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Second-line treatment outcomes after progression from first-line chemotherapy plus immunotherapy in patients with advanced non-small cell lung cancer

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ABSTRACT

Introduction: Chemotherapy plus immunotherapy is the standard of care for patients with metastatic NSCLC. No study has evaluated the outcomes of second-line chemotherapy treatments after progression following first-line chemo-immunotherapy.

Method: This multicenter retrospective study evaluated the efficacy of second line (2L) chemotherapies after progression under first-line (1L) chemo-immunotherapy, measured by overall survival (2L-OS) and progression free survival (2L-PFS).

Results: A total of 124 patients were included. The mean age was 63.1 years, 30.6 % of the patients were female, 72.6 % had an adenocarcinoma and 43.5 % had a poor ECOG-performance status prior to 2L initiation. Sixty-four (52.0 %) patients were considered resistant to first line chemo-immunotherapy. (1L-PFS < 6 months). In 2L treatments, 57 (46.0 %) patients received taxane monotherapy, 25 (20.1 %) taxane plus anti-angiogenic, 12 (9.7 %) platinum-based chemotherapy and 30 (24.2 %) other chemotherapy.

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At a median follow-up of 8.3 months (95 %CI: 7.2–10.2), post initiation of 2L treatment, the median 2L-OS was 8.1 months (95 % CI: 6.4–12.7) and the median 2L-PFS was 2.9 months (95 %CI: 2.4–3.3). Overall, the 2L-objective response and 2L-disease control rates were 16.0 %, and 42.5 %, respectively.
Taxane plus anti-angiogenic and platinum rechallenge achieved longest median 2L-OS: not reached (95 %CI: 5.8-NR) and 17.6 months (95 %CI 11.6-NR), respectively (p = 0.05).
Patients resistant to the 1L treatment had inferior outcomes (2L-OS 5.1 months, 2L-PFS 2.3 months) compared with 1L responders (2L-OS 12.7 months, 2L-PFS 3.2 months).
Conclusion: In this real-life cohort, 2L chemotherapy achieved modest activity following progression under chemo-immunotherapy. 1L-resistant patients remained a refractory population, highlighting a need for new 2L strategies.

1. Introduction

Immunotherapy has changed the therapeutic landscape for patients with lung cancer [1–5]. The combination of platinum-based chemotherapy with anti-PD-(L)1 or in association with anti-CTLA4, have become the standard of care for patients with previously untreated advanced NSCLC with PD-L1 expression < 50 % and no driver mutations [1,2,6–8]. These combinations are also an option for patients with high PD-L1 [1,2].

Five-year survival rates following chemo-immunotherapy range between 18.4 % and 31.9 % [9,10], and progression after first line (1L) therapy occurs in the majority of patients. However, there is currently no standard of care for second line (2L) treatments in patients experiencing progression following combination therapies of platinum-doublet chemotherapy and immune checkpoint inhibitors (chemo-ICI).

After progression following chemo-ICI, 2L treatments usually incorporate chemotherapy agents previously used in the pre-ICI era, such as docetaxel alone or combined with antiangiogenic therapies, or monotherapies such as gemcitabine, and vinorelbine. In patients who initially experience disease response to 1L treatment, rechallenge with platinum-based chemotherapy is a potential option. Due to the rapid shift of focus toward ICI-based treatments over the last 5 years with ICI, there is limited research characterizing the 2L options after chemo-ICI.

Hence, we aimed to describe the efficacy of various 2L chemotherapy regimens in patients with advanced NSCLC upon progression after 1L chemo-ICI in a large retrospective cohort conducted across 14 cancer centers in 7 countries.

2. Material and methods

2.1. Study design and patients

In this multicentric international study, we retrospectively included patients from 14 centers in Canada, France, Italy, Spain, the Netherlands, the United-Kingdom and the United-States of America. This study was approved by the Ethical Committee of the CHU de Montréal. We enrolled patients aged ≥ 18 years, diagnosed with advanced NSCLC with progressive disease, who had undergone 1L chemo-ICI (anti-PD-1 alone or anti-PD-1 in combination with anti-CTLA-4) regimens and were eligible for 2L chemotherapy (including taxane +/- antiangiogenic, platinum based rechallenge, gemcitabine, vinorelbine, pemetrexed, and others) between March 2017 and January 2022. Second line targeted therapies or investigational drugs were excluded from the study (Fig. 1). Data were extracted from medical records.

2.2. Endpoints

The primary endpoint of this study was the 2L-overall survival (2L-OS) treatment, defined as the time between initiation of 2L treatment and death from any cause. Secondary endpoints were 2L-progression free survival (2L-PFS), 2L-objective response rate (2L-ORR) and 2L-disease control rate (2L-DCR) with disease response assessed by investigators. 2L-PFS was defined as the time between L2 start and progression or death whichever occurred first. ORR was defined as partial plus complete responses according to the investigator's discretion as per clinical practice of each center (every 8–12 weeks). DCR was defined as ORR plus stable disease as per clinical practice of each center.

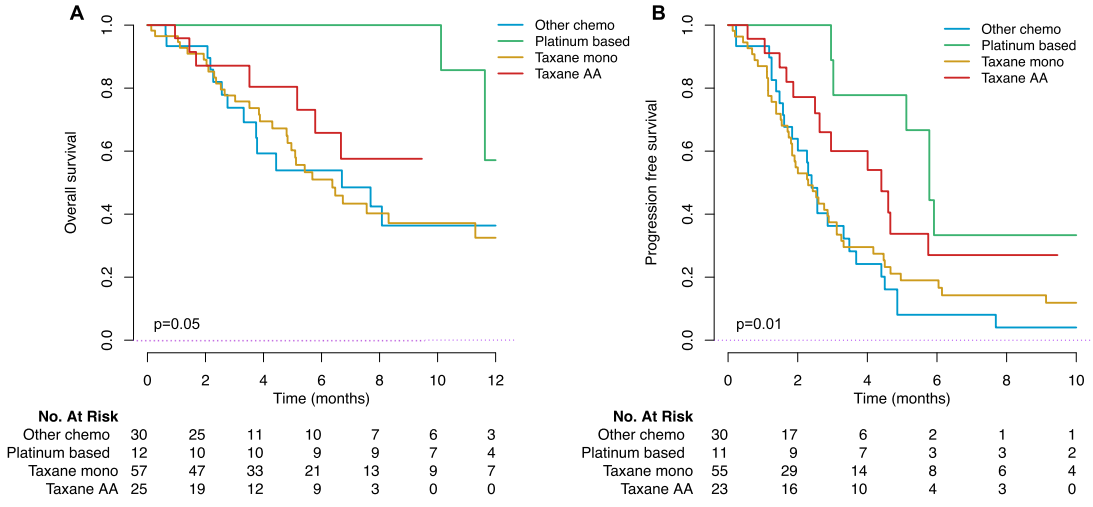

Fig. 1. Kaplan Meier curves for overall and progression free survival according to the second line treatments.

2.3. Subgroup analysis

We performed subgroup analysis according to the type of treatment received (platinum rechallenge, taxane +/- anti angiogenic, other chemotherapy regimens), and to PFS to first line treatment (1L-PFS) outcomes, with a resistant group defined as patients with 1L-PFS inferior to 6 months, and a responder group if the 1L-PFS was higher than 6 months. We also evaluated outcomes according to the histological type (adenocarcinoma and squamous cell carcinoma). Finally we performed a subgroup analysis according to the PD-L1 expression defined as high if expression was ≥ 50 %, intermediate for expression between 1 % and 49 %, and low if expression was < 1 %.

2.4. Statistical analysis

Median values (interquartile range) and frequencies (percentage) were provided for descriptions of continuous and categorical variables, respectively. Mean and proportions were compared using the Student's *t*-test and chi-square test (or Fisher's exact test, if appropriate), respectively. OS and PFS were estimated using the Kaplan-Meier method and described using median values with their 95 % confidence intervals (95 % CI). Follow-up was calculated using the reverse Kaplan-Meier method.

All statistical analyses were performed with R studio version 2.15.2, p-values < 0.05 were considered statistically significant and all tests were two-sided.

3. Results

3.1. Characteristics of the study population

A total of 124 patients were included in the analysis (Flowchart available as Supplementary Fig. 1 and Supplementary Text). The mean age was 63.1 years, 30.6 % of the patients were female and 72.6 % had an adenocarcinoma. Performance status (PS) prior to 2L initiation was 2 or 3 in 37 (43.5 %) patients. Among the 124 patients, 64 (52.0 %) patients had a tumor considered resistant to first line chemo-ICI. The main characteristics of the population are summarized in Table 1.

As second line treatments, 57 patients (46.0 %) received taxane monotherapy, 25 (20.1 %) taxane plus anti-angiogenic, 12 (9.7 %) platinum-based chemotherapy and 30 (24.2 %) other chemotherapy drugs. Patients with squamous cell carcinomas did not receive anti angiogenic containing regimens. Patients with brain metastasis at

Table 1
Characteristics of the study population according to the second-line regimen received.

		Total population (N=124)	Taxane monotherapy (N=57)	Other chemotherapy drugs (N=30)	Taxane + anti-angiogenic (N=25)	Platinum based (N=12)	p
Age at L2 start	> 65 years	52 (51.5%)	27 (57.4%)	11 (52.4%)	9 (42.9%)	5 (41.7%)	0.62
Gender	Female	38 (30.6%)	16 (28.1%)	10 (33.3%)	10 (40%)	2 (16.7%)	0.09
Smoking status	Never	8 (6.5%)	3 (5.3%)	3 (10%)	1 (4%)	1 (8.3%)	0.92
Histology	Adenocarcinoma	90 (72.6%)	42 (73.7%)	13 (43.3%)	24 (96%)	11 (91.7%)	<0.001
	Squamous	19 (15.3%)	7 (12.3%)	11 (36.7%)	0 (0%)	1 (8.3%)	
	Other	15 (12.1%)	8 (14%)	6 (20%)	1 (4%)	0 (0%)	
PD-L1 expression	0%	56 (49.1%)	26 (47.3%)	15 (60%)	13 (52%)	2 (22.2%)	0.45
	1 to 49%	48 (42.1%)	24 (43.6%)	8 (32%)	11 (44%)	5 (55.6%)	
	≥ 50%	10 (8.8%)	5 (9.1%)	2 (8%)	1 (4%)	2 (22.2%)	
	Missing	10	2	5	0	3	
Molecular alterations	*KRAS* mutation	33 (32.1%)	21 (43.8%)	6 (27.3%)	5 (21.7%)	1 (10%)	0.21
	Missing	21	9	8	2	2	
	BRAF mutation	3 (3%)	1 (2.2%)	0 (0%)	1 (4.2%)	1 (10%)	0.41
	Missing	24	11	10	1	2	
	ROS1 rearrangement	1 (1%)	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	1
	Missing	22	10	10	0	2	
	ALK rearrangement	1 (0.9%)	0 (0%)	0 (0%)	1 (4.0%)	0 (0%)	0.23
	Missing	14	6	8	0	0	
First line chemotherapy combined with type of immune checkpoint inhibitor	CTLA4 + PD1 combination	1 (0.8%)	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0.04
	PD1 inhibitor	78 (62.9%)	30 (52.6%)	18 (60%)	22 (88%)	8 (66.7%)	
	PDL1 inhibitor	45 (36.3%)	26 (45.6%)	12 (40%)	3 (12%)	4 (33.3%)	
First line outcome	Resistant (1L PFS < 6 months)	64 (52.0%)	13 (52.0%)	17 (56.7%)	29 (51.8%)	5 (41.7%)	0.86
	Responder (1L PFS ≥ 6 months)	59 (48.0%)	12 (48.0%)	13 (43.3%)	27 (48.2%)	7 (58.3%)	
	Missing	1	0	0	1	0	
Metastatic location	Bone	59 (47.6%)	25 (43.9%)	14 (46.7%)	16 (64%)	4 (33.3%)	0.44
	Liver	17 (13.7%)	8 (14%)	4 (13.3%)	3 (12%)	2 (16.7%)	0.95
	Brain	26 (21.0%)	6 (10.5%)	5 (16.6%)	10 (40.0%)	5 (41.7%)	0.005
Number of metastatic sites	> 2	67 (57.8%)	33 (58.9%)	16 (59.3%)	15 (60%)	3 (37.5%)	0.71
	Missing	8	1	3	0	4	
Performance status at 2L initiation	0	13 (15.3%)	10 (23.3%)	1 (4.5%)	2 (12.5%)	0 (0%)	0.03
	1	35 (41.2%)	16 (37.2%)	6 (27.3%)	9 (56.2%)	4 (100%)	
	2-3	37 (43.5%)	17 (39.5%)	15 (68.2%)	5 (31.2%)	0 (0%)	
	Missing	39	14	8	9	8	

second line onset received more platinum rechallenge and taxane plus anti angiogenic as 2L-treatment. Finally, patients with poor PS were more frequently treated with monotherapy (other chemotherapy group) in the 2L setting (Table 1). More information regarding the 5 patients that received ICI rechallenge are available in the Supplementary Text.

3.2. Survival and response endpoints

After a median follow-up of 8.3 months (95 % CI: 7.2–10.2) post initiation of 2L treatment, sixty patients had died, and the median 2L-OS was 8.1 months (95 % CI: 6.4–12.7). According to the regimen administered, median 2L- OS was: 6.4 months (95 % CI: 5.0–12.9) in the taxane monotherapy group, 6.7 months (95 % CI: 3.7-not reached (NR)) in the other chemotherapy group, NR (5.8-NR) in the taxane plus anti-angiogenic group, and 17.6 months (95 % CI: 11.6-NR) in the platinum-based chemotherapy group (Log Rank p = 0.05) (Table 2 and Fig. 1).

The median 2L-PFS was 2.9 months (95 %CI: 2.4–3.3). According to the regimens administered, median 2L-PFS was: 2.3 months (95 %CI: 1.8–3.1) in the taxane monotherapy group, 2.4 months (95 %CI: 1.8–3.7) in the other chemotherapy group, 4.4 months (95 % CI: 2.6-NR) in the taxane plus anti-angiogenic group, and 5.8 months (5.1-NR) in the platinum-based chemotherapy group (Log Rank p = 0.01) (Table 2 and Fig. 1).

2L-ORR and 2L-DCR were 16.0 %, and 42.5 %, respectively (Table 3). 2L-ORR was numerically higher in the taxane monotherapy group (22.2 %, p = 0.08) and 2L-DCR was the highest in the platinum-based group (81.8 %, p = 0.006), Table 3 and Supplementary Fig. 2. Only one patient with an ECOG-PS 3 received a second line treatment in our cohort, with progression as best response.

3.3. Subgroup analysis by 1L chemo-ICI response

Baseline characteristics were well balanced between resistant and responders subgroup. Patients with resistant tumors to first line chemo-ICI had poorer ECOG-PS (p = 0.02) compared with patients with responding tumors (Table 4).

Resistant subgroup: In this subgroup, median 2L-OS and 2L-PFS were 5.1 months (95 % CI: 3.9–8.3) and 2.3 months (95 % CI: 1.7–3.0), respectively (Table 2). Objective response was obtained in 11.3 % of the patients, and disease control in 31.7 %, (Table 3 and Fig. 2). In this subgroup, taxane + anti angiogenic and platinum based chemotherapy achieved the best outcomes compared with the other regimens, in term of 2L-OS, 2L-PFS and response (Tables 2 and 3).

Responders subgroup: Median 2L-OS and 2L-PFS were 12.7 months (8.1-NR) and 3.2 months (2.9–5.8), respectively (Table 2). Objective response was obtained in 21.1 % of the patients, and disease control in 35.0 %, (Table 3 and Fig. 2). Similarly to the resistant subgroup, taxane + anti angiogenic and platinum based achieved the best outcomes compared with the other regimens.

3.4. Subgroup analysis by histology

Adenocarcinomas: Median 2L-OS and 2L-PFS were 11.6 months (95 % CI: 6.7–13.4) and 3.1 months (95 %CI: 2.6–4.7), respectively (Supplementary Table 1). In this subgroup, ORR was 18.8 % and DCR 47.6 %, Supplementary Table 2.

Squamous cell carcinoma: Median 2L-OS and 2L-PFS were 6.7 months (95 %CI: 5.0-NR) and 2.6 months (95 % CI: 1.8-NR), respectively (Supplementary Table 1). In this subgroup, ORR was 7.7 % and DCR 29.4 %, Supplementary Table 2.

3.5. Subgroup analysis by PD-L1 expression

Among the 114 patients with available PD-L1 status, 10 had high PD-L1 expression (≥50 %). The median 2L-OS was numerically longer in high PD-L1 subgroup (10.1 vs 8.3 and 6.4 months for high, intermediate and low PD-L1 groups, respectively; p = 0.5), Supplementary Table 1. The same trend was observed for 2L-PFS (9.7 vs 2.6 and 2.3 months for high, intermediate (1 % to 49 %) and low (<1%) PD-L1 groups, respectively; p = 0.1). Patients with high PD-L1 expressing tumors had higher ORR compared with intermediate and low PD-L1 expressing tumors (44.4 %, 17.1 % and 9.3 %, respectively; p = 0.003). Similar results were observed for the DCR, that was numerically higher in the high PD-L1 expression subgroup as compared to the intermediate and low ones (70.0 %, 35.7 % vs and 36.7 %, respectively; p = 0.14) Supplementary Table 2.

Table 2
Median l2 overall and progression free survival in the overall population and subgroups.

	Progression free survival, months Median (95%CI)	p	Overall survival, months Median (95%CI)	p
Overall population (n=124)	**2.9 (2.4-3.3)**		**8.1 (6.4-12.7)**	
- Taxane monotherapy	2.3 (1.8-3.1)	0.01	6.4 (5.0-12.9)	0.05
- Taxane + anti-angiogenic	4.4 (2.6-NR)		Not reached (5.8-NR)	
- Platinum-based chemo	5.8 (5.1-NR)		17.6 (11.6-NR)	
- Other chemotherapies	2.4 (1.8-3.7)		6.7 (3.7-NR)	
Primary resistance to chemo-ICI population (n=64)	**2.3 (1.7-3.0)**		**5.1 (3.9-8.3)**	
- Taxane monotherapy	1.8 (1.4-2.9)	0.02	5.0 (2.7-NR)	0.3
- Taxane + anti-angiogenic	4.0 (2.6-NR)		5.8 (5.2-NR)	
- Platinum-based chemo	5.9 (3.2-NR)		10.1 (NR-NR)	
- Other chemotherapies	2.0 (1.4-3.7)		3.7 (2.6-NR)	
Responder to chemo-ICI population (n=59)	**4.4 (2.8-5.7)**		**12.7 (8.1-17.6)**	
- Taxane monotherapy	2.8 (2.0-12.9)	0.4	7.6 (5.4-NR)	0.2
- Taxane + anti-angiogenic	4.6 (2.5-NR)		NR (NR-NR)	
- Platinum-based chemo	5.8 (5.1-NR)		17.6 (11.6-NR)	
- Other chemotherapies	2.8 (2.4-NR)		12.6 (7.7-NR)	

Table 3
Response endpoints in the overall population and subgroups.

	Objective response rate % (n)	p	Disease control rate % (n)	p	PFS 6 months % (95%CI)	OS 6 months % (95%CI)
Overall population (n=124)	**16.0% (15)**		**42.5% (48)**		**19.0 (12.6-28.6)**	**59.3% (50.2-70.0)**
- Taxane monotherapy (n=57)	20.8% (11)	0.09	32.1% (17)	0.006	19.0 (10.7-33.7)	51.0 (38.5-67.5)
- Taxane + anti-angiogenic (n=25)	22.2% (4)		59.1% (13)		27.0 (12.0-60.8)	65.8 (46.1-93.9)
- Platinum-based chemo (n=12)	0%		81.8% (9)		33.3 (13.2-84.0)	100%
- Other chemotherapies (n=30)	0%		33.3% (9)		8.1 (2.-30.3)	53.9 (36.6-79.3)
Missing	30		11			
Primary resistance to chemo-ICI population (n=64)	**11.3% (6)**		**31.7% (19)**		**10.6 (4.7-23.7)**	**45.0 (33.0-61.5)**
- Taxane monotherapy (n=29)	10.7% (3)	0.16	21.4% (6)	0.02	7.2 (2.0-27.3)	41.2 (25.6-66.5)
- Taxane + anti-angiogenic (n=13)	30.0% (3)		58.3% (7)		28.6 (9.7-83.8)	49.4 (25.4-96.0)
- Platinum-based chemo (n=5)	0%		75.0% (3)		33.3% (6.7_100)	100%
- Other chemotherapies (n=17)	0%		18.8% (3)		0%	34.1% (15.1-77.1)
Missing	11		4			
Responder to chemo-ICI population (n=59)	**20.0% (8)**		**53.8% (28)**		**26.8 (16.7-43.3)**	**73.6 (61.6-87.8)**
- Taxane monotherapy (n=27)	29.2% (7)	0.50	41.7% (10)	0.22	30.3 (16.0-57.3)	59.1 (41.5-84.1)
- Taxane + anti-angiogenic (n=12)	12.5% (1)		60.0% (6)		27.0% (8.4-86.5)	90.0% (73.2-100)
- Platinum-based chemo (n=7)	0%		85.7% (6)		33.3 (10.8-100)	100%
- Other chemotherapies (n=13)	0%		54.5% (6)		18.2 (5.2-63.7)	78.7% (56.4-100)
Missing	19		7			

Table 4
Baseline characteristics according to the first line treatment outcome.

		Whole population (N=124)	Resistant to 1L (N=64)	Responders to 1L (N=59)	p
Age at L2 start	> 65 years	52 (51.5%)	25 (45.5%)	26 (57.8%)	0.22
Gender	Female	38 (30.6%)	23 (35.9%)	14 (23.7%)	0.14
Smoking status	Never	8 (6.5%)	4 (6.2%)	4 (6.8%)	1
Histology	Adenocarcinoma	90 (72.6%)	46 (71.9%)	43 (72.9%)	0.991
	Squamous	19 (15.3%)	10 (15.6%)	9 (15.3%)	
	Other	15 (12.1%)	8 (12.5%)	7 (11.9%)	
PD-L1 expression	0%	56 (49.1%)	34 (53.1%)	21 (42.9%)	0.455
	1 to 49%	48 (42.1%)	24 (37.5%)	24 (49%)	
	≥ 50%	10 (8.8%)	6 (9.4%)	4 (8.2%)	
	Missing	10	0	10	
First line chemotherapy combined with type of immune checkpoint inhibitor	CTLA4 + PD1 combination	1 (0.8%)	1 (1.6%)	0 (0%)	0.02
	PD1 inhibitor	78 (62.9%)	46 (71.9%)	31 (52.5%)	
	PDL1 inhibitors	45 (36.3%)	17 (26.6%)	28 (47.5%)	
Metastatic locations	Bone	59 (47.6%)	31 (48.4%)	28 (47.5%)	0.93
	Liver	17 (13.7%)	9 (14.1%)	8 (13.6%)	1
	Brain	26 (21.0%)	14 (21.9%)	12 (20.3%)	0.66
Type of second line	Other chemo	30 (24.2%)	17 (26.6%)	13 (22%)	0.85
	Platinum based	12 (9.7%)	5 (7.8%)	7 (11.9%)	
	Taxane	57 (46%)	29 (45.3%)	27 (45.8%)	
	Taxane + AA	25 (20.2%)	13 (20.3%)	12 (20.3%)	
Number of metastatic sites	> 2	67 (57.8%)	35 (58.3%)	31 (56.4%)	0.83
	Missing	8	4	4	
Performance status at L2 initiation	0	13 (15.3%)	4 (8.5%)	9 (24.3%)	0.02
	1	35 (41.2%)	17 (36.2%)	18 (48.6%)	
	2-3	37 (43.5%)	26 (55.3%)	10 (27%)	
	Missing	39	17	22	

Resistant to L1: defined as 1L-PFS < 6 months, Responders to L1: defined as 1L PFS ≥ 6 months.

4. Discussion

In this multicenter retrospective study, we reported the activity of 2L therapy regimens in patients with NSCLC upon progression after chemo-ICI (median 2L-OS of 8.1 months). We observed significant difference when we segregated patients into groups according to 1L treatment responses, with a median OS of 5.1 months for 1L-resistant patients and 12.7 months for the responders.

To date, very few studies have explored the efficacy of 2L chemotherapy after progression following 1L chemo-ICI in advanced NSCLC. In the pre-immunotherapy era, Rothschild et al., reported on the outcomes to 2L chemotherapy after 1L platinum-based chemotherapy in a large cohort of 576 patients, which showed very similar results to our findings (median 2L-OS 9.5 months, median 2L- PFS 3.2 months, ORR 16.2 %) [11].

Similar to what we observed in our study, the 1L-resistant group had poor prognosis compared to the responder group following 2L treatments (median 2L-OS of 10.1 months and 2L-PFS of 2.5 months, disease control in 28 %).

In our cohort, patients treated with platinum-based chemotherapy (rechallenge) or taxanes (alone or combined to antiangiogenic) had better outcomes compared to other chemotherapies as 2L treatments, particularly in the responder group. This is in line with previous reports (pre-ICI) that demonstrated the activity of platinum rechallenge with an ORR of 27.5 % [12]. Regarding taxane combined with anti-angiogenic therapy, another retrospective study showed that this regimen had an interesting efficacy profile when administered directly after progression

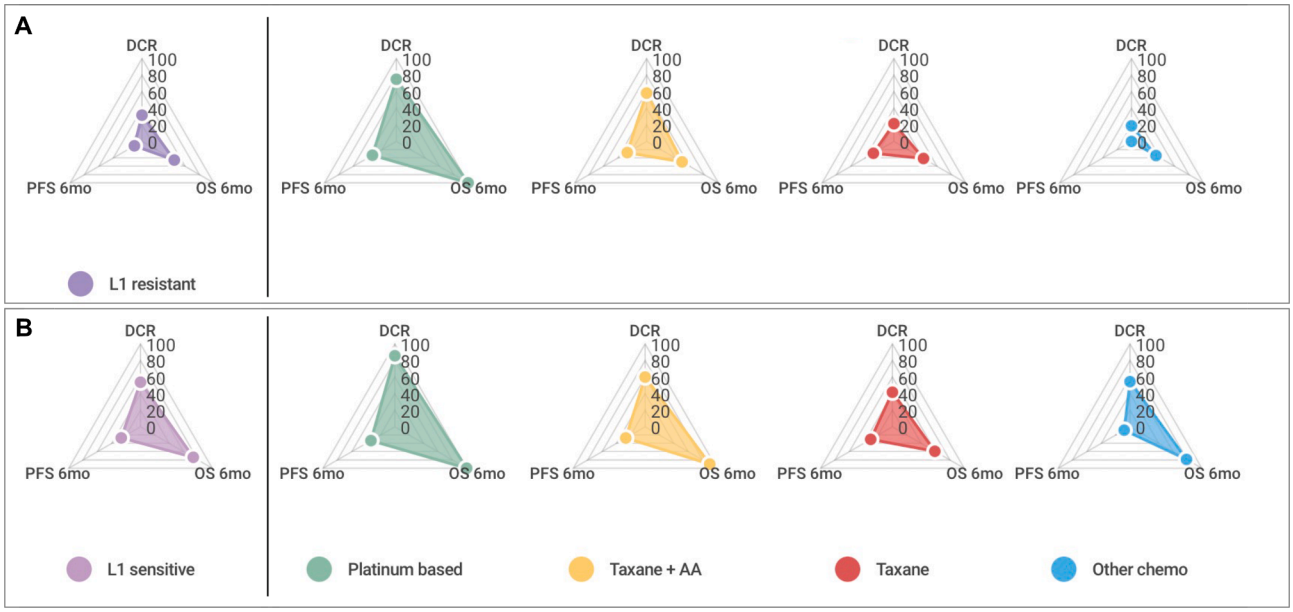

Fig. 2. Response endpoints according to each treatment in the l1 resistant (a) and l1 responders (b) populations. *Legend: PFS: Progression Free Survival, OS: Overall Survival, DCR: Disease Control Rate, AA: Anti-angiogenic, mo: months.*

under ICI (DCR 82 %, median PFS 7.0 months, median OS 13.0 months) [13]. This was also found with the combination of docetaxel plus nintedanib after progression under chemo-ICI in NSCLC (ORR 37.5 %, DCR 72.5 %), confirming the potential interest of taxane and antiangiogenic in this setting [14]. Another retrospective study showed similar results with a median 2L-OS of 7.2 months [15]. However, they did not find any benefit in term of 2L-PFS regarding platinum based chemotherapy rechallenge compared with other chemotherapy regimens.

Our results highlight the need for new strategies in second line treatments for NSCLC. New combinations of immunotherapy and anti-angiogenic agents have been explored recently as a promising treatments after immunotherapy progression [16,17]. In a phase 2 study including 136 patients, the combination of pembrolizumab plus ramucirumab conferred an OS benefit compared to second line standard of care [16]. However, the ORR was 22 %, and no PFS benefit was observed, especially in patients that received first line chemotherapy plus immunotherapy. The results of the phase 1b COSMIC-021 study were in line with this first study [17]. Indeed, in the 89 patients receiving cabozantinib plus atezolizumab after progression under immunotherapy, the ORR was 19 % and median OS and PFS were 13.8 months and 4.5 months, respectively. In our cohort, the only anti-angiogenic containing group (taxane plus anti-angiogenic, n = 25) had a comparable objective response rate of 22.2 %, suggesting that the combination therapies with anti-angiogenics in the second line setting may be an additional option after progression.

PD-L1 is considered a prognostic factor [18], as well as a predictive biomarker of response to immunotherapy [7]. However the clinical value of PD-L1 expression after progression post immunotherapy remains unexplored. In our study, patients outcomes correlated with expression of PD-L1 in tumors, with better outcomes in high PD-L1 expressing patients. This suggests that PD-L1 may not be a poor prognostic factor beyond immunotherapy progression. In our cohort, the lower rate of PD-L1 $\geq$ 50 % expressing tumors was due to the access to chemo-ICI is restricted to patients with PDL1 $<$ 50 % in European countries (representing the majority of the patients enrolled), and this could explain the response rate slightly lower compared to other studies.

Identifying the mechanism of resistance may be the clue to increase the efficacy of second line treatments. Indeed, primary resistance and secondary resistance may have different mechanisms. Karasides et al proposed some leads by describing the hallmarks of resistance to immune checkpoint inhibitors [19]. The better description of the resistance mechanism will help clinician improve clinical trials.

In our study, patients with adenocarcinoma had better outcomes compared with patients with squamous cell carcinoma. This difference may be explained by the higher number of drugs available for adenocarcinomas (pemetrexed, anti-angiogenic).

Our study is the first to explore the efficacy of distinct 2L treatments in NSCLC progression after 1L chemo-ICI combination, but also has several limitations, mainly due to its retrospective nature. Some data were unavailable, and as we only assessed patients who received 2L, we were unable to compare outcomes with 2L-ineligible patients. Moreover, assessments of disease response were not centrally performed, and the sample size was too small to draw solid conclusion in the subgroup analyses.

5. Conclusion

Second line chemotherapy after progression following 1L chemo_ICI achieved a modest activity in patients with NSCLC. Rechallenge with platinum-based chemotherapy or taxane plus anti-angiogenic may be effective option for selected populations. Patients with tumors resistant to 1L treatments remain a refractory population that requires to be enrolled in clinical trials. Our results highlight the need for new combinations and strategies in 2L after progression following 1L combination of chemo-ICI.

DOIs:

EA: Board: Amgen, Sanofi Genzyme.

MT: Travel, Accommodation, Expenses from Roche, Bristol-Myers Squibb, AstraZeneca, Takeda, Eli Lilly. Honoraria as medical writer for Novartis, Amgen, MSD.

RGC: Consulting advisory role: AZ, BMS, Novartis, Lilly, MSD, Jansen, Sanofi, Pfizer, Takeda, Roche. Speaker's bureau: AZ, BMS, Novartis, Lilly, MSD, Jansen, Sanofi, Pfizer, Takeda, Roche. Research funding: BMS.

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RL: Consulting advisory role: AZ, BMS, Novartis, MSD, Pfizer, Takeda, Roche, Pierre-Fabre. Speaker's bureau: AZ, BMS, Novartis, MSD, Pfizer, Takeda, Roche, Pierre-Fabre.

HA: Advisory roles: Astra Zeneca. Clinical trial coordination: Ferrer

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CRediT authorship contribution statement

Edouard Auclin: Data curation, Formal analysis, Methodology, Writing – original draft, Project administration. **Jose Benitez-Montanez:** Data curation, Writing – review & editing. **Marco Tagliamento:** Data curation, Writing – review & editing. **Francesca Parisi:** Data curation, Writing – review & editing. **Teresa Gorria:** Data curation, Writing – review & editing. **Rosario Garcia-Campelo:** Data curation, Writing – review & editing. **Naomi Dempsey:** Data curation, Writing – review & editing. **David J. Pinato:** Data curation, Writing – review & editing. **Roxana Reyes:** Data curation, Writing – review & editing. **Víctor Albarrán-Artahona:** Data curation, Writing – review & editing. **Filippo Dall'Olio:** Data curation, Writing – review & editing. **Davide Soldato:** Data curation, Writing – review & editing. **Lizza Hendriks:** Data curation, Writing – review & editing. **Frank Aboubakar Nana:** Data curation, Writing – review & editing. **Marion Tonneau:** Writing – review & editing. **Rafael Lopez-Castro:** Data curation, Writing – review & editing. **Ernest Nadal:** Data curation, Writing – review & editing. **Suzanne Kazandjian:** Data curation. **Thierry Muanza:** . **Félix Blanc-Durand:** Data curation. **Elizabeth Fabre:** Data curation. **Natalia Castro:** Data curation, Writing – review & editing. **Hugo Arasanz:** Data curation, Writing – review & editing. **Adrien Rochand:** Data curation, Writing – review & editing. **Benjamin Besse:** Data curation, Supervision, Writing – review & editing. **Bertrand Routy:** Writing – review & editing. **Laura Mezquita:** Supervision, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2023.02.002.

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