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Qualification en ONCOLOGIE MEDICALE

Outcomes in patients treated with taxane regimen after failure of immune checkpoint inhibitors in advanced or metastatic non-small cell lung cancer

Données de survie des patients traités par taxanes après échec de l'immunothérapie dans le CBPNPC avancé ou métastatique

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Né le 20 Juillet 1990 à Angers

Sous la direction de monsieur le Docteur Frédéric BIGOT

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« Survie des patients traités par taxanes après échec de l'immunothérapie dans le CBPNPC avancé ou métastatique »

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List of abbreviations

95% CI	95% confidence interval
ALK	Anaplastic lymphoma kinase
EGFR	Epithelial growth factor receptor
HR	Hazard ratio
ICI	Immune Checkpoint Inhibitor
ICO	« Institut de Cancérologie de l'Ouest »
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
KRAS	Kirsten rat sarcoma virus
LDH	Lactate dehydrogenase
NLR	Neutrophil to lymphocyte ratio
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death 1
PD-L1	Programmed death-Ligand 1
PFS	Progression-free survival
PS	Performans Status
RECIST	Response Evaluation Criteria in Solid Tumors

CONTENTS

Outcomes in patients treated with taxane regimen after failure of immune checkpoint inhibitors in advanced or metastatic non-small cell lung cancer

Keywords: Immune checkpoint inhibitor, taxane chemotherapy, non-small cell lung cancer, survival, palliative care

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ABSTRACT

Introduction: Anti PD-1/PD-L1 immune check point inhibitors (ICI) had dramatically changed the survival of patients with advanced non-small cell lung cancer (NSCLC). After platinum-based chemotherapy and ICI failure, taxane regimen remains the standard of care. Some data have suggested an increase in the activity of chemotherapy received after ICI. Nevertheless, taxane appears to have only modest benefit in pre-treated patients. We aimed to assess survival outcomes with taxane chemotherapies after ICI exposure and to identify prognostic and predictive factors that may influence response to those regimens.

Material and method: In this multicentric retrospective study, we included patients with stage IIIB or higher NSCLC who received subsequently taxane after ICI failure. Primary end points were progression-free survival on taxane (Taxane PFS) and overall survival on taxane (Taxane OS). Secondary end points were Taxane PFS to ICI PFS ratio, to evaluate benefit of subsequent taxane, and identification of clinical data associated with better survival on taxane.

Results: We included 110 patients, mostly men (71.8 %) with a median age of 63. Patients mostly had stage IVB (65.5%) and adenocarcinoma was the predominant histologic subtype (59.1%). Docetaxel was the taxane chosen in 70% of cases. Median Taxane PFS was 3.6 months (2.7-4.8) and Taxane OS was 7.3 months (6.1-10.3). Only 36.4% of patients had a ratio Taxane PFS to ICI PFS greater than 1.3 without clinical difference in this subgroup, except for age (60.2 versus 63.9; p=0,021). A number of ICI cycles at 6 or above was an independent factor associated with better Taxane PFS and OS. Similarly, in multivariate model, performans status at 2 or higher (PS ≥ 2) and a 2g/dL loss of haemoglobin between the start of ICI and taxane initiation were associated with poorer Taxane OS. Only PS ≥ 2 was associated with a poorer Taxane PFS.

Conclusion: Effectiveness of further treatment with taxane was observed only in a limited subgroup of patients. Factors associated with good health condition and a long exposure to ICI appeared to be predictive of better survival on taxanes.

INTRODUCTION

Lung cancer is the second most common cause of cancer in men, after prostate cancer, and the third most common cause of cancer in women, after breast cancer and colorectal cancer [1]. The incidence in France was 46,363 new cases in 2018 and the prognosis remains poor with a 5-year survival rate between 10 and 20%, mainly due to advanced or metastatic diagnosis[1–3]. Platinum-based chemotherapy was until recently the standard of care in first-line treatment of advanced or metastatic non-small cell lung cancers (NSCLC). New therapeutic have emerged through immunotherapy and drugs targeting oncogenic addiction pathways such as EGFR, ALK or ROS-1. Immune checkpoint inhibitors (ICI), specifically monoclonal antibodies targeting the PD-1/PD-L1 axis, have significantly changed the management of many cancers including NSCLC. ICI have been first approved as monotherapy in second-line treatment after failure of first-line platinum-based chemotherapy and have shown superiority over docetaxel in both squamous and non-squamous cell lung cancer [4–7]. More recently, ICI in first-line treatment have shown greater survival outcomes either in combination with platinum-based chemotherapy or as monotherapy in tumours with PD-L1 expression ≥50%, leading to a new standard of care [8–12].

Long-lasting response to ICI have been observed but unfortunately concerns a minority of patients and subsequent chemotherapy are often required [13]. Taxane regimen and in particular docetaxel were initially used as second-line therapy and still represent standard of care for subsequent therapies after ICI and platinum-based chemotherapy failure. Nevertheless, prior to the ICI era, second-line docetaxel showed only modest benefit either in the Tax 317 study or in control arms of Checkmate trials [4,5,14,15]. However, previous exposure to ICI may favourably affect the response to subsequent treatment. This may explain in part the better overall survival observed in ICI phase III trials, which is not always associated with better progression-free survival or better objective response rate (ORR). Some retrospective data suggest an

increase in efficacy of subsequent treatments with a higher ORR for chemotherapy received after ICI [16–18]. Currently, there are no robust studies comparing the benefit of salvage chemotherapy after ICI and platinum-based chemotherapy failure to best supportive care. The therapeutic decision between continuation of oncologic treatments or best supportive care remains challenging and there are no validated predictive factors to help physicians in this choice. The aim of this work was to assess in real life the benefit of subsequent chemotherapy with taxane after failure of ICI. We hypothesised that ICI exposure may favourably affect patient outcomes on taxane. We then attempted to identify factors associated with better survival on taxane that could assist clinicians in their decision-making.

MATERIAL AND METHOD

Study population

We conducted a multicentric retrospective study on patients followed at the Institut de Cancérologie de l'Ouest in Angers and in Saint-Herblain, at the Cholet hospital and at Le Mans hospital. Patients with advanced unresectable or metastatic non-small cell lung carcinoma were included if they had been treated with anti PD-1 or anti PD-L1 immune checkpoint inhibitors (ICI) alone or in combination with chemotherapy, followed by a taxane-based chemotherapy, from the 1st of January 2015 to the 18th of December 2020. Patients receiving first-line ICI monotherapy followed by taxane-based chemotherapy because tumours PD-L1 expression over 50% were excluded. Patients were identified from pharmacy records and data were extracted from hospitals charts. The project has been approved by the Ethics Committee of the University Hospital Centre of Angers. The participating centres were responsible for patient consent, either through institutional approval or no objection basis.

Data collection

Information on biometric data, health conditions via Performans Status (PS), histology and molecular biology of tumours, blood analysis as well as treatment history were collected. Primary endpoints were progression-free survival and overall survival with taxane treatment (respectively Taxane PFS and Taxane OS). Secondary endpoints were survival outcomes according to prior response on ICI and identification of clinical or biological factors associated with better outcomes on taxane treatment. The characteristics studied during ICI treatments were as follows: PFS (ICI PFS), number of cycles of ICI received, overall response rate (ICI ORR), delay between the end of ICI interruption and taxanes treatment initiation. We analysed Taxane PFS to ICI PFS ratio to assess the benefit of subsequent taxane regimen.

Taxane PFS was measured from taxane initiation to progressive disease or death and ICI PFS was measured from initiation of ICI to progressive disease. Taxane OS was defined as the time from taxane initiation to the death for any cause. The Taxane and ICI objective response rate (ORR) were defined respectively as the sum of complete and partial response observed with taxane chemotherapy or ICI regimens. Data concerning progressive disease, stable disease, partial response and complete response were extracted from the medical reports according to RECIST or iRECIST criteria.

Statistical analysis

Quantitative variables were summarised using median, range, interquartile, mean and standard deviation. Categorical and binary variables were summarised using counts and percentages. Patients alive at the cut-off date were censored at that date and patients lost during follow-up were censored on the date of last follow-up. Survival data were summarised using Kaplan Meier method. Regression models were used to quantify the association between studied variables and survival outcomes on taxane: cox regression model for censored data (to estimate hazard ratio (HR), 95% confidence interval (95% CI) and p-value) and logistic regression for binary variables (to estimate odds ratio, 95% CI and p-value). After a first univariate analysis, variables with less than 20% missing data and univariate p-value lower than 0.25 were introduced in a crude complete multivariate model and an automatic stepwise backward selection model was computed to identify the final multivariate model.

All analyses were computed using R version 3.6.2 (R Core Team (2019); R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria; URL: https://www.R-project.org/). No imputation of missing data was realised. In this observational study, a p-value lower to 0.05 was considered as statistically significant.

RESULTS

Population description at taxane initiation

We included 110 consecutive patients who received both ICI and subsequent taxane-based chemotherapy in the following four French hospitals: ICO Angers (n=26), Le Mans hospital (n= 38), ICO Saint-Herblain (n = 18) and Cholet hospital (n = 28). Baseline characteristics of the cohort are summarized in Table 1. The median age at taxane initiation was 63 (interquartile range (IQR): 57-67). Patients were predominantly male (79%) with a sex ratio at 2.54. Performans status (PS) was as follow 0-1: 61 patients (57%); 2-3: 46 patients (43%). Adenocarcinomas were the predominant histologic subtype (59.1%) whereas 35.5% were squamous cell lung cancer. Others histological subtypes were large cell lung carcinomas (2.7%) and undifferentiated lung carcinomas (2.7%). PD-L1 status were available in half of case and 50.9% of tumours had a PD-L1 expression under 1%. Molecular detection of BRAF, KRAS or EGFR mutations were available for around 40% of patients. KRAS mutation were found in 28.9% of tumours whereas 6.5% had BRAF mutation and none of samples presented a ROS-1 or ALK alteration.

At taxane initiation, almost all the patients had a locally advanced (stage IIIC) or metastatic (stage IVA and IVB) NSCLC. Two patients had an IIIB stage. One of them presented a squamous cell lung cancer T2N2M0 without any surgery or a radiotherapy issues and received first-line platinum-based chemotherapy followed by Nivolumab and then Docetaxel. The second presented a recurrent squamous cell lung cancer after concomitant chemo-radiotherapy treated by first-line chemotherapy followed by Nivolumab and then Docetaxel. Three patients (2.7%) received Durvalumab after platinum-based chemo-radiotherapy. They received taxane in third line for metastatic recurrence. Nine (8.2%) patients received an immuno-chemotherapy combination followed by taxane-based treatment in second-line.

Patients with EGFR mutation received a tyrosine kinase inhibitor at first-line but none of patients with tumour BRAF mutation received a target therapy.

Taxane treatment outcomes

Docetaxel was preferentially used for 77 patients (70%), and six patients (5.5%) received paclitaxel in association with carboplatin. At the time of analysis, only 19 patients (17.3%) were alive. The median taxane treatment duration was 2 months (IQR: 1-4) and the median of follow up was 30.6 months. Figure 1 represented OS and PFS Kaplan Meier survival curves. The median Taxane OS was 7.3 months (95% CI: 6.1-10.3). The median Taxane PFS and ICI PFS were respectively 3.6 months (95% CI: 2.7-4.8) and 3.8 months (95% CI: 2.8-6.0). Taxane discontinuation was due to progression in 39 patients (37.1%), side effects in 12 patients (11.4%) or death during taxane treatment in 18 patients (17.1%). At the time of taxane discontinuation, 14 patients (13.3%) had controlled disease. Of these, 7 died during the surveillance. On the other hand, 22 patients (21%) were referred to palliative care. The objective response rate (ORR) with taxane was available in 91 patients and was 26.4% compared to 19.6% with ICI (data available in 102 patients).

Relationship between taxane response and prior ICI exposure

We then analysed the Taxane PFS to ICI PFS ratio to appreciate the benefit of taxane treatment according to prior exposure to ICI. Forty patients (36.4%) had a Taxane PFS/ICI PFS ratio upper than 1.3 and 61 patients (55.4%) had a ratio lower than 1 (Figure 2a). Baseline characteristics of patients in the >1.3 subgroup were not different from those in the <1.3 subgroup except for the age (60.23 versus 63.89 respectively; p=0.021). Patients with a 6 months or greater PFS on taxane was considered as long-responders. The median ICI PFS was 5 months for taxane long-responders subgroup versus 2 months for the other subgroup (figure 2b).

We hypothesised that the duration of ICI exposure, the ICI ORR and the time between the end of ICI and the initiation of taxane may influence patient outcomes. The results are shown in table 3. As expected, ICI treatment duration of 3-6 months or longer was associated with better OS on taxane compared to patients who received ICI less than 3 months (Hazard Ratio (HR) 0.43 (95% CI: 0.25-0.75); p<0.01 and 0.54 (95% CI: 0.32-0.93); p<0.05 respectively). As well this parameter was also associated with a Taxane PFS improvement (HR 0.6 (95% CI: 0.37-0.98); p<0.05 and 0.55 (95% CI: 0.34-0.9); p<0.05, respectively). Similarly, patients with 6 or more cycles of ICI compared to less than 6 cycles experienced better OS on taxane (HR 0.41 (95% CI: 0.26-0.64); p<0.0001) and better PFS on taxane (HR 0.5 (95% CI: 0.33-0.75); p<0.001). Interestingly, none of these previous parameters appeared to influence the taxane ORR. Similarly, the ICI ORR did not influence Taxane PFS, Taxane OS or Taxane ORR. The time between the interruption of ICI and the first cycle of taxane was not associated with a significant change in survival with taxane. First-line immuno-chemotherapy combination did not appear to affect outcomes on subsequent taxane regimen, but the limited number of patients must be considered.

Identification of factors associated with taxane efficacy

We sought to identify factors associated with longer Taxane PFS and Taxane OS. We analysed in a univariate model both clinical and biological variables at taxane initiation (table 3). A PS lower than two (PS <2) was a positive prognostic factor of both PFS and OS on taxane compared to PS ≥2 (p<0.0001). Concerning biological variables, we identified haemoglobin loss of more than 2g/dL between the start of ICI and the start of taxane, an increase in LDH level of more than 100 Ui/L and a neutrophil-to-lymphocytes ratio (NLR) ≥3 as predictors of poorer Taxane PFS. Hypoalbuminemia ≤35g/L or loss of 5g/L of albumin between the start of ICI and the start of taxane, haemoglobin level ≤10g/dL or loss of haemoglobin greater than 2

g/dL, increase in LDH greater than 100 Ui/L, and NLR ≥3 were also associated with poorer Taxane OS (Table 3).

In multivariate model, PS ≥2 (HR 2.73 (95% CI: 1.67-4.45); p=0.0001) and haemoglobin loss greater than 2g/dL (HR 3.07 (1.34-7.05); p=0.008) appeared to be pejorative factors for Taxane OS. Only PS ≥2 (HR 2.89 (95% CI: 1.8-4.65); p<0.0001) was a clinical factor associated with poorer Taxane PFS. ICI treatment duration was also included in multivariate model; a number of 6 cycles of ICI or greater was associated with both better OS and PFS on taxane (HR 0.31 (95% CI: 0.18-0.54); p<0.0001, and HR 0.44 (95% CI: 0.27-0.71); p=0.0009, respectively).

DISCUSSION AND CONCLUSION

To our knowledge, this is the largest study evaluating the benefit of taxane-based chemotherapy after progression on ICI in locally advanced or metastatic NSCLC. Most retrospective studies evaluating the benefit of antineoplastic regimens after ICI were based on heterogeneous cohorts. Indeed, these cohorts consisted of heavily pre-treated patients who had received a wide range of treatments after ICI [16–21]. Few studies have specifically evaluated taxane as second or third-line therapy. We decided to generate a relatively homogeneous cohort of patients receiving taxane regimen after failure of ICI and platinum based chemotherapy. Prior to the ICI era, taxane regimens were the standard of care in second-line after failure of platinum-based chemotherapy but showed modest benefit with an OS below than one year in selected patients [14,15]. The relevance of subsequent chemotherapy in patients with short life expectancy remains uncertain. More recently, studies had underlined that the addition of anti-angiogenic therapy to taxanes, such as bevacizumab, ramucirumab and nintedanib, improved survival of patients [22–24]. In our real-life cohort, the median Taxane OS after ICI failure was 7.3 months and was slightly lower than those observed in studies evaluating the combination of taxane and anti-angiogenic agents [22–24]. Some patients in our study received bevacizumab in combination with paclitaxel but unfortunately, we did not identify these patients. Our median Taxane PFS of 3.6 months was similar to most others retrospective studies [16,18–20]. Freeman et al. showed a low PFS of 1.5 months, probably explain by the predominant use of anti EGFR therapy in EGFR wild type patients [21]. Moreover, our median Taxane PFS in third-line therapy was relatively close to those observed with second-line taxane treatment before the ICI era [14,15,23,25]. This result may suggest that taxane-based chemotherapies remain a valuable treatment option after ICI failure.

Nevertheless, our results suggested that only a subset of patients appeared to benefit from subsequent taxanes. The ratio of Taxane PFS to ICI PFS (PFS2/PFS1) was used to assess

taxane regimen benefit compare to prior ICI exposure. Considering the decrease in efficacy that occurs across treatment lines, a PFS2/PFS1 ratio >1.3 can be considered as subsequent treatment benefit [26]. However, this ratio is not always correlate with clinical benefit, especially in case of short PFS1. A ratio >1.3 was observed in 36.4% of patients in our cohort without significant difference in baseline characteristics between the two subgroups determined by this ratio. The challenge remains to identify patients who will experience long-lasting response with taxane and we sought to identify clinical and biological predictive factors associated with better taxane PFS and OS. Unsurprisingly, we assessed that only patients with good functional condition (PS ≤1) seem to benefit with greater extent from taxane regimen. Performans status has been widely described as an important prognostic factor in NSCLC [27]. In our cohort, there were no PS 4 and few PS 3 patients at taxane initiation because chemotherapy are often avoid in this case and best supportive care still remains the standard. PS ≥2 is often used as exclusion criteria in clinical studies and survival outcomes in this subgroup are needed. Similarly, although less toxic than chemotherapy, ICI appeared to offer benefits only in a limited number of PS 3 and 4 patients [28]. Interestingly, an increase in LDH level and hypoalbumin under 35g/L or an albumin loss greater than 5g/L is associated with worse Taxane OS in univariate analysis. These variables take place in several validated scores such as the pronopall score [29]. The pronopall score combines PS, number of metastatic sites with blood albumin and LDH levels to estimate life expectancy of palliative care patients. This score is therefore used as a guide before the initiation of additional chemotherapy. Unfortunately, these variables were not included in our multivariate analysis due to excessive missing data. Other biological data were also associated with poor outcomes such as the neutrophil-to-lymphocytes ratio (NLR) at 3 or higher and anemia. High NLR is associated with shorter survival both on ICI and chemotherapies in several studies [30,31]. Similarly to the albumin decreasing, the loss of 2g/dL of haemoglobin was independently associated with poorer Taxane OS. However, these

variables are more likely to be associated with a negative prognostic impact related to the general and inflammatory state of patients. We did not find any specific predictor of response to taxanes.

Thus, several studies suggest a synergy between ICI and subsequent chemotherapy [17,32,33]. Hypotheses put forward are that chemotherapy may induce a modification of the tumour microenvironment and the generation of new danger signals promoting an anti-tumour immune response [34]. Park et al reported this synergistic effect. In this study, ORR observed with chemotherapy used in a post-ICI fashion was higher than ORR observed with chemotherapy used prior to ICI administration in the same cohort (ORR: 53.4% vs 34.9% respectively; p=0.03) [16]. Moreover, in the KEYNOTE-189 study, patients receiving immuno-chemotherapy combination showed higher response rate than those receiving chemotherapy alone (47.6% versus 18.9%, respectively) [8]. Similarly, in the KEYNOTE 024 study patients who received a pembrolizumab followed by chemotherapy sequence showed a longer PFS compared to a chemotherapy followed by pembrolizumab sequence [35]. In our cohort the Taxane ORR was significantly lower than the one observed in Park's cohort for salvage chemotherapy after ICI, but we both showed that Taxane ORR was not influenced by duration of exposure to ICI [16]. We showed that the duration of ICI treatment and the number of ICI cycles were independent factors associated with better Taxane OS and Taxane PFS. We also observed that long-responders with taxanes (PFS ≥6 months) tended to have a better ICI PFS. These observations need to be interpreted with caution because patients with primary immuno-resistance may sometimes benefit from subsequent chemotherapy. Alternatively, our observations may be explain by the selection of patients with less aggressive or indolent diseases. Finally, nivolumab is described as remaining bound to its ligand for approximately 2 months [36]. In our cohort, a delay of more than 2 months between the end of ICI and the initiation of taxane did not influence survival data, which could suggest a residual effect of ICI.

Our study has several limitations. First, the retrospective inclusion, heterogeneous practices within each hospital and the long inclusion period lead to missing data for PD-L1 analysis, which may affect the statistical analysis. We did not perform a centralized review of the radiological data which may lead to variability in the assessment of the objective response. Secondly, by including patients regardless of their duration of response to ICI, we included patients with hyperprogression on ICI. Moreover, we did not establish a control group with patients who did not receive taxane after ICI or with patients who received taxane without ever receiving ICI. Finally, ICI monotherapy in patients with PD-L1 high expressing tumours or chemotherapy in combination with ICI regardless of PD-L1 status have become new standard of care in first-line treatment for patients without a targetable driver mutation. Our cohort is therefore no longer representative of this new standard in which taxanes will be used as second-line treatment. Nevertheless, we showed some signal that second-line taxane may be reserved for healthy patients and long-responders on ICI. New perspectives are emerging considering that ICI could also act synergistically with taxane regimens. ICI management at disease progression could be consider in combination with taxanes instead of a discontinuation. In conclusion, patients with progressive NSCLC after ICI and platinum-based chemotherapy are often eligible for further chemotherapy but with limited efficacy and short life expectancy. The expected clinical benefit of subsequent treatment with taxanes is observed in a limited number of patients. Factors associated with good health condition and long-time exposure to previous therapies appeared to be predictive for better outcomes with subsequent taxane treatment. Those factors could offer assistance for clinician in their decision-making. These exploratory work should be validate in a larger and independent cohort.

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TABLES AND FIGURES

Table 1: Patient baseline characteristics at taxane initiation

Variable	Category	n (%)
Age	Median (IQR)	63 (57;67)
Gender	Male	79 (71.8%)
	Female	31 (28.2%)
Performans status	0	11 (10.3%)
	1	50 (46.7%)
	2	38 (35.5%)
	3	8 (7.5%)
	MD	3
Smoking status	Never	10 (9.5%)
	Current smoker	44 (41.9%)
	Former smoker	51 (48.6%)
	MD	5
Histologic type	Adenocarcinoma	65 (59.1%)
	Squamous cell carcinoma	39 (35.5%)
	Large cell carcinoma	3 (2.7%)
	Undifferentiated carcinoma	3 (2.7%)
Metastatic sites	Lung	88 (80%)
	Liver	30 (27.3%)
	Pleura	36 (32.7%)
	CNS	37 (33.6%)
	Bone	47 (42.7%)
	Adrenal gland	30 (27.3%)
	Thoracic lymph nodes	93 (84.5%)
Stage at taxane initiation	III B	2 (1.8%)
	III C	4 (3.6%)
	IV A	32 (29.1%)
	IV B	72 (65.5%)
Mutational status	EGFR mutation	2 (2.9%)
	MD	41
	ALK mutation	0 (0%)
	MD	40
	ROS1 mutation	0 (0%)
	MD	41
	KRAS mutation	18 (28.6%)
	MD	47
	BRAF mutation	4 (6.5%)
	MD	48
PD-L1 status	<1%	28 (50.9%)
	1-50%	16 (29.1%)
	>50%	11 (20%)
	MD	55

IQR: Interquartile range; MD: missing data; IC 95%: 95% confidence interval; CNS: central nervous system; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; PD-L1: programmed death-Ligand 1.

Table 2: Treatment characteristics

Variable	Category	Description
ICI treatment type	Nivolumab	77 (70%)
	Pembrolizumab	19 (17.3%)
	Atezolizumab	11 (10%)
	Durvalumab	3 (2.7%)
Chemotherapy and ICI combination	Pembro with chemo	9 (8.2%)
ICI treatment duration (months)	Mean (sd)	5 (6)
	Median (IQR)	3 (1;6)
	Range	0 - 39
	<3 months	54 (49.1%)
	3 to 6 months	28 (25.5%)
	>6 months	28 (25.5%)
Number of ICI cycles	Mean (sd)	11 (12)
	Median (IQR)	6 (4;12)
	Range	1-86
	<6 cycles	43 (39.1%)
	≥6 cycles	67 (60.9%)
Delay between the end of ICI and the start of taxanes (day)	Mean (sd)	60 (73)
	Median (IQR)	36 (21;55)
	Range	7 - 453
Taxane treatment name	Docetaxel	77 (70%)
	Paclitaxel	27 (24.5%)
	Paclitaxel and carboplatin	6 (5.5%)
Taxane treatment duration (months)	Mean (sd)	3 (3)
	Median (IQR)	2 (1;4)
	Range	0 - 18
	Missing data	1
Reason for stopping taxane	Disease progression	39 (37.1%)
	Death	18 (17.1%)
	Side effects	12 (11.4%)
	Surveillance	14 (13.3%)
	Palliative care	22 (21%)
	Missing data	5

sd: standard derivation; IQR: interquartile range; ICI : immune checkpoint inhibitors.

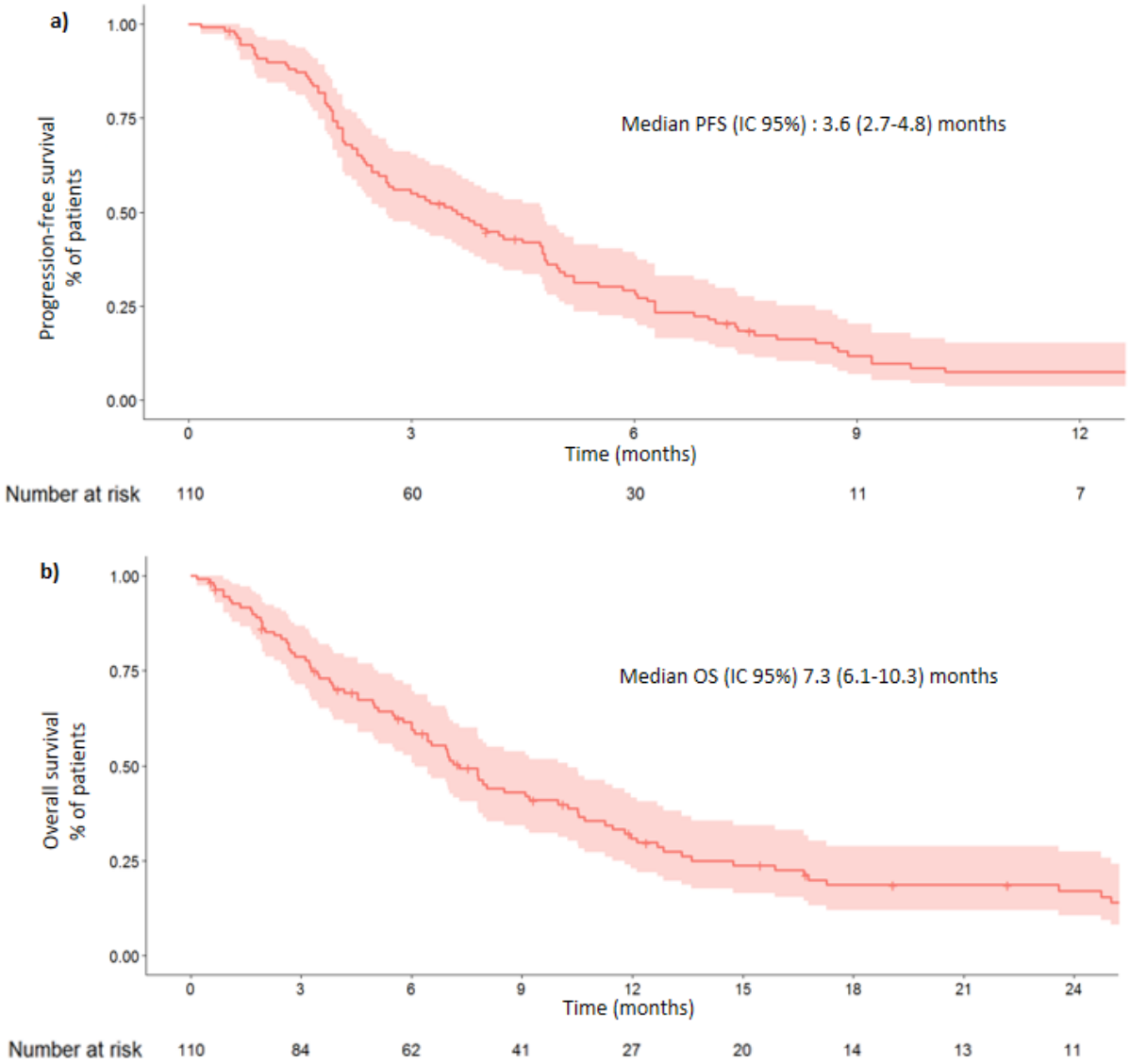

Figure 1: Kaplan-Meier curves showing a) progression-free survival and b) overall survival in patients treated by taxane.

95% CI: 95% confidence interval; PFS: progression-free survival; OS: overall survival.

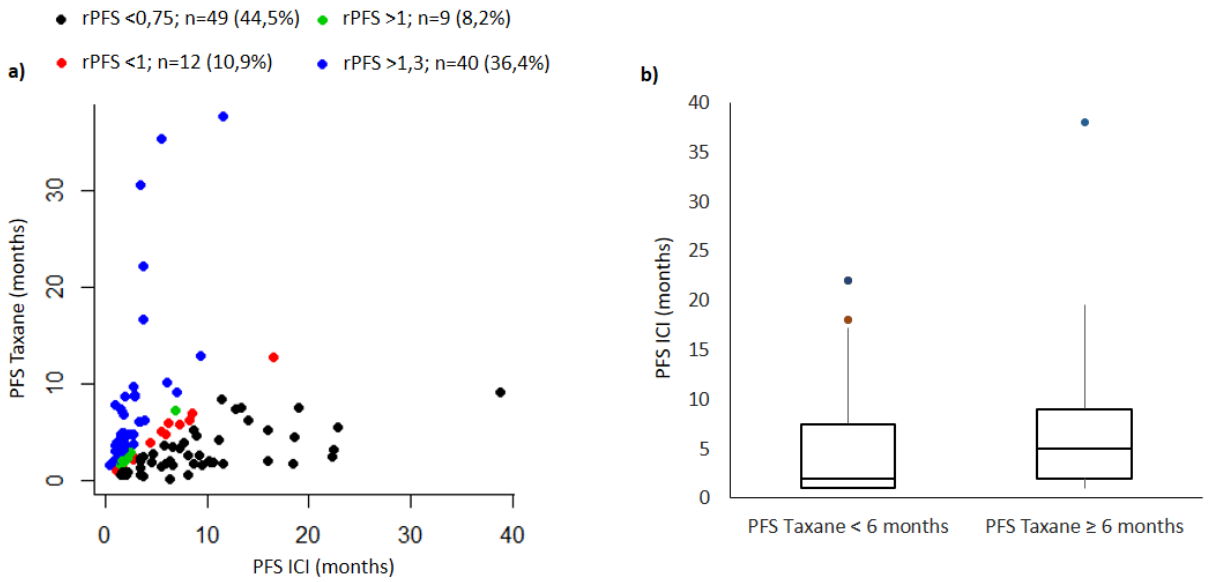

Figure 2: Analysis of PFS on ICI versus PFS on taxane. a) Dot plot showing PFS on taxane to PFS on ICI ratio (rPFS). b) Box plots show PFS on ICI according to PFS on Taxane. Individual points represent outliers.

PFS Taxane: Progression-free survival on taxane; PFS ICI: Progression-free survival on ICI; rPFS: ratio between PFS Taxane and PFS ICI.

Table 3: PFS, OS and ORR on taxane according to prior ICI exposure

	Taxane PFS		**Taxane OS**		**Taxane ORR**	
	HR (95% CI)	p value	HR (95% CI)	p value	OR (95%CI)	p value
ICI treatment duration (compare to <3 months)						
3 to 6 months	0.6 (0.37-0.98)	**0.0414**	0.43 (0.25-0.75)	**0.0031**	1.15 (0.95-1.38)	0.1608
>6 months	0.55 (0.34-0.9)	**0.0179**	0.54 (0.32-0.93)	**0.0250**	0.99 (0.82-1.2)	0.9455
Number of ICI cycles (compare to < 6 cycles)						
>=6 cycles	0.5 (0.33-0.75)	**0.0009**	0.41 (0.26-0.64)	**0.0001**	1.01 (0.86-1.19)	0.8583
Objective response on ICI (compare to SD ou PD)						
ORR on ICI	0.84 (0.5-1.41)	0.5079	0.95 (0.54-1.68)	0.8711	1.03 (0.84-1.27)	0.7726
Time between the end of ICI and taxane initiation (compare to <1 month)						
1 to 2 months	1.23 (0.78-1.92)	0.3715	0.79 (0.48-1.28)	0.3352	1.19 (1-1.41)	0.0568
>2 months	0.99 (0.59-1.66)	0.9608	0.8 (0.46-1.38)	0.4215	0.96 (0.78-1.17)	0.6777

ICI: Immune checkpoint inhibitor; PFS: progression-free survival; OS: overall survival; ORR: objective response rate; 95% CI: 95% confidence interval; HR: hazard ratio; OR: odds ratio.

Table 4: Univariate analysis of factors associated with Taxane PFS and OS

			Taxane PFS		Taxane OS	
		n	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Age ϒ	≥70 vs <70	110	0.68 (0.39-1.21)	0.1930	0.65 (0.34-1.26)	0.2045
PS ϒ	**≥ 2 vs <2**	**107**	**2.51 (1.66-3.8)**	**<0.0001**	**2.83 (1.82-4.42)**	**<0.0001**
Weight loss	> 5 kg vs no	103	1.3 (0.83-2.06)	0.2512	1.15 (0.7-1.9)	0.5864
Metastatic site						
Bone	Yes vs no	110	1.08 (0.73-1.61)	0.6897	1.1 (0.72-1.69)	0.6567
CNS ϒ	Yes vs no	110	1.31 (0.87-1.98)	0.1992	0.98 (0.63-1.54)	0.9394
Adrenal glands ϒ	Yes vs no	110	1.47 (0.95-2.28)	0.0827	1.06 (0.67-1.7)	0.7943
Lung	Yes vs no	110	1.01 (0.62-1.65)	0.9692	1.05 (0.62-1.79)	0.8591
Pleura	Yes vs no	110	0.99 (0.65-1.5)	0.9476	1.21 (0.77-1.89)	0.4089
Liver ϒ	Yes vs no	110	1.45 (0.94-2.23)	0.0938	1.31 (0.83-2.08)	0.2428
Thoracic lymph nodes ϒ	**Yes vs no**	**110**	**2.03 (1.16-3.56)**	**0.0132**	1.7 (0.9-3.21)	0.1044
Extra thoracic metastases	Yes vs no	110	1.42 (0.89-2.25)	0.1369	1.07 (0.65-1.75)	0.7833
EGFR mutation*	Yes vs no	69	1.3 (0.31-5.37)	0.7184	2.19 (0.52-9.23)	0.2857
KRAS mutation*	Yes vs no	33	1.12 (0.63-2.01)	0.6949	1.29 (0.68-2.43)	0.4348
PD-L1 expression*	1-50% vs 0	55	0.77 (0.39-1.53)	0.4570	0.98 (0.45-2.15)	0.9680
	>50% vs 0		1.65 (0.79-3.48)	0.1842	1.51 (0.68-3.35)	0.3056
Haemoglobin level	>10g/dL vs ≤ 10	100	1.68 (0.94-2.99)	0.0813	**2.44 (1.31-4.56)**	**0.0051**
Hb change ϒ	**loss ≥2g/dL**	**94**	**2.43 (1.11-5.33)**	**0.0265**	**3.22 (1.44-7.19)**	**0.0045**
LDH*	↗100Ui/L	**67**	**1.1 (1.02-1.19)**	**0.0115**	**1.14 (1.06-1.24)**	**0.0007**
Albumin level*	>35g/dL vs ≤35	84	1.51 (0.96-2.37)	0.0764	**2.33 (1.41-3.87)**	**0.0011**
Albumin change *	loss ≥5 g/dL	68	1.72 (0.95-3.09)	0.0711	**2.98 (1.57-5.65)**	**0.0008**
Lymphocytes*	≤750 vs >750/mm^3	73	1.22 (0.65-2.27)	0.5377	1.06 (0.53-2.11)	0.8699
NLR *	**≥3 vs <3**	**73**	**2.36 (1.3-4.25)**	**0.0045**	1.71 (0.92-3.15)	0.0877

*ϒ: variables included in the full multivariate model before automatic statistical selection; * variables not included in the final multivariate model. PFS: progression-free survival; OS: overall survival; HR: hazard ratios; 95% CI: 95% confidence interval; PS: performans status; CNS: central nervous system; EGFR: epidermal-growth factor; PD-L1: program death ligand 1; Hb: haemoglobin; NLR: neutrophil-lymphocytes ratio.*

Table 5: Multivariate analysis of factors associated with Taxane PFS and OS

		Taxane PFS		Taxane OS	
		HR (95%CI)	**p-value**	**HR (95%CI)**	**p-value**
PS	≥ 2 vs <2	2.89 (1.8-4.65)	**<0.0001**	2.73 (1.67-4.45)	**0.0001**
Number of ICI cycles	≥ 6 vs <6	0.44 (0.27-0.71)	**0.0009**	0.31 (0.18-0.54)	**<0.0001**
Metastatic site					
Thoracic lymph nodes	Yes vs no	3.08 (1.55-6.1)	**0.0013**	2.01 (0.96-4.2)	0.0635
Hb change	loss ≥ 2	NS	NS	3.07 (1.34-7.05)	**0.0080**

PFS: progression-free survival; OS: overall survival; HR: hazard ratios; 95% CI: 95% confidence interval; PS: performans status; ICI: immune checkpoint inhibitor; Hb: haemoglobin; NS: not significant.

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Données de survie des patients traités par taxanes après échec de l'immunothérapie dans le cancer broncho-pulmonaire non à petites cellules avancé ou métastatique

RÉSUMÉ

Introduction : Depuis l'avènement de l'immunothérapie (IO), la survie des patients traités pour un cancer du poumon non à petites cellules (CBPNPC) de stade avancé s'est considérablement améliorée. Des réponses prolongées ont été décrites mais en cas de progression sous IO la chimiothérapie par taxane reste le traitement de référence avec un bénéfice souvent limité. Plusieurs études suggèrent une synergie d'action entre l'IO et la chimiothérapie reçue ultérieurement. L'objectif était d'évaluer la survie des patients traités par taxane après échec d'une IO dans les CBPNPC avancés et d'identifier des facteurs prédictifs de réponse.

Matériels et méthodes : Nous avons mené une étude rétrospective, multicentrique. Les patients présentant un CBPNPC stade IIIB minimum ont été inclus s'ils avaient reçu une chimiothérapie par taxane faisant suite à une IO. Le critère de jugement principal était la survie globale (SG) et la survie sans progression (SSP) sous taxanes. Les objectifs secondaires étaient (1) de déterminer le bénéfice des taxanes via le calcul du rapport Taxane SSP/ IO SSP, (2) d'identifier les variables clinico-biologiques associées à une meilleure survie sous taxanes.

Résultats : Nous avons inclus 110 patients, principalement des hommes (71,8 %) et l'âge médian était de 63 ans. L'adénocarcinome était le sous-type histologique majoritaire (59,1 %) et le stade tumoral IVB était retrouvé à 65,5 %. Les patients avait reçu du docétaxel dans 70 % des cas. La médiane de SSP médiane était de 3,6 mois (2,7-4,8) et la médiane de SG de 7,3 mois (6,1-10,3). Seulement 36,4% des patients avaient un rapport de SSP entre taxane et IO supérieur à 1,3 et nous n'avons pas mis en évidence de différence clinique notable dans ce sous-groupe, excepté pour l'âge (60,2 ans contre 63,9 ans ; p=0,021). Les patients ayant reçu 6 cycles ou plus d'IO avait une SG et SSP significativement augmentée. Dans notre modèle multivarié, le performans status à 2 ou plus (PS ≥ 2) et une perte de 2g/dL d'hémoglobine entre le début de l'IO et l'initiation du taxane étaient associés à une moins bonne SG. Seul le PS ≥2 était associé à une moins bonne SSP sous Taxane.

Conclusion : Un bénéfice à l'utilisation des taxanes après échec de l'IO ne semble être observé que parmi un sous-groupe limité de patients. La durée d'exposition à l'IO et l'état général des patients apparaissent associés à une meilleure survie sous taxanes.

Mots-clés : Immunothérapie, taxanes, cancer broncho-pulmonaire non à petites cellules, données de survie, soin palliatif

Outcomes in patients treated with taxane regimen after failure of immune checkpoint inhibitors in advanced or metastatic non-small cell lung cancer

ABSTRACT

Introduction: Anti PD-1/PD-L1 immune check point inhibitors (ICI) had dramatically changed the survival of patients with advanced non-small cell lung cancer (NSCLC). After platinum-based chemotherapy and ICI failure, taxane regimen remains the standard of care. Some data have suggested an increase in the activity of chemotherapy received after ICI. Nevertheless, taxane appears to have only modest benefit in pre-treated patients. We aimed to assess survival outcomes with taxane chemotherapies after ICI exposure and to identify prognostic and predictive factors that may influence response to those regimens.

Material and method: In this multicentric retrospective study, we included patients with stage IIIB or higher NSCLC who received subsequently taxane after ICI failure. Primary end points were progression-free survival on taxane (Taxane PFS) and overall survival on taxane (Taxane OS). Secondary end points were Taxane PFS to ICI PFS ratio, to evaluate benefit of subsequent taxane, and identification of clinical data associated with better survival on taxane.

Results: We included 110 patients, mostly men (71.8 %) with a median age of 63. Patients mostly had stage IVB (65.5%) and adenocarcinoma was the predominant histologic subtype (59.1%). Docetaxel was the taxane chosen in 70% of cases. Median Taxane PFS was 3.6 months (2.7-4.8) and Taxane OS was 7.3 months (6.1-10.3). Only 36.4% of patients had a ratio Taxane PFS to ICI PFS greater than 1.3 without clinical difference in this subgroup, except for age (60.2 versus 63.9; p=0,021). A number of ICI cycles at 6 or above was an independent factor associated with better Taxane PFS and OS. Similarly, in multivariate model, performans status at 2 or higher (PS ≥2) and a 2g/dL loss of haemoglobin between the start of ICI and taxane initiation were associated with poorer Taxane OS. Only PS ≥2 was associated with a poorer Taxane PFS.

Conclusion: Effectiveness of further treatment with taxane was observed only in a limited subgroup of patients. Factors associated with good health condition and a long exposure to ICI appeared to be associated with better survival on taxanes.

keymords: Immune check point inhibitor, taxane chemotherapy, non-small cell lung cancer, survival, palliative care

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