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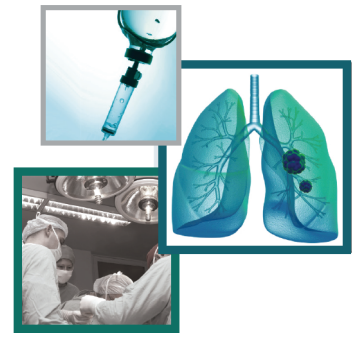
Lung Cancer Management



A comparative study of immunotherapy as second-line treatment and beyond in patients with advanced non-small-cell lung carcinoma

Jerónimo Rafael Rodríguez-Cid*[1,3], Sonia Carrasco-Cara Chards[13], Iván Romarico González-Espinoza[6], Vanessa García-Montes[4], Julio César Garibay-Díaz[7], Osvaldo Hernández-Flores[8], Rodrigo Riera-Sala[1,5], Anna Gozalishvili-Boncheva[11], Jorge Arturo Alatorre-Alexander[1,5], Luis Manuel Martínez-Barrera[1], Carla Paola Sánchez-Ríos[1,5], Adriana Martinez-Camacho[10], José Fabián Martínez-Herrera[5,12], Jordi Guzmán-Casta[1,5], Rodrigo Rafael Flores-Mariñelarena[3], Julián Diaz-Rico[9] & Patricio Santillán-Doherty[2]

[1]Clínica de Oncología Torácica, Instituto Nacional de Enfermedades Respiratorias, Dr Ismael Cosío Villegas, Mexico City, Mexico
[2]Medical Director, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico
[3]Centro Oncológico, Hospital Médica Sur, Mexico City, Mexico
[4]Departamento de Oncología, Hospital Español, Mexico City, Mexico
[5]Health Pharma Professional Research, Mexico City, Mexico
[6]Departamento de Oncología, Hospital Ángeles Puebla, Puebla, Mexico
[7]Hospital MAC, Puebla, Mexico
[8]Oncología Integral Satélite, Estado de México, Mexico
[9]Hospital Central Norte de Pemex, Mexico City, Mexico
[10]Hospital General Dr Manuel Gea González, Mexico City, Mexico
[11]Hospital H+, Los Cabos, Baja California, Mexico
[12]Centro Médico ABC Observatorio Centro de Cáncer, Mexico City, Mexico
[13]Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico
*Author for correspondence: cidjeronimo@yahoo.com.mx

Background: Immunotherapy has demonstrated an improved overall survival (OS) and progression-free survival (PFS) as second-line treatment and subsequent lines compared with chemotherapy. **Materials and methods:** This was a retrospective review among eight medical centers comprising 100 patients with a confirmed diagnosis of non-small-cell lung carcinoma, in their second-line treatment or beyond with immune checkpoints inhibitors treatment. The current study aimed to analyze effectiveness of immunotherapy in second-line treatment or further in the Mexican population, using PFS rate, OS rate and the best objective response to treatment by RECIST 1.1 as a surrogate of effectiveness. **Results:** In total, 100 patients met the criteria for enrollment in the current study. From the total study population, 49 patients (49.0%) were male and 51 (51.0%) were female, with an average age of 60 years and stage IV as the most prevalent clinical stage at the beginning of the study. A total of 61 patients (61.0%) had partial response; 11 (11.0%) stable disease; 2 (2.0%), complete response, 4 (4.0%), progression; and 22 (22.0%) were nonevaluable. We found a median PFS of 4 months (95% CI: 3.2–4.7 months) and an OS of 9 months (95% CI: 7.2–10.7 months). **Conclusion:** The response to immunotherapy is similar, with an improvement in OS and PFS, independent of which drug is used. Patients using nivolumab had a better survival, although that was not statistically significant.

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Keywords: atezolizumab • avelumab • immune checkpoint inhibitors • immunotherapy • lung cancer • nivolumab • NSCLC • pembrolizumab • second-line treatment

Lung cancer remains the leading cause of cancer in 2020, representing almost 12% of all cancers in the world. In Mexico, the incidence of lung cancer was 4.3–6.8/100,000 person-years in the latest epidemiological report

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and across the globe, there were over 2 million new cases of lung cancer in 2019 with 1.7 million deaths to worldwide statistics [1,2]. Smoking is the most recognized risk factor for lung cancer, although it is not the only one. Among others, exposure to wood smoke and work-related exposure such as asbestos, silica and coal have also been implicated [3,4].

Non-small-cell lung carcinoma (NSCLC) represents 80–85% of lung cancers. There are three subtypes of NSCLC: adenocarcinoma, squamous cell carcinoma and large cell carcinoma. These subtypes are grouped together as NSCLC because their treatment and prognoses are often similar [5]. One of the reasons for the lethality of this cancer is that it is often diagnosed at advanced stages (III or IV), so the treatments available as first-line are not sufficient enough to keep it under control.

Every tumor cell with variable neoantigens is recognized as nonself and is attacked by the immune system; however, to avoid elimination, tumor cells may express programmed death-1 ligand (PD-L1), a transmembrane protein on their surface [6]. Programmed death-1 (PD-1), a member of the CD28 immunoglobulin family expressed by $CD4^+$ and $CD8^+$ T cells, links to PD-L1, which is expressed on tumor cells and antigen presenting cells such as dendritic cells, macrophages, B cells and activated T cells [7]. In addition to the PD-1/PD-L1 checkpoint pathway, cytotoxic T lymphocyte antigen 4 (CTLA-4 or CD152) is a receptor also expressed by $CD4^+$ and $CD8^+$ T cells that modulates T-cell activation. CTLA-4 binds to B7 molecules, expressed on the surface of antigen presenting cells, and inhibits T-cell responses [8,9]. By doing so, neoplastic cells avoid antitumor immunity by suppressing T-cell proliferation and cytokine secretion. In this way, the immune system cannot recognize cancer cells and therefore cannot eliminate them. The prevalence of PD-L1 expression in NSCLC patients ranges from 24 to 60% [10]. Since some of the mechanisms in which cancer cells avoid immune recognition and elimination have been discovered, the development of new treatments is expected to increase the overall survival (OS) of cancer patients, especially those with advanced disease.

In the past decade, immunotherapy has proven to be a promising treatment for those patients with advanced disease that have failed a first-line treatment. Immunotherapy has improved OS in patients with locally advanced and metastatic disease and based on the Keynote 001, Keynote 010, OAK, Poplar, CheckMate 017 and CheckMate 057 trials, the US FDA and the European Medicines Agency have approved immunotherapies as second-line treatment for these patients [11]. Pembrolizumab, a humanized monoclonal anti PD-1 antibody has demonstrated a remarkably longer survival and fewer adverse events in patients with advanced NSCLC and PD-L1 expression on 1–50% of tumor cells [12] and has recently been approved as first-line treatment in tumors with $\geq$50% PD-L1 expression or in combination with chemotherapy, regardless of PD-L1 expression [13]. Nivolumab, a fully human anti-PD-1 IgG4 antibody that diminishes the inhibitory signaling through the PD-L1 pathway by causing immune checkpoint blockade [12], and atezolizumab, a humanized anti-PD-L1 IgG1 monoclonal antibody, have been proven to have benefit on OS in patients with advanced NSCLC (nonsquamous or squamous histologies), regardless of PD-L1 status, who had progressive disease after a previous chemotherapy regimen [11,13,14]. The first-in-class immunotherapeutic for blockade of CTLA-4 is ipilimumab, a fully human IgG1 monoclonal antibody that, in solid tumors, can stimulate tumor-specific T-cell proliferation, which leads to the infiltration of these cells into the tumor and achievement of tumor regression [15].

Materials & methods

This was a descriptive, observational, retrospective, multicenter study among eight medical centers comprising 100 patients with a confirmed diagnosis of advanced lung cancer, comparing different immunotherapy second-line treatments. The study population met the following criteria: patients older than 18 years of age with a confirmed histopathologic diagnosis of lung cancer, Eastern Cooperative Oncology Group status (ECOG) 0–2, at their second-line therapy line, locally advanced and/or metastatic disease. The following clinical and pathologic variables were reviewed: sex, age, smoking status, asbestos exposure, diagnosis, number of previous treatment lines, type of immune checkpoints inhibitors (ICI), ECOG 0–2, tumor node metastasis, clinical stage at diagnosis, response to treatment, progression-free survival (PFS) and response as per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) using computed tomography scan. SPSS software version 24.0 (IBM, NY, USA) was used for analysis, including the univariate and multivariate analysis. The variables were expressed as median values, together with total values and percentages. PFS and OS were graphed using a Kaplan–Meier plot. The criterion for statistical significance was $p < 0.05$. All financially related issues from the study were absorbed by the investigation group.

Table 1. Baseline characteristics of 100 patients treated with second-line immunotherapy.

Characteristic	Patients, n (%)
Age, years, mean (SD)	60
Sex	
Female	51 (51.0%)
Male	49 (49.0%)
Smoking status	
Smoker	46 (46.0%)
Nonsmoker	54 (54.0%)
Asbestos exposure	
Yes	23 (23.0%)
No	77 (77.0%)
ECOG	
0	35 (35.0%)
1	46 (46.0%)
2	18 (18.0%)
3	1 (1.0%)
Clinical stage at diagnosis	
II	2 (2.0%)
III	7 (7.0%)
IV	91 (91.0%)
Diagnosis	
Lung adenocarcinoma	93 (93.0%)
Lung squamous cell carcinoma	7 (7.0%)
Immunotherapy treatment	
Nivolumab	70 (70.0%)
Pembrolizumab	7 (7.0%)
Atezolizumab	16 (16.0%)
Avelumab	4 (4.0%)
Other	3 (3.0%)
Immunotherapy line number	
Second-line treatment	51 (51.0%)
Third-line treatment	38 (38.0%)
Fourth-line treatment	9 (9.0%)
Fifth-line treatment	2 (2.0%)

ECOG: Eastern Cooperative Oncology Group; SD: Standard deviation.

Results

A total of 100 patients were included in the study, from eight medical centers in Mexico. From the total study population, 49 patients were male (49.0%) and 51 were female (51.0%). The average age was 60 years old with a range of 24–89 years. About 46 patients (46.0%) had a confirmed history of tobacco use (current or former smoker). Twenty three patients (23.0%) had confirmed history of asbestos exposure. Thirty five patients (35.0%) had an ECOG 0, 46 patients (46.0%) an ECOG 1, 18 patients (18.0%) an ECOG 2 and one patient (1.0%) an ECOG 3. Of all 100 patients, 91 (91.0%) were at clinical stage IV, seven patients (7.0%) at clinical stage III and two patients (2.0%) were at clinical stage II according to the 8th edition of the tumor node metastasis classification for lung cancer provided by the International Association for the Study of Lung Cancer (IASLC) (Table 1).

Patients with different types of lung cancer were studied, with 93 (93.0%) patients were diagnosed with lung adenocarcinoma and seven (7.0%) with lung squamous cell carcinoma. 70 (70.0%) patients received nivolumab, seven (7.0%) patients received pembrolizumab, 16 (16.0%) received atezolizumab, four (4.0%) received avelumab and three (3.0%) received other immunotherapy. For 51 (51.0%) patients it was the second-line treatment, for 38 (38.0%), the third-line, for nine patients (9.0%) it was the fourth-line treatment and for two patients (2.0%), the fifth-line.

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Table 2. Best objective response to treatment by RECIST 1.1 of 100 patients after use of immunotherapy.

Objective response rate	Patients, n (%)
Complete	2 (2%)
Partial	11 (11%)
Stable disease	61 (61%)
Progressive disease	4 (4%)
Unevaluable	22 (22%)

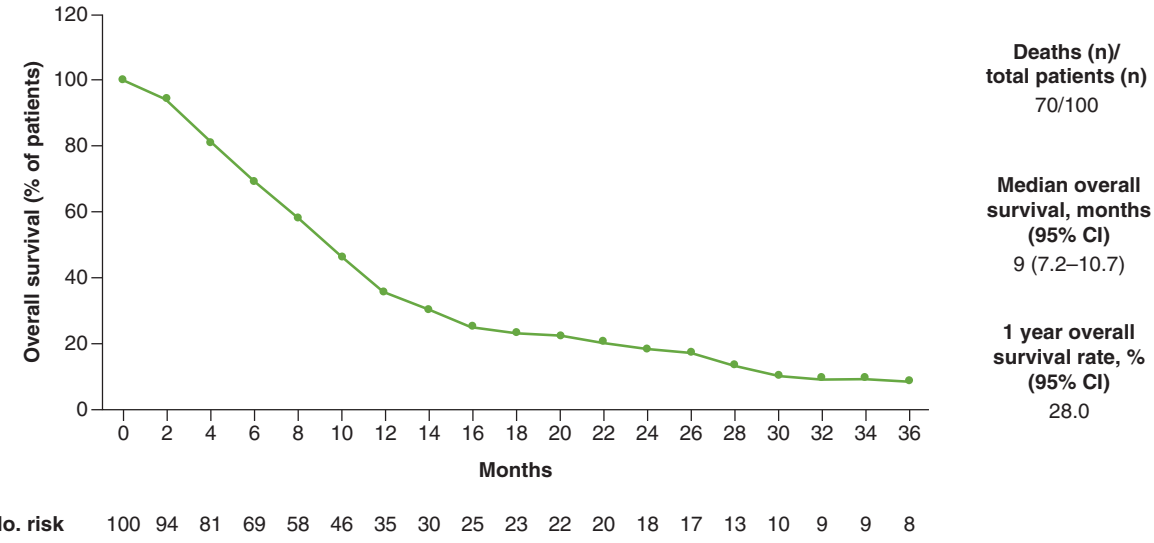

Figure 1. Kaplan–Meier Curve for overall survival.

After evaluating the response to immunotherapy by RECIST 1.1, we found 11 patients (11.0%) with partial response, 61 (61.0%) with stable disease, two (2.0%) with complete response, four (4.0%) with progression and 22 (22.0%) who were nonvaluable (Table 2).

The median PFS was 4 months (95% CI: 3.2–4.7 months) and the median OS was 9 months (95% CI: 7.2–10.7). Of all patients included in the study, 16 (16.0%) had a PFS of 1 year, seven (7.0%) of 2 years and four (4.0%) of 3 years (Figure 1). In addition, 28 (28.0%) had an OS of 1 year, 15 (15.0%) of 2 years and seven (7.0%) of 3 years (Figure 2).

Nivolumab was the most common immunotherapy. It showed an OS of 10 months (95% CI: 7.9–12.0) and a PFS of 4 months (95% CI: 3.4–4.5). Pembrolizumab had an OS of 7 months (95% CI: 0.0–17.2.0) and a PFS of 6 months (95% CI: 0.0–13.6). The use of atezolizumab demonstrated an OS of 9 months (95% CI: 5.0–12.9) with a PFS of 4 months (95% CI: 2.4–5.5) while avelumab showed an OS of 8 months (95% CI: 5.0–10.9) and a PFS of 5 months (95% CI: 4.1–5.8). Others had similar results with an OS of 6 months (95% CI: 1.1–10.8) and a PFS of 3 months (Figure 3 & 4).

For the 51 patients in their second-line treatment the OS was 9 months (95% CI: 6.5–11.4) and a PFS of 5 months (95% CI: 3.3–6.6), compared with the 49 patients in third, fourth and fifth-line treatment which showed an OS of 10 months (95% CI: 7.9–12.4) and a PFS of 4 months (95% CI: 3.9–4.9) (Figures 5 & 6).

Univariate analysis showed no statistical significance in any variable for median PFS and for PFS rate. At 3 years the only variable with statistical significance was clinical stage at diagnosis ($p = 0.01$) with a hazard ratio (HR) of 0.79. For OS, female gender had a HR of 0.76 and was statistically significant ($p = 0.008$). In addition to that, clinical stage at diagnosis was also statistically significant ($p = 0.01$) with a HR of 0.70. For OS rate at 3 years, clinical stage at diagnosis and immunotherapy used showed statistical significance ($p = 0.000$; HR: 0.66 and $p = 0.056$; HR: 0.84, respectively) (Table 3). Neither median PFS, PFS rate at 3 years, median OS nor OS rate at 3 years showed statistical significance for a benefit in receiving second-line or subsequent ICI treatment. Multivariate analysis showed $p = 0.008$ for gender, $p = 0.003$ for clinical stage at diagnosis and $p = 0.002$ in immunotherapy used (Table 4).

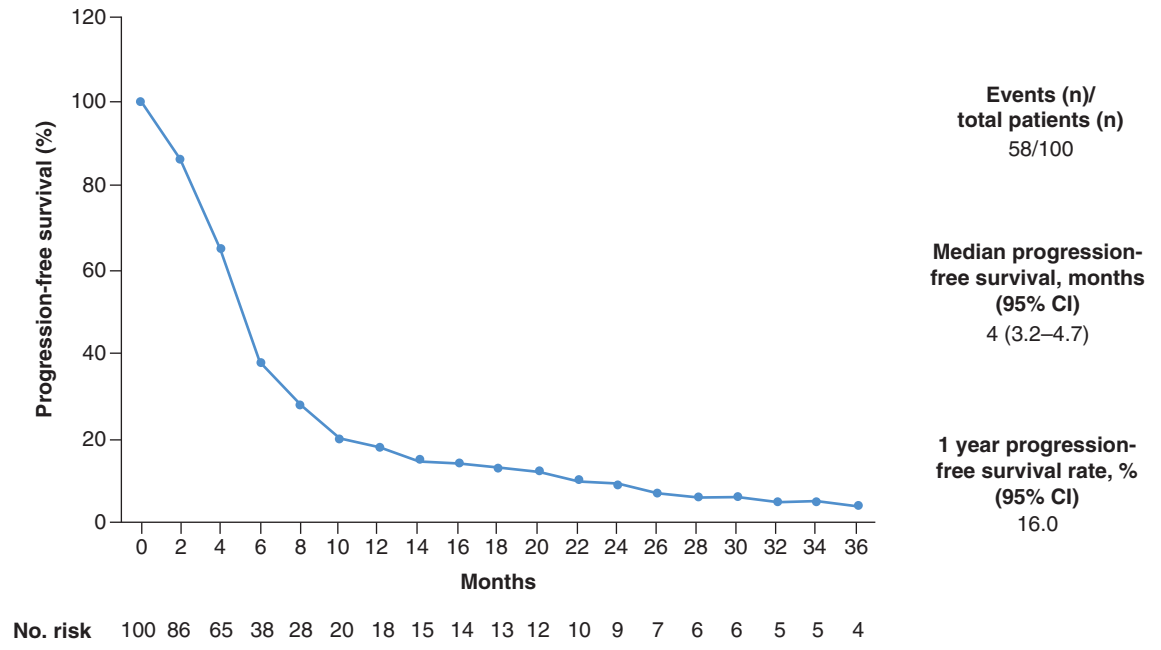

Figure 2. Kaplan–Meier curve for progression-free survival.

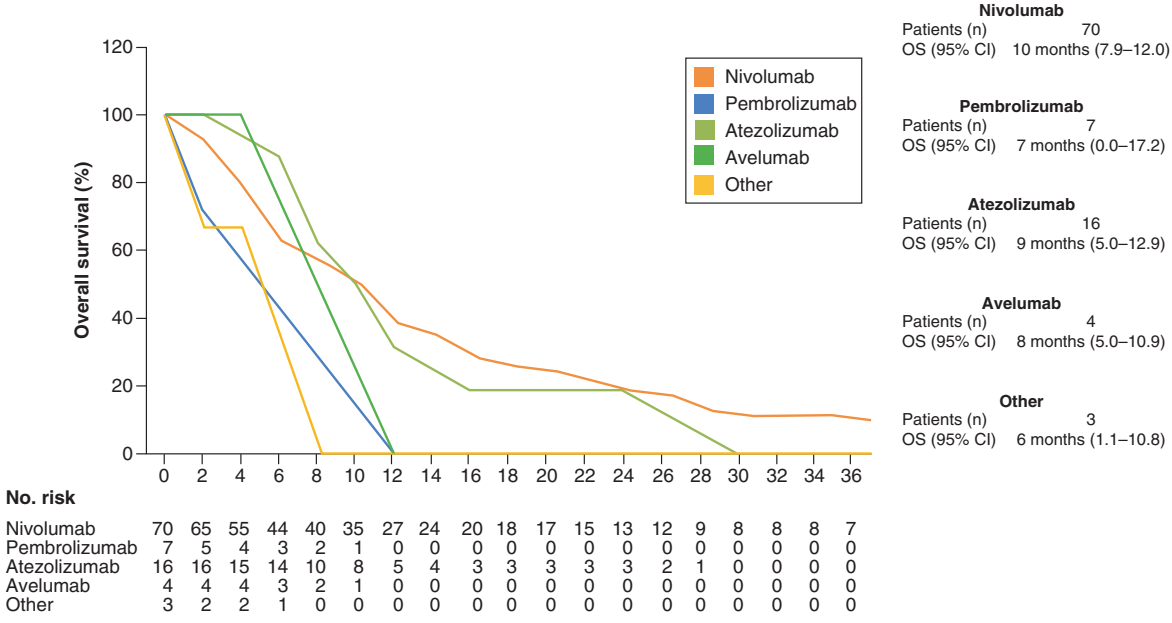

Figure 3. Kaplan–Meier Curve for overall survival with the immunotherapies used.
OS: Overall survival.

Table 3. Univariable analysis of factors that had an impact on overall survival and progression-free survival.

	PFS (months)		3-year PFS rate		OS (months)		3-year OS rate	
	$p < 0.05$	HR (95% CI)	$p < 0.05$	HR (95% CI)	$p < 0.05$	HR (95% CI)	$p < 0.05$	HR (95% CI)
Gender (female/male)	0.210	0.082	0.484	0.004	**0.008**	**0.76**	0.133	0.112
Clinical stage	0.182	0.092	**0.016**	**0.214**	**0.001**	**0.306**	**0.000**	**0.341**
Drug used	0.422	0.020	0.119	0.119	0.150	0.105	**0.056**	**0.160**

Boldface values indicate statistical significance.
HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival.

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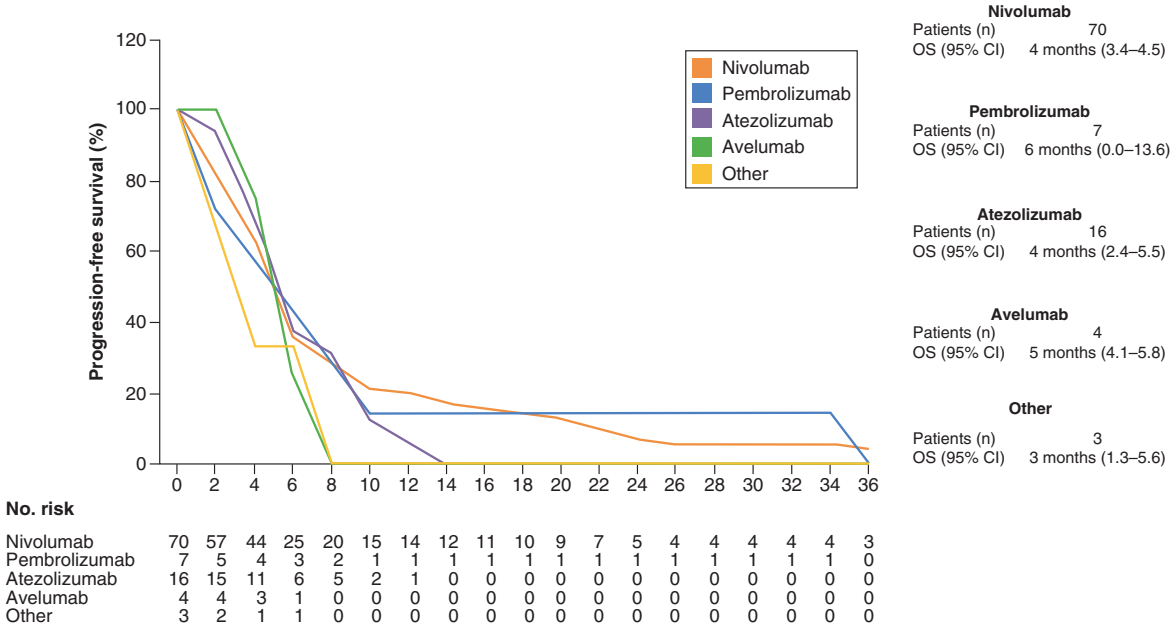

Figure 4. Kaplan–Meier curve for progression-free survival with the immunotherapies used.
OS: Overall survival.

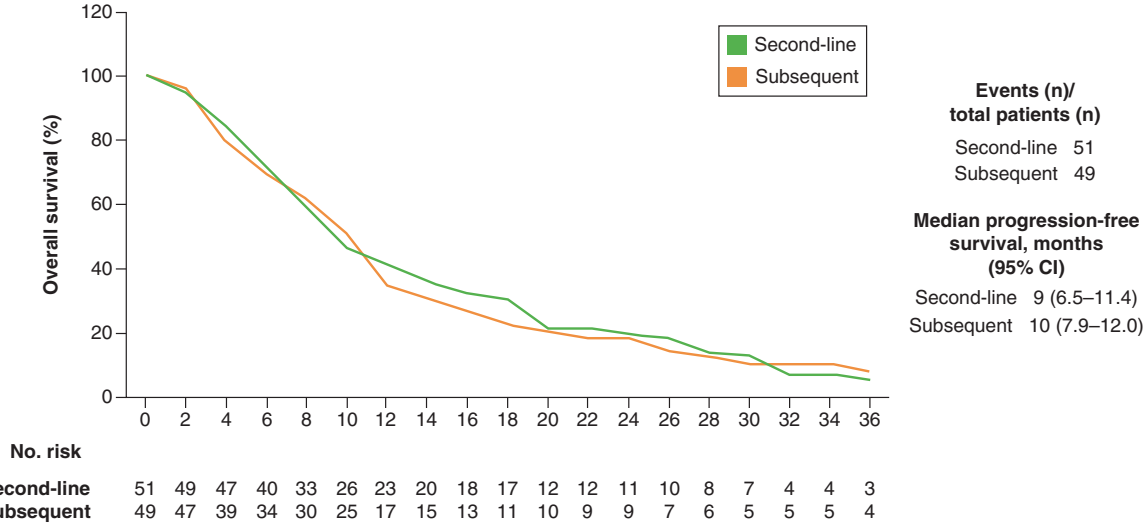

Figure 5. Kaplan–Meier curve for overall survival in second-line treatment versus subsequent treatments.

Table 4. Multivariable analysis of factors that had an impact on overall survival.

Clinical stage	p = 0.008
Gender	p = 0.003
Immunotherapy used	p = 0.002

Discussion

The number of treatment options for NSCLC has increased in the last decade but despite that, there has been a minimal improvement in OS since the approval of docetaxel as the standard of treatment for previously treated patients with advanced NSCLC with a median OS rates of 22% at 1 year and 5% at 2 years [16].

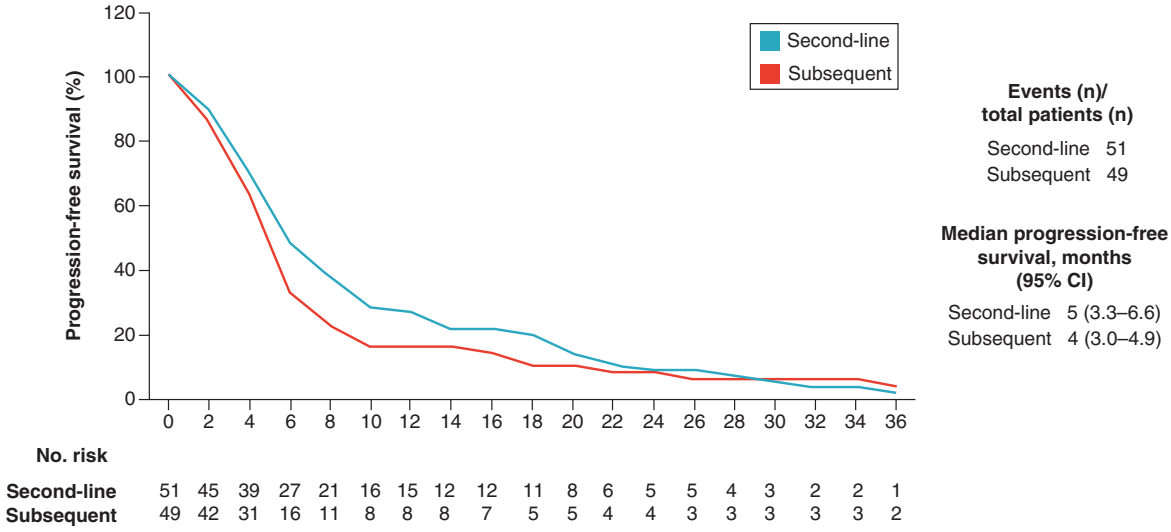

Figure 6. Kaplan–Meier curve for progression-free survival in second-line treatment versus subsequent treatments.

In our study, we report results of patients from eight oncological centers whose general characteristics are consistent with previous reports described in the literature. Stage IV was the most prevalent clinical stage at the beginning of the immunotherapy treatment, and the average age was 60 years (range: 24–89 years). After evaluating patients with second-line and further immunotherapy treatment, we found that the median OS in this trial was lower than previous studies, at 9 months compared with 9.2 months in CheckMate 017 [17], whose study population were patients with squamous histology, 12.2 months in CheckMate 057 [18], 13.8 months in OAK [19] and 14.9 months in Keynote 010 [20]. The median rate of OS at 1 year was 31.8% in our study, while CheckMate 017 reported a 1-year rate of 42%, CheckMate 057 51 %, OAK with an overall 1-year survival rate of 55% and Keynote 010 reported an OS median rate of 43.2%. The difference between our study and CheckMate 017, CheckMate 057, Keynote 010 and OAK in OS, PFS and the percentage of long-term survivors may be due to the fact that in our study population, almost 10% were patients with squamous cell carcinoma, which has a worse prognosis. In addition, in our study we included population in their second-line treatment or beyond. Regarding PFS, in our study we found a median of 4 months and a 19.6% rate at 1 year, very similar to what previous studies have shown (CheckMate017 with 3.5 months with a rate of 21%, CheckMate 057 at 2.3 months and a 1-year PFS rate of 19%, OAK at 2.8 months and Keynote 010 with a median progression-free survival of 5 months). In addition, we compared OS and PFS between patients in second-line treatment and subsequent treatments to evaluate if there is a benefit at receiving immunotherapy in earlier lines. An OS of 9 months and a PFS of 5 months was found in second-line treatment while for patients in subsequent treatments the OS was 10 months and PFS 4 months [17–20].

To evaluate the objective response, RECIST 1.1 was used, in which we found that the objective response rate was lower than previous studies at 13.1%, while in CheckMate 017 it was 20%; CheckMate 057, 19%; OAK, 18 % and Keynote 010, 18%. There is a proportion of patients considered long-term survivors; in our study we followed up at 2 years and the percentage of these patients is 15%, compared with a previous study that saw 25% for OAK and CheckMate 057. In addition to the aforementioned, the difference in the objective response could lie in the fact that the percentage of smokers in our study is lower than the percentage of the population in previous studies (46% in our study vs 92% in CheckMate 017, 79% CheckMate 057, 79% in Keynote 010 and 82% OAK).

Nivolumab had an OS of 10 months and a PFS of 4 months in our trial versus an OS of 9.2 months and PFS of 3.5 months in CheckMate 017 and 12.2 months of OS and 2.3 months of PFS in CheckMate 057 which also studied the use of nivolumab as second-line treatment. In Keynote 010, a trial that evaluated the use of pembrolizumab as second-line treatment, the OS was 14.9 months and the PFS was 2.8 months versus our trial with 7 months of OS and 5 months of PFS. For the use of Atezolizumab, the results for PFS showed a similarity in our trial versus OAK study (4 vs 2.8 months) but for OS, OAK was superior than us (13.8 vs 9 months). In our

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trial, avelumab and tislelizumab demonstrated similar results, with an OS of 8 and 6 months and a PFS of 5 and 3 months, respectively.

In the univariate analysis for OS, a negative correlation in clinical stage was found with a HR of 0.70 statistically significant (p = 0.001) when comparing stage III with stage IV, therefore, it can be concluded that patients who had been diagnosed in a stage III disease have 30% protection over those diagnose in stage IV. Moreover, gender showed a negative correlation with a HR 0.76 statistically significant (p = 0.008) favoring the female gender, so female patients have 24% less risk of death compared with male patients. We found that the use of nivolumab has a tendency to improve OS over the rest of immunotherapies studied, with a HR of 0.84, but it was not statistically significant (p = 0.056). For PFS, patients diagnosed at stage III disease have 21% protection over those patients diagnosed at stage IV disease, with a HR of 0.79 and p = 0.016. Multivariate analysis confirmed those results with significance less than 0.05 in the variables studied.

It should be noted that in our country, only a small proportion of patients has access to this type of medication, so the population sample taken into account for this study is small compared with international studies.

Conclusion

In conclusion, our results are comparable with previously reported studies. The response to immunotherapy is similar with an improvement in OS and PFS, independently of which drug is used, although we found that patients with nivolumab had a better survival but it was not statistically significant.

Future perspective

The tendency toward the use of immune checkpoints inhibitors indicates that in the near future the standard of treatment will be these drugs used in first line setting, and the future will be the use of these drugs in combination with multiple resistance inhibitors or synergistic medications. As our results show, the use of Nivolumab (although not statistically significant) demonstrated an increase in OS and PFS, so we hope that more research can be done in this regard.

Summary points

- Lung cancer remains the leading cause of cancer in 2020, representing almost 12% of all cancer in the world.
- Patients who develop non-small-cell lung carcinoma (NSCLC) usually have several comorbidities and a poor performance status.
- Immunotherapy or biological therapy, stimulates or restores the ability of the immune system to fight cancer, some infectious diseases or to protect the body from some of the side effects of treatment.
- The number of treatment options for NSCLC has increased in the last decade, but despite that, there has been a minimal improvement in overall survival (OS) since the approval of docetaxel as the standard of treatment for previously treated patients with advanced NSCLC with median OS rates of 22% at 1 year and 5% at 2 years.
- Second-line immunotherapy is the standard of care, if previously not used, for patients with NSCLC.
- This was a descriptive, observational, retrospective, multicenter study among eight medical centers comprising 100 patients with a confirmed diagnosis of advanced lung cancer, comparing different immunotherapy second-line treatments.
- The response to immunotherapy is similar with an improvement in OS and progression-free survival, independently of which drug is used.

Author contributions

Conception and design: R-CJ Rafael, G-EI Romarico, G-M Vanessa, G-DJ César, H-F Osvaldo, A-AJ Arturo; administrative support: R-CJ Rafael, G-EI Romarico, G-M Vanessa, G-DJ César, H-F Osvaldo; provision of material or patients: all authors; collection and assembly of data: R-CJ Rafael, C-C Sonia, F-MR Rafael; data analysis and interpretation: R-CJ Rafael, C-C Sonia.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The study design was approved by Instituto Nacional de Enfermedades Respiratorias Institutional Ethics Board following the Declaration of Helsinki, Fortaleza Brazil, 2013, for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Data sharing statement

Each individual participant data collected during the trial is available, including study protocol, statistical analysis plan, informed consent form, clinical study report and analytic code immediately following publication with no end date. Proposals should be directed to cidjeronimo@yahoo.com.mx. To gain access, data requestors will need to sign a data access agreement.

References

Papers of special note have been highlighted as: • of interest

1. World Health Organization (WHO). The Global Cancer Observatory. (2018). *Cancer Today – Lung Cancer Facts.* https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf
2. Yang Y. Cancer immunotherapy: harnessing the immune system to battle cancer. *J. Clin. Invest.* 125(9), 3335–3337 (2015).
3. National Lung Screening Trial Research Team; Aberle DR, Adams AM *et al.* Reduced lung-cancer mortality with low-dose computed tomographic screening. *N. Engl. J. Med.* 365(5), 395–409 (2011).
4. *The MD Anderson Manual of Medical Oncology* (3rd Edition). Kantarjian Hagop M, Wolff Robert A (Eds). Section IV, Chapter 18, McGraw Hill (2016).
5. Bareschino MA, Schettino C, Rossi A *et al.* Treatment of advanced non-small-cell lung cancer. *J. Thorac. Dis.* 3(2), 122–133 (2011).
6. Hyojin K, Jin-Haeng C. PD-L1 testing in non-small-cell lung cancer: past, present, and future. *J. Pathol. Transl. Med.* 53(4), 199–206 (2019).
7. Ramagopal UA, Liu W, Garrett-Thomson SC *et al.* Structural basis for cancer immunotherapy by the first-in-class checkpoint inhibitor ipilimumab. *Proc. Natl Acad. Sci. USA* 114(21), E4223–E4232 (2017).
8. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. *J. Exp. Med.* 182, 459–465 (1995).
9. Walunas TL, Lenschow DJ, Bakker CY, Linsley PS, Freeman GJ, Green JM *et al.* Pillars article: CTLA-4 can function as a negative regulator of T-cell activation. *J. Immunol.* 1, 405–413 (1994). J. Immunol. (Baltimore, Md: 1950). 187, 3466–74 (2011).
10. Yu H, Boyle TA, Zhou C, Rimm D, Hirsch FR. PD-L1 expression in lung cancer. *J. Thorac. Oncol.* 11(7), 964–975 (2016).
11. Gridelli C, Ascierto PA, Grossi F *et al.* Second-line treatment of advanced non-small-cell lung cancer non-oncogene addicted: new treatment algorithm in the era of novel immunotherapy. *Curr. Clin. Pharmacol.* 13(2), 76–84 (2018).
12. Kwok G, Yau TC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). *Hum. Vaccin. Immunother.* 12(11), 2777–2789 (2016).
13. Chen R, Tao Y, Xu X *et al.* The efficacy and safety of nivolumab, pembrolizumab, and atezolizumab in treatment of advanced non-small-cell lung cancer. *Discov. Med.* 26(143), 155–166 (2018).
14. Rajan A, Kim C, Heery CR, Guha U, Gulley JL. Nivolumab, anti-programmed death-1 (PD-1) monoclonal antibody immunotherapy: role in advanced cancers. *Hum. Vaccin. Immunother.* 12(9), 2219–2231 (2016).
15. Shah NJ, Kelly WJ, Liu SV, Choquette K, Spira A. Product review on the Anti-PD-L1 antibody atezolizumab. *Hum. Vaccin. Immunother.* 14(2), 269–276 (2018).
16. Penrod JR, Korytowsky B, Petrilla A *et al.* Survival of U.S. Medicare patients with advanced non-small-cell lung cancer by line of therapy. *J. Clin. Oncol.* 32(Suppl. 15), Abstract, 6582 (2014).
17. Brahmer J, Reckamp KL, Baas P *et al.* Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N. Engl. J. Med.* 373(2), 123–135 (2015).

• **One of the most releveant studies on immunotherapy with which we compared our results.**

18. Borghaei H, Paz-Ares L, Horn L *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N. Engl. J. Med.* 373, 1627–1639 (2015).

• **One of the most releveant studies on immunotherapy with which we compared our results.**

19. Rittmeyer A, Barlesi F, Waterkamp D. *et al.* Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a Phase III, open-label, multicentre randomised controlled trial. *Lancet* 389, 255–265 (2017).

• **One of the most releveant studies on immunotherapy with which we compared our results.**

20. Herbst RS, Baas P, Kim DW *et al.* Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 387(10027), 1540–1550 (2016).

- **One of the most releveant studies on immunotherapy with which we compared our results.**