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Original Article

Real-world characteristics and outcomes of *ERBB2*-mutant NSCLC in Latin American patients (CLICaP)

Erick F. Saldanha[1,2,‡], Vladmir C. Cordeiro de Lima[1,‡,*], Aline Fares[3,4], Marcelo Corassa[1,5], Leonardo Gil-Santana[1], Oscar Arrieta[6], Joao Soler[6], Diego F. Chamorro[7], July Rodrigues[7], Helano Carioca Freitas[1], Leonardo Rojas[8], Jairo Zuluaga[8], Andres F. Cardona[8]

[1]Division of Thoracic Medical Oncology, A.C. Camargo Cancer Center, São Paulo 01509-900, Brazil,
[2]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada M5G 2M9,
[3]Hospital de Base São José do Rio Preto, São Jose do Rio Preto 15090-000, Brazil,
[4]BC Cancer Agency, Abbotsford, British Columbia, Canada,
[5]Hospital Beneficência Portuguesa, São Paulo 01323-001, Brazil,
[6]Thoracic Oncology Unit, National Cancer Institute (INCan), Mexico City, 14080, Mexico,
[7]Foundation for Clinical and Applied Cancer Research – FICMAC, Bogota, 110111, Colombia,
[8]Thoracic Oncology Unit, Luis Carlos Sarmiento Angulo Cancer Treatment and Research Center – CTIC, Bogota, 169-49, Colombia

[*]Corresponding author: Vladmir Cláudio Cordeiro de Lima, MD PhD, Division of Thoracic Medical Oncology, A.C. Camargo Cancer Center, Rua Prof. Antônio Prudente, 211 - Liberdade, São Paulo, SP 01509-010, Brasil (vladmir.lima@accamargo.org.br).
[‡]These authors contributed equally to the study.

Abstract

Introduction: *ERBB2-mutant non-small cell lung cancer (NSCLC) represents approximately 1*%-4% of all lung adenocarcinomas (LUADs) and has emerged as a distinct molecular subtype. Little is known about NSCLC harboring *ERBB2* mutations in Latin America. This study aimed to characterize the real-world clinical characteristics and outcomes of *ERBB2*-mutant NSCLC in Latin America.

Materials and methods: Patients with NSCLC harboring ERBB2 mutations detected by next-generation sequencing in tumors or cfDNA were identified in databanks from 3 Latin American countries (Brazil, Colombia, and Mexico). Demographic, clinical, and pathological data were retrieved from electronic medical records.

Results: Of 1245 patients with NSCLC included from January 2015 to September 2022, 35 (2.8%) patients had tumors with *ERBB2* mutations. The median age was 60 years (IQR: 49-69), 54.2% of patients were females, 59.4% were never smokers, 51.3% had baseline performance status ECOG 0, 91.5% were diagnosed with stage IV disease, and 29.7% had de novo brain metastasis. The most common *ERBB2* mutations were A775_G776insYVMA (40%) and G780_P781dupGSP (20%). The most often co-mutated gene was *TP53* (17.1%), and the median tumor mutation burden was 2 mut/Mb (IQR: 1-4). PD-L1 tumor proportion score was ≥50%, 1%-49%, and <1% in 11.4%, 54.2%, and 31.4%, respectively. Regarding treatment patterns, 74.2% of patients received chemotherapy (CT) plus immune checkpoint blockade (ICB) in the first line, and 42.8% received antibody-drug conjugates (ADC) targeting *ERBB2* in further lines of therapy, especially trastuzumab emtansine (37.1%) and trastuzumab deruxtecan (5.7%). The median real-world progression-free survival (rwPFS) to the first line was 6.7 months (95%CI, 5.65-8.48). The median real-world overall survival (rwOS) for the entire cohort was 25.9 months (95% CI, 24.4-27.9).

Conclusion: This study demonstrated that *ERBB2*-mutant NSCLC is uncommon among Latin American patients. Despite the vast majority of patients being treated with chemo-immunotherapy (ICB) in the first line, the median rwOS was similar to that reported for non-oncogene-addicted NSCLC.

Key words: NSCLC; *ERBB2*-mutation; oncogene-addicted NSCLC; Latin America; real-world.

Implications for Practice

While rare ERBB2-mutant non-small cell lung cancer (NSCLC) represents a recently identified class of oncogene-addicted NSCLC with approved targeted therapy available for patients. A deeper understanding of the landscape of *ERBB2* alterations in NSCLC is crucial for optimal therapeutic decisions and to fast-track drug development. Our study reports the real-world treatment patterns and clinical outcomes for the largest cohort of patients diagnosed with advanced ERBB2-mutant NSCLC and treated in Latin America (LATAM). Our findings highlight the dire need for equitable access to comprehensive genomic profiling in LATAM and provide relevant insights into the genomic characteristics and response to treatment for patients with ERBB2-mutant NSCLC.

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Introduction

Lung cancer remains one of the most frequently diagnosed malignancies and is the leading cause of cancer-related death globally.[1] Significant advancements in precision oncology, primarily driven by innovative treatment options, have dramatically changed the treatment landscape of this malignancy. These advancements include targeted therapies directed against genetic alterations in oncogenic drivers that have notably improved survival outcomes for patients with advanced lung cancer.[2-4] In this context, the US Food and Drug Administration (FDA) and other regulatory agencies worldwide have approved multiple targeted therapeutic agents for non-small cell lung cancer (NSCLC), representing substantial progress in treating this complex disease.[5]

Among the various genomic alterations detected in NSCLC, the human epidermal growth factor receptor 2 (*ERBB2; HER2)* gene has recently been identified as a potential therapeutic target.[6] Strikingly different from other solid tumors like breast cancer and gastric cancer, where *ERBB2* protein expression and amplification are well-established biomarkers for targeted therapies,[7,8] in NSCLC, HER2 exhibits multiple activating mechanisms, including *ERBB2* overexpression (2%-30%), amplification (2%-5%), and mutations (1%-4% of cases).[9-12] Therefore, compared to other oncogene-addicted NSCLC subtypes, *ERBB2* has emerged as a distinct molecular subtype with multiple studies investigating HER2 targeting strategies in NSCLC yielding limited benefits with standard therapies such as immune checkpoint blockade (ICB), HER2-directed tyrosine kinase inhibitors, anti-HER2 monoclonal antibodies (trastuzumab and pertuzumab), and the antibody-drug conjugate (ADC) trastuzumab emtansine (T-DM1).[13-24]

The biological and clinical heterogeneity of *ERBB2*-mutant NSCLC may explain the limited and heterogeneous activity of *ERBB2*-targeted therapies. Despite its importance, there is a lack of studies due to the low incidence of this oncogene driver in NSCLC. This gap is particularly evident in populations with diverse genomic backgrounds, such as those from Latin America (LATAM).[25] Understanding the incidence, clinical, and genomic characteristics of *ERBB2*-mutant NSCLC in such a mixed population is crucial.

Our study evaluates the incidence, clinical characteristics, and treatment outcomes in the largest LATAM cohort of NSCLC patients with *ERBB2* mutations detected by next-generation sequencing (NGS) in 3 comprehensive cancer centers from Brazil, Colombia, and Mexico.

Material and methods

Study design and patient population

We conducted a multicenter, multinational, retrospective cohort study of Latin American NSCLC patients utilizing electronic medical records to collect clinical, demographic, and genomics data within 3 comprehensive cancer centers in Brazil, Colombia, and Mexico. The cohort assembled included only patients with age ≥18 years with a pathologically confirmed diagnosis of metastatic LUADs at initial presentation (stages IVA or IVB) or at the time of recurrence from January 1, 2015, to September 30, 2022. Only patients with LUADs whose tumors harbored ERBB2 mutations detected by NGS in tumors or blood were included.

Tumor sample preparation and genomic profiling

The samples were collected and subjected to the initial pathological evaluation in each country's reference center. A trained thoracic pathologist assessed formalin-fixed paraffin-embedded tumor samples and subsequently microdissected them to guarantee malignant sample representation. Comprehensive genomic profiling was performed using next-generation sequencing (NGS) targeted panels, such as FoundationOne CDx, Oncomine Focus Assay, FoundationOne CDx Liquid, and Guardant360, in a reference laboratory accredited by the College of American Pathologists (CAP), with validated methods.[26,27]

PD-L1 and tumor mutational burden (TMB) assessment

The PD-L1 tumor proportion score (TPS) was determined by immunohistochemistry using the validated anti-PD-L1 antibodies: 22C3 (Dako North America Inc.) or SP263 (Ventana, Roche Diagnostics). TMB, defined as the number of somatic, coding, base substitution, and indel mutations per megabase (Mb) of genome examined, was determined using commercial FoundationOne CDx, FoundationOne CDx Liquid, or Guardant 360 panels in paraffin-embedded tissue or liquid biopsy. Samples tested with Oncomine Focus Assay did not have TMB data. As previously described, TMB distributions were harmonized between the platforms using a standard transformation and standardization to *Z-Z*-scores.[24] For the analysis, TMB-H was defined as ≥10 mutations/megabase [mut/Mb]. We employed the same cutoff used in the KEYNOTE-158 study.[28]

Statistical analysis

No formal sample size calculation was performed. Categorical and continuous variables were summarized descriptively using percentages and medians. The Wilcoxon-Rank Sum and the Kruskal-Wallis tests were used to test for differences between continuous variables. Fisher's exact test was used to test for associations between categorical variables. Real-world overall survival (rwOS) was defined as the time from NSCLC diagnosis to death by any cause. Real-world progression-free survival was defined as the time from diagnosis till disease progression (as recorded by the patient's assistant physician) or death by any cause. The Kaplan-Meier method was used to estimate time-to-event distributions. Log-rank tests were used to test for differences in time-to-event distributions. Cox proportional hazard models were fitted to obtain estimates of hazard ratios in univariate and multivariable analysis. The Cox proportional hazards model assumption was inspected by calculating the Schoenfeld residuals. All *P* values are 2-sided, and CIs are at the 95% level, with statistical significance defined as $P < .05$. All statistical analyses were conducted with R software version 4.3.1 and GraphPad Prism 8.0.1.

Results

Patient population

From January 2015 to September 2022, 1245 patients with advanced NSCLC whose tumors were submitted to tissue or liquid gene-targeted NGS-based panel tests were retrieved from the electronic medical records of participating institutions. We identified 35 patients (2.8%; 35/1245) with

advanced *ERBB2*-mutant NSCLC (Brazil *N* = 10/35, 28.5%; Colombia *N* = 23/35, 65.7%; and Mexico *N* = 2/35, 5.7%). The median age was 60 years (range 49-69), and 54.2% of the patients were women. Twenty-two patients were never smokers (62.8%) and 51.3% had baseline performance status ECOG 0. Most patients were diagnosed at stage IV (91.4%) and 29.7% of the patients had brain metastasis. The baseline characteristics are shown in Table 1.

Pathological and genomic characteristics

The tumor histology was LUAD for all *ERBB2*-mutant patients. Genomic profiling was conducted using tissue biopsy for 33 patients (91.4%) and liquid biopsy for 2 patients (8.5%). The most common *ERBB2* mutations were *ERBB2* exon 20 insertions (94.3%), including A775_G776insYVMA (40%) and G780_P781dupGSP (20%) as the most common (Figure 1). Co-mutations were frequent and were detected in 62.8% of samples. The most prevalent co-mutations were *TP53* mutations (22.8%) and *CDKN2A/B* loss or mutation (11.4%). Additionally, 30 samples (85.7%) had more than one co-mutation (Figure 2).

Most patients had PD-L1 tumor proportion scores (TPS) between 1% and 49% (54.2%), and tumors had low TMB in general (median TMB = 2mut/Mb, IQR: 1-4 Mut/Mb) (Table 1).

Treatment characteristics and outcomes

In this cohort, 26 (74.2%) patients received (CT) plus ICB, and 8.5% received only CT as the first line of treatment. The median number of lines of therapy was 3. Fifteen (42.8%) patients received ADC targeting *ERBB2*, trastuzumab emtansine (37.1%), and trastuzumab deruxtecan (5.7%) as second or later lines of treatment. The median rwPFS in the first line of therapy (Figure 3) in the entire cohort was 6.7 months (95% CI, 5.65-8.48). There were no significant differences in the rwPFS associated with the presence of brain metastasis ($P = .6$), smoking status ($P = .3$), PD-L1 status ($P = .2$), and type of treatment (CT + ICB vs ICB, $P > .9$). The median rwOS (Figure 3) for the entire cohort was 25.9 months (95% CI, 22.6-27.9). The PD-L1 expression (Figure 4) was associated with improved rwOS with a median rwOS of 26.9 months (95% CI, 26-NA) for PD-L1 ≥ 1% vs 20.3 months (95% CI, 19.1-NA) for PD-L1 < 1% ($P = .03$). The rwOS was not impacted by the presence of brain metastasis

Table 1. Demographics and clinical characteristics (*N* = 35).

Characteristics	Number (%)
Gender	
Male	16 (45.8)
Female	19 (54.2)
Age (years), median [range]	60 [49-69]
Smoking	
Never-smoker	22 (59.4)
Former/ever smoker	13 (40.6)
Histology	
Adenocarcinoma	35 (100)
ECOG	
0	19 (51.3)
1	14 (37.8)
2	4 (10.8)
PD-L1 expression	
≥50%	4 (11.4)
1-49%	19 (54.2)
<1%	11 (31.4)
Stage at diagnosis	
I-III	3 (8.5)
IV	32 (91.5)
Brain metastasis at diagnosis	
Yes	11 (29.7)
No	24 (70.3)
Treatment lines—median [IQR]	3 [3-4]
Received ICB	25 (71.4)
ERBB2 mutation detection	
Tissue	33 (94.3)
Blood	2 (5.7)

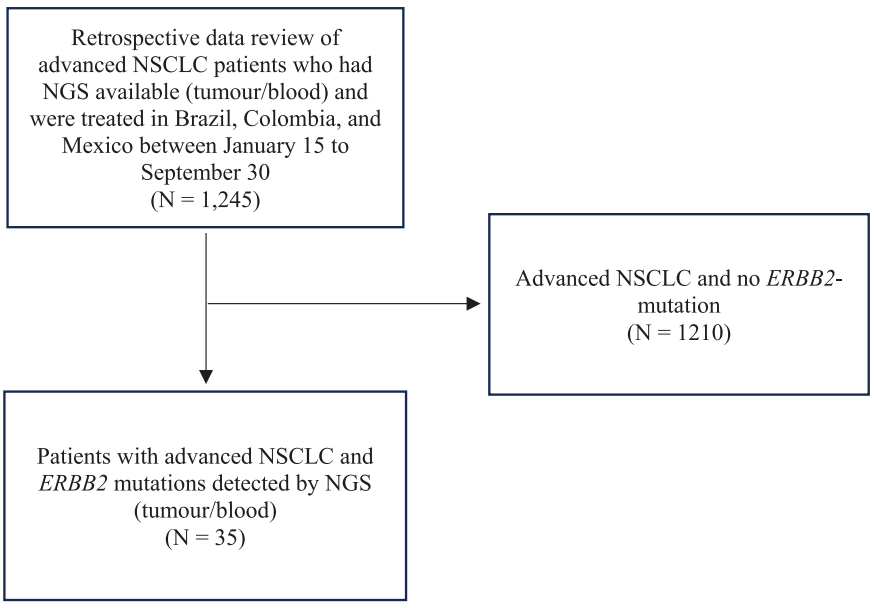

Figure 1. Study flowchart.

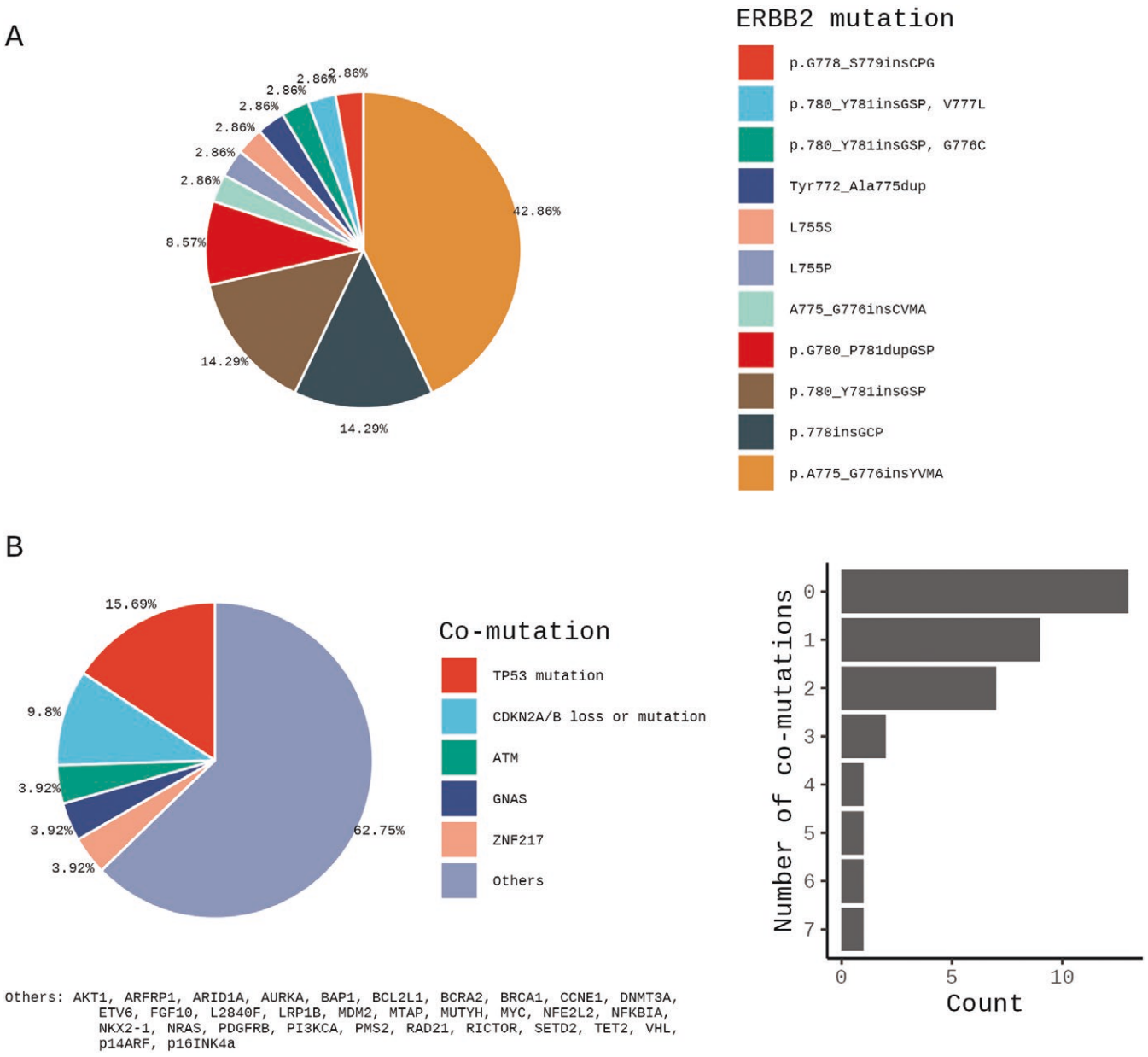

Figure 2. (A) Frequency and distribution of *ERBB2* mutations (*N* = 35). (B) Frequency of co-mutations in *ERBB2*-mutant NSCLC (*N* = 35).

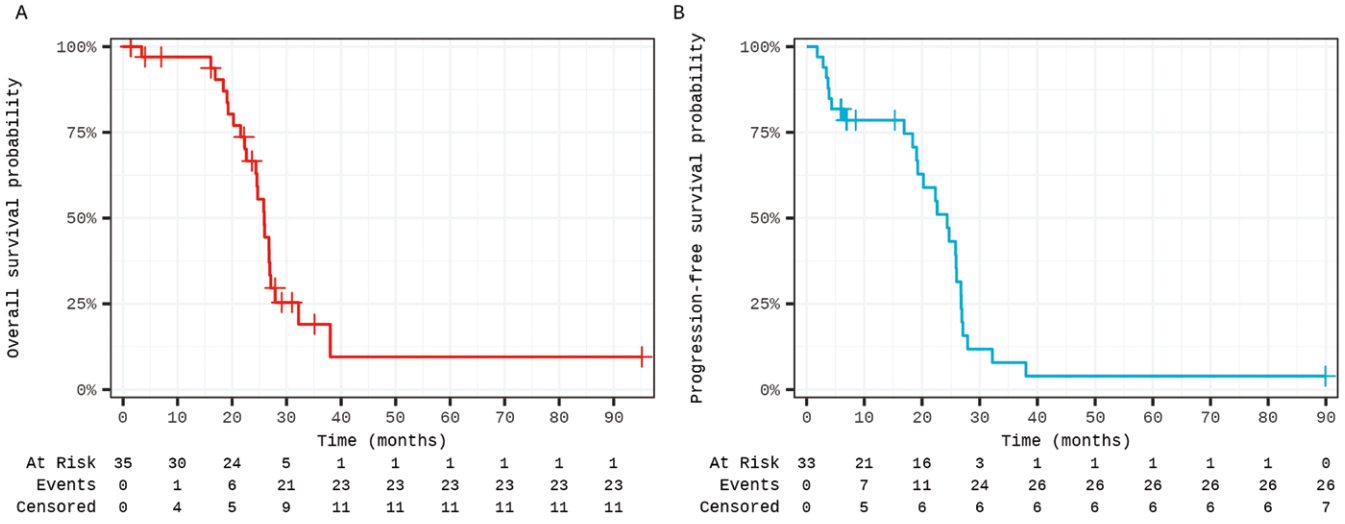

Figure 3. Progression-free survival (rwPFS) to the first line (A). Overall survival (rwOS) in the entire study cohort (B).

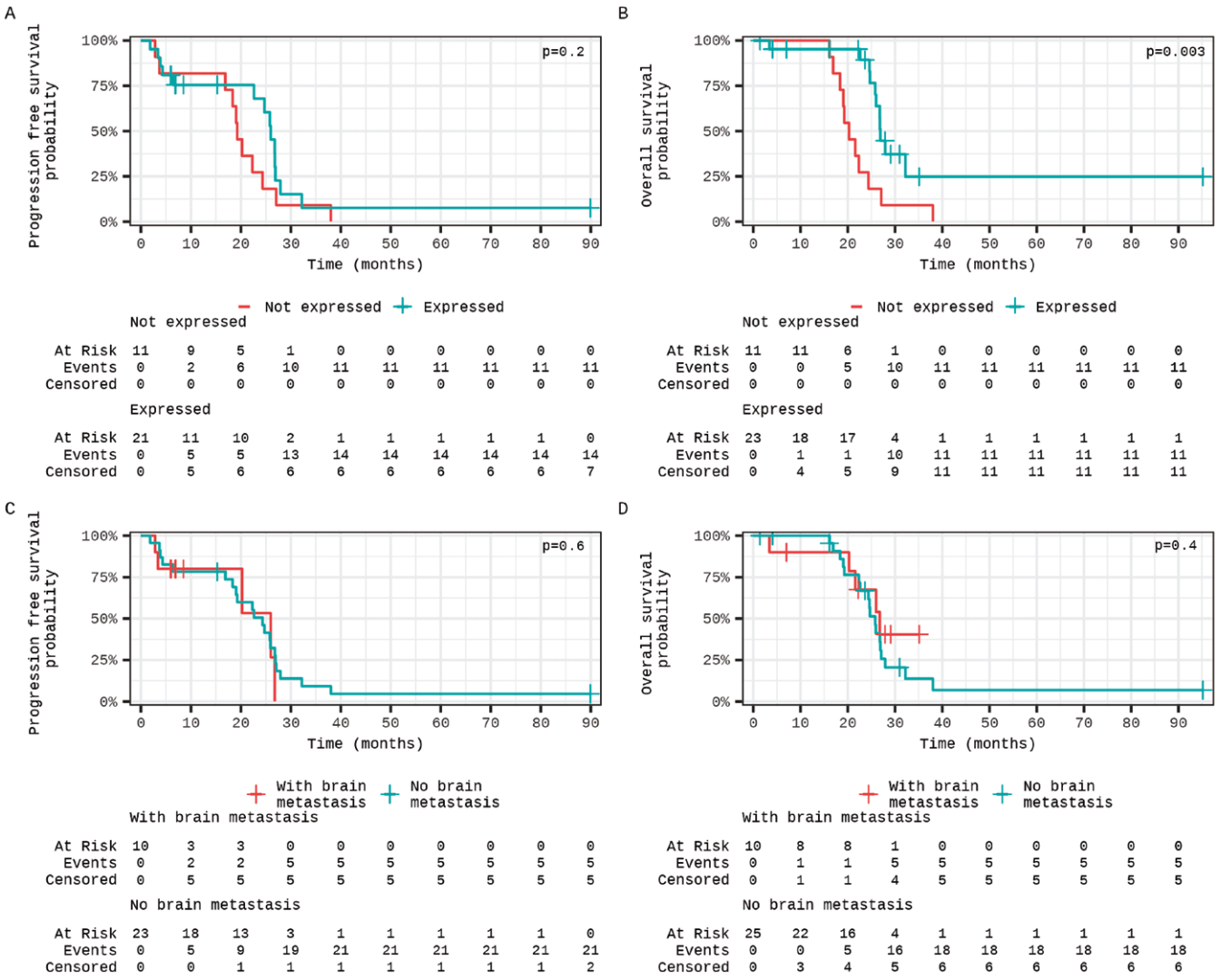

Figure 4. rwPFS to the first line according to the PD-L1 expression levels (A). rwOS according to the PD-L1 expression levels (B). rwPFS to the first line according to the presence of brain metastasis (C). rwOS according to the presence of brain metastasis (D).

(*P* = .4), type of treatment in the first line (CT + ICB vs ICB, *P* = .6), or smoking status (*P* = .3). Multivariable analysis for rwOS demonstrated that PD-L1 expression was an independent predictor of longer rwOS (HR 0.33, 95% CI, 0.11-0.97, *P* = .044). Table 2 shows the results of the multivariable analysis for rwPFS (first line of therapy) and rwOS. The median follow-up of the entire cohort was 35 months.

Discussion

In this multicenter cohort study evaluating the clinical characteristics and outcomes of advanced NSCLC patients with *ERBB2* mutation identified by NGS, we provide comprehensive real-world evidence among this subset of patients treated in tertiary institutions from LATAM (Brazil, Colombia, and Mexico). To the best of our knowledge, this is the first and largest real-world cohort to report the clinical characteristics, treatment patterns, and outcomes of *ERBB2*-mutant NSCLC patients treated in Latin America.

We showed that among advanced non-squamous NSCLC patients, *ERBB2* mutations were identified in 2.8%, consistent with the frequency reported in the literature.[6,11,29] Although a recent meta-analysis evaluating the prevalence of oncogenic driver mutations in LATAM patients reported an overall prevalence of *ERBB2* mutations of 4%,[30] this frequency must have been overestimated due to patient selection (exclusion of patients with *EGFR* mutations detected by PCR and *ALK* rearrangements detected by FISH or immunohistochemistry). We also demonstrated that the *ERBB2* exon 20 insertion mutations were the most prevalent subtype of *ERBB2* mutations. These findings are aligned with those reported in the literature.[11,12] Furthermore, our cohort was predominantly composed of females and never-smokers with tumors with low TMB and adenocarcinoma histology. These features are like those described in other oncogene-addicted NSCLCs and are similar to reports from previous studies.[31-34]

Noteworthy, the *ERBB2* mutation traits reported in this cohort reveal important biological insights that significantly aid physicians in therapeutic decision-making and patient selection for treatment, given that the most common *ERBB2* mutations, such as *ERBB2* exon 20 insertions, have a poor response to ICB. In contrast, uncommon *ERBB2* mutations have higher TMB, with a smoking mutational signature, and could potentially benefit from treatment with ICB.[11]

Table 2. Multivariable Cox regression for rwPFS and rwOS in Latin American NSCLC patients harboring *ERBB2* mutations.

	OS				PFS			
Characteristic	*N*	HR	95% CI	*P*-value	*N*	HR*1*	95% CI	*P*-value
Gender								
Male	15	—	—		15	—	—	
Female	17	0.77	0.29, 2.05	.6	17	1.39	0.51, 3.80	.5
Brain metastasis								
No	22	—	—		22	—	—	
Yes	10	1.02	0.32, 3.28	>.9	10	0.91	0.26, 3.15	.9
Smoking status								
Never smoker	21	—	—		21	—	—	
Former/ever smoker	11	0.43	0.12, 1.55	.2	11	1.31	0.44, 3.88	.6
Number of co-mutations	32	1.08	0.68, 1.71	.7	32	1.35	0.88, 2.07	.2
Anti-HER2 treatment								
Without anti-HER2	9	—	—		9	—	—	
With anti-HER2	23	0.55	0.19, 1.63	.3	23	1.03	0.37, 2.85	>.9
TMB	32	0.79	0.55, 1.14	.2	32	0.7	0.49, 1.02	.062
PD-L1								
Not expressed	11	—	—		11	—	—	
Expressed	21	0.33	0.11, 0.97	.044	21	1.06	0.37, 3.00	>.9
ECOG								
0	18	—	—		18	—	—	
≥1	14	1.09	0.34, 3.47	.9	14	1.03	0.36, 2.95	>.9

Abbreviation: HR, hazard ratio.

Nonetheless, in our cohort, many patients (74.2%) received chemotherapy plus immunotherapy (ICB) as the first line of therapy. Conversely, real-world studies evaluating treatment patterns among patients with advanced *ERBB2*-mutant NSCLC report a markedly lower number of patients (15.4%-42.0%) receiving ICB-based treatment regimens as the first line of treatment.[32,34-37] The reasons for such discrepancy are the lack of consensus regarding the activity of ICB in *ERBB2*-mutant NSCLC and the limited available targeted agents for these tumors at the time most of these patients were treated. Even nowadays, there is restricted access to *ERBB2*-directed therapy for *ERBB2*-mutant NSCLC in LATAM. While ICB is the mainstay of treatment for non-oncogene-addicted NSCLC, the benefit of ICB is overall limited in oncogene-addicted NSCLC.[31] Real-world studies that included *ERBB2*-mutant NSCLC showed inferior outcomes with ICB as a single treatment in these patients.[14,33] However, despite most patients in this cohort receiving chemotherapy plus ICB treatment, the median rwPFS to the first line of therapy was 6.7 months. No significant differences were seen in rwPFS based on treatment type, PD-L1 expression, smoking status, and the presence of brain metastasis. The median overall survival for this entire cohort was 25.9 months, akin to that observed in patients with non-oncogene-addicted NSCLC.[38] Thus, ICB combined with chemotherapy as first-line therapy seems to be a viable treatment option, given the results observed.

Interestingly, PD-L1 expression (PD-L1 ≥ 1%) was significantly associated with survival benefit in our cohort. The prognostic association of PD-L1 expression seen in our study is not in line with previous reports from real-world studies.[39,40] Moreover, data regarding the PD-L1 expression in patients with NSCLC harboring *ERBB2* mutations is heterogeneous, with multiple studies limited to small sample sizes, and some studies could not capture PD-L1 expression levels. Hence, further studies are needed to investigate the effect of PD-L1 expression status and its correlation with treatment and survival outcomes.

Approximately one-third of patients included in our cohort had brain metastasis. Several previous real-world studies have reported similar frequencies of brain metastasis.[32-36] *ERBB2* mutations are associated with brain metastasis in NSCLC, and the exon 20 YVMA mutation is mainly associated with a high incidence of brain metastasis.[41] Not surprisingly, this mutation was the most frequently reported in our cohort. Collectively, our study results highlight the importance of access to comprehensive genomic profiling for patients with advanced NSCLC in LATAM. Ensuring equitable access to CGP can improve treatment outcomes by optimal patient selection in populations with diverse genomic traits and provide avenues for advancing biomarker-driven clinical trials and access to therapies in LATAM.[42-44]

Our study should be interpreted in the context of its limitations. Our study was retrospective, and we only analyzed patients treated at 4 tertiary comprehensive referral cancer centers in LATAM, which may limit generalizability. To this end, we emphasize that the cohort of patients reported in our analysis might be biased, given their access to comprehensive genomic sequencing as reflected by the receipt of care in referral centers in LATAM. While reporting comprehensive patient-level data, we could not capture safety data and treatment outcomes such as response rate and progression-free survival among the multiple lines of treatment. Nonetheless,

these limitations were also present in previous real-world studies. Finally, a few patients in this cohort had access to *ERBB2*-directed therapy, hampering our ability to better ascertain its efficacy in this population.

Conclusion

This multicenter real-world study evaluating LATAM patients with NSCLC harboring *ERBB2* mutations showed that this subset of oncogene-addicted NSCLC is rare and occurs at a similar rate observed in non-Latin American populations. Our study further underscores the importance of having access to comprehensive genomic profiling and its ability to inform treatment selection.

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Author contributions

Erick Figueiredo Saldanha, Vladmir Cláudio Cordeiro de Lima, and Andres F. Cardona (Conceptualization, formal analysis, data curation, writing—original draft), Erick Saldanha, Marcelo Corassa, Leonardo Gil Santana, Oscar Arrieta, Aline Fares, João Soler, Diego F. Chamorro, J Rodrigues, Leonardo Rojas, and Jairo Zuluaga (Writing—review & editing, data curation). All authors (Writing & review)

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Conflict of interest

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Data availability

The data underlying this article will be shared at a reasonable request by the corresponding author.

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