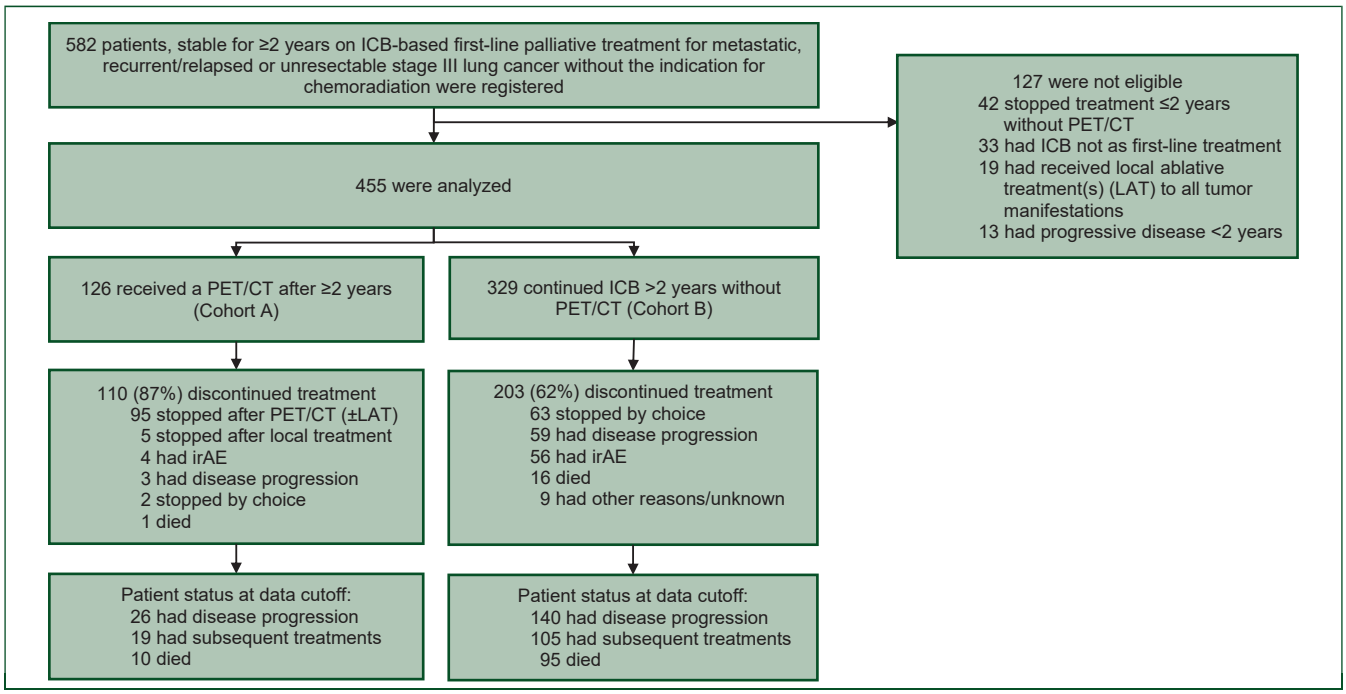


Figure 1. CONSORT diagram.
ICB, immune checkpoint blockade; irAE, immune-related toxicities; LAT, local ablative treatment; PET/CT, 18F-fluorodeoxyglucose positron emission tomography.

with progression after ICB discontinuation), with limited tissue quantity or quality being the main reasons for non-eligibility. Tumor-specific analyses included paired comprehensive genomic profiling before and after ICB ($n = 32$) and estimation of tumor mutational burden (TMB, $n = 25$). Tumor microenvironment (TME) analyses comprised paired quantification of tumor-infiltrating lymphocytes (TILs) on hematoxylin–eosin-stained slides ($n = 29$). Integrative profiling of tumor and microenvironment was carried out using spatial single-cell gene expression analysis on well-preserved tumor resections or large biopsies with minimal fragmentation ($n = 13$), including matched pre- and post-ICB samples ($n = 5$) (Supplementary Figure S11, available at https://doi.org/10.1016/j.annonc.2025.12.011). A detailed description of the respective methods is provided in the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2025.12.011.

Statistical analysis

Categorical variables were described and compared using Pearson's Chi-square test or Fisher's exact test, whereas continuous and ordinal variables were analyzed using the Mann–Whitney *U* test and Kruskal–Wallis test, respectively. Follow-up time was calculated using the reverse Kaplan–Meier method. To ensure an appropriate and unbiased survival analysis, we combined landmark and dynamic Kaplan–Meier estimation to model PET/CT as a time-dependent covariate. The 24-month mark was set as baseline. In cohort A, time to PET/CT was assigned to cohort B, with survival counted from PET/CT onward. Univariable and multivariable Cox models assessed clinical, tumor-, and treatment-related factors. Propensity score matching was carried out as additional sensitivity analysis. Analyses were carried out in SPSS version 29 (IBM, Armonk, NY, USA), with $P < 0.05$ considered significant. Unless otherwise specified, results are presented as medians with corresponding 95% confidence intervals (CI), with data reported for cohort A first, followed by cohort B.

Ethics statement

The study complied with the Declaration of Helsinki and was approved by the Charité ethics committee (EA4/027/23). Informed consent was obtained when required.

RESULTS

Baseline characteristics

For this observational study, 455 lung cancer patients with sustained disease control for ≥2 years following ICB-based first-line therapy were included, 126 in cohort A (PET/CT) and 329 in cohort B (control) (CONSORT diagram, Figure 1). Median age at ICB initiation was 65 years, 45% were female, 92% had a smoking history, and 71% presented with non-squamous NSCLC, thus reflecting a typical lung cancer population without actionable genomic alterations. Baseline and treatment characteristics were largely balanced between cohorts. The study population was characterized by a high PD-L1 TPS (median 65%; <1% TPS occurred in 14%; 1%-49% TPS occurred in 20%; ≥50% TPS occurred in 66% of patients) as well as prevalence of KRAS mutations (47%, including 25% KRAS G12C) among non-squamous cancers. Classical resistance-associated alterations such as STK11 and KEAP1 were comparatively rare (9% and 7%,

Table 1. Baseline characteristics

Variable	All patients ($N = 455$)	PET ($n = 126$)	Control ($n = 329$)	P value
Age[a] years, median (range)	65 (34-86)	65 (34-83)	65 (35-86)	0.26
Sex	—	—	—	0.30
Female, *n* (%)	206 (45.3)	62 (49.2)	144 (43.8)	—
Male, *n* (%)	249 (54.7)	64 (50.8)	185 (56.2)	—
ECOG PS, 0-1 versus ≥2	—	—	—	0.70
0, *n* (%)	199 (43.7)	50 (39.7)	149 (45.3)	—
1, *n* (%)	209 (45.9)	67 (53.2)	142 (43.2)	—
≥2, *n* (%)	36 (7.9)	9 (7.1)	27 (8.2)	—
Missing	11 (2.5)	0	11 (3.3)	—
Smoking history	—	—	—	0.24
Never, *n* (%)	22 (4.8)	10 (7.9)	12 (3.6)	—
Ever, *n* (%)	420 (92.3)	115 (91.3)	305 (92.8)	—
Missing	13 (2.9)	1 (0.8)	12 (3.6)	—
PY, median (range)	40 (0-125)	40 (0-100)	40 (0-125)	1.00
Histology	—	—	—	0.04[c]
Non-squamous NSCLC	324 (71.2)	79 (62.7)	245 (74.5)	—
Squamous/NOS NSCLC	94 (20.7)	32 (25.4)	62 (18.8)	—
SCLC	37 (8.1)	15 (11.9)	22 (6.5)	—
PD-L1 expression, median (95% CI)	65 (60-70)	60 (40-77)	65 (60-70)	0.48
0%[b]	56 (12.3)	16 (12.7)	40 (12.2)	0.29
1%-49%	81 (17.8)	24 (19.0)	57 (17.3)	—
≥50%	271 (59.6)	68 (54.0)	203 (61.7)	—
Missing	47 (10.3)	18 (14.3)	29 (8.8)	—
Initial stage at start ICB, IV versus III/rr	—	—	—	0.38
IV, *n* (%)	383 (84.2)	103 (81.7)	280 (85.1)	—
III/rr, *n* (%)	72 (15.8)	23 (18.3)	49 (14.9)	—
Brain metastases at start ICB, Y versus N	—	—	—	0.36
Y, *n* (%)	96 (21.1)	23 (18.3)	73 (22.2)	—
N, *n* (%)	359 (78.9)	103 (81.7)	256 (77.8)	—
First-line treatment	—	—	—	0.25
ICB monotherapy, *n* (%)	222 (48.8)	56 (44.4)	166 (50.5)	—
ICB+chemotherapy, *n* (%)	233 (51.2)	70 (55.6)	163 (49.5)	—
Platinum cycles, *n* (range)	4 (1-7)	4 (1-6)	4 (1-7)	0.30
Local treatment before/during ICB, Y versus N	—	—	—	0.12
Y, *n* (%)	148 (32.5)	48 (38.1)	100 (30.4)	—
N, *n* (%)	307 (67.5)	78 (61.9)	229 (69.6)	—
DoT until end of any LT, mo. (95% CI)	0 (0-0)	0 (0-0)	0 (0-0)	0.43

95% CI, 95% confidence interval; DoT, duration of treatment; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICB, immune-checkpoint blockade; LT, local treatment; N, no; (N)SCLC, (non-) small-cell lung cancer; PD-L1, programmed death ligand 1; PET, positron emission tomography; PY, package years; rr, recurrent/relapsed; Y, yes.
[a]At the start of ICB-based treatment.
[b]Tumor proportion score (TPS).
[c]$P < 0.05$.

respectively). Additional baseline characteristics are summarized in Table 1 and Figure 2A.

Treatment characteristics and outcomes of PET/CT in cohort A

The initial treatment approaches were evenly distributed, with 49% of patients receiving ICB monotherapy and 51% receiving immunochemotherapy. One-third (33%) of patients had received local treatment measures, predominantly for metastatic sites, before or during ICB therapy. Best ORR to ICB were 95% (A) and 87% (B), respectively ($P = 0.01$), corresponding with a median decrease in sum target lesions of 69% (range 64%-73%) and 59% (range 54%-63%) ($P < 0.001$) (Figure 2A and B, Supplementary Figure S1, available at https://doi.org/10.1016/j.esmogo.2025.100297).

A total of 126 patients in cohort A once underwent a PET/CT after a median of 25.6 months (range 25.1-26.9 months) (Supplementary Figure S2A, available at https://doi.org/10.1016/j.annonc.2025.12.011) and 78 (62%) achieved a CMR (Figure 2C). Tracer avidities in non-CMR patients were predominantly observed in the originally affected primary tumor sites and lymph nodes (Supplementary Figure S2B, available at https://doi.org/10.1016/j.annonc.2025.12.011). Additional biopsies were carried out in most non-CMR patients (36/48, 75%), with findings evenly split between viable tumor ($n = 19$) and non-malignant changes such as unspecific inflammation or anthracosilicosis ($n = 17$). Among 19 patients with viable tumor, 14 received LATs [stereotactic body radiation therapy (SBRT) $n = 8$, surgery $n = 6$], three palliative radiotherapy, and two systemic treatment only.

At the time of data cut-off, 16 (13%) and 126 patients (38%) were still receiving ICB, with a median treatment duration of 27.2 months (range 25.7-28.8 months) and 44.6 months (range 41.1-48.0 months), respectively ($P < 0.001$) (Figure 2D). In cohort A, the main reason for stopping treatment was PET/CT-guided decision-making (95/110 patients, 86%), whereas in cohort B it was primarily patient preference (63/203, 31%), disease progression (59/203, 29%), or intolerable immune-related toxicities (irAE; 56/

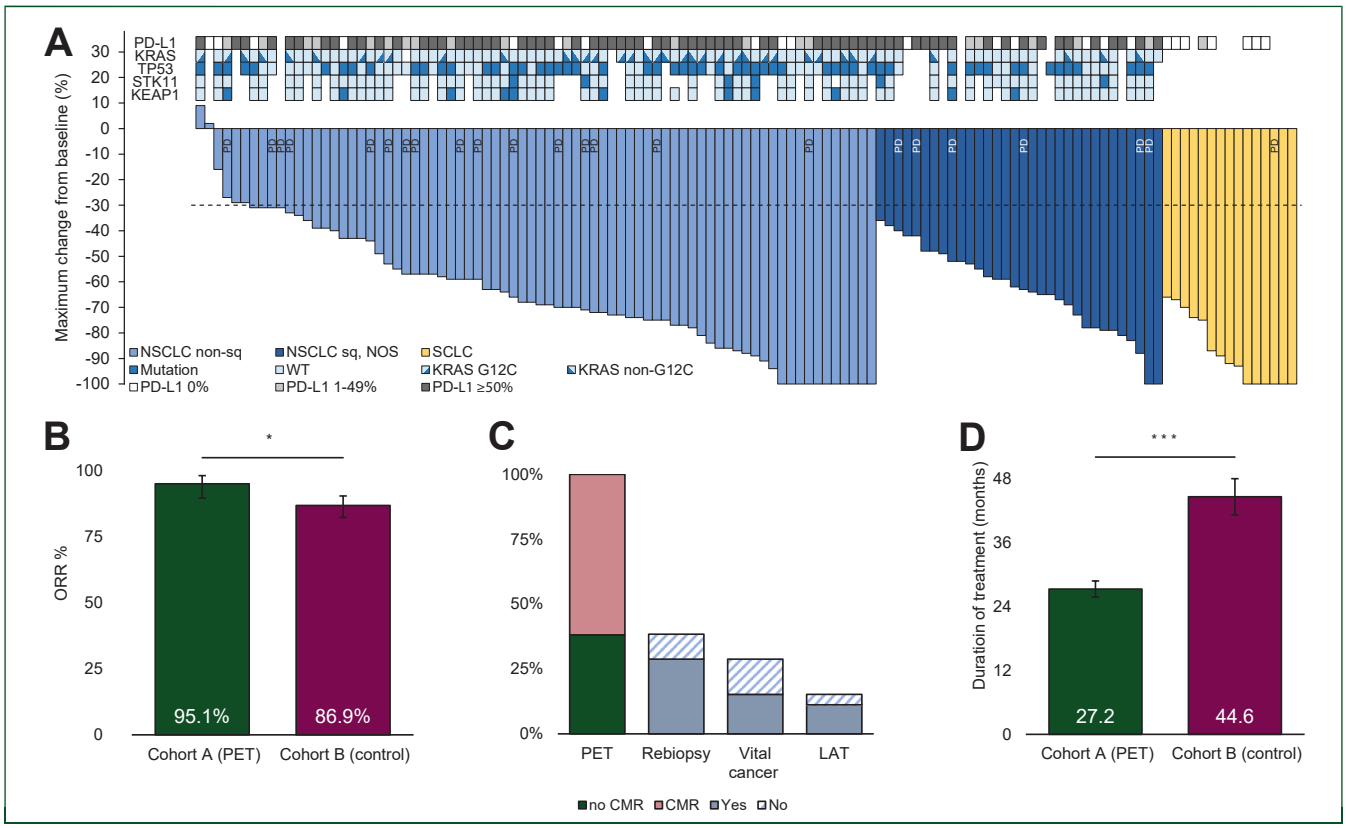


Figure 2. Clinical responses to ICB-based treatments, PET/CT imaging outcomes and treatment duration. (A) Waterfall plot illustrating best responses to first-line ICB-based treatments according to RECIST. (B) ORR in both cohorts. (C) Distribution of PET/CT outcomes with display of the respective clinical consequence and outcomes of re-biopsy. (D) Duration of treatment. * $P < 0.05$; *** $P < 0.001$.
CMR, complete metabolic response; ICB, immune checkpoint blockade; LAT, local ablative treatment; non-sq, non-squamous; NOS, not otherwise specified; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; PET/CT, 18F-fluorodeoxyglucose positron emission tomography; SCLC, small-cell lung cancer; sq, squamous; WT, wild type.

203, 28%). Of note, only 4% (4/110) of patients in cohort A discontinued ICB due to irAE. ICB-limiting irAE occurred after a median of 31 months of treatment, with one-third being grade ≥3 (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2025.12.011).

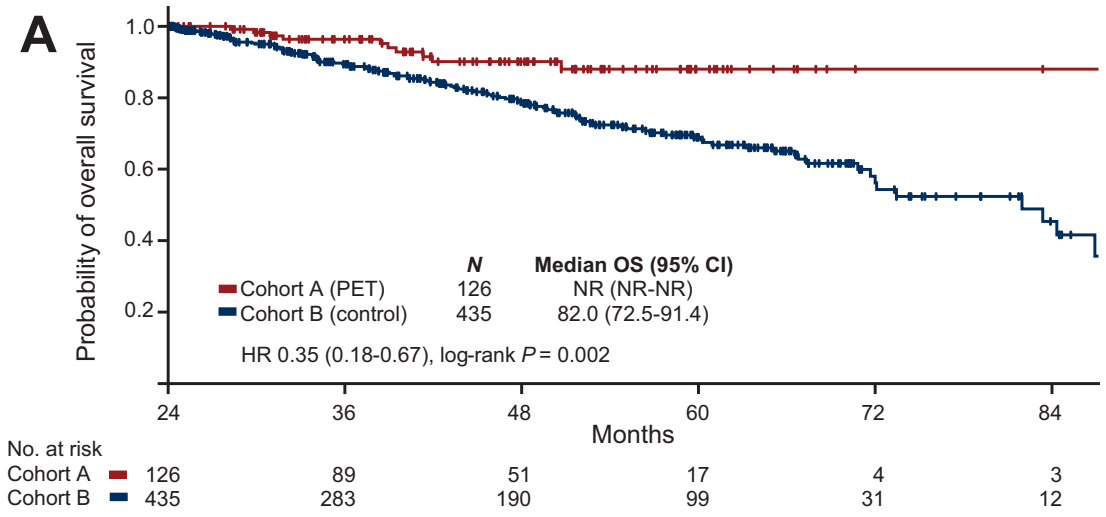
Survival analyses in cohort A and B

After a median follow-up of 55 months (range 52-57 months), 10 (8%) and 95 (29%) patients had died. Median OS was not reached in cohort A and was 82.0 months in cohort B (range 72.5-91.4 months), with 3-, 4-, and 5-year OS rates of 96%, 90%, and 88% versus 89%, 79%, and 69% (Figure 3A), translating into a 65% reduction in all-cause mortality in favor of cohort A (hazard ratio 0.35, [95% CI 0.18-0.67]; $P = 0.002$). These findings were consistently reproduced across all subgroups (Figure 3B), and their robustness was further supported by propensity score matching as a sensitivity analysis (Supplementary Table S11, available at https://doi.org/10.1016/j.esmogo.2025.100297, Figure S4). Survival outcomes did not differ according to the PET/CT prescription strategy (systematic versus individualized), the institutional setting (academic center versus community-based hospital), and outcome of PET/CT (Supplementary Figure S5A-C, available at https://doi.org/10.1016/j.annonc.2025.12.011).

Given that a substantial proportion of patients did not succumb to the underlying lung cancer (41 out of 165 OS events, 25%) and had competing causes of death, we additionally analyzed lung cancer-specific OS. This analysis demonstrated an even more pronounced survival benefit in cohort A (HR 0.22, [95% CI 0.08-0.61], $P = 0.004$), suggesting that alternative causes of death become increasingly relevant in long-term responders (Supplementary Figure S6A, available at https://doi.org/10.1016/j.annonc.2025.12.011).

Disease progression occurred in 26 (21%) and 140 patients (43%) in cohorts A and B, respectively. Median PFS was not reached in cohort A and was 63.0 months in cohort B (range 53.1-74.1 months) with 3-, 4-, and 5-year PFS rates of 86%, 78%, and 69% versus 78%, 60%, and 52%, respectively (Supplementary Figure S7A, available at https://doi.org/10.1016/j.annonc.2025.12.011). The 46% overall risk reduction for progression or death (HR 0.54, [95% CI 0.36-0.82]; $P = 0.004$) was consistently confirmed across all subgroups (Supplementary Figure S7B, available at https://doi.org/10.1016/j.annonc.2025.12.011).

Both univariable and multivariable Cox regression analyses confirmed the PET/CT-guided strategy as an independent predictor of OS and PFS (Supplementary Figure S8A and B, available at https://doi.org/10.1016/j.annonc.2025.12.011). Moreover, it emerged as the only



B

	HR	(95% CI)	*P* value	*n*	Events
OS					
Cohort A versus B	**0.35**	**(0.18-0.68)**	**0.002***	455	105
Age,years					
<65	0.40	(0.16-1.04)	0.06	237	43
≥65	0.33	(0.13-0.82)	0.02*	218	62
Sex					
Female	0.44	(0.17-1.13)	0.09	249	62
Male	0.30	(0.12-0.75)	0.01*	206	43
ECOG					
0	0.56	(0.20-1.58)	0.27	199	37
1	0.26	(0.10-0.67)	0.005*	209	50
≥2	0.51	(0.07-4.13)	0.63	36	10
Histology					
non-sq NSCLC	0.32	(0.14-0.73)	0.13	324	75
sq-NSCLC/NOS	0.46	(0.16-1.35)	0.16	94	26
SCLC	NE	(NE-NE)		37	4
PD-L1 expression					
0%	0.25	(0.03-1.97)	0.19	55	12
1%-49%	0.29	(0.07-1.27)	0.10	78	21
≥50%	0.43	(0.20-0.95)	0.04*	271	65
Unknown/SCLC	NE	(NE-NE)		46	7
Initial stage at start ICB					
IV	0.40	(0.20-0.81)	0.01*	383	84
III/recurrent	0.21	(0.03-1.58)	0.13	72	21
Brain metastases					
Yes	0.18	(0.02-1.34)	0.09	96	19
No	0.41	(0.20-0.81)	0.01*	359	86
Local treatment before/during ICB					
Yes	0.53	(0.22-1.30)	0.17	148	35
No	0.24	(0.09-0.65)	0.005*	307	70
Response (RECIST)					
PR/CR	0.46	(0.24-0.89)	0.02*	368	76
SD	NE	(NE-NE)		44	17

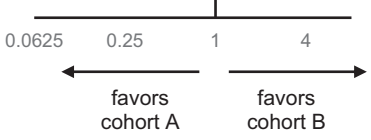


Figure 3. Overall survival. (A) Dynamic Kaplan—Meier plot for OS in both cohorts. (B) Forest plot displaying various subgroups (patient-related, tumor-related). * $P < 0.05$.

CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ICB, immune checkpoint blockade; NE, not estimable; NEC, neuroendocrine carcinoma; non-sq, non-squamous; NOS, not otherwise specified; NR, not reached; NSCLC, non-small-cell lung cancer; PD-L1, programmed death ligand 1; PR, partial response; SCLC, small-cell lung cancer; SD, standard deviation.

significant determinant for PFS, alongside well-established prognostic factors such as age, performance status, and RECIST-defined outcome for OS. Notably, initial histology and PD-L1 expression had no significant impact on survival in long-term responders.

Subsequent treatments

Of the 166 patients with PD, subsequent treatments were assessed in 124 patients where death was not the PFS-defining event. Rates of further treatments were 100% (19/19) and 82% (86/105, $P = 0.04$) (A versus B). Progression patterns among treated patients were comparable, with the majority presenting with localized oligo-progression (80% versus 70%, Supplementary Table S13A, available at https://doi.org/10.1016/j.annonc.2025.12.011). However, treatment approaches differed, with exclusive local therapy used in 53% versus 17% and systemic treatments (with or without local treatment) in 47% versus 83% (A versus B). Overall, drug regimens were similar, including ICB (Supplementary Table S13B, available at https://doi.org/10.1016/j.annonc.2025.12.011). OS2 in subsequently treated patients was not reached in cohort A and was 17.9 months in cohort B (range 6.5-29.2 months, HR 0.47, [95% CI 0.19-1.19], $P = 0.11$) (Supplementary Figure S6B, available at https://doi.org/10.1016/j.annonc.2025.12.011).

Secondary malignancies

Whereas the primary disease remained well controlled, 26 patients (5.7%) in both cohorts eventually developed secondary malignancies (Supplementary Figure S9A, available at https://doi.org/10.1016/j.annonc.2025.12.011). Of these, 18 were SPLC (cohort A: 10/126, 8%; cohort B: 8/329, 2%) and 8 non-thoracic malignancies (cohort A: 3/126, 2%; cohort B: 5/329, 2%). Due to early detection during structured radiological follow-up, the majority ($n = 17$, 65%) were eligible for curative-intended treatments such as surgery or SBRT (Supplementary Figure S9B, available at https://doi.org/10.1016/j.annonc.2025.12.011).

Histological and mutational features of lung cancers before and after ICB

In light of the limited evidence on morphological and functional transformation of tumors following prolonged ICB, we investigated histological and mutational features within three predefined clinical subgroups: persistence or progression of the initial primary tumor and SPLC. SPLC, an increasingly recognized phenomenon in long-term survivors, accounted for 9 of 32 cases (28%) (Figure 4A). Most SPLCs displayed divergent histomorphology and mutational profiles compared with the initial primaries (Figure 4B). Three shared histology but carried distinct driver mutations and were only clearly identifiable as SPLC through molecular profiling (Figure 4C, Supplementary Figure S10, available at https://doi.org/10.1016/j.annonc.2025.12.011). Primary tumors acquired additional mutations with a slight TMB increase after ICB, whereas SPLC showed a trend toward lower TMB than their corresponding primaries (Figure 4D). PD-L1 expression (TPS) was highly variable in primary tumors with overall lower pre- and post-ICB expression levels in progressive cases compared with persistent tumors. In contrast, SPLC displayed significantly lower TPS than the initial primaries (Figure 4E).

Tumor microenvironment dynamics in lung cancers before and after ICB therapy

The TME before and after ICB was explored by spatial transcriptomic profiling (Figure 4F), which revealed assembly of tumor-, immune-, and stroma-rich niches (Figure 4G). Both the distribution of spatial niches and histological TIL densities showed substantial heterogeneity before and after ICB (Figure 4H and I). Matched data revealed a significant correlation between histological TIL density and both the frequency of B and T cells as well as the extent of immune-rich spatial niches (Supplementary Figure S11C, available at https://doi.org/10.1016/j.annonc.2025.12.011). In samples taken after treatment from cases of persistence (patients p122 and p123) and progression (p173 and p174), immune-rich niches were notably expanded (Figure 4H). In contrast, SPLC (patient p121) showed a marked reduction in both TILs and immune-rich niches (Figure 4H and J), accompanied by an immunosuppressive TME with reduced expression of proinflammatory chemokines *CXCL9* and *CXCL10* in monocyte-derived macrophages (mo-Macs), and increased expression of *NT5E* (encoding CD73) in tumor cells (Figure 4K). Regardless of clinical course, persistent or progressive primary tumors were characterized by upregulation of different combinations of alternative immune checkpoints, including CTLA4, IDO1, LAG3, TIGIT, TIM-3, and VISTA (Figure 4K).

DISCUSSION

This study investigated in an explorative way the non-inferiority of a PET/CT-guided discontinuation strategy compared with continuous ICB beyond 2 years in lung cancer long-term responders. Our key findings demonstrated not only non-inferior OS but even substantially improved outcomes in patients managed according to the PET/CT-based approach. Importantly, this benefit was accompanied by an almost 50% reduction in treatment duration and a substantial decrease in long-term irAE. Remarkably, early detection of localized second primary tumors during follow-up allowed for curative local therapies, even in a formally incurable setting.

One of the most intriguing clinical phenomena in ICB is the emergence of long-term responders characterized by sustained tumor control or durable remissions over multiple years. Although this subgroup exemplifies the long-term potential of immunotherapy, it also poses a major clinical and biological challenge. At present, no reliable biomarkers exist to prospectively identify these patients. Common markers such as PD-L1, TMB, or immune-related gene expression signatures have shown limited predictive capacity in this specific context.[37] As a result, long-term response largely remains a retrospective observation

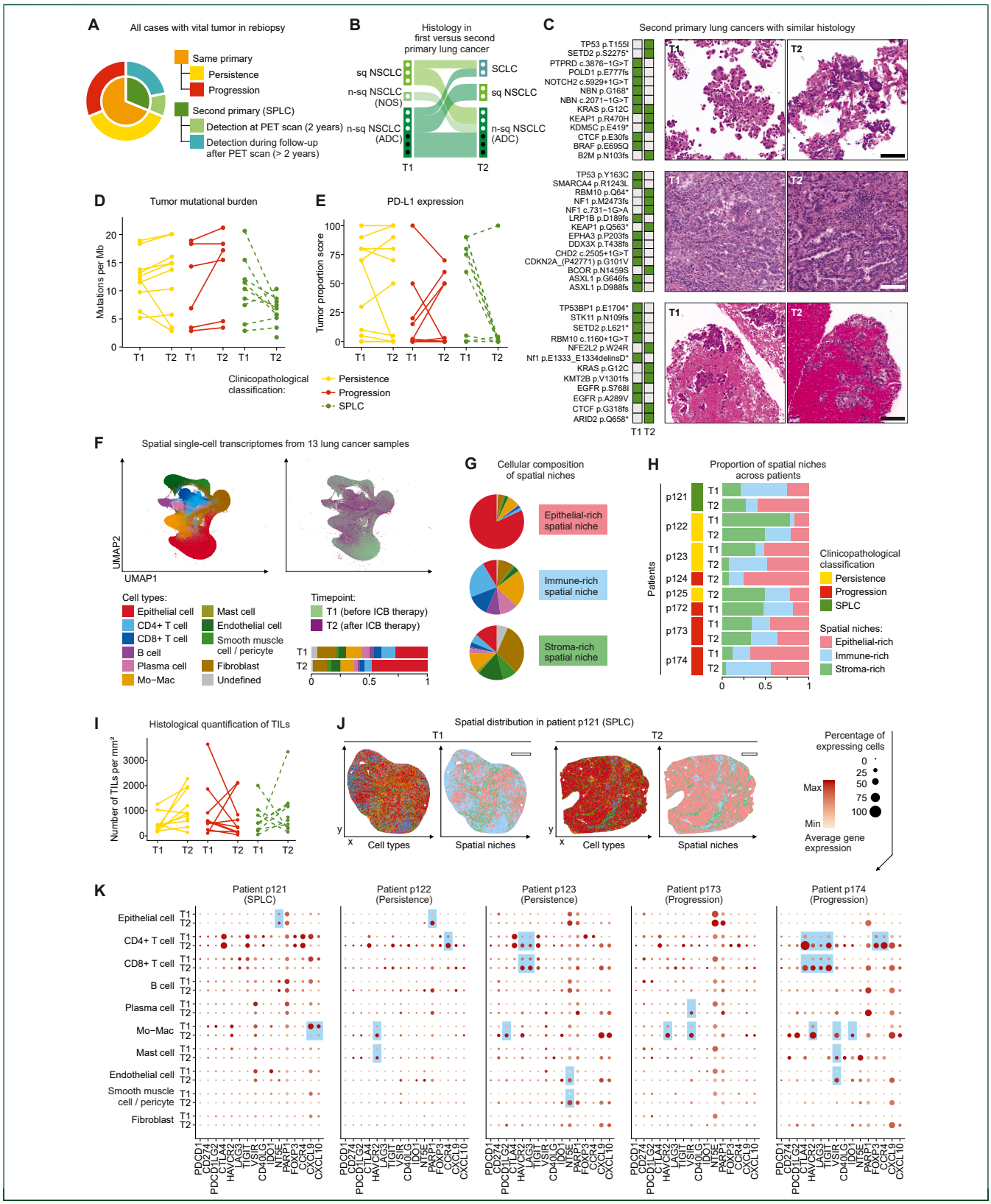


Figure 4. Molecular and pathological classification and spatial gene expression analysis of lung cancers before (T1) and after (T2) ICB. (A) Following ICB treatment, biopsies ($n = 32$) comprised the same primary tumors, categorized as persistent at the (≥2-year) PET/CT or progressive during extended follow-up, and second primary lung cancers (SPLCs). (B) Among patients with SPLCs ($n = 10$), no consistent histological pattern was observed, except for *de novo* SCLC, absent in initial primaries. (C) Three cases shared the same histological subtype (adenocarcinoma) but harbored a distinct mutational profile, leading to correct classification as SPLCs rather than persistent/progressive primaries (scale bar indicates 100 μm). (D) TMB showed a slight, non-significant increase in same primaries, whereas SPLCs had lower TMB than corresponding primaries [persistence (T1 versus T2): 12.33 ± 4.44 versus 14.34 ± 6.37, $P = 0.96$ (paired *t*-test), progression (T1 versus T2): 10.61 ± 7.32 versus 16.34 ± 7.50, $P = 0.16$ (paired *t*-test), SPLC (T1 versus T2): 10.32 ± 5.52 versus 6.88 ± 2.06, $P = 0.10$ (unpaired *t*-test)]. (E) PD-L1 tumor proportion score (TPS) was heterogeneous in same primaries but frequently lower in SPLCs diagnosed during or after ICB therapy [persistence (T1 versus T2): 70 ± 39.6 versus 50 ±

rather than a prospectively definable phenotype in the absence of molecular guidance.

Radiological depth of response and early tumor shrinkage have been identified as potential surrogate markers of durable benefit in melanoma and lung cancer, two malignancies linked by biological parallels including exogenous carcinogenic exposure and susceptibility to ICB.[38-41] In line with this, response rates exceed 80% among long-term responders with NSCLC, both in clinical trials[24-26] and this real-world investigation. However, these observations remain exploratory, and to date, no structured strategy exists to translate treatment response into treatment duration. Most research has focused on predefined treatment exposure and its association with clinical outcomes, rather than on response-adapted approaches. A recent meta-analysis demonstrated comparable survival with fixed 2-year ICB treatment versus indefinite ICB across tumor types and patient subgroups, suggesting that treatment discontinuation may represent an overall safe, patient-centered, and economically sustainable option.[42]

Yet, many patients progressing after completing 2 years of ICB in registrational trials highlight the clinical dilemma of identifying those with minimal residual disease (MRD) who may require extended or intensified therapy.[24-26] MRD, assessable via circulating tumor DNA (ctDNA), may serve as a valuable tool to individualize treatment duration in ICB long-term responders. In resectable lung cancer, ctDNA predicts pathological response and correlates with outcomes after neoadjuvant chemoimmunotherapy,[43,44] and has more recently emerged as a promising biomarker in metastatic disease.[45,46] However, due to limited specificity and lack of assay standardization, ctDNA monitoring is not yet ready for routine clinical use and imaging-based strategies have gained increasing relevance for response-adapted treatment approaches. PET/CT, an established and guideline-endorsed staging tool[33,47,48] may help distinguish non-viable remnants from active disease, particularly in a setting where complete responses are rare. In this regard, our PET/CT-based approach, combined with LAT for OPD, may help prevent immune escape in otherwise controlled but not fully eradicated disease. In this context, viewing oligo-persistence and oligo-progression as two sides of the same coin, the addition of LAT to ICB following oligo-progression has recently been shown to improve survival in the randomized CURB trial.[49]

Current trials aiming to limit ICB administration in NSCLC are exploring either time-restricted or dose-restricted strategies, but do not incorporate MRD assessment.[50,51] Based on our findings, a prospective randomized non-inferiority trial is currently being prepared within the nNGM network. This study (PENELOPE: PET-guided treatment in lung cancer long-term responders to checkpoint inhibitors) will compare the described PET/CT-based approach against standard-of-care treatment, with OS as the primary endpoint.

Beyond the potential economic impact on health care systems, individual toxicity represents a major yet widely underrecognized issue, particularly when delayed or chronic, affecting up to 40% of patients.[52] Although late toxicities have often been regarded as clinically less relevant due to their predominantly low-grade and smoldering nature, our findings challenge this perception. In our control group, one-third of patients discontinued treatment during extended follow-up due to irAEs, compared with only 4% in cohort A, and one-third of these toxicities were grade $\geq$3. This underscores that clinically meaningful late toxicity is not uncommon in long-term responders and may substantially affect general health and quality of life. Of particular concern is the potential for late-onset cardiovascular toxicity, which may significantly contribute to overall morbidity in a population already burdened by cardiovascular comorbidities.[53,54] In clinical routine, the attribution of such events to prior immunotherapy remains challenging. To address this, the incidence of chronic and delayed irAEs has been defined as a key secondary endpoint in the upcoming PENELOPE trial.

Furthermore, our findings highlight the importance of rebiopsy and comprehensive molecular profiling to distinguish early-stage SPLC from true progression of stage IV disease. Although the clinical consequence in both scenarios should be the evaluation of LAT, the psychological difference between facing progression of a controlled metastatic disease and being diagnosed with a potentially curable second primary cancer should not be underestimated. Patients may perceive the latter not as a recurrence, but rather as a new, isolated and actionable event, potentially associated with hope and closure rather than chronic uncertainty.[55] Whereas SPLCs have been reported after treatment of non-metastatic lung cancer with an annual incidence of 1%-2%,[56] this phenomenon is relatively new in stage IV disease and likely remains

44.3, $P = 0.08$ (paired *t*-test), progression (T1 versus T2): 2 $\pm$ 32.6 versus 1.5 $\pm$ 30.0, $P = 0.66$ (paired *t*-test), SPLC (T1 versus T2): 67.5 $\pm$ 42.1 versus 0 $\pm$ 33.1, $P = 0.046$ (unpaired *t*-test)]. (F) Two-dimensional UMAP of 843 443 single cells from 13 tissue samples, including five paired pre- and post-ICB biopsies, demonstrates cluster-wise representation of major tumor-microenvironment cell types. (G) On the basis of spatial proximity of cells, three niches, epithelial-, immune-, and stroma-rich, were identified, (H) and their distribution was quantified across patients before and after ICB. (I) Semi-automated histological quantification of tumor-infiltrating lymphocytes (TILs) per mm^2 in persistent, progressive, and secondary primaries revealed dynamic changes pre- and post-ICB [persistence (T1 versus T2): 378 $\pm$ 371 versus 895 $\pm$ 697, $P = 0.03$ (paired *t*-test), progression (T1 versus T2): 563 $\pm$ 1079 versus 340 $\pm$ 787, $P = 0.59$ (paired *t*-test), SPLC (T1 versus T2): 506 $\pm$ 606 versus 681 $\pm$ 931, $P = 0.36$ (unpaired *t*-test)]. (J) Representative spatial maps of patient p121 illustrate differences in cell-type composition and niche distribution in an SPLC after ICB. (K) The SPLC in patient p121 was characterized by lower expression of proinflammatory cytokines CXCL9 and CXCL10 in monocyte-derived macrophages (Mo-Macs). In contrast, persistent or progressive primary tumors exhibited varying patterns of alternative immune checkpoint upregulation following ICB. Specifically, in patient p122, HAVCR2 (TIM-3) was upregulated in Mo-Macs and mast cells, PARP1 in tumor epithelial cells, and CCR4 in CD4+ T cells. In patient p123, upregulation was observed for HAVCR2 and LAG3 in T cells, PDCD1LG2 (PD-L2) in Mo-Macs, and NT5E (CD73) in endothelial and smooth muscle cells/pericytes. Patient p173 showed increased expression of VSIR (VISTA) in plasma cells and Mo-Macs, and HAVCR2 in Mo-Macs. In patient p174, multiple alternative checkpoints were upregulated, including VSIR across various cell types; CTLA4, HAVCR2, LAG3, and TIGIT in T cells; HAVCR2 and IDO1 in Mo-Macs, and NT5E in mast cells.
ADC, antibody-drug conjugates; ICB, immune checkpoint blockade; NOS, not otherwise specified; non-sq, non-squamous; NSCLC, non-small-cell lung cancer; PET, positron emission tomography; SCLC, small-cell lung cancer; sq, squamous.

underrecognized. Consequent re-biopsies more than doubled SPLC detection in cohort A, highlighting the value of systematic surveillance for early diagnosis and providing a plausible explanation for the superior survival in this cohort.

In addition, re-biopsy of tumor lesions following ICB treatment provides a unique opportunity to study resistance mechanisms in long-term responders, a context previously underexplored. In general, various patterns of resistance to ICB have been described, including intrinsic and extrinsic mechanisms.[57] Acknowledging the highly selected nature of the translational subgroup, our findings nonetheless suggest distinct patterns of resistance that align with clinical trajectories. ICB rapidly restores T-cell effector function but does not permanently reprogram exhausted T cells, thus limiting additional immunological gains beyond the initial response. Consequently, the elimination of residual cancer cells is unlikely to occur during extended treatment.[58,59] Acquired resistance appeared extrinsically driven, with persistent and progressive tumors exhibiting largely overlapping mutational profiles and only a modest increase in TMB. Resistance did not arise through late-acquired drivers but rather reflects plastic transformation of the TME with upregulation of alternative checkpoints and preserved lymphocyte infiltration within a dysfunctional proinflammatory milieu.[60,61] Persistent and progressive tumors may therefore represent different positions along a shared continuum of immune control. By contrast, SPLCs following ICB treatment displayed features of intrinsic resistance, characterized by low TMB and PD-L1 expression, both well-established markers of primary resistance.[62] Applying LAT to all detectable sites with active cancer to bypass intrinsic or acquired resistance may prevent the clinical manifestation of widespread escape, thereby contributing to the observed survival benefit in cohort A. Although evidence from consolidative LAT in induced oligo-residual disease under ICB has been inconsistent,[63,64] these studies were carried out early during systemic therapy, when resistance biology may be less pronounced, potentially attenuating the effect of LAT.

Despite the considerable scientific value of structured re-biopsies after ICB treatment, both PET/CT and invasive tissue sampling come with important limitations and potential pitfalls. Single-timepoint PET/CT is prone to biologically driven false-positive uptake, particularly in lymph nodes, even when applying standardized uptake value-based criteria, which may trigger unnecessary diagnostic procedures. Moreover, periprocedural risks associated with biopsy are especially relevant in this comorbid population, with real-world data from lung cancer screening programs demonstrating complication rates of 16%-20%, largely attributable to older age and cardiopulmonary comorbidities.[65] These considerations underline the need for rigorous imaging standardization, careful target selection, and optimized diagnostic pathways.

Given its retrospective design, this study carries methodological limitations that should be acknowledged when interpreting the findings. Firstly, the non-randomized cohort assignment entails a risk of selection bias, as PET/CT use, specific PET/CT prescription policies, and discontinuation decisions were left to local investigators. However, all of these factors were addressed in multiple sensitivity analyses, which consistently confirmed the robustness of our findings. Secondly, metabolic response and biopsy indications were not centrally reviewed, and the interpretation of CMR was not standardized. Thirdly, tissue analyses were limited to a subset of patients with available archival material and therefore remain exploratory. Fourthly, potential procedure-related complications associated with re-biopsies were not systematically captured, precluding a comprehensive risk—benefit assessment; this will be predefined as a secondary endpoint in the prospective PENELOPE trial. Finally, documentation of chronic irAEs and second primary malignancies was based on structured but non-predefined follow-up procedures, introducing a possibility of reporting bias.

Conclusion

A PET/CT-guided discontinuation strategy maintains outcomes despite shorter treatment and may identify high-risk patients through systematic re-biopsies. Including a large real-world cohort, it provides the rationale for the prospective PENELOPE trial, which, if successful, holds the potential to reduce both individual toxicity and health care-related costs.

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DATA SHARING

Individual, de-identified participant data and data dictionary can be made available upon reasonable request. Requests can be made to nikolaj.frost@charite.de. Spatial transcriptomic data and code used for data analysis are available on https://doi.org/10.5281/zenodo.17818852.

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