Original Article

Response to platinum-based therapies in second-line after immunotherapy in advanced or metastatic non-small-cell lung cancer PD-L1 ≥50%

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Background: Platinum-based therapies for patients with advanced non-small-cell lung cancer (NSCLC) have classically provided overall survival (OS) rates of six to nine months and objective response rates (ORRs) of 20–30%. Whether prior immunotherapy determines a different response to platinum is currently unknown. This study aimed to analyse the current response characteristics to platinum as a second-line treatment for advanced NSCLC (PD-L1 ≥50%) after first-line immunotherapy.

Methods: This retrospective study was conducted at the University Hospital of Salamanca (CAUSA) between 2016 and 2023 with patients who had advanced NSCLC (PD-L1 ≥50%) treated with second-line platinum-based therapies after immunotherapy (without mutations in *EGFR*, *ALK* or *ROS1* and with Eastern Cooperative Oncology Group (ECOG) ≤1 during the first- and second-line treatments). Survival and response correlation analyses (Kaplan-Meier and log rank tests in SPSS v. 25) were performed. Subsequently, the results were compared with historical cohorts (PubMed, COCHRANE, ScienceDirect, Embase, and the clinical trial registry) who had received platinum-based therapies for advanced NSCLC.

Results: Seventeen patients were analysed (11 male and 6 female). Their median age was 67 years (interquartile range, 50–77 years). Fifteen patients (88.2%) were smokers or former smokers. The patients' main histology was adenocarcinoma (9 patients, 52.9%). All first-line treatments applied pembrolizumab (median dose: 12 cycles). Second-line platinum-based therapy achieved OS of 25 months (95% CI: 7–45 months) and progression-free survival (PFS) of 6 months (95% CI: 2.5–95 months). The ORR was 47.1% [seven patients with a partial response (PR) and one patient with a complete response (CR)]. Of the patients with PRs or CRs, 75% were treated with platinum plus pemetrexed. The one-year survival rate was 58.8%. The historical OS for first-line platinum-based doublets is 7 to 12 months, with PFS of three to five months and an ORR of 17–30%.

Conclusions: The current response to second-line platinum-based therapies for patients with advanced NSCLC after immunotherapy appears to achieve favourable response rates and be an optimal treatment after

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progression to immunotherapy. Prior immunotherapy appears to enhance these patients' platinum response, though future confirmatory studies are necessary.

Keywords: Platinum-based therapies; non-small-cell lung cancer (NSCLC); second-line treatment; immunotherapy

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Introduction

According to the World Health Organization (WHO), lung cancer is currently the leading cancer in terms of its incidence and mortality worldwide, accounting for over 2.4 million diagnoses per year and 1.8 million deaths (1). Of lung cancer diagnoses, 80–85% indicate non-small-cell lung cancer (NSCLC), which the introduction of immunotherapy has revolutionised in recent years (2).

The current treatments for advanced or metastatic NSCLC without driver mutations are generally based on first-line chemo-immunotherapy targeting tumours with PD-L1 expression <50% and immunotherapy if PD-L1 ≥50% (3). Alongside immunotherapy, the other key pillar of lung cancer treatment is platinum. Several clinical trials in the 1980s demonstrated platinum's superiority over the best supportive care (BSC); cisplatin monotherapy was the initial standard treatment, followed by combinations (4). While combinations with etoposide or vinblastine were the most widely used in the United States, the combination of cisplatin with vindesine was the most standard in Europe.

Highlight box

Key findings

- The efficacy of platinum-based chemotherapy for non-small-cell lung cancer (NSCLC) in the post-immunotherapy era is similar to that in the pre-immunotherapy era, although the data suggest a possibly greater effect.

What is known and what is new?

- Platinum-based therapies have first-line efficacy both alone and in combination with immunotherapy.
- Platinum-based therapies after first-line immunotherapy in advanced NSCLC are equally effective in second-line as in first-line.

What is the implication, and what should change now?

- Current treatment guidelines using second-line platinum therapies after immunotherapy appear to be the correct treatment sequence.

Later, in the 1990s, the appearance of drugs such as paclitaxel, docetaxel, vinorelbine, gemcitabine or irinotecan led to the new combinations that are mostly used today alongside immunotherapy (5).

Platinum-based therapies for advanced NSCLC have classically provided overall survival (OS) rates of six to nine months and objective response rates (ORRs) of 20–30% (6). However, whether these rates remain steady due to the use of platinum doublets after immunotherapy for advanced NSCLC is currently unknown (*Figure 1*). One of the most important studies in this field was by Park *et al.* (7). It showed an increase in classical responses to chemotherapy after treatment with PD-1/PD-L1 inhibitors (ORR: 66.7% through platinum doublet therapy).

The mechanism through which chemotherapy appears to lead to an increased response after immunotherapy is unknown. Several mechanisms have been proposed as the main causes of immunosuppressive cells decreasing in the tumour microenvironment, such as myeloid-derived suppressor cells (MDSCs) or regulatory T-cells (8,9). Therefore, chemotherapy—especially platinum-based chemotherapy—seems to be the most reasonable option for patients with advanced NSCLC who have progressed to first-line immunotherapy (PD-L1 ≥50%) despite the lack of studies in this regard.

This study aimed to analyse the current characteristics of responses to platinum as a second-line treatment for advanced NSCLC (PD-L1 ≥50%) after first-line immunotherapy. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-513/rc).

Methods

Data source and cohort construction

This prospective study was conducted with a population registered through the data system of the University

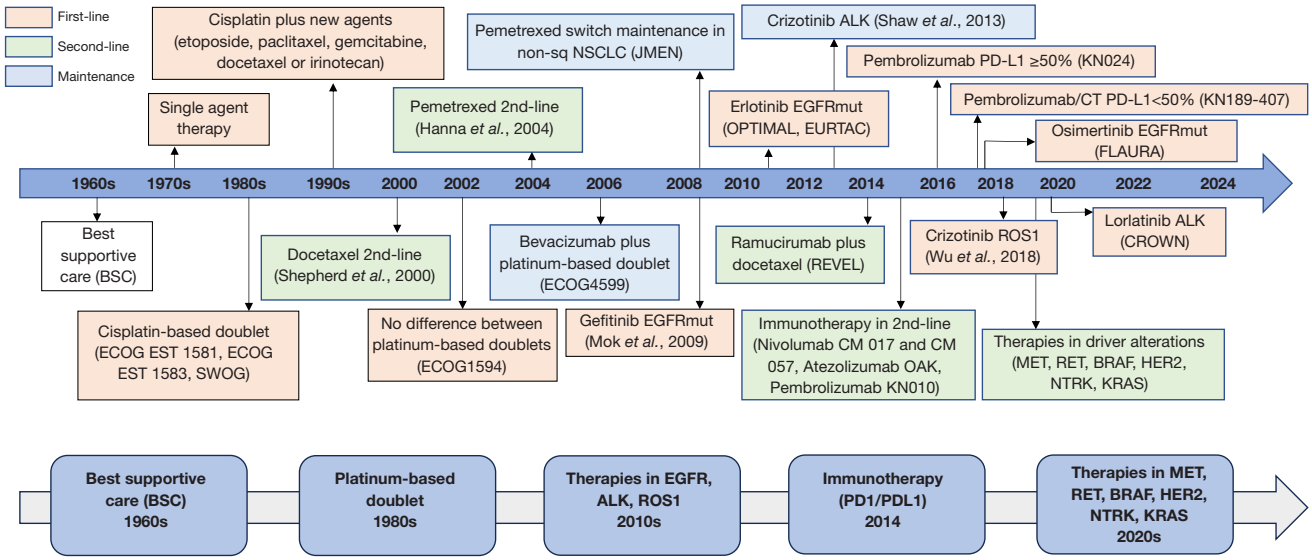

Figure 1 Development of therapies in advanced or metastatic NSCLC from the early 1960s to the present day. CM, CheckMate; *EGFR*mut, *EGFR* mutated; KN, KEYNOTE; non-sq NSCLC, non-squamous non-small-cell lung cancer.

Hospital of Salamanca (Salamanca, Spain). The patient cohort was established through hospital discharge records collected between January 1, 2016, and December 31, 2023. Patients who had been diagnosed with NSCLC (PD-L1 ≥50%) and treated with second-line platinum-based therapies after immunotherapy were selected. The collected data were provided by the Department of Medical Oncology of the University Hospital of Salamanca. They comprised patients' age (years), sex, toxic habits (smoking and alcohol use), tumour (location, stage, histology, oncological treatment, type of immunotherapy, doses of immunotherapy, type of platinum therapy, doses of platinum therapy and toxicity), general condition [Eastern Cooperative Oncology Group (ECOG) scale], OS and progression-free survival (PFS) after tumour diagnosis (months), date of death and better response through immunotherapy (RECIST1.1) and toxicity (CTCAE v. 4.0). The patients selected for the study had been treated at the Department of Medical Oncology at the University Hospital of Salamanca, and their treatment until the time of the study's data analysis was considered. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study's research protocol was approved by the Ethics Committee of the University Hospital of Salamanca (PI 2022 10 1155) and informed consent was taken from all the patients.

Inclusion and exclusion criteria

The study's patient inclusion criteria were as follows:

- Age ≥18 years, diagnosis with advanced or metastatic NSCLC, and agreement to study inclusion, as well as a signature indicating informed consent.
- Expression of PD-L1 ≥50% in a tumour or immune cells.
- First-line immunotherapy monotherapy treatment with current European Medicines Agency approval (pembrolizumab, atezolizumab or cemiplimab).
- The absence of previous systemic treatment with chemotherapy for NSCLC.
- The previously mentioned criteria's inclusion in clinical history records.

The study's patient exclusion criteria were as follows:

- Prior systemic treatment with chemotherapy for NSCLC (though a prior platinum treatment ≥5 years before the initiation of platinum treatment for NSCLC was allowed).
- First-line treatment with chemo-immunotherapy.
- The absence of clinical variables required for the study's analysis.

Response, survival and toxicity definitions

- PFS: time in months from the start of a treatment

(first-line immunotherapy or second-line platinum-based therapy) until the patient progression or was lost to follow-up.

- OS: time in months from the start of a treatment (first-line immunotherapy or second-line platinum-based therapy) until the patient died or was lost to follow-up.
- Response Evaluation Criteria for Solid Tumours (RECIST v1.1): the response of patients was graded according to four types of response—complete response (CR), partial response (PR), disease stabilisation (SD) and progression (PD).
- Common Terminology Criteria for Adverse Events (CTCAE v.4.0): toxicity was measured according to the CTCAE criteria into five toxicity groups, from the lowest grade to the highest grade.

Statistical analysis

The calculations of differences between populations at the epidemiological level were estimated using comparative statistical tests of medians and percentages. Survival rates were calculated in months and expressed as medians with 95% confidence intervals (CIs). Survival was calculated using the Kaplan-Meier method (log rank and the Breslow test) and Cox regression. Given the limited sample and the possibility of a crossover between the survival curves, an a priori decision determined to perform two statistical tests (log rank and Breslow). Comparisons were made between platinum-based therapies, not with platinum monotherapy due to the current standard of treatment based on the combination. The study's statistical significance level was established a priori at $P<0.05$. The software used was SPSS, version 28 (IBM, Armonk, NY, USA). The results were expressed using the log rank test except in cases specifically indicated for the Breslow test.

Historic cohorts in platinum-based therapies

Subsequently, results were compared with historical cohorts of platinum-based therapies in advanced NSCLC. The clinical trials collected were selected prior to the introduction of immunotherapy [2014–2015] from those assessing responses to platinum doublets as a first-line treatment for advanced or metastatic NSCLC. The included clinical trials and studies were found by searching several databases: PubMed, COCHRANE, ScienceDirect, Embase, and the clinical trial registry (www.clinicaltrials.gov). Studies and trials presented at the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) conferences were also included. Only studies published before December 31, 2023, were included.

Various text and medical subject heading (MeSH) combinations were used in the search: 'Lung cancer OR lung OR NSCLC', 'Platinum therapies OR platinum-based therapies OR platinum combinations OR platinum' and 'clinical trials OR approved drugs OR review'. Several combinations were used to search the databases: '(Lung Cancer OR NSCLC) "AND" (Platinum therapies OR platinum-based therapies OR platinum combinations OR platinum) "AND/OR" (clinical trials OR approved drugs OR review)'.

Results

General sample characteristics

In total, 17 patients were studied (*Table 1*). Their mean age was 67 years (interquartile range, 50–77 years). Eleven were male (64.7%), and six were female (35.3%). Fifteen were smokers or ex-smokers (88.2%). The patients' main histology was adenocarcinoma (9 patients, 52.9%), followed by squamous tumours (7 patients, 41.2%). All patients had ECOG scores of 0–1 at the time of the first- and second-line treatments. The most frequent site of metastatic involvement was the bone (8 of 17 patients, 47.1%). Only one patient experienced liver involvement, and one patient experienced central nervous system involvement. At the time of the study's data analysis, 9 of the 17 patients had died (52.9%).

All the patients were treated with pembrolizumab as a first-line approach (median dose: 12 cycles). The OS for first-line treatment was 41 months (95% CI: 14–68 months), with a PFS of 10 months (95% CI: 8–12 months) and an ORR of 88.2%. Of the patients treated with immunotherapy, five developed immune-related toxicity (29.4%), and three developed toxicity of grade ≥2 (17.6%).

Historical cohorts

Different platinum combinations have been studied. From the first combinations with drugs such as vindesine, vinorelbine or etoposide in the 1990s to the later ones with next generation drugs such as docetaxel or pemetrexed in the 2000s have demonstrated their efficacy *vs.* monotherapy

Table 1 General characteristics of the sample

Variables	Overall sample	Platinum-pemetrexed	Platinum-paclitaxel	Platinum monotherapy
Number of patients	17 (100%)	10 (100%)	4 (100%)	3 (100%)
Age, years	67 (50–77)	67 (50–73)	67.5 (64–76)	68 (68–77)
Sex (male/female)	11/6 (64.7%/35.3%)	5/5 (50%/50%)	3/1 (75%/25%)	3/0 (100%/0%)
Smokers/never smokers	15/2 (88.2%/11.8%)	8/2 (80%/20%)	4/0 (100%/0%)	3/0 (100%/0%)
Drinkers/never drinkers	5/12 (29.4%/70.6%)	3/7 (30%/70%)	1/3 (25%/75%)	1/2 (33.3%/66.7%)
Histology (ADC)	9 (52.9%)	7 (70%)	0 (0%)	2 (66.7%)
Metastases localization				
Lung	5 (29.4%)	4 (40%)	1 (25%)	0 (0%)
Pleura	3 (17.6%)	1 (10%)	2 (50%)	0 (0%)
Bone	8 (47.1%)	4 (40%)	2 (50%)	2 (66.7%)
Liver	1 (5.9%)	1 (10%)	0 (0%)	0 (0%)
Adrenal	3 (17.6%)	2 (20%)	0 (0%)	1 (33.3%)
CNS metastases	1 (5.9%)	1 (10%)	0 (0%)	0 (0%)
EGFR/*ALK* mutations	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PD-L1 (≥50%)	17 (100%)	10 (100%)	4 (100%)	3 (100%)
ECOG (0–1)	17 (100%)	10 (100%)	4 (100%)	3 (100%)
First-line treatment (pembrolizumab)	17 (100%)	10 (100%)	4 (100%)	3 (100%)
First-line median doses	12 (1–35)	12 (3–35)	12 (1–19)	12 (4–12)
Immunotoxicity				
Any grade	5 (29.4%)	3 (30%)	2 (50%)	0 (0%)
Grade ≥2	3 (17.6%)	1 (10%)	2 (50%)	0 (0%)

Data are presented as number of patients (%) or median (interquartile range). ADC, adenocarcinoma; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group.

or BSC. The median number of patients in the clinical trials, all of them phase 3, was 403 patients (range, 135–1,218). The different studies analyzed present an OS between 7.2–12.5 months and an ORR 12.5–43.7%. The clinical trials that evaluated chemotherapy triplets did not demonstrate a survival or response benefit over platinum doublets. The main studies that evaluated the differences between platinum combinations found no difference between them with similar ORR and OS from previous studies (16–32% and 7.4–9.9 months respectively).

Second-line platinum-based therapy

The treatment most commonly used in combination with platinum was pemetrexed (10 of 17 patients, 58.8%), followed by paclitaxel (23.5%). Of the 17 patients, five used cisplatin (29.4%), and 12 used carboplatin (70.6%). Platinum monotherapy was used for three of the 17 patients (carboplatin in all cases, 17.6%). The median number of cycles administered, including pemetrexed maintenance, was 6 (IQR, 2–64). The OS was 25 months (95% CI: 7–45 months), with a PFS of 6 months (95% CI: 2.5–95 months) and an ORR of 47.1% (seven patients with a PR and one patient with a CR). Of the patients with a PR or CR, 75% were treated with platinum plus pemetrexed. The one-year survival rate was 58.8%, and the two-year survival rate was 29.4%.

A comparison of treatment regimens (*Table 2*) revealed an OS of 25 months for patients treated with platinum plus pemetrexed (95% CI: 1.5–48.5 months), a PFS of

Table 2 Overall results of platinum-based therapies in advanced or metastatic NSCLC after first-line immunotherapy

Regimen	Patients	OS (m)	PFS (m)	ORR (%)	1-year survival (%)	Toxicity (grade ≥2, %)	P value
Platinum + pemetrexed	10	25	7	60	70	20	0.03*
Platinum + paclitaxel	4	6	3	50	25	25	
Carboplatin monotherapy	3	4	3	33.4	33.4	33.4	
Global	17	25	6	47.1	58.8	23.5	

*, Breslow test. NSCLC, non-small-cell lung cancer; m, months; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

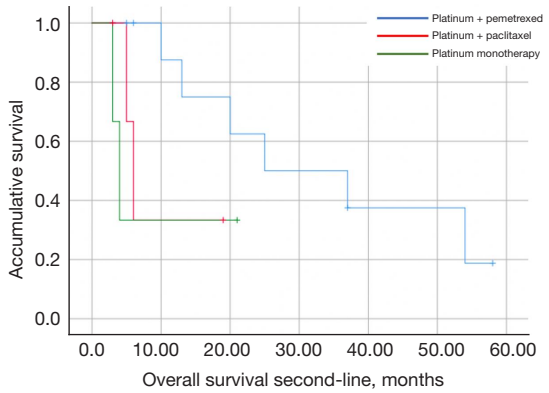

Figure 2 Kaplan-Meier curve of overall survival for the different second-line platinum-based therapies arms.

7 months (95% CI: 0–16.5 months) and an ORR of 60%. For the platinum plus paclitaxel combination, the OS was 6 months (95% CI: 4.5–7.5 months), the PFS was 3 months (95% CI: 0–6 months) and the ORR was 50%. For platinum monotherapy, the OS was 4 months (95% CI: 2.5–5.5 months) with a PFS of 3 months (95% CI: 0–6 months) and an ORR of 33.4%. A comparison between treatments showed that the combination with pemetrexed was statistically significantly superior to paclitaxel in terms of both OS (log rank test: P=0.06; Breslow test: P=0.03) and PFS (log rank test: P=0.02; Breslow test: P=0.02) (*Figure 2*). The Cox regression showed a hazard ratio (HR) 0.186 (95% CI: 0.025–1.357) for OS and a HR 0.273 (95% CI: 0.065–1.141) for PFS.

In total, six patients developed some form of treatment toxicity (35.3%). Four patients experienced toxicity of grade ≥2 (23.5%). Of the patients who developed toxicity, two did so with the combination of pemetrexed (11.8%), one with the paclitaxel combination (5.9%) and one patient with carboplatin monotherapy (5.9%). One patient had to discontinue treatment due to cisplatin hypersensitivity.

Third and subsequent treatment lines

Of the 17 patients who received treatment, nine (53%) received a third-line treatment, and seven received a fourth-line treatment (41.2%). Of the 17 patients who received second-line platinum treatment, only one patient did not progress or died during second-line treatment (5.9%). Of the remaining 16 patients, 9 received a third line (53%) and 7 patients died during treatment (41.2%).

The most-used third-line therapies were docetaxel (three patients, 33.3%), followed by paclitaxel (two patients, 22.2%) and gemcitabine (two patients, 22.2%). For the third-line treatments, the OS was 21 months (95% CI: 0–49 months) with a PFS of four months (95% CI: 1–7 months) and an ORR of 47.1%. None of the patients who received third-line treatments experienced toxicity of grade ≥2.

For the seven patients who received a fourth-line treatment, the most frequently used combination was gemcitabine in monotherapy (five patients, 71.4%). The OS for the fourth-line therapies was four months (95% CI: 0–14 months), the PFS was three months (95% CI: 1.5–4.5) and the ORR was 16.6%. None of the patients who received a fourth-line treatment experienced toxicity of grade ≥2.

Discussion

The treatment sequence for advanced NSCLC after first-line immunotherapy is based on the classic treatment for NSCLC using platinum combinations (10). However, the studies that have examined these therapies have mostly involved patients who had not received any systemic oncologic treatment; therefore, how a previous therapy could influence the response to chemotherapy, particularly with platinum, was unknown. For advanced NSCLC with PD-L1 ≥50% treatment is, with few exceptions, based on immunotherapy, whose influence on the immune system

and the tumour microenvironment seems theoretically to cause a greater response to the chemotherapy used in NSCLC (platinum, docetaxel, gemcitabine, vinorelbine or paclitaxel) (11).

The first studies evaluating platinum-based doublets were performed in the 1980s. The clinical ECOG trial EST 1581, ECOG trial EST 1583 and SWOG trial evaluated more than 1,900 patients, with overall ORRs of 6–31% and a mean OS of 24.5–31 weeks with no statistically significant differences across the studies (12,13). Subsequently, Le Chevalier *et al.* conducted the first study to evaluate platinum doublets with new-generation drugs (14). They studied the efficacy of cisplatin plus vinorelbine *vs.* cisplatin plus vindesine and vinorelbine as monotherapy. From this trial, two important conclusions were drawn for subsequent studies: the combination of cisplatin with a new-generation drug, such as vinorelbine, increased survival and the response among patients, and treatment with platinum doublets exhibited clear superiority to monotherapy using any chemotherapy type.

Subsequently, multiple phase 3 clinical trials were performed between the 1990s and 2000s using different combinations of cisplatin and carboplatin plus drugs such as etoposide, paclitaxel, gemcitabine, docetaxel or irinotecan (14-25) (*Table 3*). These studies showed a median survival of 7.2–13.4 months and an ORR of 12.5–43.7%. The one-year survival ranged from 25% to 43%. Especially relevant due to its number of patients was the TAX 326 clinical trial, in which 1,218 patients were randomly chosen to receive cisplatin or carboplatin plus docetaxel *vs.* cisplatin plus vinorelbine. The ORR was superior in the docetaxel arm compared to the vinorelbine arm (31.6% *vs.* 24.5%; P=0.029). However, the combination with docetaxel did not achieve better survival than vinorelbine (OS: 11.3 *vs.* 10.1 months; two-year survival: 21% *vs.* 14%) (21).

Following these clinical trials, four major studies specifically sought to compare different platinum doublets in patients with advanced NSCLC as a first-line treatment (26-29) (*Table 4*). Schiller *et al.* (28) conducted the most important of these studies, comparing results for 1,155 patients who received cisplatin plus paclitaxel, cisplatin plus gemcitabine, cisplatin plus docetaxel or carboplatin plus paclitaxel. In this study, no differences in response rates or survival were observed between across treatment regimens. The patients' ORR was 19% with an OS of 7.9 months and a one-year survival of 33%.

Following these studies, pemetrexed was introduced in combination with platinum (JMDB and JMEN trials). JMDB was the main study conducted that evaluated the efficacy of the pemetrexed combination *vs.* the gemcitabine combination for 1,725 patients. It showed the first combination's superiority in a subgroup of patients with the non-squamous subtype (11.0 *vs.* 10.1 months; HR: 0.84) and a more favourable toxicity profile. Subsequently, the efficacy of maintenance pemetrexed was evaluated in these patients after their response to four cycles of platinum–pemetrexed doublet, mainly in the JMEN and PARAMOUNT studies. The JMEN trial showed an OS of 13.9 months for pemetrexed maintenance *vs.* 11.0 months for placebo (one-year survival rates of 58% *vs.* 45%). These data were similar to that of the PARAMOUNT study (30) with an OS of 13.9 *vs.* 11.9 months (HR: 0.78; 95% CI: 0.64–0.96). Following these data, for non-squamous NSCLC, the platinum-pemetrexed combination was preferentially established as a first-line treatment in the metastatic setting.

After the previous clinical trials that, for two decades, defined the first-line treatment for advanced NSCLC, no changes were observed until the introduction of immunotherapy. The data on second-line platinum doublets after first-line immunotherapy were, therefore, based on all of these clinical trials. The results of our study show a global OS of 25 months with a PFS of 6 months. Likewise, the one-year survival rate was 58.8%, which shows that, at higher response or PFS rates, the responses are sustainable, or the patients present a preserved general condition such that a third- or fourth-line treatment can be initiated. An important point in our study's data is that the results seem statistically significantly dependent and more favourable for the combination with pemetrexed. Although these data were statistically significant only by Breslow's test, the data suggest that if there were an increase in sample size there would probably be overall statistical significance. Multiple factors influence the longer survival of pemetrexed patients, the first of which is maintenance on monotherapy after combination with platinum. In addition, adenocarcinoma histology, a higher proportion of female patients, younger age and a lower proportion of smokers are known key factors that have influenced the study data.

Overall, these data are superior to those previously obtained, and the previous effect of immunotherapy with consequent alterations in the antitumor immune system and tumour microenvironment likely influenced these data. The usefulness, for example, of angiogenesis inhibitors together with immunotherapy is already known and studied, there being a synergistic effect between both therapies both in combination and sequentially (31,32).

Table 3 Main studies with platinum-based therapies in advanced or metastatic NSCLC

Study	Year	Phase	Patients	Regimen	Response rate (%)	Median OS (m)
Le Chevalier (14)	1994	3	612	Vinorelbine	14	7.2
				Cisplatin + vindesine	19	7.4
				Cisplatin + vinorelbine	30	9.3
Bonomi (15)	1997	3	599	Cisplatin + etoposide	12.5	7.6
				Cisplatin + paclitaxel	25	9.5
				Cisplatin + paclitaxel + G-CSF	28	10.1
Giaccone (16)	1998	3	332	Cisplatin + teniposide	28	9.9
				Cisplatin + paclitaxel	41	9.7
Belani (17)	1998	3	369	Cisplatin + etoposide	14	9.9
				Carboplatin + paclitaxel	22	9.5
Crinò (18)	1999	3	307	Mitomycin + ifosfamide + cisplatin	28	8.8
				Cisplatin + gemcitabine	40	8.1
Cardenal (19)	1999	3	135	Cisplatin + etoposide	22	7.2
				Cisplatin + gemcitabine	41	8.7
Kelly (20)	2001	3	408	Cisplatin + vinorelbine	27	8
				Carboplatin + paclitaxel	27	8
Fossella (21)	2003	3	1,218	Platinum + docetaxel	31.6	11.3
				Cisplatin + vinorelbine	24.5	10.1
Negoro (22)	2003	3	398	Cisplatin + irinotecan	43.7	12.5
				Cisplatin + vindesine	31.7	11.4
				Irinotecan	20.5	11.5
Kubota (23)	2004	3	311	Cisplatin + docetaxel	37	11.3
				Cisplatin + vindesine	21	9.6
Scagliotti (JMDB) (24)	2008	3	1725	Cisplatin + pemetrexed	30.6	10.3 (non-sq 11.0)
				Cisplatin + gemcitabine	28.2	10.3 (non-sq 10.3)
Ciuleanu (JMEN) (25)	2009	3	663	Platinum + pemetrexed (maintenance)	–	13.4
				Platinum + pemetrexed	–	10.6

NSCLC, non-small-cell lung cancer; OS, overall survival; m, months; G-CSF, granulocyte colony-stimulating factor; non-sq, non-squamous.

However, with chemotherapy, this synergy or potentiating effect has not been demonstrated and although at a theoretical level there is data in favor of it, new studies are still needed. Some studies have tested combinations of therapies with antiangiogenic agents plus chemotherapy plus immunotherapy, such as the IMpower150 clinical trial, although they have not been definitive (33,34).

These findings found in our study can be influenced by multiple factors, such as the fact that immunotherapy has always seemed less effective for squamous carcinomas PD-L1 negative, with practically no difference in OS (5-year OS rate chemo-immunotherapy 10.7% *vs.* chemotherapy 13.1%; HR 0.61–1.13) for PD-L1-negative squamous tumours in the KEYNOTE-407 clinical trial (5-year

Table 4 Major clinical trials comparing the efficacy of combination therapy with cisplatin or carboplatin

Study	Year	Phase	Patients	Regimen	Response rate (%)	Median OS (m)	P value
Klastersky (26)	1990	3	228	Cisplatin + etoposide	27	NA	>0.05
				Carboplatin + etoposide	16		
Rosell (27)	2002	3	618	Cisplatin + paclitaxel	28	9.8	>0.05
				Carboplatin + paclitaxel	25	8.5	
Schiller (28)	2002	3	1,155	Cisplatin + paclitaxel	21	7.8	>0.05
				Cisplatin + gemcitabine	22	8.1	
				Cisplatin + docetaxel	17	7.4	
				Carboplatin + paclitaxel	17	8.1	
Scagliotti (29)	2002	3	612	Cisplatin + gemcitabine	30	9.8	>0.05
				Carboplatin + paclitaxel	32	9.9	
				Cisplatin + vinorelbine	30	9.5	

OS, overall survival; m, months; NA, not available.

update) (35). These data were not statistically significant in OS but were statistically significant in PFS (5-year OS rate chemo-immunotherapy 7.1% *vs.* chemotherapy 6.7%; HR 0.52–0.95), so the data should be treated with caution. Furthermore, pemetrexed can be maintained as a monotherapy after a combination with platinum at a low toxicity; together with other factors, this fact means that adenocarcinomas have a better prognosis than squamous cell carcinomas in both the pre- and post-immunotherapy eras (36). Therefore, platinum chemotherapy may have a greater effect after immunotherapy than before the immunotherapy era.

Importantly, however, our study's limitations should be considered. It involved a retrospective cohort with a limited sample size (17 patients) and the use of historical cohorts that did not allow for the validation of these results. Comparison between patients in our sample with historical cohorts should be taken with caution because of the differences between the target populations of the clinical trials and our analysis. Therefore, no direct statistical analyses have been performed and the data for the efficacy comparison are indirect.

Conclusions

The efficacy of platinum-based chemotherapy for NSCLC in the post-immunotherapy era is similar to that in the pre-immunotherapy era, although the data suggest a possibly greater effect in terms of both survival and response. Immunotherapy's effect on the immune system may exert a key influence on the subsequent chemotherapy response; therefore, platinum is a second-line treatment with long response options, especially in pemetrexed maintenance. These treatment schemes' use over the years, allowing for prospective real-life studies, will be key to better understanding NSCLC treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-513/rc

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have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study's research protocol was approved by the Ethics Committee of the University Hospital of Salamanca (PI 2022 10 1155) and informed consent was taken from all the patients.

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