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Are the Different Immunotherapies Used in Second Line Treatment of Metastatic Lung Cancer Equivalent?

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Abstract

Background: Immune Checkpoint Inhibitors (ICIs) have changed the management of Non-Small Cell Lung Cancer (NSCLC). Nivolumab, pembrolizumab, and atezolizumab have been shown to be effective in second line treatment of metastatic NSCLC compared with docetaxel, improving response rate, Progression-Free Survival (PFS), Overall Survival (OS), and quality of life compared with chemotherapy.

Methods: This retrospective study was conducted from 2015 to 2021 on 165 patients with metastatic or locally advanced NSCLC in progression after a 1st line of chemotherapy without immunotherapy, who received a second line of ICIs at the University Hospital of Dijon.

Results: The response rate with nivolumab, pembrolizumab and atezolizumab was 15.7%, 16.3% and 5.4% respectively. Pembrolizumab had a better PFS (median of 190 days [28.5;604], p=0.0426) compared with the 2 other ICIs. There was no significant difference in OS between the 3 ICIs, even when survival analyses were performed with PDL1 ≥ 1. Incidence of grade ≥ 3 toxicities were 10.2%, 6.12%, and 3.1% with nivolumab, pembrolizumab, and atezolizumab respectively.

Conclusion: This study shows a better "real-life" PFS with pembrolizumab compared to nivolumab and atezolizumab in metastatic or locally advanced NSCLC progressing after 1st line chemotherapy. Atezolizumab appears to be less effective than the 2 others anti PD1 agents but offers less severe toxicities.

Keywords: Immunotherapy; Non-small cell lung cancer; Second line; Efficacy

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Introduction

Until 2015, the recommended second line NSCLC treatment was, in the absence of available oncogenic addiction, second line chemotherapy, according the molecule used in first line treatment [1]. The development of immunotherapy and monoclonal antibodies has broadened the range of treatments available for NSCLC, with new therapies available for second line treatment of locally advanced or metastatic NSCLC [2].

Immune Checkpoint Inhibitors (ICIs), stimulates the patient's immune response to destroy the tumor. This therapy is already used in other cancers such as melanoma, colon cancer or urothelial tumors [3]. The inflammatory response results from the encounter between a T cell and the antigen presented by the MHC [4]. Two proteins are involved: Anti-Programmed Death-1 (PD1), a transmembrane protein found on the surface of T cells, but also on other immune cells such as B cells, dendritic cells, and TILS; and the protein PDL1 or programmed death-ligand 1, found on the surface of tumor cells. PD1 can bind to PDL1 and PDL2. This binding inhibits tumor cell apoptosis, induces depletion of peripheral effector T cells, and stimulates the conversion of effector T cells into regulatory T cells, leading to immunotolerance, which is conducive to tumor growth [3,4]. Inhibiting this interaction therefore plays a key role in controlling tumor proliferation. Since the fall of 2015, ICIs have been available in standard practice for the management of lung cancer [5] (Figure 1).

Three molecules have already demonstrated superior efficacy and safety compared to standard chemotherapy in second line treatment of metastatic or locally advanced NSCLC not amenable to

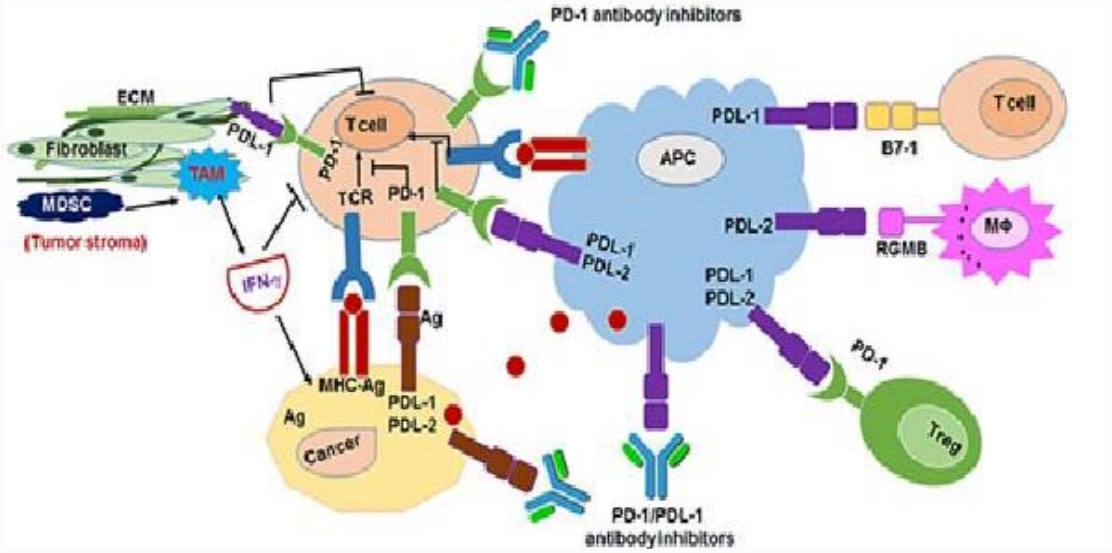

Figure 1: Interaction between PDL1/PDL2, and PD1.

local therapy (stages IIIB/IV), after failure of first-line chemotherapy, in patients without oncogenic addiction (or previously treated and progressing) [6-8].

There are very few real-life data in the literature comparing the OS and safety of nivolumab, pembrolizumab, and atezolizumab in pre-treated metastatic NSCLC in an unselected patient population [9], and to our knowledge no data on the RR and PFS, observed with these different immunotherapies. Studies compare indirectly [10,11], with data from previous studies [6-8], OS and PFS between nivolumab, pembrolizumab and atezolizumab. The Italian study by Franchi and al, compared OS and cost effectiveness between nivolumab, pembrolizumab and atezolizumab in pre-treated advanced NSCLC in an unselected patient cohort. There was no significant difference in OS between these three treatments [9].

The objective of our work is to compare the response rate, OS and PFS of our patients undergoing nivolumab, pembrolizumab and atezolizumab, to eventually identify, in a "real life" patient population, preferential therapeutic orientations for the management of progressive NSCLC after a first line of chemotherapy, according to PDL1 status. We also aim to compare the tolerability of these three treatments.

Material and Methods

This is a retrospective, single center study conducted at the University Hospital Center of DIJON-BOURGOGNE, in the Department of Thoracic Oncology, from December 2015 to December 2021.

Population

We included:

- Patients with primary non-small cell lung cancer, adenocarcinoma, squamous cell, large cell neuroendocrine and NOS,
- Progressing after first line chemotherapy (without immunotherapy) and having received second line immunotherapy alone, in the Department of Thoracic Oncology
- Tumor stage III not targetable to local treatment (surgery and/or radiotherapy) or IV
- Age of 18 years old or older.

We excluded:

- Other Cancer than primary lung cancers (mesothelioma, sarcomatoid tumors, unknown etiology)
- Patients who could be treated locally (surgery and/or radiotherapy) after their first line of chemotherapy
- Other systemic treatment than nivolumab, pembrolizumab or atezolizumab in second line
- Patients included in a research protocol
- Patients with missing data

Treatments

The first immunotherapy marketed in this indication, was nivolumab, in intravenous infusion, initially in a weight dose of 3 mg/kg every two weeks, then in a flat dose of 240 mg every two weeks (or 480 mg every 4 weeks off label, notably during the SARS-CoV-2 pandemic, to limit patient visits to hospital); pembrolizumab by intravenous infusion, also in a weighted dose when it was first marketed, at 2 mg/kg every three weeks, then in a flat dose of 200 mg every three weeks, or 400 mg every six weeks; and finally atezolizumab by intravenous infusion, at a dosage of 1200 mg every three weeks.

Data collection

We recorded sex, age and date of birth, smoking and number of pack year, histology (adenocarcinoma, squamous cell, large cell neuroendocrine, undifferentiated type NOS), oncogenic addictions and molecular biology (PDL1 status, EGFR mutation, ALK, ROS 1, MET amplification, TP 53 mutation, CD8+ infiltrate, KRAS, BRAF, RB1 status, HER2). The performance status before the first line treatment was recorded, as well as the type of first line treatment. Maintenance treatment after first line therapy and/or monitoring during following period was recorded. The type of immunotherapy (nivolumab, pembrolizumab and atezolizumab), the start date, the recurrence, the dose (weight dose, flat dose, double dose), and the number of injections were recorded.

Table 1: Patient's feature according immunotherapies.

		nivolumab (n=86)	pembrolizumab (n=50)	atezolizumab (n=29)	n	p
Median age [Q25-75]		69.0 [61.1-75.0]	66.0 [57.5-71.6]	62.0 [59.0-69.0]	165	0.16
Sex, n	Females	22 (26%)	11 (22%)	10 (34%)	43	0.47
	Males	64 (74%)	39 (78%)	19 (66%)	122	-
Smoking status, n	No	5 (5.8%)	2 (4%)	3 (10%)	10	0.55
	Yes	81 (94%)	48 (96%)	26 (90%)	155	-
PDL1, n	Negative	61 (71%)	0 (0%)	19 (66%)	80	<0.001
	1-49%	9 (10%)	34 (67%)	10 (34%)	53	-
	≥ 50%	0 (0%)	16 (32%)	0 (0%)	16	-
	Unknow	16 (19%)	0 (0%)	0 (0%)	16	-
Histology, n	Adenocarcinoma	55 (64%)	35 (70%)	20 (69%)	110	0.8
	Epidermoid	25 (29%)	14 (28%)	9 (31%)	48	-
	NE	4 (4.7%)	0 (0%)	0 (0%)	4	-
	NOS	2 (2.3%)	1 (2%)	0 (0%)	3	-
Brain localization, n	No	52 (60%)	38 (76%)	22 (76%)	112	0.1
	Yes	34 (40%)	12 (24%)	7 (24%)	53	-
CD8 rate, n	Negative	3 (3.5%)	0 (0%)	2 (6.9%)	5	0.52
		8 (9.3%)	7 (14%)	4 (14%)	19	-
	Moderate	1 (1.2%)	1 (2%)	0 (0%)	2	-
	Unknow	74 (86%)	42 (84%)	23 (79%)	139	-
ALK, n	Negative	80 (93%)	45 (90%)	29 (100%)	154	0.36
	Positive	1 (1.2%)	0 (0%)	0 (0%)	1	-
	Unknow	5 (5.8%)	5 (10%)	0 (0%)	10	-
EGFR, n	Negative	79 (92%)	43 (86%)	28 (97%)	150	0.53
	Mutated	2 (2.3%)	1 (2%)	0 (0%)	3	-
	Unknow	5 (5.8%)	6 (12%)	1 (3.4%)	12	-
K RAS, n	Negative	59 (69%)	27 (54%)	15 (52%)	101	0.14
	Positive	19 (22%)	14 (28%)	12 (41%)	45	-
	Unknow	8 (9.3%)	9 (18%)	2 (6.9%)	19	-
ROS1, n	Negative	81 (94%)	45 (90%)	29 (100%)	155	0.2
	Unknow	5 (5.8%)	5 (10%)	0 (0%)	10	-

A patient was a responder to immunotherapy if, from the start of treatment, he or she showed: Stabilization of the disease; or a decrease (in size and/or number) of lesions; or a heterogeneous evolution of the disease, with lesions that could decrease in size, while others increased (partial responder). The complete response to treatment corresponded to the disappearance of tumor lesions visible on the re-evaluation CT scan during follow up. The toxicities of each immunotherapy were reported, as well as their grades, and the necessity or not to stop the treatment if the severity of the toxicity imposed it. The date of progression under immunotherapy were taken into account. Third line treatment, continuation of immunotherapy, or comfort care could be considered depending on the response to immunotherapy and the patient's general condition. The date of the end of follow-up, or if applicable, the death of the patient, was reported. Demographic characteristics and first line chemotherapies are sum up in Table 1, 2.

Table 2: Descriptive table of first line chemotherapies and targeted therapies.

First line chemotherapy	Patient's treated, n
Cisplatin and pemetrexed	62
Carboplatin and pemetrexed	18
Carboplatin and gemcitabine	13
Cisplatin and gemcitabine	6
Gemcitabine alone	10
Carboplatin and paclitaxel	32
Cisplatin and vinorelbine	1
Carboplatin and etoposide	2
Cisplatin and docetaxel	12
Carboplatin and docetaxel	3
Docetaxel alone	1
Vinorelbine	1
Afatinib	3

Endpoints

The primary endpoint was the difference OS and PFS, between

Table 3: Patients evolution at the study end point.

		nivolumab (n=86)	pembrolizumab (n=50)	atezolizumab (n=29)	n	p
Patient's status, n	Dead	48 (56%)	20 (40%)	18 (62%)	86	0.1
	Alive	38 (44%)	30 (60%)	11 (38%)	79	-
Evolution, n	Progression and implementation of a 3rd line treatment*	35 (41%)	10 (20%)	11 (38%)	56	0.046
	Continued immunotherapy**	22 (26%)	19 (38%)	4 (14%)	45	-
	Discontinuation of immunotherapy for palliative care***	22 (26%)	16 (32%)	10 (34%)	48	-
	Discontinuation of immunotherapy for toxicity, initiation of corticosteroids****, or patient's wish	7 (8%)	5 (10%)	4 (14%)	16	-

*If tumor progression and general condition allow continuation of curative treatment
**in the absence of known tumor progression or persistent clinical benefit, continuation of current immunotherapy
***if general condition does not allow continuation of curative treatment
****corticosteroid therapy on cerebral progression alone, at a dose greater than 10 mg per day of prednisone equivalent, contraindicating the continuation of immunotherapy

Table 4: Toxicities according to the immunotherapy used.

		nivolumab (n=86)	pembrolizumab (n=50)	atezolizumab (n=29)	n	p
Toxicity, n	No	70 (81%)	42 (84%)	23 (79%)	135	0.86
	Yes	16 (19%)	8 (16%)	6 (21%)	30	-

Table 5: Progression free survival according patients age (>67 years or =67 years) under immunotherapy during the study.

	=67 y (n=73)	>67 y (n=92)	n	p
Median PFS(d) [Q25-75]	84.0 [50.0; 329]	82.5 [28.0; 224]	165	0.2

Table 6: Progression free survival according to smoking status.

	Smokers (n=155)	Non-smokers (n=10)	n	p
Median PFS(d) [Q25-75]	84.0 [41.5; 281]	82.5 [26.2; 156]	165	0.4

nivolumab, pembrolizumab, and atezolizumab in study patients. The outcome is given in number of days and visualized on survival curves.

The secondary endpoint includes the difference in response rate, PFS and OS between nivolumab and atezolizumab combined, *vs.* pembrolizumab, for tumors PDL1 positive, and safety of each immunotherapy. We also investigated among our patient cohort, factors that may predict better response to immunotherapy.

Statistical analyses

We used the p-value statistical software to perform our descriptive analyses. Chi-2, Kruskal-Wallis, Fisher, Welch, Wilcoxon rank and Mann-Whitney tests were used by the software to obtain the descriptive results. The results are presented with medians (first quartile-third quartile). Survival curves were made in RStudio and analyzed with the Kaplan Meier method. We determined overall survival and progression-free survival between nivolumab, pembrolizumab and atezolizumab immunotherapies, and stratified the results for some curves according to PDL1 status. Results were considered significant if the p value was less than or equal to 0.05.

Results

423 patients received immunotherapy during their management in the thoracic oncology department of Dijon University Hospital. 177 patients received second line immunotherapy. 12 patients were excluded: 5 because having a diagnosis other than lung carcinoma (2 mesotheliomas, 2 cancers of unknown origin and one sarcoimatoid tumor), 4 because of missing data, 1 because he was part of a research protocol and 2 because having locally advanced tumors accessible to local treatment. One hundred sixty-five patients were eligible and included in the analysis. This population was divided into 3 groups: 86 patients in the nivolumab group, 50 patients in the pembrolizumab group and 29 patients in the atezolizumab group (Figure 2).

Assessment of PFS, OS and therapeutic response under immunotherapies

There was no significant difference in OS between the nivolumab, atezolizumab, and pembrolizumab groups (p=0.089), however survival on pembrolizumab and atezolizumab appeared quite different (Figure 3). PFS was significantly better in the pembrolizumab group compared to the nivolumab and atezolizumab groups (p=0.025), the latter two immunotherapies being highly comparable (Figure 4). There was also a significant difference in PFS in favor of the pembrolizumab group compared with the combined data from the nivolumab and atezolizumab groups (p=0.0079) (Figure 5).

When comparing progression-free survival for a positive PDL1 level, there was no significant difference in progression-free survival between the 3 groups (p=0.25) (Figure 6).

In our study, the response rate (partial or complete) to immunotherapy was 38% (62 patients). The response rates were of 15.7%, 16.3%, and 5.4% for nivolumab, pembrolizumab, and atezolizumab, respectively (Figure 7).

Patients' evolution at the study endpoint

More people died in the atezolizumab group (62% of the group, 18 patients), than in the 2 others groups. Almost as many patients experienced disease progression in the nivolumab and atezolizumab arms, with respectively 41% patients in the group nivolumab and 38% patients in the group atezolizumab. The details of the evolution of the patients according each group of immunotherapy is available in Table 3.

Adverse events and tolerance to immunotherapies

In our study, 98 patients (59%) had at least one immunotherapy related toxicity. Of these, 68 patients (41%) experienced dysthyroidism. The occurrence rate of grade ≥ 3 toxicities was 10.2%, 6.12%, and 3.1%

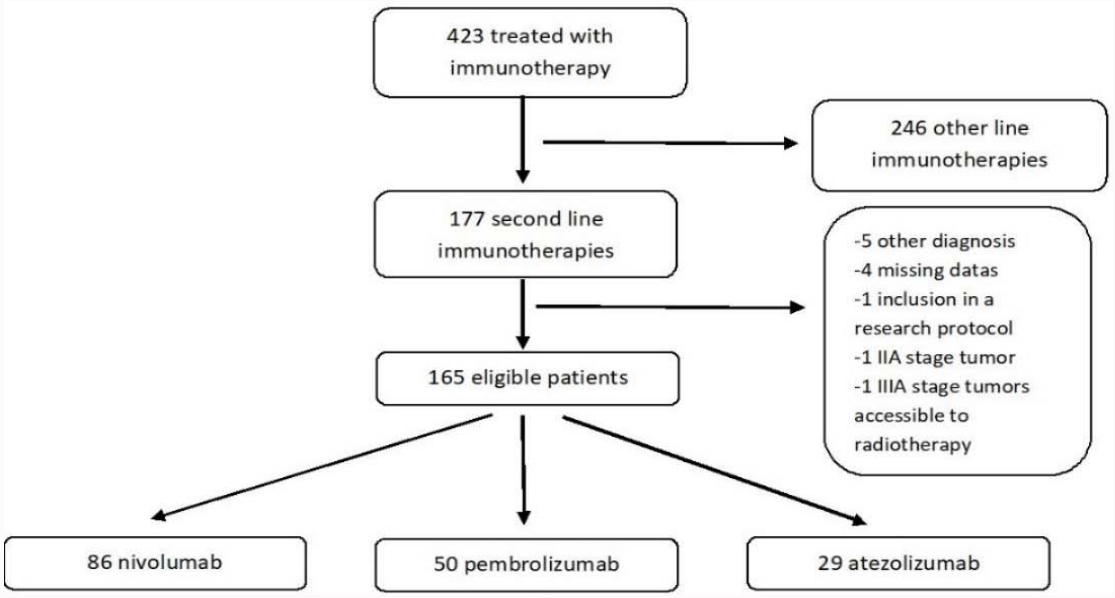

Figure 2: Flowchart.

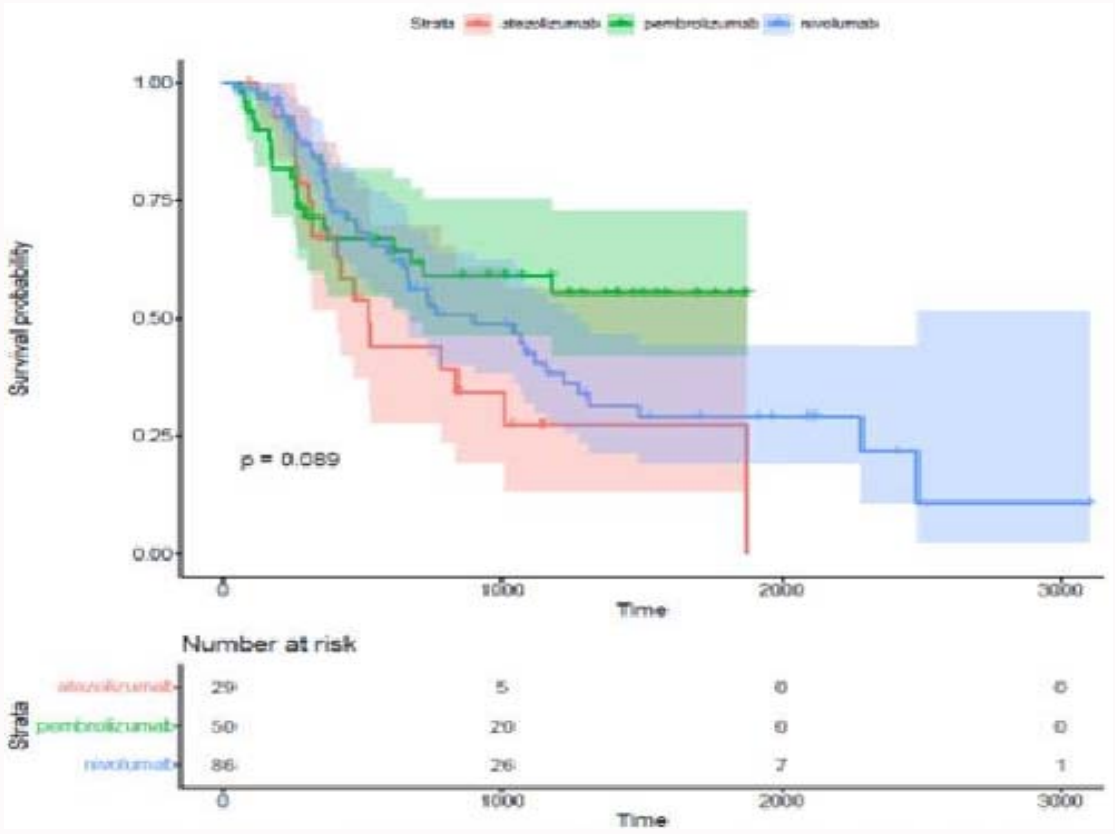

Figure 3: Comparison of OS according immunotherapy (nivolumab, pembrolizumab and atezolizumab).

under nivolumab, pembrolizumab, and atezolizumab, respectively. We find 8 cholestatic hepatitis (1 in the atezolizumab group, 2 in the pembrolizumab group, and 5 in the nivolumab group), 5 cytolytic hepatitis (1 in the pembrolizumab group and 4 in the nivolumab group), 5 pneumopathies (1 in the atezolizumab group and 2 in the pembrolizumab and nivolumab groups), 2 pericarditis in the nivolumab arm, 3 colitis (1 in the atezolizumab arm and 2 in the nivolumab arm), 1 allergic reaction in the atezolizumab arm, 1 joint involvement in the pembrolizumab arm, 7 skin toxicities (3 in the nivolumab arm and 2 in the atezolizumab and pembrolizumab arms). Twenty-two treatments were discontinued for serious adverse events (3 dysthyroidisms, 2 pericarditis, 3 cholestatic hepatitis, 1 pseudo erysipelas, 1 bullous pemphigoid, 3 pneumopathies, 1 inflammatory rheumatism, 4 cytolytic hepatitis, 3 colitis and 1 allergic reaction).

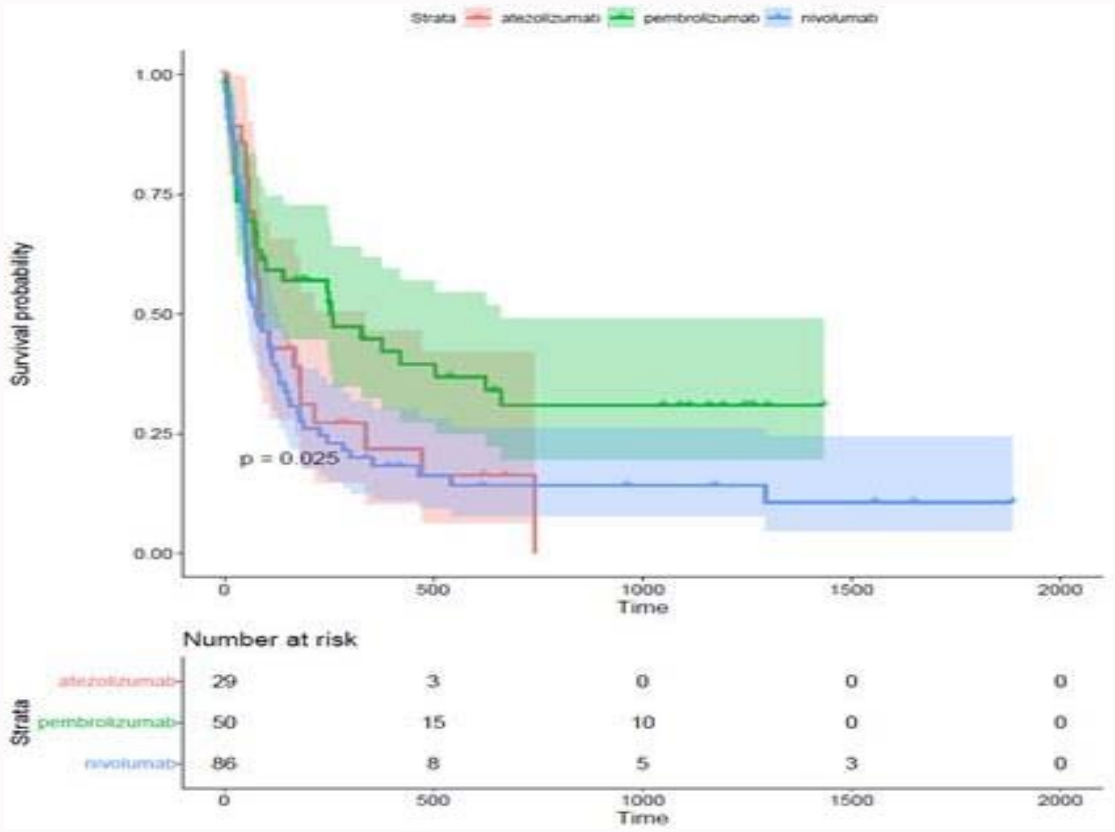

Figure 4: Comparison of PFS according immunotherapy (nivolumab, pembrolizumab and atezolizumab).

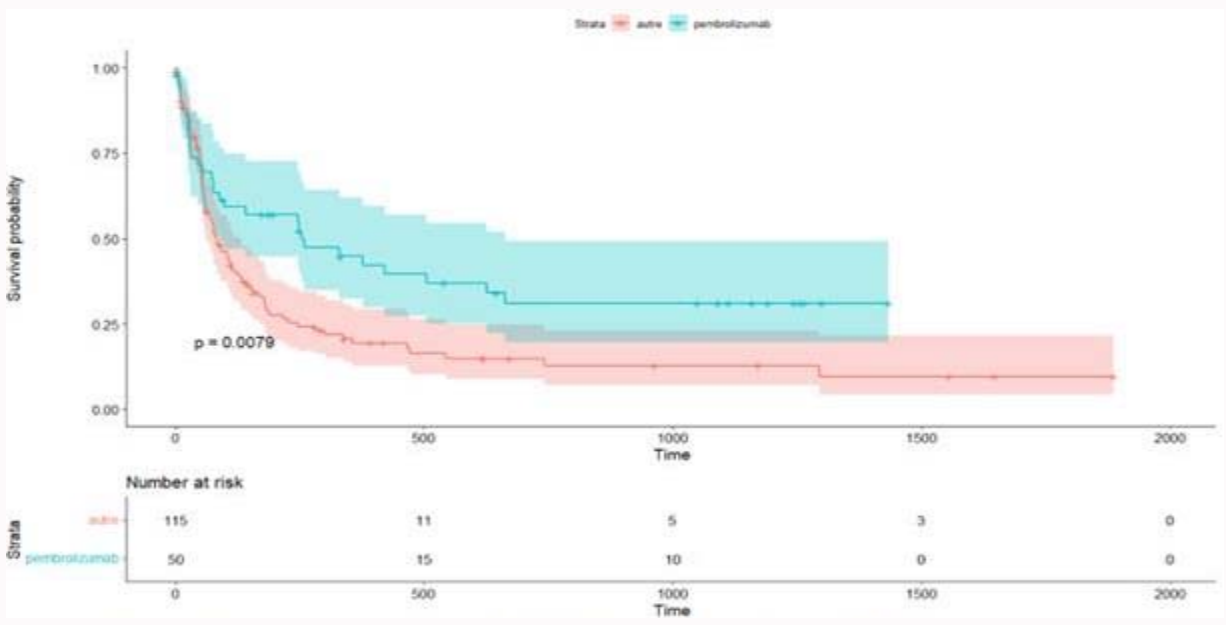

Figure 5: Comparison of PFS of pembrolizumab alone *vs.* PFS of nivolumab and atezolizumab combined.

There was no significant difference in the occurrence of toxicities between the 3 groups (Table 4).

Survival according to age and smoking status

The median age of study population is 67 years. This is the value we have chosen to analyze the response to immunotherapy. In our study, 73 patients (44%) are 67 years old or younger, and there is no significant difference in progression free survival but only a trend towards better PFS in the group ≤ 67 years old compared to patients >67 years old (median PFS 84.0 days [50.0; 329], p=0.2). There was no significant difference in progression free survival based on smoking status (Table 5, 6).

We looked at whether there was a difference in survival under

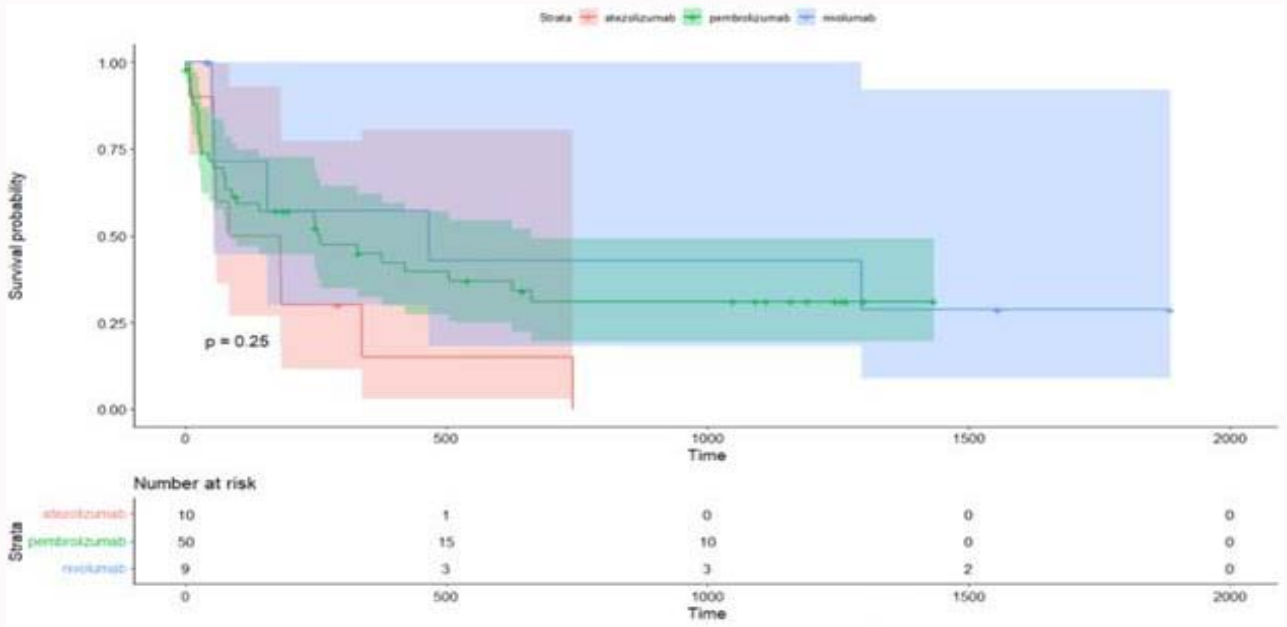

Figure 6: Comparison of PFS in the nivolumab, pembrolizumab and atezolizumab groups, for tumors PDL ≥ 1.

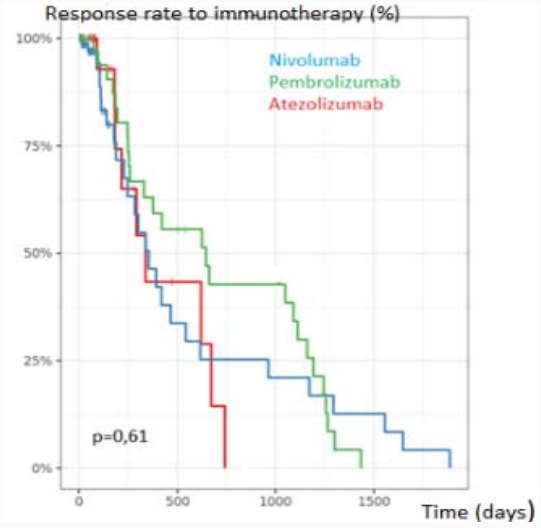

Figure 7: Response rate to ICIs, from immunotherapy initiation until progression.

immunotherapy according to the histology of our patients' bronchial tumors. We did not find any difference in survival depending on the histology (Figure 8).

Discussion

To our knowledge, this work is the first to directly compare OS and PFS of "real-life" patients with pretreated locally advanced or metastatic NSCLC undergoing nivolumab, pembrolizumab and atezolizumab in second line treatment. It was motivated by an unfavorable clinical feeling of the department's practitioners regarding the responses and survivals of patients on anti PDL1 (atezolizumab), by comparison with the experience gained with PD1 blockers (nivolumab and pembrolizumab) since 2015.

We highlighted:

- A lower response rate in the atezolizumab arm compared to the nivolumab and pembrolizumab arms.
- Significantly better PFS in the pembrolizumab arm compared with the nivolumab and atezolizumab arms.
- No significant difference in OS between the 3 groups.
- No significant difference in PFS between the 3 groups for analyses with PDL1 rate ≥ 1.
- No significant difference in the occurrence of adverse events between the 3 groups.

We showed a gain in PFS in favor of pembrolizumab compared with nivolumab or atezolizumab. This conclusion is reinforced in survival analyses performed when combining the nivolumab and atezolizumab arms versus pembrolizumab (Figure 6, p=0.0079). Patients are treated for a shorter period with atezolizumab, suggesting that disease in this group progress more rapidly and patients have an earlier deterioration in general condition. In our study, the response rate of patients treated with nivolumab was 15.7%, 16.3% with pembrolizumab and 5.4% with atezolizumab. These results are comparable to those in the literature and the primary studies, except for atezolizumab, which presents in our work, a half as good response compared to others studies. The meta-analysis of Passiglia and al. comparing the combined data of the OAK, Checkmate 017 and 057, and KEYNOTE-010 studies did not show a significant difference in PFS or OS between the three treatments. Nivolumab and pembrolizumab are associated with a better RR compared with atezolizumab (RR of 19%, 15.5%, and 13.6%, respectively) [10]. The study by Franchi and al investigated OS with nivolumab, pembrolizumab and atezolizumab in a cohort of 1,607 patients with pretreated advanced NSCLC, and showed no significant difference in survival [9].

Survival analyses for PDL1 rate ≥ 1, do not show better PFS for PDL1-positive patients treated with pembrolizumab (curves rather in favor of nivolumab, although not significant, Figure 7, p=0.25). It probably does not justify pembrolizumab systematic use for the treatment of PDL1-positive tumors, to the detriment of the other

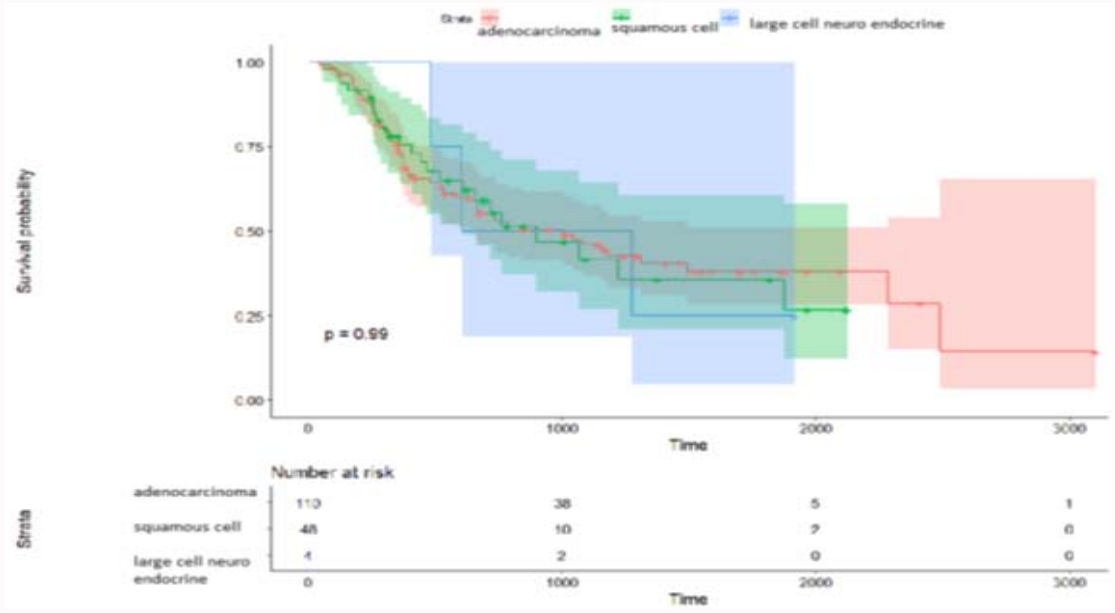

Figure 8: Comparison of OS on nivolumab, pembrolizumab and atezolizumab, according tumor histology.

two molecules. However indirectly, Peng et al. showed in a meta-analysis comparing the efficacy and safety of the use of nivolumab and pembrolizumab in locally advanced or metastatic NSCLC progressing after at least one line of treatment that there was no significant difference in OS or PFS between these two treatments regardless of PDL1 level, but that for a PDL1 rate ≥ 50% there was a significant improvement in the objective response rate (OR: 2.58, 95% CI, 1.22-5.49) in favor of pembrolizumab [11].

One of the arguments in favor of a poorer response with the atezolizumab is that it has no action on PD1 or PDL2, leaving these two pathways available to promote tumor proliferation [7,12]. The study by Duan et al. showed in a meta-analysis of 19 studies, a poorer OS of the anti PDL1 compared to PD1 blockers, but no difference in tolerance between the 2 classes of ICIs [13].

Dysthyroidism was the most common toxicity found in our study, affecting 41% of patients in the study population. This is the most common adverse event encountered with the use of ICIs in the literature [14]. Overall, toxicities appeared more severe and frequent in the nivolumab and pembrolizumab groups, compared with the atezolizumab group, with an occurrence rate for grade ≥ 3 toxicities of 10.2%, 6.12%, and 3.1% respectively in the study population [6,8]. Asthenia was the main toxicity reported in the atezolizumab arm, making it the best-tolerated treatment in our study. Fatigue was also the most frequently reported toxicity in the POPLAR study by Fehrenbacher et al. This work compared the safety of docetaxel and atezolizumab in patients treated for stage IIIB/IV NSCLC. Grade ≥ 3 events were, as in our study, infrequent, with an incidence of occurrence of 1% to 3% in the study population [15]. The study by Shankar et al. presenting the predictive factors for the development of adverse events on ICIs, identified a direct relationship between the duration of ICI treatment and the development of toxicities [16]. The apparent better tolerance of atezolizumab compared with PD1 blockers in our study may be the consequence that patients were treated for a shorter time in the atezolizumab group.

In our study, wo notice more severe (grade ≥ 3) adverse event in the nivolumab and pembrolizumab arms, but also better PFS, marking the existence of a link between the occurrence of adverse events and the efficacy of immunotherapy. In the meta-analysis by Zhang et al., which included all adverse events occurring with PD1 and PDL1 blockers in the treatment of NSCLC, it was shown that PFS and OS were significantly improved in the development of adverse events (PFS: HR=0.55, 95% CI=0.51-0.60, p<0.001 and OS: HR=0.74, 95% CI=0.68-0.81, p<0.001). Only PFS was improved with the occurrence of severe adverse events (grade ≥ 3) [17].

Age may also have an impact on the survival of patients undergoing ICIs, and we have shown in our study the tendency for a better PFS for patients aged 67 years or less. The study by Rosanne et al. showed the existence of a physiological decrease with age of PD1 expression and memory CD4+ cells [18]. The Daste et al. study replicated the results of the OAK, KEYNOTE 0-10, and CHECKMATE 017 and 057 pilot studies, and showed a trend toward poorer treatment efficacy in people over 65 years old [19].

Ninety-four percent of our study population are active or past smokers. Results in the literature remain heterogeneous regarding the impact of smoking status on the efficacy of ICIs. According to the work of Leighl et al. in the KEYNOTE-001 study comparing pembrolizumab and docetaxel in pre-treated NSCLC, there is a better median OS in the pembrolizumab arm for the smokers' groups (active or past smokers) compared to the non-smokers group [20]. The study by Rizvi et al. showed that in patients with pretreated NSCLC and treated with pembrolizumab, there is a molecular signature of smoking, which would induce a high tumor mutational burden and thus a better response to immunotherapy [21]. In contrast, in the OAK study by Rittmeyer et al. in the atezolizumab arm, the median OS was better in the non-smoking group (16.3 months, HR 0.71 (0.47-1.08)) than in the smoking group (13.2 months, HR 0.74 (0.61-0.88)) [7]. Smoking status is not, to date, one of the criteria that can be used to identify "good responders" to ICI therapy [22].

In our study, there was a trend towards better PFS in patients receiving first-line platinum and pemetrexed chemotherapy. This is

the most common first-line chemotherapy combination in our study. The administration of chemotherapy, by inducing cell death, leads to a specific anti-tumor immune response, similar to the vaccine [23], proliferation and maturation of antigen presenting cells [24], and the attraction of CD8 T cells to the tumor site [25], making the tumor environment more immunogenic. To date, no study has shown which treatment prior to immunotherapy would be the most immunogenic [26].

Finally, we did not find any significant difference in OS of our patients under immunotherapy, depending on the histology of the tumors. However, the study of Lee et al. studying the predictive factors of good response to immunotherapy, shows that squamous tumors have worse OS as demonstrated in the control (docetaxel) arm of CheckMate 017 trial (median OS, 6.0 months), than those with non-squamous tumors, as demonstrated in the control arm of CheckMate 057 trial (median OS, 9.4 months) [22].

This study as some limitations. This a single-center and retrospective study, leading to a selection bias. The population is limited, especially for the atezolizumab arm, which makes the 3 groups hardy comparable.

Pembrolizumab can only be used in second-line treatment for NSCLC in PDL1 positive tumors. This point leads to a bias, regarding survival analyses between the three molecules when PDL1 positivity is not considered.

Conclusion

This "real life" study on unselected patients shows a global equivalence of the three immunotherapies currently used in second line treatment of metastatic Non-Small Cell Lung Cancer (NSCLC) in progression after a first line of chemotherapy. However, the response rate with PDL1 blocker (atezolizumab), is lower than that observed with PD1 blocker (nivolumab and pembrolizumab), as well as the response rate observed in the pivotal OAK study. PFS and OS tend to be worse with PDL1 blocker than with the other two molecules, but the sample size of our study is insufficient to achieve a significant difference in OS. However, these data support the clinician's perception that PDL1 blocker is less effective.

In our study, pembrolizumab was the drug most likely to significantly prolong PFS in patients, but this result was biased by its use only in PDL1-expressing tumors, and there was no difference between the three molecules after considering PDL1 positivity.

There does not seem to be existing a real difference between nivolumab and pembrolizumab in survival, for PDL1-expressing tumors. A larger study would help define which PD1 blocker is the most effective in PDL1 positive tumors.

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