Survival outcomes in a cohort of metastatic non-small cell lung cancer patients with limited access to immunotherapy and targeted therapy in a low and middle-income country.

Diego F. Ballen, MD[1]; Carlos Carvajal-Fierro, MD[2]; Rafael Beltrán, MD[2]; Martha L. Alarcón, MD[3]; Camilo Vallejo-Yepes, MD[3]; Ricardo Brugés-Maya, MD[3]

[1]Clinical Oncology Fellow, Instituto Nacional de Cancerología, Universidad el Bosque. Bogotá D.C. (Colombia).

[2]Thoracic Surgeon, Instituto Nacional de Cancerología, Bogotá D.C. (Colombia)

[3]Clinical Oncologist, Instituto Nacional de Cancerología, Bogotá D.C. (Colombia)

Corresponding Author: Diego F. Ballen, MD, address for correspondence: Instituto Nacional de Cancerología, Cl. 1 #9-85, Bogotá D.C., Colombia

Mobile number: (+57 3152931879),

e-mail: diegoballenmd@gmail.com

Clinical Oncology Department, Instituto Nacional de Cancerología, Bogotá D.C., Colombia.

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Abstract

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Diego-Felipe Ballen, MD[1]; Carlos Carvajal-Fierro, MD[2]; Rafael Beltrán, MD[2]; Martha-Liliana Alarcón, MD[3]; Camilo Vallejo-Yepes, MD[3]; Ricardo Brugés-Maya, MD[3]

Purpose: To describe the survival outcomes in a cohort of metastatic non-small cell lung cancer (NSCLC) patients with limited access to immunotherapy and target therapy treated between 2013 and 2018 in a reference cancer center in Bogota, Colombia.

Methods: Observational study of a retrospective cohort of metastatic NSCLC patients. A complete description of the population was made. Survival curves were performed using the Kaplan-Meier method. Log-rank test was used to evaluate differences between subgroups.

Results: 209 patients were included. 79,5% patients had adenocarcinoma (ADC) and 14,8% squamous cell carcinoma (SCC). The most used first-line treatment was cytotoxic chemotherapy (50.2%), followed by anti-EGFR therapy (14.8%), chemoimmunotherapy (1.9%) and ALK target therapy (1.4%). 31.6% received best supportive care (BSC). Median overall survival (OS) was 11.2 months, 13 months for ADC and 2.5 months for SCC. The median OS for patients that received any type of treatment was 26.9 months (95%CI,14.9–38.8) versus 1.4 months for BSC (95%CI,1.1–1.8). Progression-free survival was 9.3 months without significant differences with respect to the type of first-line therapy used. The median time-to-treatment was 55 days and only 54% of patients with an actionable mutation in EGFR received an anti-EGFR therapy as the first line treatment.

Conclusions: Cytotoxic chemotherapy was the most used treatment for the management of metastatic NSCLC, however a third of patients received BSC. SCC was the subgroup with worse prognosis and their access to immunotherapy is imperative. In our population, use of targeted therapies has been restricted by access to molecular diagnosis and remained low until 2018.

Key words: non-small cell lung cancer, overall survival, progression-free survival, chemotherapy, immunotherapy, molecular diagnosis, adenocarcinoma, squamous cell carcinoma, molecular targeted therapy.

Introduction

Lung cancer is the leading cause of cancer mortality in the world with 1,796,144 deaths reported in 2020 (1). Advances in translational oncology have made non-small cell lung cancer (NSCLC) a disease whose adverse outcomes have been favorably modified by incorporating molecular diagnostic methods and personalized treatment, especially in the advanced and metastatic setting. This has been recently demonstrated in United States, where a reduction in mortality related to NSCLC has been documented, since 2013, when approval of targeted therapies was given for actionable mutations such as EGFR or ALK (2).

In low- and middle-income countries (LMICs) we have a high heterogeneity in access to diagnostic tests, biomarkers, and access to treatments like immunotherapy and targeted therapy that make implementation of personalized therapy a big challenge (3,4). However,

the impact of the development of personalized therapies on the survival of our patients has been poorly described.

The aim of this study was to describe the survival outcomes of metastatic NSCLC patients with limited access to immunotherapy and target therapy treated between 2013 and 2018 in a cohort of patients treated in a reference cancer center in Bogota, Colombia.

Materials and methods

We did a retrospective cohort study including patients with metastatic NSCLC treated at Instituto Nacional de Cancerologia (INC) in Bogota, Colombia, between 2013 and 2018. We excluded patients under 18 years of age, without institutional review of the pathology, extra-institutional treatment, lack of follow-up or with other synchronous tumors except for non-melanoma skin cancer managed with local therapies.

RedCap 7.1.2 platform was used to collect data obtained from clinical records. Continuous variables were described in medians and interquartile ranges (IQR) and categorical variables in absolute values and percentages. Data were analyzed using SPSS version 19 with the support of INC statistical team. Overall survival (OS) was defined as the time between the date of the biopsy report of NSCLC and the date of death recorded in the clinical records or censored on the last day of follow-up. Progression-free survival (PFS) was calculated as the time between the date of initiation of first-line systemic therapy with palliative intention until the date of progression, death, or last follow-up if disease progression was not documented. Additionally, time-to-treatment was defined as the time between the date of the pathological report confirming NSCLC to the date of the initiation of first-line systemic therapy. Survival analysis was performed using Kaplan-Meier curves and log-rank test to assess differences between subgroups. A cox regression was performed in search of factors related to progression-free survival and overall survival.

The protocol was approved by institutional ethics committee (No CEI-00554-19) before collecting data from clinical records, and it was supervised by an independent clinical monitoring group.

Results

Between December 2013 and December 2018, 209 patients with newly diagnosis, treatment-naive metastatic NSCLC were included (Table 1). The median age was 65 years (IQR=55-72), 55.5% were women, half of the patients had active or past smoking history and 39.2% had an Eastern Cooperative Oncology Group (ECOG) performance status ≥2. The most frequent subtype was adenocarcinoma (ADC) in 79.5% of patients, followed by squamous cell carcinoma (SCC) in 14.8% and others in 5.7%.

EGFR mutation status was the most tested biomarker in 70.8% of patients with a positivity rate of 39% for the samples studied, the ALK tested frequency was 24.9% with a positivity rate of 25%. PD-L1 was performed in 11% of the cases. The most used first-line treatment was cytotoxic chemotherapy (50.2%), followed by anti-EGFR therapy (14.8%), chemoimmunotherapy (1.9%), and ALK-targeted therapy (1.4%). 31.6% of the patients did not receive specific cancer treatment and were managed with best supportive care (BSC). The median time of follow up was 13 months. The median overall survival for the total population was 11.2 months (95% CI 7.9 - 14.4) and 34% of patients were alive at 2 years, Figure 1A. For the ADC group the median OS was 13.0 months (95% CI 8.1 - 17.9) and 38% of patients were alive at 2 years. For the SCC group the median OS was 2.5 months (95% CI % 0.6 - 4.4) and only 8% of patients were alive at 2 years, Figure 1B. Women had a better median overall survival compared to men (14.7 months vs. 5.7 months, $p < 0.014$).

SCC was more likely to receive BSC as the only treatment compared to ADC, a difference that was statistically significant (p = 0.003).

The median OS for the subgroup of patients that received any type of treatment was 26.9 months (95% CI 14.9 – 38.8) versus 1.4 months for BSC (95% CI 1.1 – 1.8) (p < 0.001).

Among the 143 patients who received any kind of treatment, the median time-to-treatment was 55 days (IQR 30 to 105). Although, median OS of patients with chemotherapy and anti-EGFR therapy was 20.8 (95% IC 8.5 – 33.0) and 27.2 (95% IC 14.5 – 39.9) months respectively, this difference was not statistically significant (p = 0.270).

The median PFS for the total population was 9.3 months (95% CI 7.9 - 10.7). Median PFS was 8.7 months (95% CI 6.7 - 10.7) in chemotherapy subgroup and 9.3 months (95% CI 5.4 - 13.2) in EGFR therapy subgroup, this difference was not statistically significant (p = 0.362), Figure 2.

A first-generation tyrosine kinase inhibitor was used in 80% of patients who received first-line anti-EGFR therapy (Erlotinib 45%, Gefitinib 35%), followed by the second-generation ITK Afatinib in 20%. No patient received Osimertinib as first-line treatment. The use anti-EGFR therapy in the second line treatment was 33% (n = 19), including four patients receiving Osimertinib.

Cox regression model, which included variables sex, age, ECOG, histology and type of first-line therapy, showed that SCC histology was an independent factor for worst OS (HR: 1.8, 95% CI 1.073 – 3.035, p = 0.026) and worst PFS (HR:3.4, 95% CI 1.568 – 7.596).

Discussion

The treatment approach to patients with metastatic NSCLC is changing year by year with the development of personalized therapies. The frequent use of molecular diagnostic techniques has taught us that the term NSCLC brings together many entities with different clinical and biological behavior. These advances are experienced in a particular way in

LMICs, where there are other ethnic, socio-economic, environmental, and geographic factors that make real-life studies a valuable tool for evaluating the impact that these new approaches really have on the care of our patients.

The most widely used treatment in our patients continues to be cytotoxic chemotherapy (50.2%). On the other hand, a third of our patients did not receive a first-line treatment and were treated with BSC, these data are similar to those reported in other cohort of Latin American patients with metastatic NSCLC (5). The interpretation of these data needs carefully attention to histology, since BCS was the only treatment received by 54% of patients with SCC compared to 27.7% of patients with ADC, a difference that was statistically significant ($p = 0.003$).

Differences according to histology were also found in overall survival, with a statistically significant difference in median OS of 13.0 months in ADC versus 2.5 months in SCC. Several factors of SCC patients could explain this gap: they were mainly men (74.2%), smokers (80.6%) and had a worse performance status (ECOG ≥ 3, 16,1%). Furthermore, the fact that actionable mutations are not an important therapeutic target in SCC makes the incorporation of immunotherapy into treatment the most impactful strategy (6), even if it is used after progression to first line therapy (7). The low use of immunotherapy in our population was due to the time of approval of these therapies in Colombia. PD-1 inhibitors were introduced as second-line treatment for lung cancer in 2016 and determination PDL-1 expression was not mandatory. Government approval of immune checkpoint inhibitors (ICI) as first-line monotherapy in patients with PD-L1 expression greater than 50% occurred in June 2017 and its use in combination with chemotherapy regardless of the determination of PDL-1 expression in non-SCC patients occurred in August 2018 and in SCC patients in March 2019, Figure 3. In our cohort, no patients with SCC received

immunotherapy in the first line of treatment and only one of them underwent determination of PD-L1 expression in tumor tissue, which may explain the poor outcomes found in this population and highlights the importance of improving access to immunotherapy in our patients.

Patients receiving some type of first-line treatment had a striking median OS of 26.9 months, which could be explained by the high frequency of women with adenocarcinoma histology in the general population. A retrospective study in a Latin American population between 2006 and 2014 found that women have a 16% lower risk of mortality from lung cancer compared to men, which is explained by a wide variety of factors such as younger age at diagnosis, higher probability of ADC, lower frequency of smoking, higher actionable genomic alterations, and better response to different treatment modalities (8). Another important factor is time-to-treatment. It is interesting the recent published data about interpretation of time-to-treatment in patients with NSCLC. The hypothesis that extended time-to-treatment negatively affects survival has been consistently described in early-stages specifically for surgical treatment, however, it doesn't apply for metastatic setting (9,10). This phenomenon called "waiting time paradox" (11,12), could be explained by the fact that early treated patients tend to have more severe symptoms, so the extended median time-to-treatment of 55 days in our cohort indirectly tell us that they are patients in better conditions, and this could be another reason for the OS reached in the population who received any kind of treatment. Regardless of the cause, we have observed in our population a progressive improvement in overall survival according to what has been published in previous years (13,14)

In ADC patients, a median PFS of 9.3 months reached with anti-EGFR therapy (mainly first generation ITK) is really close to PFS published in EURTAC study (15). The lack of

statistical significance in PFS between EGFR therapy and cytotoxic chemotherapy could be related to the fact that only 54% of patients with EGFR mutations received targeted therapy in the first-line scenario which implies that many patients received chemotherapy as first line treatment without perform an actionable molecular analysis. Limitations for access to an adequate molecular diagnosis is well known in Latin America (LATAM), a recent survey conducted by IASCL shows that 74% of oncologist in LATAM answered that less than 50% of patients with NSCLC are molecular tested in their countries (16). In a recent publication of a cohort of patients with EGFR mutations in LATAM the frequency of molecular testing was 66% with a wide variation according to the country and insurance coverage (5). In the same study, Colombia had the longest turnaround time for testing with 20.4 days. We need to face different challenges to improve molecular diagnosis. First, very few laboratories have the technology and knowledge required to perform these tests. Second, the incorporation of these molecular tests in health insurance has been low and progressive, and finally, the unavailability of many target therapies to other driver mutations makes the routine use of genomic profiling a big issue.

Limitations of our study are its retrospective nature and a that includes a single center that may not represent the practice of the entire country due to the high degree of heterogeneity that exists between and within our countries. Despite this, unlike other real-life studies our work, not only shows the molecular diagnosis and treatment in a cohort of patients, but also related them to clinical outcomes which is the main goal of treatment. There is a lack of information on the type of technique used for molecular studies and the appearance of resistance mutations, mainly related to the fact that despite the INC is a cancer reference center, some tests were done outside the hospital and were not registered in the institutional medical record.

Conclusion

In our cohort, cytotoxic chemotherapy continues to be the most widely used treatment for the management of metastatic NSCLC. In addition, a large proportion of patients received better supportive care. Squamous cell carcinoma histology was a special subgroup of poor prognosis and the addition of immunotherapy in this population is imperative. The use of targeted therapies has been limited by access to molecular diagnosis and remained low until 2018 in our population, a barrier that we hope to have overcome since then.

Figure legends

Table 1. Demographics and clinical characteristics of metastatic non-small cell lung cancer (NSCLC) patients.

Figure 1. A. Overall survival (OS) of complete cohort of patients. B. Overall survival according to histology: adenocarcinoma (ADC) or squamous cell carcinoma (SCC)

Figure 2. Progression free survival (PFS) according to the type of fist-line therapy.

Figure 3 (Online Only). Approval timeline of anti EGFR and immunotherapy treatments for metastatic NSCLC in Colombia.

Table 1

Characteristic	**Complete cohort Frequency (%) n = 209**	**Adenocarcinoma Frequency (%) n = 166**	**Escamocelular Frequency (%) n = 31**
Age (Median)	65 years RIQ 55 - 72	64 years RIQ 54 - 72	67 years RIQ 61 - 73
Gender			
Men	93 (44,5%)	64 (38,6%)	23 (74,2%)
Women	116 (55,5%)	102 (61,4%)	8 (25,8%)
Smoking (active o history)	103 (49,3%)	74 (44,6%)	25 (80,6%)
Yes	106 (50,7%)	92 (55,4%)	6 (19,4%)
No			
Performance status			
ECOG 0	26 (12,4%)	20 (12%)	6 (16,1%)
ECOG 1	101 (48,3%)	81 (48,8%)	13 (41,9%)
ECOG 2	59 (28,2%)	49 (29,5%)	8 (25,8%)
ECOG 3	21 (10%)	14 (8,4%)	5 (16,1%)
ECOG 4	2 (1%)	2 (1,2%)	0 (0%)
Histology			

Adenocarcinoma	166 (79,5%)	166 (100%)	-
Squamous Cell Carcinoma	31 (14,8%)	-	31 (100%)
Others	12 (5,7%)	-	-
EGFR			
Mutated	57 (27,3%)	48 (28,9%)	1 (3,2%)
non-mutated	91 (43,5%)	89 (53,6%)	1 (3,2%)
Unknown	61 (29,2%)	29 (17,5%)	29 (93,6%)
ALK			
mutated	13 (6,2%)	12 (7,2%)	0
Non-mutated	39 (18,7%)	37 (22,3%)	0
unknown	157 (75,1%)	117 (70,5%)	31 (100%)
PD-L1			
<1%	13 (6,2%)	13 (7,8%)	0
1 - 50%	9 (4,3%)	8 (4,8%)	1 (3,2%)
> 50%	1 (0,5%)	1 (0,6%)	0
unknown	186 (89%)	144 (86,7%)	30 (96,8%)
First line therapy			
Cytotoxic chemotherapy	105 (50,2%)	85 (51,2%)	14 (45,2%)
Anti-EGFR	31 (14,8%)	28 (16,9%)	0
Anti-ALK	3 (1,4%)	3 (1,8%)	0
Immuno-chemotherapy	4 (1,9%)	4 (2,4%)	0
Best supportive care	66 (31,6%)	46 (27,7%)	17 (54,8%)

Figure 1.

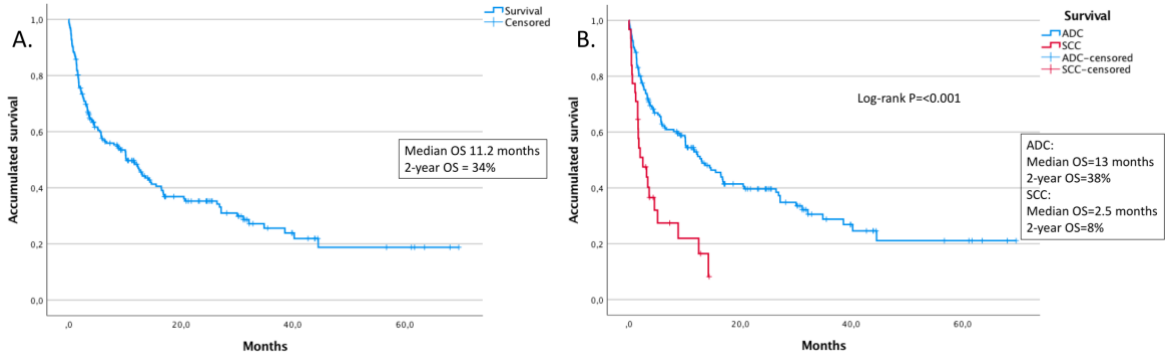
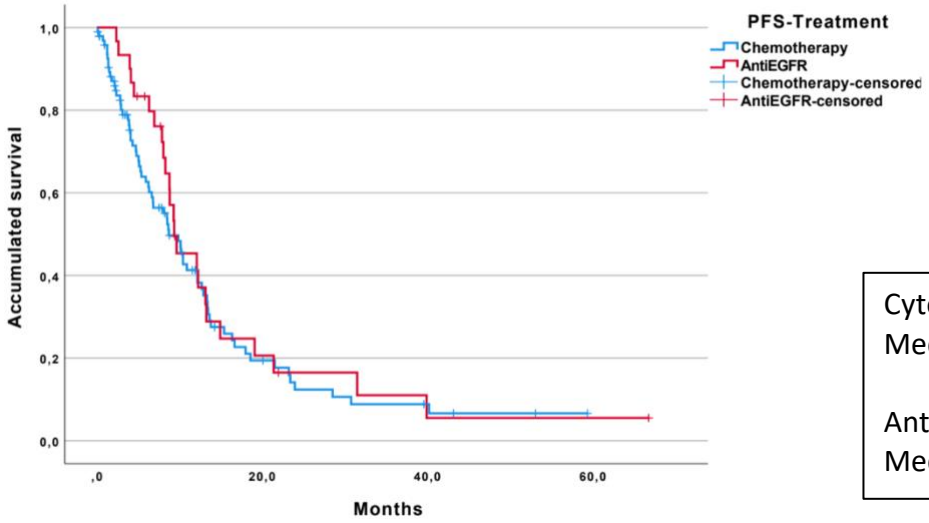


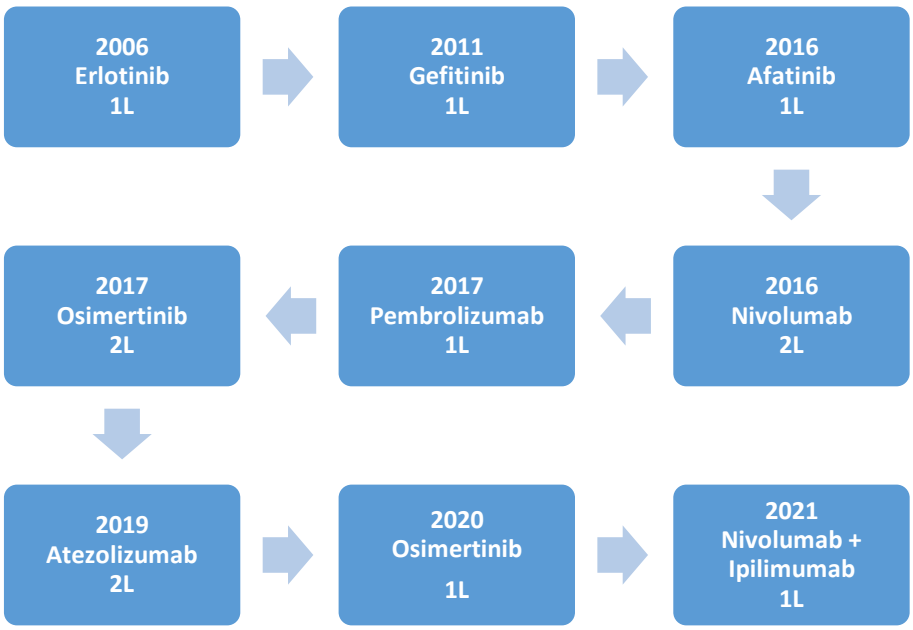
Figure 2.



Cytotoxic chemotherapy
Median PFS 8.7 months

Anti-EGFR therapy
Median PFS 9.3 months

Figure 3.


2006
Erlotinib
1L
2011
Gefitinib
1L
2016
Afatinib
1L
2016
Nivolumab
2L
2017
Pembrolizumab
1L
2017
Osimertinib
2L
2019
Atezolizumab
2L
2020
Osimertinib
1L
2021
Nivolumab +
Ipilimumab
1L

References

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [01 Nov 2021].
2. Howlader, N., Forjaz, G., Mooradian, M. J., Meza, R., Kong, C. Y., Cronin, K. A., Mariotto, A. B., Lowy, D. R., & Feuer, E. J.. (2020). The Effect of Advances in Lung-Cancer Treatment on Population Mortality. New England Journal of Medicine, 383(7), 640–649. https://doi.org/10.1056/nejmoa1916623
3. Hirsch, F. R., Zaric, B., Rabea, A., Thongprasert, S., Lertprasertsuke, N., Dalurzo, M. L., & Varella-Garcia, M.. (2017). Biomarker Testing for Personalized Therapy in Lung Cancer in Low- and Middle-Income Countries. *American Society of Clinical Oncology Educational Book*, *37*, 403–408. https://doi.org/10.1200/edbk_175243
4. Raez, L. E., Cardona, A. F., Santos, E. S., Catoe, H., Rolfo, C., Lopes, G., Barrios, C., Mas, L. A., Vallejos, C., Zatarain-Barrón, Z. L., Caglevic, C., & Arrieta, O. (2018). The burden of lung cancer in Latin-America and challenges in the access to genomic profiling, immunotherapy and targeted treatments. *Lung cancer (Amsterdam, Netherlands)*, *119*, 7–13. https://doi.org/10.1016/j.lungcan.2018.02.014
5. Claudio, M., Mauricio, C., Olga, B., Gonzalo, R., Sandra, A., Herman, P., Susana, S., Carlos, B., Francisco, O., Susana, B., Virginia, G., Alvaro, G., Ernesto, K., Maycos, Z., Juan, C., Eric, O., Susana, G., & Florencia, R.. (2021). Real-world evaluation of molecular testing and treatment patterns for EGFR mutations in non-small cell lung cancer in Latin America. *Molecular and Clinical Oncology*, *16*(1). https://doi.org/10.3892/mco.2021.2439

6. Chen R-L, Zhou J-X, Cao Y, Li S-H, Li Y-H, Jiang M, et al.. The efficacy of PD-1/PD-L1 inhibitors in advanced squamous-cell lung cancer: a meta-analysis of 3112 patients. Immunotherapy 2019;11(17):1481–90.
7. Ruiz-Patiño, A., Arrieta, O., Cardona, A. F., Martín, C., Raez, L. E., Zatarain-Barrón, Z. L., … Rosell, R. (2020). Immunotherapy at any line of treatment improves survival in patients with advanced metastatic non-small cell lung cancer (NSCLC) compared with chemotherapy (Quijote-CLICaP). Thoracic Cancer, 11(2), 353–361. https://doi.org/10.1111/1759-7714.13272
8. Costa, G. J., Silva, G., Ferreira, C. G., Mello, M., Bergmann, A., & Thuler, L. (2021). Brazilian Women With Lung Cancer Have a Higher Overall Survival Than Their Male Equivalents: A Cohort Study. Clinical lung cancer, 22(3), e313–e319. https://doi.org/10.1016/j.cllc.2020.05.022
9. Cushman, T. R., Jones, B., Akhavan, D., Rusthoven, C. G., Verma, V., Salgia, R., Sedrak, M., Massarelli, E., Welsh, J. W., & Amini, A. (2021). The Effects of Time to Treatment Initiation for Patients With Non-small-cell Lung Cancer in the United States. *Clinical lung cancer*, *22*(1), e84–e97. https://doi.org/10.1016/j.cllc.2020.09.004
10. Hall, H., Tocock, A., Burdett, S., Fisher, D., Ricketts, W. M., Robson, J., Round, T., Gorolay, S., Macarthur, E., Chung, D., Janes, S. M., Peake, M. D., & Navani, N.. (2021). Association between time-to-treatment and outcomes in non-small cell lung cancer: a systematic review. *Thorax*, thoraxjnl-2021-. https://doi.org/10.1136/thoraxjnl-2021-216865
11. Neal, R. D., Tharmanathan, P., France, B., Din, N. U., Cotton, S., Fallon-Ferguson, J., Hamilton, W., Hendry, A., Hendry, M., Lewis, R., Macleod, U., Mitchell, E. D., Pickett, M., Rai, T., Shaw, K., Stuart, N., Tørring, M. L., Wilkinson, C., Williams, B., Williams, N., … Emery, J. (2015). Is increased time to diagnosis and treatment in symptomatic

cancer associated with poorer outcomes? Systematic review. *British journal of cancer*, *112 Suppl 1*(Suppl 1), S92–S107. https://doi.org/10.1038/bjc.2015.48

12. Anggondowati, T., Ganti, A. K., & Islam, K. M. M.. (2020). Impact of time-to-treatment on overall survival of non-small cell lung cancer patients—an analysis of the national cancer database. *Translational Lung Cancer Research*, *9*(4), 1202–1211. https://doi.org/10.21037/tlcr-19-675
13. Cardona, A. F., Carranza, H., Vargas, C. A., Otero, J. M., Reveiz, L., Reguart, N., … Castro, C. (2010). Supervivencia de pacientes con cáncer de pulmón de célula no pequeña en cuatro instituciones de Colombia. Revista Venezolana de Oncologia, 22(1), 66–83.
14. Pino LE, Ospina Serrano AV, Triana IC. Real-world evidence in the treatment of metastatic non-small cell lung cancer in a single institution of Colombia in the period august 2015 to august 2018. JCO. 2019;37(15):e18204. https://doi.org/10.1200/JCO.2019.37.15_suppl.e18204.
15. Rosell, R., Carcereny, E., Gervais, R., Vergnenegre, A., Massuti, B., Felip, E., Palmero, R., Garcia-Gomez, R., Pallares, C., Sanchez, J. M., Porta, R., Cobo, M., Garrido, P., Longo, F., Moran, T., Insa, A., De Marinis, F., Corre, R., Bover, I., Illiano, A., … Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica (2012). Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *The Lancet Oncology*, *13*(3), 239–246. https://doi.org/10.1016/S1470-2045(11)70393-X
16. Smeltzer, M. P., Wynes, M. W., Lantuejoul, S., Soo, R., Ramalingam, S. S., Varella-Garcia, M., Meadows Taylor, M., Richeimer, K., Wood, K., Howell, K. E., Dalurzo, M. L., Felip, E., Hollenbeck, G., Kerr, K., Kim, E. S., Mathias, C., Pacheco, J., Postmus,

P., Powell, C., … Hirsch, F. R.. (2020). The International Association for the Study of Lung Cancer Global Survey on Molecular Testing in Lung Cancer. *Journal of Thoracic Oncology*, *15*(9), 1434–1448. https://doi.org/10.1016/j.jtho.2020.05.002