ORIGINAL ARTICLE

Salvage Immunotherapy With Pembrolizumab in Patients Hospitalized for Life-Threatening Complications of NSCLC

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ABSTRACT

Introduction: It is not known whether patients with NSCLC who are hospitalized because of cancer-related complications are liable to benefit from salvage immunotherapy.

Methods: This is a multicenter observational study including five centers, which involve all patients with advanced-stage NSCLC exhibiting a level of programmed death-ligand 1 (PD-L1) greater than or equal to 1%, having been hospitalized because of complications attributed to the evolution of the NSCLC, and having started pembrolizumab treatment during their hospitalization because of a risk of clinical deterioration in the short term. The analysis measured overall survival (OS) and the rate of discharge to home at 3 months.

Results: The study included 33 patients, including 28 (85%) with metastatic NSCLC and 27 (82%) under first-line treatment. The main causes of hospitalization were deterioration of the general condition (52%), acute respiratory failure (18%), and an uncontrolled infection owing to the tumor (15%). A total of 20 patients (60%) had a performance status greater than or equal to 2 and 15 (45%) were under oxygen therapy. A total of 29 patients (88%) had a PD-L1 greater than or equal to 50%. Five patients (15%) started pembrolizumab in the intensive care unit. The median OS was 4.3 months (95% confidence interval [CI]: 0.9–not reached), and the 6-month and 1-year OS rates were 41.5% (95% CI: 27.5%–62.6%) and 32.6% (95% CI: 19.0%–55.9%), respectively. The home discharge rate at 3 months was 39% (95% CI: 23%–58%).

Conclusions: Even when initiated in patients hospitalized for a life-threatening clinical deterioration, pembrolizumab seems to prolong the survival of certain patients with high PD-L1 NSCLC. Prospective, controlled data are necessary to confirm these results.

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Introduction

Lung cancer, whose most common histologic type is NSCLC,[1] is the most frequent and deadly cancer worldwide.[2]

This cancer is often diagnosed at an advanced stage, in patients whose general condition has deteriorated. In a prospectively recorded cohort in North Glasgow from 2009 to 2012,[3] 20% of patients harbor, at diagnosis, a performance status (PS) of 3, and 31% of these are receiving active treatment. According to the U.S. National Cancer Database, 24.7% of patients with stage IV NSCLC never receive any anticancer treatment.[4] Several guidelines specify that systemic treatments should not be introduced in patients with PS greater than 2,[5,6] given the lack of any illustrated benefit in this population.[7–9]

Furthermore, advanced cancers are associated with complications other than worsening of the general condition, such as respiratory failure, sepsis, and uncontrolled bleeding. In such patients, systemic treatment is associated with a 2-month mortality rate of 60% and with aggressive end-of-life care.[10,11]

The management of advanced-stage NSCLC without oncogene addiction has undergone a major evolution since the implementation of immunotherapy. Immune checkpoint inhibitors, validated initially for second-line treatment[12,13] after the failure of platin-based chemotherapy, and later as first-line monotherapy in patients with programmed death-ligand 1 (PD-L1) greater than or equal to 50%[14] or in association with chemotherapy regardless of PD-L1 expression level, have a central place in the management of NSCLC.[5] Immunotherapy is better tolerated and safer than chemotherapy, and has been reported to prolong disease control in some patients.[12–14] These results prompted clinicians to expose as many patients as possible to immunotherapy.

It is noteworthy, however, that studies evaluating immunotherapy are carried out on strictly selected patients in good general condition (Eastern Cooperative Oncology Group PS 0–1), whose disease exhibit kinetics compatible with the timing of inclusion in trials.[14–17]

Thus, it is difficult to extrapolate the results of pivotal trials to a real population of patients with more serious deterioration of their general condition or with cancer-related complications that require hospitalization and may be life-threatening (acute respiratory failure, lung infection, hemoptysis, pulmonary embolism, and symptomatic metastasis, notably to the brain).

In real-life cohort studies, nivolumab as second-line and further treatment of NSCLC[18,19] exhibited a lower efficacy in patients with PS 2 than in patients PS 0 to 1, without any increase in adverse effects. Pembrolizumab, as a first-line treatment for patients with PS 2,[20] was associated with an objective response rate of 27% and immunotherapy-related toxicity in 28% of patients.[20] Immunotherapy has never been evaluated, however, in patients with PS greater than 2 or in patients hospitalized for cancer-related complications.

The aim of this study was to investigate the potential benefits of salvage immunotherapy with pembrolizumab started in patients hospitalized for a complication of advanced-stage NSCLC.

Materials and Methods

Study Population

This was a multicenter observational study conducted at five centers, including patients having started pembrolizumab treatment in the inpatient setting. Medical records were identified through the hospital electronic register and were screened for the following inclusion criteria: (1) patients at least 18 years old; (2) a histologically proven stage IIIB, IIIC, or IV NSCLC (TNM eighth edition), pretreated or not; (3) hospitalized for a complication attributed to the evolution of their NSCLC; and (4) first injection of pembrolizumab monotherapy administrated during hospitalization as semiemergency treatment justified by the short-term risk of clinical deterioration.

Short-term cancer-related risk of clinical aggravation was defined as any of the following: (1) the deterioration of the patient's general condition requiring hospitalization; (2) acute respiratory failure; (3) a tumor-related uncontrolled infection (abscessed tumor, obstructive pneumopathy); (4) tumoral bleeding with no possible hemostasis; (5) refractory hypercalcemia; and (6) spinal cord compression. Patients who had received pembrolizumab less than 48 hours before discharge were excluded, as they could be viewed as ambulatory patients at the time treatment began. Finally, to minimize the subjectivity linked to the notion of short-term risk of clinical aggravation, the medical record of each eligible patient was subjected to independent blind reviews by two investigators (Drs. Roborel De Climens and Gauvain). In cases of disagreement, a blind review by a third investigator (Dr. Dhalluin) was performed.

The pembrolizumab injections were administered at 200 mg every 3 weeks until progression, until a total of 35 injection cycles was reached, or until treatment was stopped because of unacceptable toxicity or as per the decision of the referring doctor. The patients received, if necessary, the usual care delivered in the context of cancerology. If necessary, therapeutic limitations were

applied on a case-by-case basis according to the severity of the patient's condition.

Collected Data and Duration of Follow-Up

The data collected were sex, age, PS, age-adjusted Charlson index,[21] histological subtype, cancer stage, the presence of brain metastases, the PD-L1 status, the presence of oncogene addiction, the cause of hospitalization, the department of hospitalization, respiratory support, body mass index, albumin (g/liter), previous corticotherapy of at least 10 mg/day, antibiotic treatments in the 2 months preceding pembrolizumab start, the neutrophil-to-lymphocyte ratio, the necessity of associated radiotherapy, previous lines of treatment, consultation with the palliative care team during hospitalization, and the possibility, if any, of specific active treatment for the complication (e.g., drainage, radiotherapy).

The minimal duration of patient follow-up in the absence of death was 3 months. This duration seemed pertinent to the short-term prognosis in this population.

End Points

The primary end point was overall survival (OS), defined as the time between the first pembrolizumab injection and death from any cause. The secondary end points were the following: (1) the 3-month rate of discharge to home, defined as the proportion of patients who were alive and at home at 3 months; (2) progression-free survival (PFS), defined as the time between the first pembrolizumab injection and disease progression or death from any cause; and (3) the occurrence of toxicity assessed according to Common Terminology Criteria for Adverse Event.

Statistical Analysis

Qualitative data are recorded as numbers and percentages. Estimated proportions are expressed with their 95% confidence intervals (95% CIs). Quantitative data with a normal distribution are described with means and standard deviations; quantitative data with a nonnormal distribution are described with median and range. The Kaplan-Meier method was used to estimate OS and PFS. For the analysis of PFS, the data pertaining to living patients with no progression or to patients lost to follow-up were censored from the time of their last tumor evaluation. For the analysis of OS, the data pertaining to living patients or to patients lost to follow-up were censored from the time of the last contact with the patient. Given the small number of patients (implying a potential lack of statistical power) and to limit inflation of the alpha risk, the study of subgroups of interest was restricted to a graphical approach with the help of swimmer plots instead of statistical tests.

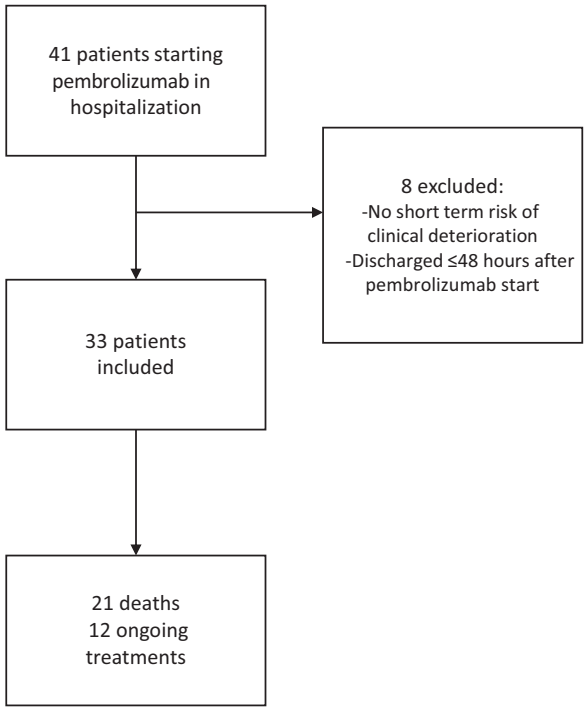

Figure 1. A flowchart of the study.

Ethical Considerations

The study was carried out in agreement with the ethics regulations applicable in France. A statement relating to the computerized processing of data was filed (under reference DEC19-072) with the Data Protection Delegate of the Lille University Hospital Center. Patients were informed that their data could retrospectively be used for research purposes in the absence of their opposition; owing to the retrospective nature of the study, no signed consent was required.

Results

Patients

Between December 2017 and April 2019, a total of 41 patients started pembrolizumab monotherapy under hospitalization in the five participating centers. A review of medical records (requiring a call on the third reviewer in six cases) identified 33 patients who met the eligibility criteria and were included in the analysis (Fig. 1). The mean age was 62 plus or minus 12 years, most were men (76%), and most had a PS greater than or equal to 2 (60%) (Table 1). A total of nine patients (27%) had brain metastases and six patients (24%) had previously received at least one line of treatment. The median age-adjusted Charlson index was 9 (range: 6–15). The histological subtype of cancer was adenocarcinoma for 24 patients (73%), squamous cell carcinoma for three patients (9%), NSCLC not otherwise specified in 3 (9%), sarcomatoid carcinoma in 2 (7%), and large cell carcinoma in 1 (3%).

Table 1. Baseline Characteristics of Patients

Variables	N = 33
Male Sex	25 (76)
Age (mean ± SD)	62 ± 12
PS (ECOG PS)	
0-1	11 (33)
2	11 (33)
3-4	9 (27)
NA	2 (7)
Histological subtype	
Adenocarcinoma	24 (73)
Squamous cell carcinoma	3 (9)
Other	6 (18)
Gene alteration	
None	18 (55)
EGFR	1 (3)
ALK	1 (3)
KRAS	5 (16)
Other	2 (6)
Cancer stage	
IIIB-C	5 (15)
IV	28 (85)
PD-L1, %	
≥90	14 (42)
50-89	15 (46)
1-49	4 (12)
Charlson index (median, range)	9 (6-15)
Complication motivating hospitalization (Main reason)	
Deterioration of general condition	17 (52)
Acute respiratory failure	6 (18)
Uncontrolled infection	5 (15)
Uncontrolled bleeding	3 (9)
Hypercalcemia	1 (3)
Spinal cord compression	1 (3)
Hospital unit	
Conventional care	28 (85)
Intensive care	5 (15)
Respiratory support	
None	18 (55)
Conventional oxygen therapy	9 (27)
High-flow nasal oxygen therapy	5 (15)
Invasive ventilation	1 (3)
Patient known to a palliative care team	3 (9)
Long-term systemic corticotherapy ≥0 mg/day	5 (15)
Antibiotics in the 2 months preceding the beginning of pembrolizumab	20 (60)
Prior systemic treatments	6 (18)
1 single line of treatment	5 (15)
7 lines of treatment	1 (3)
BMI (kg/m^2)	
18-25	12 (36)
25-30	13 (40)
≥30	4 (12)
NA	4 (12)
Albumin (N = 35-45 g/liter), mean ± SD	25.2 ± 7.5
NLR, median (range)	8.3 (0.3-150.5)

Note: Values are given in n (%) unless indicated otherwise.
BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; NA, not applicable; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death-ligand 1; PS, performance status.

The most frequent gene alteration retrieved was *KRAS* in five patients (16%). Two patients harbored common targetable addiction: one had *EGFR* mutation and one had *ALK* rearrangement. None had *ROS1* rearrangement.

Five patients (15%) had long-term systemic corticosteroid therapy greater than or equal to 10 mg/day when starting treatment with pembrolizumab (four for symptomatic metastatic neurologic lesions and one for superior vena cava syndrome). There was no short-term corticosteroid therapy. In the months after the initiation of pembrolizumab, three patients started corticosteroid therapy—none within the first month. Two patients started corticosteroid therapy to treat immune-related adverse events (AEs): grade 2 colitis and grade 3 eosinophilia. One patient received corticosteroid because of carcinomatous lymphangitis.

Survival

Regarding follow-up, the median observation time was 3.7 (range: 0.2–19.5) months in the whole population, and the observation time in event-free patients was 13.4 (range: 3.6–19.5) months. The median OS was 4.3 (95% CI: 0.9–not reached) months, the proportions of patients alive at 3 months, 6 months, and 1 year were 54.5% (95% CI: 39.9%–74.5%), 41.5% (95% CI: 27.5%–62.6%), and 32.6% (95% CI: 19.0%–55.9%), respectively (Fig. 2). A total of nine patients died during initial hospitalization. For patients discharged from hospitalization during the initial hospital stay, the median time between the first pembrolizumab injection and discharge was 7 (range: 2–73) days.

Secondary End Points

A total of 18 patients were able to return home, and six patients were transferred to rehabilitation unit hospitals. The home discharge rate at three months was 39% (95% CI: 23%–58%).

The median PFS was 2.1 (95% CI: 0.8–8.3) months and PFS at 3 months was 45% (95% CI: 31.3%–66.1%). At 6 months and 1 year, the PFS rates were 39% (95% CI: 25.3%–59.9%) and 23.9% (95% CI: 12.5%–45.8%), respectively.

Figure 3 depicts the OS according to various parameters of interest. Of the eight patients still alive 1 year after the start of treatment, four had exhibited a PS of two or more when treatment began (Fig. 3*A*), two had required oxygen support (Fig. 3*B*), and one of these two had been hospitalized in a reanimation unit (Fig. 3*C*). The PD-L1 level was 90% or more in four of these patients, between 50% and 89% in three of them, and between 1% and 49% in one of them (Fig. 3*D*). The distribution of these parameters did not seem to differ from that observed in the whole studied population. The analysis

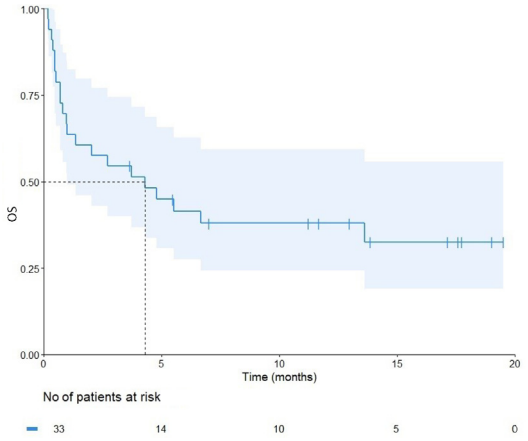

Figure 2. OS (Kaplan-Meier estimation with 95% CI). CI, confidence interval; OS, overall survival.

of albumin, body mass index, neutrophil-to-lymphocyte ratio, and antibiotic treatment in the 2 months before immunotherapy start in the patients still alive after 1-year follow-up did not retrieve substantial differences with the overall population either. None of these long survivors were under corticosteroids when they started immunotherapy.

Four patients (12%) exhibited immunotherapy-linked toxicity (grade 1 dysthyroidism, grade 2 colitis, grade 2 skin rash, grade 3 hypereosinophilia) and two required systemic corticosteroids.

Discussion

The efficacy of immunotherapy has been established in patients with NSCLC with a good general condition. Whether these results can be extrapolated to less carefully selected populations is less clear. In the present retrospective multicenter study of patients hospitalized for a complication of their cancer, we have noted, unsurprisingly, a high short-term mortality rate, with close to 50% mortality in the first 3 months; but we have also noted a prolonged benefit in some patients, with 41.5% survival at 6 months and 32.6% at 1 year. More than a third of the patients having received emergency pembrolizumab therapy were back at home 3 months after the start of treatment. These results suggest a benefit of immunotherapy in some patients hospitalized for a life-threatening complication of cancer.

The patients treated in this study were mostly patients (88%) with PD-L1 greater than or equal to 50%. This is a factor predictive of response to immunotherapy and might explain, on the one hand, the observed results, and on the other hand, the clinicians' choice to try this treatment, which was much less used for patients with a low PD-L1 expression. However, this very low proportion of PD-L1 less than 50% in our study population does not permit any conclusion in this specific subset of patients.

One should note, however, that prognosis was very heterogeneous, with a sharp contrast between a high early mortality rate and prolonged survival for a third of the patients. However, the search for variables explaining this heterogeneity was considerably limited by low statistical power. Yet, the analysis of individual data suggests an unfavorable role of poor general condition and dependence on oxygen support, but no discriminating effect of a high PD-L1 level ($\geq$90%), in contrast to observations made on a less severely affected population.[22] These data, however, do not enable us to isolate real prognostic factors.

This heterogeneity may also certainly be explained by the variability of the clinical picture, with 15% of patients hospitalized in intensive care or and 27% of patients with a PS of 3 or 4 contrasting with 33% with a PS 0 to 1. This high proportion of low PS in hospitalized patients might seem unexpected and is probably explained by an increased risk of symptom underestimation by caregivers in the hospitalized patient compared with outpatients.[23] In addition, deterioration of general condition was not the only reason for hospitalization. Other patients were admitted because of life-threatening complications that are not necessarily associated with poor PS but nevertheless requiring the initiation of specific treatment and urgent supportive care. Despite this high proportion of low PS, the severity of this population remains real and is reflected by the high 3-month mortality rate, the rate of patients requiring oxygen support, or intensive care admission. The severity of the included population was indeed ensured by the double-blind selection of patients on the basis of medical records but allowed a certain heterogeneity in patients. However, this heterogeneity of the included population represents a pragmatic approach as it corresponds to the real clinical situation, in which the question of initiating semiemergency treatment arises.

Only five patients (15%) had long-term systemic corticosteroid therapy greater than or equal to 10 mg/day when starting treatment with pembrolizumab, which can seem low given the severity of the population, with 18% of patients in intensive care. However, here, the prescription of corticosteroids was limited to strict indications (e.g., symptomatic brain metastases) so as not to reduce the effectiveness of immunotherapy. Acute respiratory distress or major oxygen referral were not, in themselves, indications for corticosteroid therapy in the absence of a favorable recommendation.[24,25] As a consequence, this low proportion of patients under corticosteroids does not allow any analysis regarding the impact of systemic steroids on immunotherapy in severe patients, even if we note that none of the long survivors underwent systemic corticosteroid therapy when they started immunotherapy.

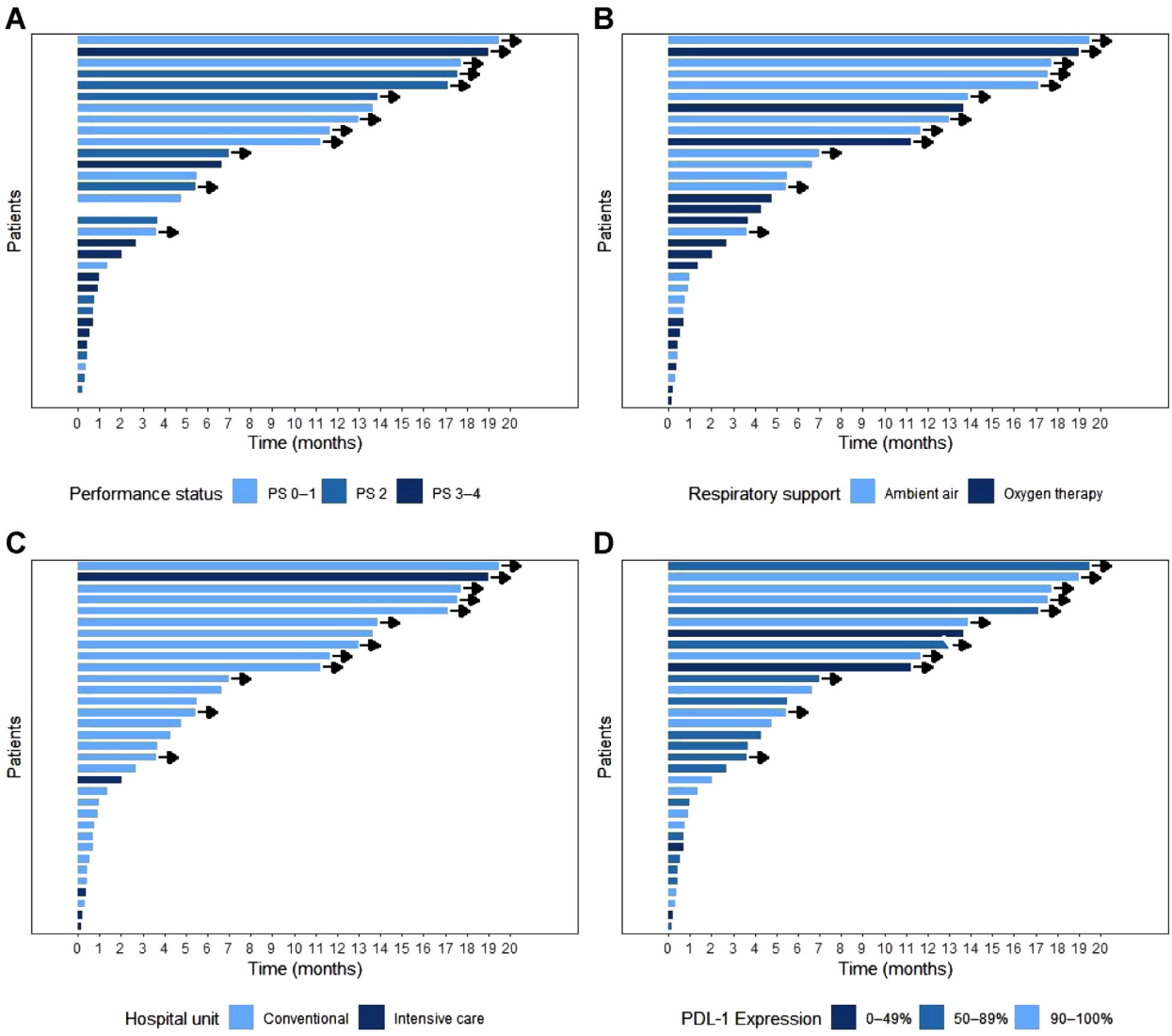

Figure 3. Swimmer plots illustrating the OS of patients according to *(A)* PS, *(B)* whether they required respiratory support, *(C)* the department where they were hospitalized, and *(D)* PD-L1 expression. OS, overall survival; PD-L1, programmed death-ligand 1; PS, performance status.

In this study, only 12% of the patients experienced an immune-related AE. This is low compared with the rates reported in randomized prospective trials.[14] It may be because of the fact that a large number of patients died shortly after the start of treatment, before developing immune complications, which usually seem later. Another explanation might be the retrospective character of data collection, which probably led to underestimating any less serious AEs.

The clinical improvement allowing hospital discharge on the part of the patients might be owing partly to the initiation of supportive care[26] rather than the early efficacy of pembrolizumab. The good tolerance profile of immunotherapy permits its use in deteriorated patients without impacting the efficacy of supportive care undertaken simultaneously, contrary to chemotherapy. It is, thus, possible to start treating the cause of clinical deterioration without hindering the symptomatic treatment of such clinical alteration. This situation is akin to the introduction of targeted therapy in patients with PS 3 or 4 exhibiting oncogene addiction with conserved efficacy in these populations.[27–30]

Thus, the results of this study suggest that starting immunotherapy in patients hospitalized for a complication of a high PD-L1 NSCLC can result in a prolonged benefit and does not seem to constitute unreasonable obstinacy.

To our knowledge, no other study has investigated the effect of immunotherapy specifically started during hospitalization of patients with advanced-stage NSCLC. Studies evaluating nivolumab immunotherapy have evidenced shorter OS in patients with PS 2 as compared

with patients having PS 0 to 1, without an increase in toxicity.[18,19] The Pembrolizumab in Patients With Non-Small Cell Lung Cancer and a Performance Status 2 study[20] reported a median PFS of 4.4 months in PS 2 patients treated with pembrolizumab for NSCLC, but to be included, patients could not have exhibited any clinical deterioration during the 2 weeks preceding treatment, and their life expectancy had to be more than 3 months. This probably explains the difference in PFS observed between this study and ours. Durbin et al.[31] have reported results of a retrospective study of 106 patients with a stage IV solid tumor, including 21 NSCLCs, treated by immunotherapy during hospitalization, but in one out of four patients, immunotherapy had begun during ambulatory care before hospitalization. The authors report 49% mortality during hospitalization or during the month after discharge and 15% survival at 6 months.

The multicenter character of the study and its "real-life–type" design strengthened its external validity and suggest that its results can be readily transposed.

This study has various limitations. First, it is a non-comparative retrospective study with some, albeit few, missing data. To ensure the homogeneity of data collection, this collection was done by a single person for all patients of all centers. The insufficient proportion of low PD-L1 NSCLC in this population prevents drawing conclusions in this particular subgroup. The small number of patients, which limits the statistical power of the study, is caused in part by the lack of recommendations in favor of treating these patients and to fear of unreasonable obstinacy. Another reproach might be that the follow-up period was relatively short, but it seemed acceptable to us in the context of severe clinical situations and it seems to have been pertinent, as it was long enough to discern patients exhibiting prolonged survival. The notion of cancer-linked complication, viewed as entailing a risk of clinical deterioration in the short term, might be considered subjective, and thus, not very reproducible. This is a problem we have tried to master by performing double-blind selection, with a third opinion in case of disagreement. Patients discharged from the hospital within 48 hours of pembrolizumab treatment were excluded from the study so as to avoid the inclusion of "quasi-ambulatory" patients. Recent studies have reported the efficacy of associating chemotherapy with immunotherapy as first-line treatment for NSCLC[15,16,32] and such association has become a standard of care resulting in fewer patients receiving immunotherapy alone. Yet, deteriorated patients and ones with a cancer complication are generally ineligible for chemotherapy. The question of whether to introduce immunotherapy in these patients, thus, remains topical. Furthermore, several prospective studies are currently addressing the question of the efficacy of immunotherapy in patients whose general condition has deteriorated (PS 2 or even PS 3).[33] Our results should prompt investigators to include in these studies patients who are hospitalized for a cancer complication.

In conclusion, this study suggests that the emergency introduction of pembrolizumab in patients hospitalized for a cancer-linked complication, with a risk of short-term clinical deterioration, and with a high expression of PD-L1, can benefit certain patients. Large-scale, controlled studies are necessary to confirm these results and explore the potential benefit in patients with PD-L1 less than 50% given the weak proportion of low PD-L1 in our study, and identify other characteristics of patients likely to benefit from this emergency immunotherapy treatment.

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