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Real-world survival outcomes with immune checkpoint inhibitors in large-cell neuroendocrine tumors of lung

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ABSTRACT

Background Little is known regarding the efficacy of immune checkpoint inhibitors (ICI) in patients with advanced large-cell neuroendocrine lung carcinoma (aLCNEC).

Methods 125 consecutive patients with aLCNEC were identified in the electronic databases of 4 participating cancer centers. The patients were divided into group A (patients who received ICI, n=41) and group B (patients who did not receive ICI, n=84). Overall survival since advanced disease diagnosis (OS DX) and OS since ICI initiation (OS ICI) were captured.

Results With a median follow-up of 11.8 months (mo) (IQR 7.5–17.9) and 6.0mo (IQR 3.1–10.9), 66% and 76% of patients died in groups A and B, respectively. Median OS DX was 12.4mo (95% CI 10.7 to 23.4) and 6.0mo (95% CI 4.7 to 9.4) in groups A and B, respectively (log-rank test, p=0.02). For ICI administration, HR for OS DX was 0.59 (95% CI 0.38 to 0.93, p=0.02—unadjusted), and 0.58 (95% CI 0.34 to 0.98, p=0.04—adjusted for age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), presence of liver metastases and chemotherapy administration). In a propensity score matching analysis (n=74; 37 patients in each group matched for age and ECOG PS), median OS DX was 12.5 mo (95% CI 10.6 to 25.2) and 8.4 mo (95% CI 5.4 to 16.9) in matched groups A and B, respectively (log-rank test, p=0.046). OS ICI for patients receiving ICI as monotherapy (n=36) was 11.0 mo (95% CI 6.1 to 19.4).

Conclusions With the limitations of retrospective design and small sample size, the results of this real-world cohort analysis suggest a positive impact of ICI on OS in aLCNEC.

BACKGROUND

Large-cell neuroendocrine carcinoma of lung (LCNEC) is a rare malignancy (<3% of all lung tumors) characterized by aggressive behavior and high recurrence rate.[1–3] According to 2015 WHO criteria, LCNEC is composed of large cells with neuroendocrine differentiation (as demonstrated by typical morphology and immunoreactivity for chromogranin, synaptophysin or CD56), and, typically, a high mitotic rate.[4] In up to 20% of cases, LCNEC demonstrates a mixed histology with an additional non-small cell lung cancer (NSCLC) component.[4] From a molecular perspective, LCNEC can be further classified as SCLC-like subtype (characterized by tumor protein p53 *(TP53)* and Retinoblastoma gene-1 *(RB1)* comutations or loss) or NSCLC-like subtype (characterized by lack of *TP53 +RB1* alterations and presence of mutations in the Kirsten rat sarcoma viral oncogene homolog, serine/threonine kinase 11, and Kelch-like ECH-associated protein 1 genes); LCNEC molecular subtype may affect response to systemic therapy.[5–7]

Systemic approach in advanced-stage LCNEC primarily includes platinum-based chemotherapy, with objective response rate (ORR) in the range of 12%–52%, median progression-free survival (mPFS) of 4.6–6.1 months and median overall survival (OS) of 10.2–11.1 months.[2 8–10] The roles of somatostatin analogs and tyrosine-kinase inhibitors (TKIs) in the management of advanced LCNEC remain limited.[2 8 9]

Anti-programmed cell death-1 (anti-PD-1)/antiprogrammed cell death ligand-1 (anti-PD-L1) immune checkpoint inhibitors (ICI) are well incorporated into treatment algorithms for advanced NSCLC and SCLC—either with or without platinum-based chemotherapy. This is based on the results of numerous randomized clinical trials demonstrating a consistent OS benefit with early incorporation of immunotherapy across histological tumor types.[11–20] The data regarding clinical activity of ICI in advanced LCNEC, while encouraging, is limited to case reports and small retrospective series.[21–31] According to the results of several retrospective analyzes, ICI administration in advanced LCNEC is associated with ORR of 13%–60%, mPFS of 4.2–14.2 months and

median OS of 11.8 months.[29–31] For instance, the non-randomized DART trial assessed the clinical activity of combination nivolumab and ipilimumab in rare tumor types and reported an objective response in two out of three patients with advanced LCNEC.[32] The impact of ICI on OS in advanced LCNEC, however, has not been fully determined. The largest report of ICI in patients with LCNEC from the American National Cancer Database, delivered in abstract form only, included only 37 patients. It did, however, suggest a positive impact of ICI on OS.[33]

Aiming to bridge this gap in the literature, we conducted a retrospective analysis of consecutive patients with advanced LCNEC treated at four tertiary cancer centers. We explored the impact of ICI on OS in this rare lung tumor type, with a keen emphasis on molecular subtype.

MATERIALS AND METHODS

Patient selection and group assignment

Electronic databases of four participating cancer centers (Institute of Oncology, Sheba Medical Center, Tel HaShomer; Davidoff Cancer Center, Rabin Medical Center, Beilinson Campus; Rambam Healthcare Campus (Israel); Lombardi Comprehensive Cancer Center, MedStar Georgetown University Hospital (USA)) were systematically searched for patients diagnosed with LCNEC between 2009 and 2019. Mixed LCNEC and small-cell neuroendocrine tumors (NET) of lung origin as well as mixed LCNEC and non-small-cell lung carcinomas with a predominating LCNEC component were also included. Only advanced-stage tumors (stage IV or stage III disease not amenable to definitive treatment, or recurrent tumors not amenable to definitive treatment) were selected. Cases with Ki-67 <30% were excluded from the analysis given that, in small biopsies, this commonly accepted cut-off is frequently used to separate high-grade LCNEC and SCLC from low-grade NET (typical and atypical carcinoid) in the presence of crush artifact and poor tissue preservation.[4 34–38]

The patients were then divided into group A (patients who received ICI as any treatment line) and group B (patients who did not receive ICI whatsoever). Group A* subcategorized patients receiving ICI administered as monotherapy or in combination with different ICI agents, thereby excluding patients who received combination ICI and chemotherapy. Additionally, patients with an available molecular tumor profile were further classified into SCLC-like subtype (defined by the presence of *TP53/RB1* co-mutations or loss) or NSCLC-like subtype (defined by the lack of *TP53/RB1* alterations).

Study design and assessments

After obtaining institutional ethical review board approval, we retrospectively reviewed patients' charts and hospital electronic medical records, and gathered baseline demographic, clinical, pathological and treatment characteristics. OS since advanced disease diagnosis (OS DX) was captured and compared between groups A and B among the whole cohort (primary endpoint) and between selected subgroups (according to age, Eastern Cooperative Oncology Group performance status (ECOG PS), presence of liver metastases and tumor molecular subtype). A propensity score matching analysis of OS DX was done, and patients in both groups were matched for age and ECOG PS. Univariate and multivariate analyzes were then performed to assess the impact of patient baseline characteristics, tumor subtype and treatment characteristics on OS DX. Additionally, OS after ICI initiation (OS ICI) was analyzed in group A* according to the tumor molecular subtype, with an additional univariate analysis exploring the impact of patient baseline characteristics, tumor subtype and treatment characteristics.

OS DX was defined as the time from advanced disease diagnosis until death or censored at last follow-up. OS ICI was calculated from the time of ICI initiation until death or censored at last follow-up. Duration of follow-up was calculated from the time of advanced disease diagnosis until last follow-up or censored at death. The cut-off date for data collection was January 13 2020.

Statistical analysis

The sample size was determined by the available patients meeting the inclusion criteria. We conducted the statistical analysis using R Core Team software (R Foundation for Statistical Computing, Vienna, Austria), version 2019.[39] Categorical variables were presented by numbers and percentiles. Continuous variables were reported by medians and ranges. Categorical variables were compared using the χ^2 method or Fisher's exact test, while continuous variables were compared using either a t-test or Mann-Whitney-Wilcoxon test. OS was assessed by the Kaplan-Meier method, with the log-rank test for comparison between groups. The propensity score matching analysis matching patients in the two compared groups for age and ECOG PS was performed with a caliper of 0.5, a 1:1 matching (ICI administration vs no ICI administration), and an AUC (area under the curve) of 0.67. Cox proportional hazards univariable models including prespecified covariates were constructed. Covariates for the multivariate Cox regression model were selected from the statistically significant covariates found in the aforementioned univariate model. P values less than 0.05 were considered statistically significant. No correction for multiple comparisons was performed.

RESULTS

Patient and tumor characteristics

One hundred eighty-four consecutive patients with histologically confirmed LCNEC diagnosed between 2009 and 2019 were identified from the four participating cancer centers. Forty-nine patients with early-stage disease were excluded from the analysis, and an additional ten cases with Ki-67 <30% were excluded as well. The selected cohort thus comprised 125 patients (Thoracic Oncology Service, Institute of Oncology, Sheba Medical Center, Tel

HaShomer, n=53; Davidoff Cancer Center, Rabin Medical Center, Beilinson Campus, n=47; Thoracic Cancer Service, Rambam Healthcare Campus, n=14; Lombardi Comprehensive Cancer Center, MedStar Georgetown University Hospital, n=11; online supplemental figure S1).

Of the selected 125 patients, 41 were treated with ICI (group A), and 84 did not receive ICI (group B). Baseline demographic, clinical and pathological characteristics for these 125 included are displayed in table 1. This cohort mainly comprised smokers (84%); the majority were males (62%). Patients with ECOG PS 2–4 at the time of advanced disease diagnosis constituted 26% of the cohort; brain metastases were present in 32%, and liver metastasis in 34% of the patients. Patients in group A demonstrated a younger median age of 63 years (IQR 58–68) compared with group B median age of 67.5 years (IQR 62–75) (p=0.003). Group A included more patients with ECOG PS 0 or 1 (75%) compared with group B (44%) (p=0.02).

Given these differences in baseline characteristics, we performed a propensity score matching analysis to account for age and ECOG PS. The matched cohort (n=74) included 37 patients in each group with a median age of 64 years for both groups (IQR 59–68 and 59–69 in matched groups A and B, respectively) (p=0.79); the proportion of matched patients with ECOG PS 0 or 1 yielded 84% and 78% in matched groups A and B, respectively (p=0.77), while the percentage of matched patients with ECOG PS 2–4 was 16% and 22% in matched groups A and B, respectively (p=0.77). No other significant differences in baseline patient and tumor characteristics between the matched groups were observed (online supplemental table S1).

Use of molecular tumor testing was generally limited. Comprehensive genomic profiling was complete for only 16 patients (39%) and 6 patients (7%) in groups A and B, respectively. PD-L1 expression was assessed in 21 patients (51%) and 14 patients (17%) in groups A and B, respectively. Tumor mutation burden was available in seven patients (17%) and one patient (1%) in groups A and B, respectively. Finally, microsatellite instability was calculated in eight patients (19%) in group A only (table 1).

Group A* comprised 36 patients. This group's baseline characteristics according to tumor molecular subtype are presented in online supplemental table S2. Since the molecular testing was likewise limited (39% of patients in group A*, n=14), tumors with NSCLC-like molecular subtype (n=9) were compared with all others (n=27, including tumors with SCLC-like subtype (n=5) and tumors with unknown molecular subtype (n=22)). In group A*, NSCLC-like tumors were more likely to have a mixed histology (p=0.03).

Treatment characteristics

ICI regimens used in group A included nivolumab (n=19, 46% of patients in group A), pembrolizumab (n=4, 10%), atezolizumab (n=6, 15%), durvalumab (n=3, 7%), nivolumab/ipilimumab (n=4, 10%), platinum/pemetrexed/pembrolizumab (n=3, 7%) and platinum/etoposide/atezolizumab (n=2, 5%).

Significantly more patients in group A (95%) compared with group B (74%) received chemotherapy (p=0.01) (table 1). The proportion of patients receiving SCLC-based chemotherapy regimens (eg, cisplatin/etoposide and carboplatin/etoposide) was numerically similar (73% and 61% in groups A and B, respectively) (p=0.40). Thirty-six percent of patients in group A and 20% of patients in group B received NSCLC-based chemotherapy regimens (p=0.11); such NSCLC-based regimens included platinum/pemetrexed (n=9), platinum/paclitaxel (n=6), platinum/pemetrexed/bevacizumab (n=4), platinum/vinorelbine (n=4), pemetrexed (n=3), paclitaxel (n=2), docetaxel (n=2), vinorelbine (n=2), platinum/docetaxel (n=1), gemcitabine (n=1), gemcitabine/paclitaxel (n=1), and capecitabine/temozolomide (n=1). Three patients in group B received somatostatin analogs. Two patients in group B and one patient in group A received epidermal growth factor receptor (EGFR) TKIs on diagnosis of an activating mutation in the *EGFR* gene (exon 19 del); two additional patients in group A received anaplastic lymphoma kinaseTKIs, though confirmatory comprehensive tumor molecular testing did not confirm the presence of a targetable abnormality, later halting such treatment. Overall, patients in group A received more lines of systemic treatment (p<0.001).

In the matched cohort (n=74), no significant differences between groups were observed in terms of chemotherapy administration or chemotherapy regimens (online supplemental table S1).

Treatment characteristics of patients in group A* are presented in the online supplemental table S2. Systemic treatments were similar between patients with NSCLC-like molecular tumor subtype and the rest of the group. Most patients received nivolumab, pembrolizumab or atezolizumab as second-line treatment.

OS since advanced disease diagnosis

After a median follow-up period of 11.8 months (IQR 7.5–17.9) for group A and 6.0 months (IQR 3.1–10.9) for group B, (p<0.001 for the comparison), 27 (66%) patients died in group A while 64 (76%) patients died in group B. Median OS DX was 12.4 months (95% CI 10.7 to 23.4) in group A and 6.0 months (95% CI 4.7 to 9.4) in group B (p=0.02) (figure 1A). In group A, projected 1-year and 2-year survival rates since advanced disease diagnosis were 55% and 25%, respectively (figure 1A). In group B, projected 1-year and 2-year survival rates since advanced disease diagnosis were 32% and 18%, respectively (figure 1A).

In the matched cohort (n=74), median follow-up comprised 12.0 months (IQR 6.5–19.9) for matched group A and 6.1 months (IQR 4.4–10.1) for matched group B, (p=0.004). Twenty-four (65%) patients in matched group A and 26 (70%) patients in matched group B died during the study period. Median OS DX was 12.5 months (95% CI 10.6 to 25.2) in matched group

Table 1 Baseline clinical, pathological and treatment characteristics of patients with advanced LCNEC divided according to exposure to ICI

	Pts treated with ICI (group A, n=41)	Pts not treated with ICI (group B, n=84)	P value	All pts (n=125)
Age, years—median (IQR)	63 (58–68)	67 (62–75)	**0.003**	66 (61–73)
Sex, n (%)			1.00	
Female	16 (39)	32 (38)		48 (38)
Male	25 (61)	52 (62)		77 (62)
Smoking history, n (%)			1.00	
Current/past smoker	36 (88)	69 (82)		105 (84)
Never smoker	5 (12)	11 (13)		16 (13)
NA	0 (0)	4 (5)		4 (3)
Histological subtype, n (%)			0.12	
LCNEC	33 (80)	73 (87)		106 (85)
Mixed LCNEC+SCLC	6 (15)	11 (13)		17 (14)
Mixed LCNEC+NSCLC	2 (5)	0 (0)		2 (1)
Stage, n (%)*			0.77	
I/II	4 (10)	11 (13)		15 (12)
III/IV	37 (90)	71 (85)		108 (87)
NA	0 (0)	2 (2)		2 (1)
ECOG PS, n (%)			**0.02**	
0/1	31 (75)	37 (44)		68 (54)
2/3/4	6 (15)	26 (31)		32 (26)
NA	4 (10)	21 (25)		25 (20)
Brain metastases, n (%)			0.97	
Yes	14 (34)	26 (31)		40 (32)
No	27 (66)	46 (55)		73 (58)
NA	0 (0)	12 (14)		12 (10)
Liver metastases, n (%)			0.80	
Yes	15 (37)	27 (32)		42 (34)
No	26 (63)	56 (67)		82 (65)
NA	0 (0)	1 (1)		1 (1)
Ki-67, %—median (IQR)†	70 (60-80)	70 (50-80)	0.39	70 (50-80)
Molecular subtype			NA	
SCLC-like	6 (15)	1 (1)		7 (6)
NSCLC-like	10 (24)	5 (6)		15 (12)
NA	25 (61)	78 (93)		103 (82)
PD-L1 TPS, n (%)			0.15	
≥50%	3 (7)	0 (0)		3 (2)
1%–49%	2 (5)	4 (5)		6 (5)
<1%	16 (39)	10 (12)		26 (21)
NA	20 (49)	70 (83)		90 (72)
TMB, mut/Mb—median (IQR)‡	14 (10–17)	21 (21)	0.38	14 (10–21)
MSI-high, n (%)§	1 (2)	NA	NA	1 (1)
Treatment details				
Chemotherapy, n (%)	39 (95)	62 (74)	**0.01**	101 (81)
SCLC-based chemotherapy, n (%)¶	30 (73)	51 (61)	0.40	81 (65)

Continued

Table 1 Continued

	Pts treated with ICI (group A, n=41)	Pts not treated with ICI (group B, n=84)	P value	All pts (n=125)
NSCLC-based chemotherapy, n (%)¶	15 (36)	17 (20)	0.11	32 (26)
Somatostatin analogs, n (%)	0 (0)	3 (3)	0.55	3 (2)
Tyrosine kinase inhibitors, n (%)	3 (7)	2 (2)	0.39	5 (4)
Systemic treatment lines, n (%)			**<0.001**	
0	0 (0)	21 (25)		21 (17)
1	5 (12)	47 (56)		52 (42)
2	26 (64)	11 (13)		37 (30)
3	7 (17)	4 (5)		11 (9)
4	1 (2)	1 (1)		2 (1)
5	2 (5)	0 (0)		2 (1)
≥1 systemic treatment lines, n (%)	41 (100)	63 (75)	**0.001**	104 (83)

Statistically significant differences are indicated in bold.
*Stage at initial diagnosis.
†Assessed in 88 patients (group A, n=33; group B, n=55).
‡Assessed in eight pts (group A, n=7; group B, n=1).
§Assessed in eight pts (group A, n=8).
¶14 patients (n=6 and n=8%–15% and 10% of groups A and B, respectively) received both SCLC-based and NSCLC-based chemotherapy.
ECOG PS, Eastern Cooperative Oncology Group performance status score; ICI, immune check point inhibitors; LCNEC, large-cell neuroendocrine tumors of lung; MSI, microsatellite instability; mut/Mb, mutations per megabase; NA, not available/not applicable; NSCLC, non-small-cell lung cancer; PD-L1, programmed-death ligand 1; pts, patients; SCLC, small-cell lung cancer; TMB, tumor mutation burden; TPS, Tumor Proportion Score.

A and 8.4 months (95% CI 5.4 to 16.9) in matched group B (p=0.046) (figure 1B). In matched group A, projected 1-year and 2-year survival rates since advanced disease diagnosis were 57% and 27%, respectively (figure 1B). For matched group B, projected 1-year and 2-year survival rates since advanced disease diagnosis were 33% and 19%, respectively (figure 1B).

Univariate and multivariate analysis of OS DX

In the univariate analysis, age (p=0.02), ECOG PS on diagnosis of advanced disease (p<0.001), presence of liver metastases (p=0.005), chemotherapy administration (p<0.001) and ICI administration (p=0.02) all demonstrated a significant correlation with OS DX, whereas sex, smoking status, molecular subtype, stage at diagnosis and presence of brain metastases did not (p>0.05) (table 2).

ICI administration (p=0.04), chemotherapy administration (p=0.002), ECOG-PS on diagnosis of advanced disease (p=0.002) and presence of liver metastasis (p=0.03) remained statistically associated with OS DX in a multivariate Cox regression analysis model that incorporated all factors found to significantly correlate with OS DX in univariate analysis (table 2).

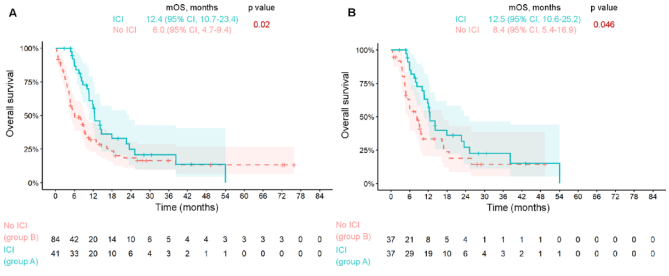

Figure 1 OS of patients with advanced LCNEC according to ICI exposure in the entire cohort (A, n=125), and in the cohort matched for age and ECOG PS (B, n-74): group A—patients who received ICI; group B—patients who did not receive ICI. ECOG PS, Eastern Cooperative Oncology Group performance status score; ICI, immune check point inhibitors; LCNEC, large-cell neuroendocrine tumors of lung; mOS, median overall survival.

OS DX in selected subgroups

We analyzed the effect of ICI exposure on OS DX in several patient subgroups (figure 2). ICI administration positively affected OS DX in elderly (≥65 years old) patients (p=0.03) and patients without liver metastases (p=0.05). A trend toward longer OS DX with ICI exposure was seen in patients with ECOG PS 0 or 1 (p=0.052). In smaller subgroups of patients younger than 65 years (p=0.45), patients with liver metastases (p=0.09), and patients with ECOG PS 2–4 (p=0.2), there was no statistically significant OS benefit seen with ICI administration. Additionally, the smaller subgroup of patients with NSCLC-like tumors did not seem to derive OS benefit from ICI administration (p=0.63) as opposed to the remainder of the cohort comprizing patients with SCLC-like or unknown molecular subtype tumors (p=0.02) (figure 2).

Table 2 Univariate and multivariate COX regression analyzes of overall survival since diagnosis of advanced disease in patients with advanced LCNEC

	Univariate analysis		Multivariate analysis	
Parameters	HR (95% CI)	P value	HR (95% CI)	P value
ICI: yes versus no	0.59 (0.38 to 0.93)	**0.02**	0.58 (0.34 to 0.98)	**0.04**
Chemotherapy: yes versus no	0.33 (0.20 to 0.52)	**<0.001**	0.41 (0.23 to 0.73)	**0.002**
Age	1.15 (1.02 to 1.29)	**0.02**	1.00 (0.97 to 1.03)	0.89
Sex: male versus female	1.23 (0.81 to 1.88)	0.34		
Smoking: yes versus no	1.00 (0.55 to 1.81)	1.00		
Stage at DX:I/II vs III/IV	1.56 (0.86 to 2.81)	0.15		
ECOG PS:2–4 vs 0/1	2.66 (1.65 to 4.31)	**<0.001**	2.3 (1.37 to 3.84)	**0.002**
Brain metastases: yes versus no	1.40 (0.89 to 2.20)	0.15		
Liver metastases: yes versus no	1.83 (1.19 to 2.80)	**0.005**	1.70 (1.06 to 2.74)	**0.03**
Molecular subtype: NSCLC-like *vs* others	0.56 (0.28 to 1.11)	0.10		

Statistically significant differences are indicated in bold.
DX, diagnosis; ECOG PS, Eastern Cooperative Oncology Group performance status score; ICI, immune check-point inhibitors; LCNEC, large-cell neuroendocrine tumors of lung; NSCLC, non-small-cell lung cancer.

OS with ICI

After a median follow-up after ICI initiation in group A* of 6.2 months (IQR 2.7–14.0), 24 (67%) patients died. In group A*, median OS ICI was 11.0 months (95% CI 6.1 to 19.4) (figure 3). The projected 1-year and 2-year survival rates after ICI initiation were 44% and 22%, respectively (figure 3).

Median follow-up after ICI initiation was 6.9 months (IQR 6.1–12.9) in patients with NSCLC-like tumors and 5.7 months (IQR 2.0–14.3) in the remainder of patients in group A* (p=0.25). Six patients (67% of patients with NSCLC-like tumor subtype) and 18 patients (67% of the rest of group A*) died. Median OS ICI was 9.3 months (95% CI 6.1 to not reached (NR)) in patients with NSCLC-like tumors, and 11.0 months (95% CI 3.7 to NR) in the rest of group A* (p=0.65) (online supplemental figure S2).

In the univariate analysis, only ECOG PS at ICI initiation (p=0.02) and presence of liver metastases (p=0.01) demonstrated a significant correlation with OS ICI. Sex, age, smoking status, stage at diagnosis, PD-L1 TPS (≥1% vs <1%), molecular subtype (NSCLC-like vs all others), presence of brain metastases, ICI type (monotherapy with an anti-PD-1/PD-L1 agent vs combination of an anti-PD-1 agent with an anticytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4) agent), administration of chemotherapy, and number of systemic treatment lines prior to ICI administration did not correlate with OS ICI (online supplemental table S3). Multivariate analysis of OS ICI was not performed because of small sample size.

DISCUSSION

To the best of our knowledge, our data set represents the largest series to date reporting on mature outcomes of ICI in advanced-stage LCNEC. It is also one of the first analyzes to assess the impact of ICI administration on OS in advanced LCNEC. We found ICI administration in LCNEC to be associated with longer OS DX in the entire cohort, as well as in the cohort matched for age and ECOG PS. The positive impact of ICI administration on OS of patients with advanced LCNEC was further supported by the results of univariate and multivariate analyzes. Since prospective randomized clinical trials focusing on patients with this rare tumor subtype are challenging to complete, these data provide valuable insight regarding possible therapeutic options for advanced LCNEC.

According to our observations, the median OS was twice as long in patients who received ICI (12.4 months, 95% CI −10.7 to 23.4) compared with those who did not (6.0 months, 95% CI −4.7 to 9.4) (p=0.02). Similar results were detected when matching patients for age and ECOG PS: the median OS was longer in patients who received ICI (12.5 months, 95% CI −10.6 to 25.2) compared with those who did not (8.4 months, 95% CI −5.4 to 16.9) (p=0.046). Projected landmark OS rates were also higher in patients who were exposed to ICI: 1-year survival rates of 55% vs 32%–33%, and 2-year survival rates of 25%–27% vs 18%–19% in patients who did and did not receive ICI, respectively. Our observations correspond to the results of the retrospective analysis of advanced LCNEC patients presented by Komiya and Powell as an ASCO 2020 virtual meeting abstract. Analysis of Komiya and Powell demonstrated that the use of ICI was associated with improved OS (p=0.0168); a landmark OS analysis in the ICI group showed 12-month and 18-month survival rates of 34% and 29%, respectively, compared with 24% and 15% in the non-ICI group.[33]

Importantly, the OS rates in patients not exposed to ICI in our cohort were consistent with historical data retrieved from the majority of large retrospective series

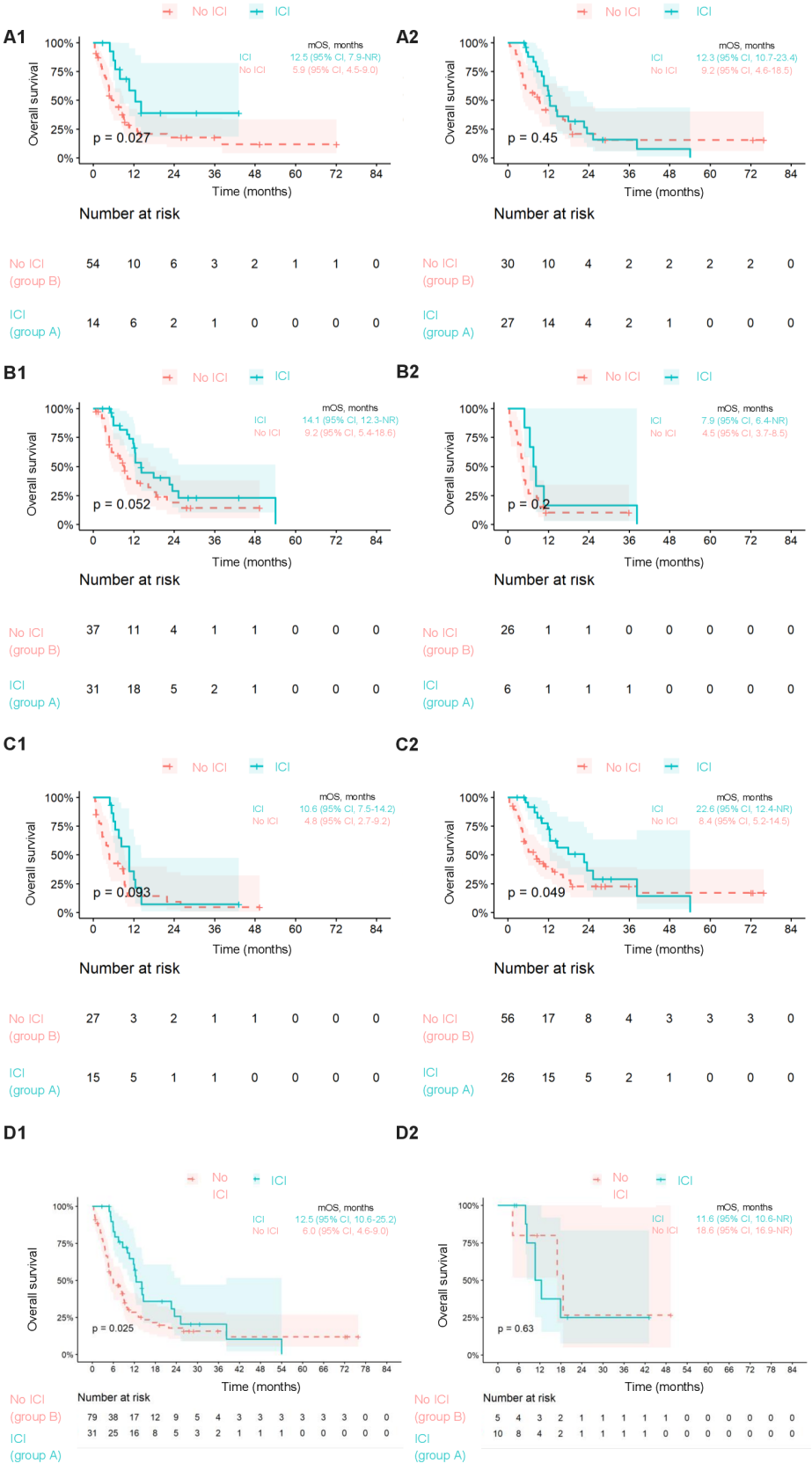

Figure 2 The effect of ICI exposure on OS of patients with advanced LCNEC in selected subgroups according to age (A1 ≥65 years; A2 ≤65 years), ECOG PS (B1-ECOG PS 0/1; B2-ECOG PS 2–4), liver metastases (C1-liver metastases present; C2-liver metastases absent) and molecular subtype (D1-SCLC-like subtype or unknown molecular subtype; D2-NSCLC-like subtype). ECOG PS, Eastern Cooperative Oncology Group performance status score; ICI, immune checkpoint inhibitors; LCNEC, large-cell neuroendocrine tumors of lung; mOS, median overall survival; NR, not reached; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

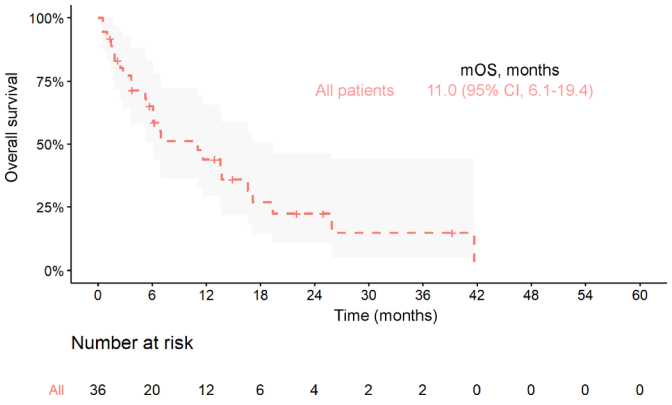

Figure 3 OS with ICI in patients with advanced LCNEC. ICI, immune checkpoint inhibitors; LCNEC, large-cell neuroendocrine tumors of lung; mOS, median overall survival.

and some prospective clinical studies assessing platinum-based chemotherapy in advanced LCNEC.[1 33 40 41] Other prospective studies which evaluated platinum-based chemotherapy in patients with advanced LCNEC reported higher OS rates compared with those we observed, probably reflecting the differences in baseline and treatment characteristics between patients in real-world cohorts and those enrolled in clinical trials.[42] Our cohort notably included patients with poor prognosis, 25% of whom did not receive any systemic treatment.

We acknowledge some differences in baseline and treatment characteristics in favor of patients treated with ICI in our presented cohort. Specifically, these patients were younger, had a better ECOG PS at the time of diagnosis of advanced disease, and were more likely to be treated with systemic therapy. However, the results of propensity score matching analysis along with multivariate analysis accounting for these imbalances confirmed a positive correlation between ICI administration and OS beyond traits including younger age, better ECOG PS, lack of liver metastases and administration of chemotherapy. Our conclusions are further supported by the analysis presented by Komiya and Powell which also demonstrated a significant correlation between ICI administration and OS in advanced LCNEC patients, along with chemotherapy administration, surgery, female sex and absence of liver metastases.[33]

We also confirmed our previous observation regarding outcomes related to IO exposure in advanced LCNEC.[31] In this expanded cohort comprised 36 patients treated with ICI administered as either anti-PD-1/PD-L1 monotherapy or in combination with anti-CTLA 4 therapy, we again observed a median OS of 11.0 months (95% CI 6.1 to 19.4)—similar to the median OS of 11.8 months (95% CI 3.7 to NR) we previously had demonstrated in the cohort of 21 patients. Our data set is the only known report to date detailing mature OS outcomes related to ICI exposure in patients with advanced LCNEC.

Of note, no significant correlation was seen between the level of PD-L1 expression and OS with ICI exposure, although the small number of cases with PD-L1 TPS available for analysis limited the value of this observation. Positive PD-L1 expression in LCNEC represents a rare event, and its prognostic value is controversial.[43–46] It is unknown if PD-L1 TPS may serve as a predictive factor in the context of ICI therapy in advanced LCNEC, and it remains to be seen whether such a relationship exists with either of the two LCNEC molecular subtypes. We hypothesize such an association might be limited to NSCLC-like LCNEC if one extrapolates known data from NSCLC and SCLC.[19 47 48]

One of the major limitations of our study is lack of comprehensive molecular tumor profiling data available for most patients, thereby weakening conclusions regarding the correlation between the established molecular LCNEC subtypes and outcomes related to ICI exposure. Based on data available from our series and another series from Sabari *et al*,[29] the NSCLC-like LCNEC subtype appears to derive less benefit from ICI compared with the SCLC-like molecular subtype. For example, the Sabari *et al* series demonstrated ORR with ICI of 43% (3/7) in SCLC-like LCNEC vs 13% (1/8) in NSCLC-like LCNEC.[29] In our series, patients with the NSCLC-like molecular subtype trended towards a numerically lower median OS with ICI (9.3 months) compared with the remainder of the patients treated with ICI (11.0 months) (p=0.65). Additionally, a numerically lower median OS DX was witnessed in NSCLC-like LCNEC patients exposed to ICI (11.6 months) compared with NSCLC-like LCNEC patients not exposed to ICI (18.6 months) (p=0.63), while the opposite held true in the rest of the cohort (ie, 12.5 months and 6.0 months for patients who received and did not receive ICI, respectively) (p=0.02). Given the overall low molecular testing rate in our cohort, these observations are only hypothesis generating.

Our analysis has additional important limitations, including retrospective nature, lack of central pathological assessment and relatively small sample size of patients treated with ICI.

Prospective phase II clinical trials are underway to assess the efficacy of anti-PD-1/PD-L1 ICI and the combination of anti-PD-1 ICI with anti-CTLA ICI in high-grade neuroendocrine tumors.[49] Some of these allow enrollment of patients with LCNEC (g, NCT03352934, NCT03190213, NCT03136055, NCT03290079 and NCT02834013). Additional questions remaining to be addressed include the correlation between ICI treatment efficacy and the LCNEC molecular subtype, as well as the value of a combined approach implementing concurrent platinum-based chemotherapy with ICI administration.

In conclusion, the results of this real-world data analysis suggest that the use of ICI to be associated with superior OS in advanced LCNEC. The impact of molecular tumor subtype on ICI outcomes requires further evaluation.

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REFERENCES

1 Derks JL, Hendriks LE, Buikhuisen WA, *et al*. Clinical features of large cell neuroendocrine carcinoma: a population-based overview. *Eur Respir J* 2016;47:615–24.
2 Lo Russo G, Pusceddu S, Proto C, *et al*. Treatment of lung large cell neuroendocrine carcinoma. *Tumour Biol* 2016;37:7047–57.
3 Kinoshita T, Yoshida J, Ishii G, *et al*. The differences of biological behavior based on the clinicopathological data between resectable large-cell neuroendocrine carcinoma and small-cell lung carcinoma. *Clin Lung Cancer* 2013;14:535–40.
4 Travis WD, Brambilla E, Nicholson AG, *et al*. The 2015 World Health organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol* 2015;10:1243–60.
5 Rekhtman N, Pietanza MC, Hellmann MD, *et al*. Next-generation sequencing of pulmonary large cell neuroendocrine carcinoma reveals small cell carcinoma-like and non-small cell carcinoma-like subsets. *Clin Cancer Res* 2016;22:3618–29.
6 Derks JL, Leblay N, Thunnissen E, *et al*. Molecular subtypes of pulmonary large-cell neuroendocrine carcinoma predict chemotherapy treatment outcome. *Clin Cancer Res* 2018;24:33–42.
7 George J, Walter V, Peifer M, *et al*. Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. *Nat Commun* 2018;9:1048.
8 Rossi G, Cavazza A, Marchioni A, *et al*. Role of chemotherapy and the receptor tyrosine kinases kit, PDGFRalpha, PDGFRbeta, and Met in large-cell neuroendocrine carcinoma of the lung. *J Clin Oncol* 2005;23:8774–85.
9 Sun J-M, Ahn M-J, Ahn JS, *et al*. Chemotherapy for pulmonary large cell neuroendocrine carcinoma: similar to that for small cell lung cancer or non-small cell lung cancer? *Lung Cancer* 2012;77:365–70.
10 Naidoo J, Santos-Zabala ML, Iyriboz T, *et al*. Large cell neuroendocrine carcinoma of the lung: Clinico-pathologic features, treatment, and outcomes. *Clin Lung Cancer* 2016;17:e121–9.
11 Brahmer J, Reckamp KL, Baas P, *et al*. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373:123–35.
12 Borghaei H, Paz-Ares L, Horn L, *et al*. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627–39.
13 Herbst RS, Baas P, Kim D-W, *et al*. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540–50.
14 Rittmeyer A, Barlesi F, Waterkamp D, *et al*. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (oak): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;389:255–65.
15 Reck M, Rodríguez-Abreu D, Robinson AG, *et al*. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016;375:1823–33.
16 Gandhi L, Rodríguez-Abreu D, Gadgeel S, *et al*. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018;378:2078–92.
17 Paz-Ares L, Luft A, Vicente D, *et al*. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018;379:2040–51.
18 Socinski MA, Jotte RM, Cappuzzo F, *et al*. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 2018;378:2288–301.
19 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;379:2220–9.
20 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;394:1929–39.
21 Mauclet C, Duplaquet F, Pirard L, *et al*. Complete tumor response of a locally advanced lung large-cell neuroendocrine carcinoma after palliative thoracic radiotherapy and immunotherapy with nivolumab. *Lung Cancer* 2019;128:53–6.
22 Wang VE, Urisman A, Albacker L, *et al*. Checkpoint inhibitor is active against large cell neuroendocrine carcinoma with high tumor mutation burden. *J Immunother Cancer* 2017;5:3–6.
23 Chauhan A, Arnold SM, Kolesar J, *et al*. Immune checkpoint inhibitors in large cell neuroendocrine carcinoma: current status. *Oncotarget* 2018;9:14738–40.
24 Daido W, Yamasaki M, Saito N, *et al*. [Effectiveness of Nivolumab in Large-Cell Neuroendocrine Carcinoma of the Lung - A Report of Two Cases]. *Gan To Kagaku Ryoho* 2017;44:59–62.
25 Zhang X, Sun Y, Miao Y, *et al*. Immune Checkpoint Inhibitor Therapy Achieved Complete Response for Drug-Sensitive *EGFR/ALK* Mutation-Negative Metastatic Pulmonary Large-Cell Neuroendocrine Carcinoma with High Tumor Mutation Burden: A Case Report. *Onco Targets Ther* 2020;13:8245–50.
26 Takimoto Sato M, Ikezawa Y, Sato M, *et al*. Large cell neuroendocrine carcinoma of the lung that responded to nivolumab: a case report. *Mol Clin Oncol* 2020;13:43–7.
27 Qin Y, Yu M, Zhou L, *et al*. Durable response to combination radiotherapy and immunotherapy in EP-resistant lung large-cell neuroendocrine carcinoma with *B2M* and *STK11* mutations: a case report. *Immunotherapy* 2020;12:223–7.
28 Oda R, Okuda K, Yamashita Y, *et al*. Long-term survivor of pulmonary combined large cell neuroendocrine carcinoma treated with nivolumab. *Thorac Cancer* 2020;11:2036–9.

29 Sabari JK, Julian RA, Ni A, *et al*. Outcomes of advanced pulmonary large cell neuroendocrine carcinoma stratified by *RB1* loss, SLFN11 expression, and tumor mutational burden. *JCO* 2018;36:e20568.
30 Levra MG, Mazieres J, Valette CA, *et al*. P1.07-012 efficacy of immune checkpoint inhibitors in large cell neuroendocrine lung cancer: results from a French retrospective cohort. *J Thorac Oncol* 2017;12:S702–3.
31 Sherman S, Rotem O, Shochat T, *et al*. Efficacy of immune checkpoint inhibitors (ICPi) in large cell neuroendocrine tumors of lung (LCNEC). *Lung Cancer* 2020;143:40–6.
32 Patel SP, Othus M, Chae YK, *et al*. Swog 1609 (dart): a phase II basket trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors. *JCO* 2019;37:TPS2658.
33 Komiya T, Powell E. Role of immunotherapy in stage IV large cell neuroendocrine carcinoma of the lung. *JCO* 2020;38:9060.
34 Pelosi G, Rindi G, Travis WD, *et al*. Ki-67 antigen in lung neuroendocrine tumors: unraveling a role in clinical practice. *J Thorac Oncol* 2014;9:273–84.
35 Pelosi G, Rodriguez J, Viale G, *et al*. Typical and atypical pulmonary carcinoid tumor overdiagnosed as small-cell carcinoma on biopsy specimens: a major pitfall in the management of lung cancer patients. *Am J Surg Pathol* 2005;29:179–87.
36 Aslan DL, Gulbahce HE, Pambuccian SE, *et al*. Ki-67 immunoreactivity in the differential diagnosis of pulmonary neuroendocrine neoplasms in specimens with extensive crush artifact. *Am J Clin Pathol* 2005;123:874–8.
37 Lin O, Olgac S, Green I, *et al*. Immunohistochemical staining of cytologic smears with MIB-1 helps distinguish low-grade from high-grade neuroendocrine neoplasms. *Am J Clin Pathol* 2003;120:209–16.
38 Helpap B, Köllermann J. Immunohistochemical analysis of the proliferative activity of neuroendocrine tumors from various organs. are there indications for a neuroendocrine tumor-carcinoma sequence? *Virchows Arch* 2001;438:86–91.
39 R Foundation for Statistical Computing. *A language and environment for statistical computing*. Vienna, Austria, 2019.
40 Derks JL, van Suylen RJ, Thunnissen E, *et al*. Chemotherapy for pulmonary large cell neuroendocrine carcinomas: does the regimen matter? *Eur Respir J* 2017;49:1601838.
41 Le Treut J, Sault MC, Lena H, *et al*. Multicentre phase II study of cisplatin-etoposide chemotherapy for advanced large-cell neuroendocrine lung carcinoma: the GFPC 0302 study. *Ann Oncol* 2013;24:1548–52.
42 Niho S, Kenmotsu H, Sekine I, *et al*. Combination chemotherapy with irinotecan and cisplatin for large-cell neuroendocrine carcinoma of the lung: a multicenter phase II study. *J Thorac Oncol* 2013;8:980–4.
43 Hermans BCM, Derks JL, Thunnissen E, *et al*. Prevalence and prognostic value of PD-L1 expression in molecular subtypes of metastatic large cell neuroendocrine carcinoma (LCNEC). *Lung Cancer* 2019;130:179–86.
44 Tsuruoka K, Horinouchi H, Goto Y, *et al*. PD-L1 expression in neuroendocrine tumors of the lung. *Lung Cancer* 2017;108:115–20.
45 Eichhorn F, Harms A, Warth A, *et al*. PD-L1 expression in large cell neuroendocrine carcinoma of the lung. *Lung Cancer* 2018;118:76–82.
46 Fan Y, Ma K, Wang C, *et al*. Prognostic value of PD-L1 and PD-1 expression in pulmonary neuroendocrine tumors. *Onco Targets Ther* 2016;9:6075–82.
47 Garon EB, Rizvi NA, Hui R, *et al*. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372:2018–28.
48 Mok TSK, Wu Y-L, Kudaba I, *et al*. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet* 2019;393:1819–30.
49 Weber MM, Fottner C. Immune checkpoint inhibitors in the treatment of patients with neuroendocrine neoplasia. *Oncol Res Treat* 2018;41:306–12.