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Original article

Immune checkpoint inhibitors versus second line chemotherapy for patients with lung cancer refractory to first line chemotherapy

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ABSTRACT

Purpose. – Anti Programmed Death-ligand (PD1/PD-L1) directed immune-checkpoint-inhibitors (ICI) are widely used to treat patients with advanced non-small cell lung cancer (NSCLC) who progress after first line chemotherapy. The best strategy after early progression under first line has not been specifically studied.
Patients and methods. – We conducted a multicenter, retrospective study including all consecutive NSCLC patients progressing within the first 3 months following introduction of first-line chemotherapy and being treated with second line ICI monotherapy or chemotherapy between March 2010 and November 2017. We analysed the clinicopathological data and outcome under second line chemotherapy *vs.* second line ICI: objective response rate (ORR), progression-free survival (PFS), overall survival (OS.
Results. – We identified 176 patients with refractory disease, 99 who received subsequent immunotherapy and 77 undergoing chemotherapy. The 2 populations were comparable regarding the main prognostic criteria, median age was 60, main histology was adenocarcimoma (68.2%). PFS was not significantly different between both treatments 1.9 [1.8–2.1] versus 1.6 month [1.4–2.0] ($P = 0.125$). Compared to chemotherapy, ICI treated patients had a superior OS ($P = 0.03$) (Median [95% CI] OS 4.6 [2.8–6.7] versus 4.2 months [3.4–5.9] and a non-significant improvement in ORR (17.2% versus 7.9%, respectively, $P = 0.072$). Poor performance status (ECOG PS ≥ 2) and a higher number of metastatic sites (≥ 3) were associated with poorer prognosis. KRAS-mutated patients did not seem to benefit more from ICI than chemotherapy.
Conclusions. – ICI appears to be the preferred second-line treatment for patients who are refractory to first line chemotherapy.

1. Introduction

Non-small cell lung cancer (NSCLC) treatment has been transformed over the last decade with the development of immune checkpoint inhibitors (ICI). The first studies were conducted in second line treatment and pembrolizumab, nivolumab (both programmed death-1 (PD-1) inhibitors [1–4], and atezolizumab (PD-L1 inhibitor), are currently registered for second line treatment [5]. Pembrolizumab monotherapy is registered in first line for those with a PD-L1 tumor proportion score of $\geq 50\%$, and has recently been approved in combination with platinum-based chemotherapy regardless of PD-L1 for non-squamous NSCLC [6]. Until recently, the only available first line strategy for advanced NSCLC patients without a targetable driver, and with a PD-L1 below 50%, was a platinum doublet based chemotherapy.

However, only 20–40% of patients have an objective response on first line platinum-doublet chemotherapy and 20–30% have refractory disease (defined as the progression occurring within the first 3 months from the beginning of the treatment) [7,8]. The standard of care in second line, for patients with good performance status (PS) and no contra-indication is progressively switching from taxanes to ICI. The ICI registered are nivolumab and atezolizumab regardless of PD-L1 status or pembrolizumab for PD-L1 positive patients. Objective response rate (ORR) to 2nd line ICI is generally below 20%, and only a minority of patients obtains long-term benefits [1–3]. Furthermore, 40% of patients treated with ICI have progressive disease (PD) as best response. Champiat et al. and later Ferrara et al. [9,10]

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also described a hyperprogressive disease pattern on PD1/PD-L1 therapy with fast growing disease and poor prognosis. In these last studies, they found negative correlation on survival with age for the first one and with the number of metastatic locations for the second one.

Some predictive factors for ICI response were proposed and validated. PD-L1 expression on tumor cells was the first one to be addressed in clinical trials. LIPI (Lung Immune Pronostic Index) score based on Derived neutrophils ratio and LDH, was recently associated with overall survival (OS) in patients treated with ICI as a prognosis factor [11]. Unfortunately, these scores have a low sensitivity and specificity and are not statistically correlated with each other [12].

Patients with an aggressive disease, non-responding to first-line platinum-based chemotherapy, have a poor prognosis. It has been reported that, if time since initiation of the latest treatment is inferior to 6 months, patients have a poor prognosis on ICI with a median OS of 4.6 months [13]. Furthermore, it has been shown that response to chemotherapy immediately before nivolumab, particularly when combined with bevacizumab, increases the likelihood of disease control under nivolumab [14].

It is unclear to date whether patients with aggressive disease (progression within 3 months of start of first line treatment) can obtain a better survival with chemotherapy or ICI.

Therefore, we analysed data from advanced NSCLC patients with progression within the first three months of first line chemotherapy initiation and who received ICI or chemotherapy as second line treatment.

2. Patients and Methods

2.1. Patient selection

We conducted a retrospective, multicentric study. We included all consecutive patients with advanced or metastatic NSCLC who had PD according to RECIST 1.1 criteria within the first 3 months following first line platinum-based chemotherapy initiation and who subsequently received either 2nd line monotherapy ICI (nivolumab, pembrolizumab or atezolizumab) or 2nd line chemotherapy (docetaxel, paclitaxel, pemetrexed, gemcitabine). The study was conducted in 4 centers: Institut Gustave Roussy (Villejuif, France), University Hospital of Toulouse and Bordeaux (France) and Maastricht University Medical Centre (MUMC, the Netherlands). Patients with a targetable molecular alteration (Anaplastic lymphoma kinase, ROS1, and Epidermal Growth Factor Receptor) were excluded.

2.2. Data Collection and response assessment

We extracted data from the medical records, including: age and Eastern Cooperative Oncology Group Performance Status (ECOG PS) at the beginning of first line chemotherapy and before the start of second line therapy, gender, smoking history, histology, molecular profiling, details of first and second line therapy including start and end date, best response according to RECIST 1.1, and date of death or last follow-up).

We included patients who had begun first line treatment between March 2010 and November 2017 (Chemotherapy: March 2010–May 2017; ICI: May 2014–November 2017). Finally, we collected post second line treatment when it was done.

2.3. Study objectives and outcomes

Each center locally assessed response to systemic therapies using RECIST v1.1 criteria, defined as a complete or partial response (CR/PR), stable disease (SD) or PD during therapy. We collected data of progression; Progression Free Survival (PFS) and Overall Survival, date of death (or last follow-up) and patients' characteristics. ORR was defined as CR or PR.

We divided the PFS on both 2nd line treatments into 3 groups: Progression within the first 2 months corresponding approximately to hyperprogressive disease description, progression between 2 and 6 months and progression after 6 months. The 2 months cut-off for PFS was used corresponding to the first evaluation in daily practice of the three major ICI drugs. 6 months being approximately the time we observed long responders PFS curve stabilisation on ICI landmark study.

The primary objective was to compare progression free survival of NSCLC patients who are refractory to first line chemotherapy and who were subsequently treated with immunotherapy single agent versus second line chemotherapy. Secondary objectives were ORR, OS, and identification of potential predictive clinical or biological factors.

2.4. Statistical methods

Demographic and clinical data were presented according to treatment modality (chemotherapy vs. ICI). Qualitative variables were summarized using counts, percent, number of missing data. Comparisons between groups were performed through chi-square or Fisher's exact test.

Association between variables and early progression (< 2 months) on ICI treatment were quantified by the Odds Ratio (ORs) and their corresponding confidence intervals (CIs) in univariable and multivariable analysis using logistic regression models.

All survival times were calculated from the initiation of second line treatment and estimated by the Kaplan-Meier method with 95% confidence intervals (CI), using the following first event definitions: progression or death from any cause for PFS and death from any cause for OS. Patients still alive without event of interest were censored at last follow-up. Time-to-event end points were analysed by using the log rank test for univariable analysis and Cox proportional hazards regression model for multivariable analysis Hazard Ratios (HR) were estimated with 95% confidence intervals.

All statistical tests were two-sided and p-values < 0.05 were considered significant. Statistical analyses were conducted using Stata®, version 13.

3. Result

3.1. Patient characteristics

We identified 176 patients who fulfilled the eligibility criteria: 99 received second line immunotherapy and 77 second line chemotherapy. The main characteristics of these two cohorts are reported in Table 1. Both populations were comparable regarding age (60 yrs in the ICI group vs. 59 yrs in the chemo group), smoking habits (97% of smokers in both groups), and histological subtypes (adenocarcinoma for 65% and 73%) and molecular subtypes (KRAS mutation). The number of patients with more than 2 metastatic sites at diagnosis was higher in the ICI group (32.3% versus 15.6% $P = 0.01$). Metastatic sites at diagnosis and before second line were not different between both groups except for adrenals and nodal metastasis (respectively 30.3% and 28.3% in ICI group, 9.1% ($P < 0.001$) and 10.3% ($P = 0.003$) in the chemotherapy group). ECOG PS was significantly better in the ICI group, 27.6% of patients having a PS score of ≥ 2 versus 44.2% in the chemotherapy group ($P = 0.022$). Additionally, LIPI score was available for 62 patients (35.2.%), the percentage of patients with a poor LIPI score (i.e. score 1 or 2) was

Table 1
Patients characteristics and association between 2nd line therapy status and clinical categorical variables (univariable analysis).

2nd Line treatment				
	Total	ICI 2nd line	CT 2nd line	
	n = 176	*n* = 99	*n* = 77	
Age (years)				0.095
≥ 60	88 (50.0%)	44 (44.4%)	44 (57.1%)	
< 60	88 (50.0%)	55 (55.6%)	33 (42.9%)	
Smoking history				0.298
Current/Former	169 (97.1%)	95 (96.9%)	74 (97.4%)	
Non-smoker	5 (2.9%)	3 (3.1%)	2 (2.6%)	
Missing	2	1	1	
Histology				0.146
Adenocarcinoma	120 (68.2%)	64 (64.6%)	56 (72.7%)	
NSCLC-other	15 (8.5%)	12 (12.1%)	3 (3.9%)	
Squamous	41 (23.3%)	23 (23.2%)	18 (23.4%)	
PD-L1 status				
PD-L1 negative	11 (28.2%)	8 (22.9%)	3 (75%)	
PD-L1 positive	28 (71.8%)	27 (77.1%)	1 (25%)	
Missing	137	64	73	
Stage at diagnosis				0.117
III	18 (10.2%)	7 (7.1%)	11 (14.3%)	
IV	158 (89.8%)	92 (92.9%)	66 (85.7%)	
KRAS mutation				0.923
Yes	52 (45.6%)	34 (45.9%)	18 (45.0%)	
No	62 (54.4%)	40 (54.1%)	22 (55.0%)	
Missing	59	25	37	
N° metastatic sites before 2nd line				< 0.001
≤ 3	93 (52.8%)	40 (40.4%)	53 (68.8%)	
> 3	83 (47.2%)	59 (59.6%)	24 (31.2%)	
Performance Status before 2nd line				0.022
0–1	114(65.1%)	71 (72.4%)	43 (55.8%)	
≥ 2	61 (34.9%)	27 (27.6%)	34 (44.2%)	
Missing	1	1	0	
dNLR >3 before 2nd line				0.126
No	71 (55.5%)	48 (60.8%)	23 (46.9%)	
Yes	57 (44.5%)	31 (39.2%)	26 (53.1%)	
Missing	48	20	28	

higher in the chemotherapy group (Chemo: 93.8% vs. ICI: 63.0%, *P* = 0.025).

3.2. Patient outcome

Median PFS [95% CI] for the chemotherapy versus the ICI subgroup was [1.9 (1.8–2.1) versus 1.6 months (1.4–2.0)] (*P* = 0.125) (Fig. 1). We divided PFS on 2nd line treatment into 3 groups: Progression within the first 2 months, progression between 2 and 6 months and progression after 6 months. The population's distribution in the various previously defined PFS groups is shown in Table 2. There were significantly more patients who did not progress at 6 months in the ICI group (22.3% vs. 10.4%, *P* = 0.006).

Overall survival was better in ICI group than in chemotherapy group (*P* = 0.031) with a median OS of 4.6 months [95%CI: 2.8; 6.7] versus 4.2 months [95%CI: 3.4; 5.9] (Fig. 2). Noteworthy, immunotherapy OS curve goes below than chimiotherapy's curve in the first three months in this figure.

The ORR was numerically increased in patients treated with ICI compared to chemotherapy: 17.2% vs. 7.9% (*P* = 0.072). These results are non significant.

3.3. Subgroup analysis

Factors associated with both poor PFS and poor OS in univariable analysis for both populations were ECOG PS ≥ 2 (*P* = 0.027 and *P* = 0.001, respectively), more than 2 metastatic sites (p = 0.022 and *P* = 0.002) and liver metastases (*P* = 0.027 and *P* = 0.014) (Table 3). High LIPI score (1 or 2) was also associated with a poor OS (*P* = 0.016). In Cox multivariable analysis after backward selection, ICI [HR 0.71 (0.51–0.98), *P* = 0.040] and ≥ 3 metastatic sites [1.52 (1.10–2.10), *P* = 0.011] were both related to PFS (Table 4).

We considered, then, the factors associated with rapid progression on ICI treatment (< 2 months). In univariable analysis, Performance Status before 2nd line [Odds Ratio OR 3.40 [1.23; 9.43] *P* = 0.019], more than 2 metastatic sites (OR 2.57 [1.12; 5.89] *P* = 0.025) and hepatic metastasis [OR 4.40 [1.50; 12.90] *P* = 0.007] were associated with a rapid progression. Multivariable model confirmed these results for hepatic metastasis [OR 5.10 (1.68; 15.45) *P* = 0.004] and Performance Status ≥ 2 [OR 3.90 (1.35; 11.28), *P* = 0.012] (Table 5)

We compared ICI and chemotherapy PFS and OS results for the 2 main histologic subtypes and for KRAS status. We did not find any difference between treatments in OS (*P* = 0.27) and PFS (*P* = 0.16) for both major histologic subtypes of NSCLC (squamous and adenocarcinoma). Patients bearing KRAS mutation (*n* = 52; 18 in chemotherapy subgroup, 34 in ICI subgroup) had a median PFS of 1.9 month [1.8;3.4] in the chemotherapy group and 1.4 month [1.1;2.0] in the ICI group (*P* = 0.509). For KRAS wild-type patients (*N* = 62; 22 in chemotherapy subgroup, 40 in ICI subgroup), even though PFS of ICI [median PFS 1.7 month (1.1;7.4)] and chemotherapy patients [1.9 months (1.4; 4.1)] (*P* = 0.129) were similar, OS in ICI treated patients was significantly better than in the chemotherapy group [median OS 6.0 (3.2; NR) *P* = 0.033] (Fig. 3).

In ICI treated patients, those with positive PD-L1 status (≥ 1%) (*n* = 27) was associated with a better PFS (*P* = 0.009) (median PFS 3.7 [1.1-not reached] versus 0.7 months [0.4–1.6] (*P* = 0.009) (*n* = 8).

3.4. Third line treatment

In the ICI group, 18 (18.2%) patients were still under treatment. 58 (58.6%) did not receive further treatment and 23 (23.2%) patients

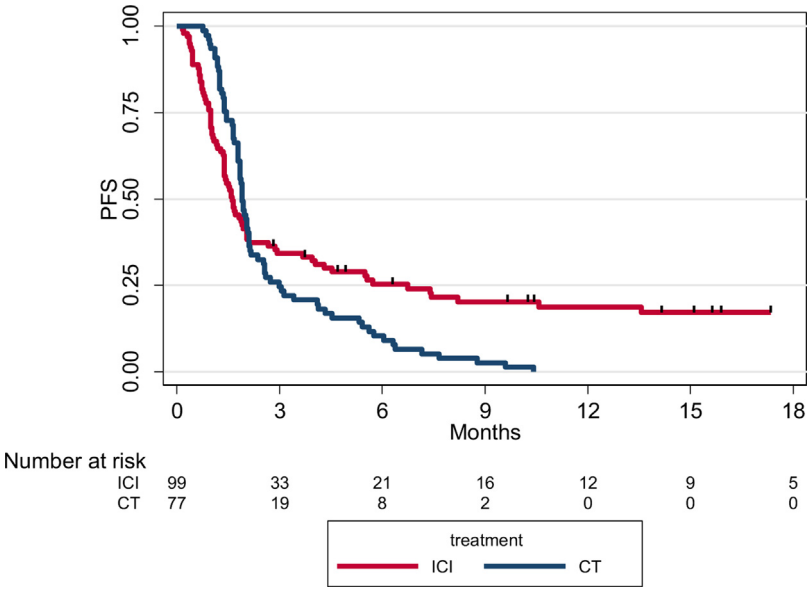

Fig. 1. Kaplan Meier curves for Progression Free survival for both ICI group and CT group.

Table 2
PFS sub-class analyses.

2nd Line treatment				
	Total	ICI 2nd line	CT 2nd line	
	n = 176	*n* = 99	*n* = 77	
PFS subdivised (3cl) (*n* = 171)				*P* = 0.006
<2 months PD	100 (58.5%)	58 (61.7%)	42 (54.5%)	
2–6 month PD	42 (24.6%)	15 (16.0%)	27 (35.1%)	
No PD at 6 months	29 (17.0%)	21 (22.3%)	8 (10.4%)	
Missing	5	5	0	

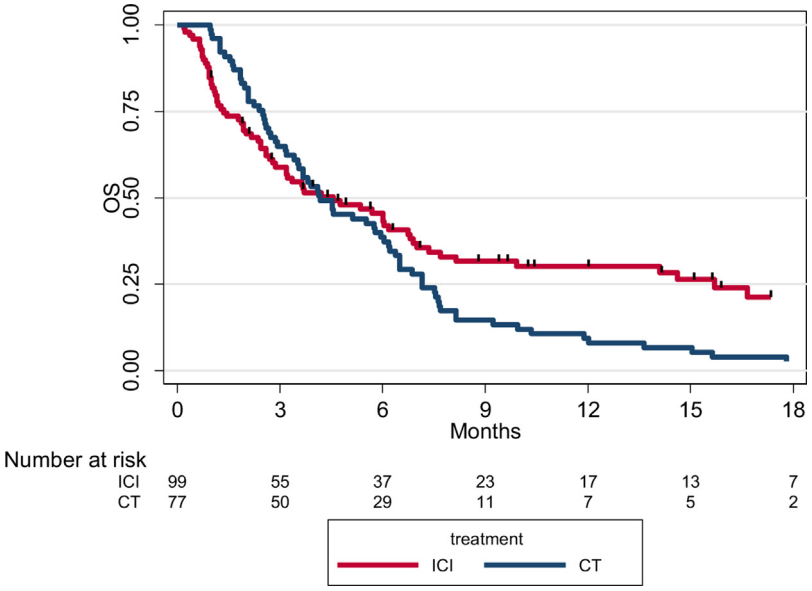

Fig. 2. Kaplan Meier curves for Overall Survival for both ICI group and CT group.

received third line treatment (chemotherapy for 21 patients and tyrosine Kinase inhibitors for 2 of them).

In the chemotherapy group, 53 patients (68.8%) didn't receive third line treatment, 24 (31.2%) received third line treatment (10 chemotherapies, 6 nivolumab and 3 Tyrosine Kinase inhibitors).

4. Discussion

Advanced NSCLC patients who are refractory to first line chemotherapy are frequent in our daily practice. The prognosis of these patients remains poor, therapeutic options are often limited and the best treatment strategy remains uncertain. No

Table 3
Univariable analysis of characteristics associated with OS and PFS.

	OS		PFS	
Variable	Median (months) [CI 95%]	*P*-value	Median (months) [CI 95%]	*P*-value
Treatment		0.0305		0.1248
Chemotherapy	4.2 [3.4;5.9]		1.9 [1.8;2.1]	
Immunotherapy	4.6 [2.8;6.7]		1.6 [1.4;2.0]	
Number of metastatic location before 2nd line		0.0017		0.0222
0-1-2 (ref)	6.4 [4.5;7.2]		2.0 [1.8;2.6]	
3 or +	2.6 [2.0;3.6]		1.5 [1.2;1.9]	
Performance Status		0.0010		0.0273
0–1	6.0 [3.8;6.9]		2.0 [1.8;2.5]	
2–3–4	2.5 [1.9;4.2]		1.4 [1.2;1.9]	
Hepatic metastases		0.0143		0.0275
No	4.8 [3.7;.2]		1.9 [1.8;2.1]	
Yes	2.9 [1.8;.0]		1.4 [1.2;1.8]	
LIPI Score		0.0158		0.1985
0	18.7 [2.6;NR]		2.6 [1.4;7.4]	
1–2	3.7 [1.9;5.9]		1.8 [1.3;2.9]	

Table 4
Final multivariable analysis of characteristics associated with OS and PFS (after backward selection method).

n = 175	OS		PFS	
Variable	HR [CI 95%]	*P*-value	HR [CI 95%]	*P*-value
Treatment		0.045		0.040
Chemotherapy (ref)	1.00		1.00	
Immunotherapy	0.70 [0.49; 0.99]		0.71 [0.51;0.98]	
Number of metastatic location before 2nd line		0.005		0.011
0-1-2 (ref)	1.00		1.00	
3 or +	1.64 [1.16;2.31]		1.52 [1.10;2.10]	
Performance Status		0.038		
0–1 (ref)	1.00			
2–3–4	1.46 [1.02;2.09]			

Table 5
Characteristics associated with fast progression (< 2 months) on ICI.

n= 98	Final model (after backward selection method)	
Variable	OR [CI 95%]	*P*-value
Performance Status		
0–1 (ref)	1.00	
2–3–4	3.90 [1.35;11.28]	0.012
Hepatic metastasis		
No (ref)	1.00	
Yes	5.10 [1.68;15.45]	0.004

studies specifically studied response to chemotherapy versus ICI in this setting. Although landmark studies have collected data regarding previous treatment response, they have not looked on best treatment approach for refractory disease patients [1–3,5] Some retrospective studies described a lower ORR with ICI in chemorefractory patients, but these studies did not address the best treatment strategy (i.e. ICI or chemotherapy 2nd line) in first line chemotherapy refractory patients [13–16].

Our multicenter, retrospective study evaluated the outcome of second line ICI and chemotherapy treatment in this specific patient population; OS was significantly improved with ICI compared with chemotherapy but non clinically relevant as it improves OS of 0,4 months. Although ORR (17.2%) on ICI was comparable to landmark trials [1–3,5], the prognosis patients who are refractory to first line chemotherapy remains poor with a mortality rate of 80% within the first year. In contrast with the landmark trials, median PFS and OS were low in our series for both chemotherapy and ICI (PFS: 1.8 and OS 4.2 months, respectively), compared with a median PFS of 4.2 (docetaxel) and 2.3 months (nivolumab), and a median OS of 9.4 (docetaxel) and 12.2 months (nivolumab) in the CheckMate 057 trial [1,2,4,5].

Treating patients who do not respond to first line chemotherapy has always been challenging [17]. In this context, results with 2nd line chemotherapy have been disappointing. Therefore, it is of interest to assess ICI efficacy in this patient population. We found that, although OS with 2nd line ICI is superior to OS with 2nd line chemotherapy, outcome remains poor. Mechanism that could explain this result is that the immune system might be overloaded by tumor aggressiveness in these immunocompromised patients. As an example, patients have frequently a poor performance status (PS $\geq$ 2 for 34.9% of patients) at the time of second line beginning due to aggressive disease with organ dysfunction and comorbidities.

It has been shown for patients progressing rapidly under first line chemotherapy that the combination of docetaxel and one of the VEGF (Vascular Endothelial Growth Factor) inhibitors nintedanib or ramucirumab was more effective than docetaxel alone, especially for first line refractory patients and in the adenocarcinoma subgroup [18,19]. In Lume–Lung 1, patients with adenocarcinoma and time since start of first line therapy (TSFLT) < 9 months, median PFS was 3.6 months for docetaxel and nintedanib association versus 1.5 months for chemotherapy alone in second line for pretreated patients. This median PFS of 1.5 months for second line docetaxel without nintedanib is closed from our results (1.6 months for second line chemotherapy arm). Interestingly our median OS result for this population is shorter in our study in chemotherapy arm (4.2 months) than LUME (7.9 months in chemotherapy alone arm). Two main reasons may explain this OS difference. First of all our patients had PS $\geq$ 2 for 34% of them on contrary of LUME-lung 1 in which only PS0-1 patients were enrolled. Second of all, we had a shorter cut-off to define refractory disease (9 months versus 3 months). Nevertheless, considering PFS and OS differences between 2nd line ICI on our study (respectively 1.9 months and 4.6 months) and 2nd line nintedanib and docetaxel in Lume-lung 1 (respectively 3.6 months

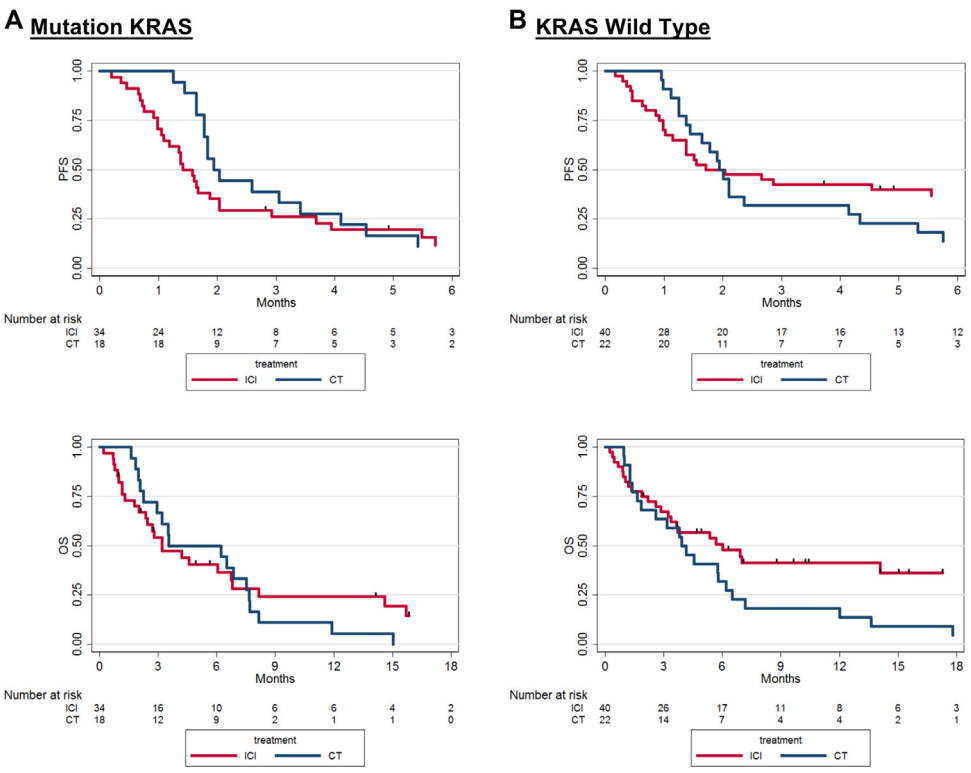

Fig. 3. Effect of treatment on KRAS mutated patients and KRAS Wild Type. PFS (2A) and OS (2B).

and 10.2 months), we might consider VEGF inhibitors in second line as an option for platinum refractory patients.

Factors related to unfavorable prognosis in our study were poor PS, 3 or more metastatic sites and especially the presence of liver metastases as already shown by Tamiya et al. [20], and Riihimäki et al.[21]. This poor prognosis on ICI after first line progression was previously reported by Garde Noguera et al. with a median OS of 4.6 months for patients progressing within the six first months of platinum-doublet first line chemotherapy [13]. The LIPI, developed by Mezquita et al. for outcome on ICI, could not be precisely studied due to missing LIPI for 64.8% of patients. Nevertheless, we found that a high LIPI is a poor prognostic factor on OS for our patients with a median OS of 3.7 months for LIPI score of 1 or 2 vs. 18.7 months for LIPI 0 in the whole population. Another feature raised by our study is a possible hyperprogressive disease patterns with a PFS cuve in disfavour of ICI in the two first months. It appears that patients with a large number of metastatic sites (≥ 3) and an altered general state ($PS \geq 2$) are predisposed to progress within the first two months. If one of these 2 prognosis factors is present, the probability of a rapid progression is 78% versus 39.2% if none of them is present. Considering that registration, following the landmark studies, need a PS of 0–1 for ICI prescription, we may stay cautious on ICI prescription for $PS \geq 2$ patients.

This data are consistent with conclusions of Ferrara et al. [9]. Our study failed to formally identify patients who may benefit more from chemotherapy than immunotherapy.

Our study has some limitations. First, it is a retrospective study with inherent selection bias and missing data, although both groups were well balanced for main clinical and biological characteristics. Most of the patients treated with chemotherapy were treated before 2015 and patients with ICI after 2015 (immunotherapy approval). Therefore, some patients undergoing second line chemotherapy did not benefit from third line ICI as it was not available at that time although some ICI patients could potentially benefit from third line docetaxel after progression. Moreover, Schvartsmann et al. [22] suggested that chemotherapy after ICI is more effective, contributing to OS improvement in ICI patients.

Noteworthy, first line therapy strategy is currently changing with the recent approval of platinum doublet and pembrolizumab combination [6]. These results let us think that the additive effect of ICI to CT will still be seen in patient refractory to chemo. Nevertheless in this last study, 22% of patients had a progressive disease at 3 months. The next challenge will thus be to determine the best strategy in patients who are refractory to the combination.

Despite its retrospective nature, this study helps to clarify the best strategy to set up in patients who are refractory to first line chemotherapy. Second line immunotherapy seems to be associated with a more durable benefit in this poor prognosis population.

Disclosure of interest

The authors declare that they have no competing interest.

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