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Clinical outcomes in Hispanic patients compared to Non-Hispanic white patients with non-small cell lung cancer treated with immune checkpoint inhibitors

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ABSTRACT

Literature is scant regarding clinical outcomes in Hispanic patients with non-small cell lung cancer (NSCLC) treated with immunotherapy. The main clinical trials for first- and second-line therapies using checkpoint inhibitors have included mostly Non-Hispanic White (NHW) populations of American or European descent. In this study, data on 436 NSCLC patients (256 Hispanics and 180 NHWs) treated with immunotherapy at five large institutions are presented. The primary endpoints of the study were: overall response rate (ORR), progression-free survival (PFS), and overall survival (OS). The roles of biomarkers PD-L1, KRAS, STK11 and TP53 mutations, the incidence of adverse events (AEs), and neutrophil/lymphocyte ratio (NLR) as potential predictive factors of response are also evaluated. Most of the patients received single-agent therapy as second-line or beyond, while a small group of patients were treated with single agent pembrolizumab as first line therapy. The analysis showed no statistically significant differences in ORR, PFS, OS, and responses according to PD-L1 status (as measured by IHC) between Hispanic and NHW patients. Disease control rate (DCR) was also not different for Hispanics or NHW regardless of histology. The absence of STK11 mutations and the presence of AEs were associated with better PFS and OS. However, there were no ethnic differences except for more hypothyroidism seen in Hispanics. We conclude that the clinical outcomes in Hispanic and NHW pts with NSCLC treated with immune checkpoint inhibitors (ICIs) are similar.

KEYWORDS: PD-1/PD-L1, check point inhibitors, minorities, disparities, Hispanics, non-small cell lung cancer.

1. INTRODUCTION

Immune-checkpoint inhibitors (ICIs) have profoundly changed the therapeutic landscape of advanced non-small cell lung cancer (NSCLC) without actionable genomic alterations. Targeting the programmed death-1/programmed death ligand-1

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(PD-1/PD-L1) axis has emerged as the standard of care, initially in second-line, then first-line therapy, with potential long-term survival in a subset of patients [1]. Following positive results in KEYNOTE-001 [2], pembrolizumab, an anti-PD-1 checkpoint inhibitor, was Food and Drug Administration (FDA)-approved as second-line monotherapy for NSCLC. Subsequently, in KEYNOTE-010, pembrolizumab confirmed an overall survival (OS) benefit, compared with second-line docetaxel in patients with tumors expressing PD-L1 in ≥1% of cells [3]. Further randomized phase III trials with atezolizumab, and nivolumab, yielded similar results compared with docetaxel in the second-line, this time including patients whose tumors did not express PD-L1 [4, 5]. In a recent pooled analysis of 3 randomized controlled trials, Borghaei *et al.* demonstrated a substantial clinical benefit and manageable safety profile with first-line pembrolizumab plus platinum-doublet chemotherapy versus chemotherapy alone in patients with PD-L1-negative NSCLC. Pembrolizumab plus chemotherapy substantially reduced the risk of death (HR for OS 0.63) and improved the median OS by ~8 months (19.0 vs. 11.4 months); it also improved PFS (HR 0.68), PFS-2 (HR 0.57), and ORR (50.0% vs. 29.8%) [6]. Besides, the updated information was recently presented for the Checkmate 227 trial, showing a 3-year median OS of 17.1 months with nivolumab plus ipilimumab compared with 14.9 months with chemotherapy, with a HR of 0.79 for PD-L1 >1% cohort. OS rates at 3 years were 33% with nivolumab plus ipilimumab, compared with 22% with chemotherapy [7]. This information was confirmed by the Checmate-9LA study which showed after a median follow-up of 12.7 months, that nivolumab and ipilimumab plus chemotherapy resulted in prolonged OS, with a median of 15.6 months compared with 10.9 months in patients receiving chemotherapy alone (HR of 0.66). The 1-year OS was 63% in the combination group compared with 47% in the chemotherapy-only group and the benefit was seen regardless of PD-L1 positivity, histology and multiple subgroups [8].

These trials represent a valuable collective effort that has changed the treatment paradigm in lung cancer. However, an analysis of their demographic composition reveals a lower representation of racial/ethnic minority patients disproportionately to incidence rates [9]. US trials' enrollment is highest for non-Hispanic whites (NHW) and Asians, and only 3% for Hispanics. This low recruitment fails to represent a growing minority of 57.5 million Americans, or 18% of the continental US and Hawaii population, which identified themselves as Hispanic or Latino in 2016 [10]. Furthermore, Verma *et al.* recently demonstrated that ICs were more likely administered to younger and healthier patients, those living farther from treating facilities, and in more educated areas ($P < 0.05$ for all). ICs were more often delivered to lung adenocarcinomas and patients who received chemotherapy but not radiotherapy. In addition to geographic differences, uninsured and Medicaid populations received ICs less often, along with African Americans and Hispanics [11].

According to the American Cancer Society (ACS), cancer remains the number one cause of death among Hispanics accounting for 21% of deaths [10]. Moreover, lung cancer is the third most diagnosed and the number one cause of cancer death among Hispanic men (fifth and second in Hispanic women, respectively). Hispanics are known to have lower lung cancer mortality and a different profile of driver mutations than NHW; hence the question of whether their response to immunotherapy is comparable to that reported in the major clinical trials remains partially answered [12]. Recently, the CLICaP showed the information of 296 patients with unresectable/metastatic NSCLC treated with either, first-, second-, third- or fourth-line of immunotherapy in several Latin American countries, finding a median OS of 12.7 months (95% CI 9.67-14 months) and PFS of 4.27 months (95% CI 3.97-5.0 months). Factors associated with increased survival included treatment with immunotherapy as first-line ($P < 0.001$), type of response ($P < 0.001$), and PD-L1 status ($P = 0.0039$). Compared with a historical cohort, immunotherapy proved to be superior in OS ($P = 0.05$) but not PFS, and hyperprogression was found in 20% of the cases (95% CI 14.5-25.1%) [13]. To narrow the information gap regarding the efficacy of ICIs in Hispanics, we present additional data collected from an admixed population of Hispanics exposed to ICIs in the US, Peru, and Argentina. From our knowledge, this is the most extensive comparison of NSCLC immunotherapy outcomes between Hispanics vs. NHW patients.

2. METHODS

A multicenter retrospective cohort study was conducted which included 436 patients diagnosed at five large institutions [Memorial Cancer Institute (Florida, US), University of Miami - Sylvester Comprehensive Cancer Center (Florida, US), H. Lee Moffitt Cancer Center (Florida, US), Instituto Nacional de Enfermedades Neoplásicas - INEN (Lima, Peru), and Centro Oncologico Riojano Integral – CORI / National University of La Rioja (La Rioja, Argentina)]. Inclusion criteria were patients over 18 years old with advanced/nonresectable or metastatic NSCLC (proven histologically) who were treated with immunotherapy agents such as nivolumab, pembrolizumab, atezolizumab, and ipilimumab/nivolumab. Most of the patients received single-agent therapy as second-line (or beyond) intervention considered the standard of care at that time, while a small group of patients was treated with first-line single-agent pembrolizumab (when the PD-L1 expression level was ≥50%). None of the patients harbored actionable genetic mutations (EGFR, ALK, ROS-1 or others). Patients were assessed for OS, PFS, overall response rate (ORR), and disease control rate (DCR). Demographic and clinical data were extracted for analysis and the results are presented in Table 1.

Serial evaluations were performed on each patient which accounted for assessment of treatment response according to the RECIST criteria and adverse effects to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [14]. For purposes of the analyses, ORR was defined as complete response (CR) or partial response (PR). DCR was defined as complete response (CR), partial response (PR) or stable disease (SD). We compared the overall survival (OS) and progressive free survival (PFS) between the two groups (i.e. Hispanics and NHWs) for each biomarker, adverse event or laboratory evaluations, mainly N/L ratio. OS was defined as the period in months between diagnosis and death; whereas PFS was defined as the period between the start of immunotherapy and the start of progressive disease. Adverse events (AEs) and neutrophil/lymphocyte ratio (NLR) were collected in a subset of 70 patients.

2.1. Tissue selection, management and evaluation

Tumor morphology and all IHC stained sections were evaluated and scored by expert pathologists and discrepancies were resolved by a complementary external evaluation (control). The standard immunohistochemical panel included at least Ck7, TTF-1, Napsin and p40. The suitability of material for mutational analysis was assessed based on

Table 1. Descriptive statistics by race/ethnicity.

Variable	Hispanic (%) n = 256 (58.7)	Non-Hispanic White (%) n =180 (41.3)
Age	64.4 ± 9.8	69.3 ± 11.2
Range	28-88	41-95
Sex		
Male	132 (51.6)	81 (45.0)
Female	124 (48.4)	99 (55.0)
Smoking Status		
Never	60 (25.6)	16 (8.9)
Former	74 (31.6)	69 (38.6)
Current	100 (42.7)	94 (52.5)
Treatment Plan		
Nivolumab	104 (44.8)	112 (62.2)
Pembrolizumab	78 (33.6)	55 (30.6)
Atezolizumab	34 (14.7)	13 (7.2)
ipilimumab+ nivolumab	4 (1.7)	-
Other	12 (5.2)	-

Table presents the number and proportion of cases except for Age which presents the mean, standard deviation, and range.

hematoxylin and eosin (H&E) stains of FFPE tissue blocks and/or cytology specimens (if available). A representative area with high frequency of malignant cells was identified, from which sections for mutational analysis was taken followed by new H&E sections to ensure that a representative material had been taken. An estimate of tumor cell content was made, with a requirement of ≥10% for the mutational analysis. In addition to FFPE tissue blocks, tissue material for mutation analysis could also originate from cytology slides, or sections from centrifuged and paraffin embedded cytology material (cell blocks). Sections were stored at -20 °C until nucleic acid extraction.

In case of preparation of cell lysate from cytology slides, a representative tumor cell-rich area of a cytology slide was identified, the slide was scanned (to enable future clinical review), and the glass cover slip was removed using xylene followed by a rehydration step in ethanol. Thereafter, the cells were lysed using 180 ul ATL Buffer from Qiagen (Qiagen, Hilden, Germany). DNA was extracted from the lysate within 24 h and stored at -20 °C.

2.2. PD-L1 expression

IHC analysis was carried out in previously deparaffinized tissue sections. Rehydration and posterior antigen retrieval was done using XS Tris Buffered Saline with Tween 20 and boiled for 20 minutes. Rabbit monoclonal primary PD-L1 antibody (Monoclonal Mouse Anti-Human PD-L1 Clone 22C3, Agilent Technologies, Santa Clara, California, US) was processed using 4 mm-thick FFPE tissue sections on a EnVision FLEX visualization system on Autostainer Link 48 (Agilent Technologies, Santa Clara, California, US) with standard antigen retrieval methods. The Signal Stain DAB substrate kit (#8959) was used according to the manufacturer's instructions. Human placenta was used as positive control. PD-L1 protein expression was determined using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining at any intensity. Tumors with ≥1% of tumor cells stained either in membrane or cytoplasm will be considered positive for PD-L1. The grading system of PD-L1 expression was: 0 (negative), 1-49%, (weak to moderate expression), and >50 (strong expression).

2.3. DNA and RNA extraction

DNA and RNA for NGS-based mutation analysis were extracted using the Qiagen AllPrep kit for FFPE tissue and automated on the QIAcube instrument (Qiagen, Hilden, Germany). The protocol was modified with an extended proteinase K digestion (overnight) for the DNA extraction to obtain higher DNA yields. DNA from cytology slides was extracted using the QiaAmp DNA Micro kit (Qiagen, Hilden, Germany). RNA was not extracted from cytology specimens. Following extraction, DNA samples were quantified using Qubit and RNA samples were quantified using a BioAnalyzer. Then, for quality assessment DNA samples were analyzed by qPCR using the Illumina FFPE QC Kit (WG-321-1001) along with a control cell line sample with a known input mass.

DNA Next-generation sequencing (NGS) was evaluated in tumor tissue by Caris Life Sciences and Foundation Medicine platforms and plasma *ct*DNA by Guardant Health NGS (analyzes were performed centrally as described elsewhere). None of the selected cases had paired evaluations using the two platforms, and sufficient evaluable tumor DNA was found in 81% of tissue. Data from platform reports were maintained in a secure network and secure files. Data from Caris were collected into columns that corresponded to gene alterations of all frequencies. Similarly, detected alterations from Guardant360 were collected considering the allelic concentration of the mutated genes. The most relevant information for this report focused on the status of KRAS, TP53 and STK11 (all included patients had no actionable abnormalities, including EGFR, ALK, ROS1, Her2, NTRK, RET, and MET).

2.4. Statistical analysis

For descriptive purposes, continuous variables were summarized as arithmetic means, medians and standard deviations. Categorical variables were reported as proportions with 95% confidence intervals (95% CIs). Inferential comparisons were performed using Student's t test. χ^2 or Fisher's exact test were used to assess the significance among categorical variables. The time-to-event variables were obtained from the Kaplan-Meier method. Differences in terms of OS and PFS were

estimated using the log-rank test or milestone analysis when applicable. After evaluation of hazard rates proportionality, Cox regression was used to evaluate survival determinants. For outcome measures Pearson Chi-Square test was used to determine whether the ORR and DCR significantly differed between Hispanics and NHWs. All analyses were completed using Stata/SE 15.1. There was no censoring since all participants' survival status was known by the end of the study.

3. RESULTS

Four hundred thirty-six patients from reference centers in three countries (3 from the US, one from Perú, and one from Argentina) were included. Of the total study group, 256 were Hispanic, and 180 were NHW. The majority was male (51%). There were no significant differences in age, smoking status, or treatment plan between Hispanics and NHW. The overall response rate was achieved in 22.9% of Hispanics and 24.4% of NHWs while DCR was seen in 68.2% of Hispanics and 61.7% of NHWs (Table 2). Neither ORR nor DCR significantly differed in the subgroups according to the line of therapy (first vs. second and beyond), histology (adenocarcinoma or squamous cell carcinoma), or PD-L1 status (negative or positive). Similarly, there were no significant differences between median OS (21.6 months for

Table 2. Comparison in clinical outcomes between Hispanics and Non-Hispanic Whites.

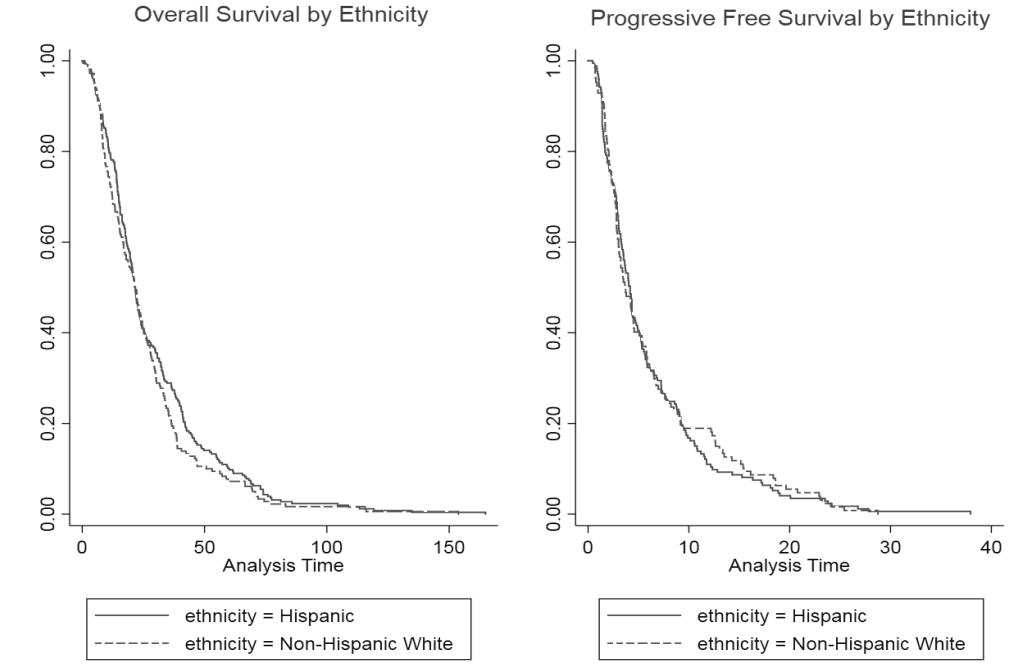
Variable	Hispanics (n = 256)	NHW (n = 180)	p-value
Sex (males)	52%	45%	0.2059
ORR	22.9%	24.4%	
First Line	35%	30%	0.6590
Second Line and beyond	18%	19%	0.3236
Adeno	22%	24%	0.6714
SQCC	24%	23%	1.0000
PDL1 (+)	29%	32%	0.4839
PDL1 (-)	5%	17%	0.3040
Median PFS	4.2m	3.7m	0.7509
Median OS	21.6m	21.5m	0.2004

Table 3. Predictive presence of clinical responses of STK11 and KRAS mutations.

Variable	STK11 (-) (n = 96)	STK11 (+) (n = 31)	p-value
PFS	6.28 m	5.6 m	0.35
OS	12.1 m	8.6 m	0.035
1-year PFS	45%	43%	0.85
1-year OS	73%	55%	0.03
	SKW (n = 63)	**SKM (n = 14)**	**p-value**
PFS	5.13 m	3.02	0.56
OS	11.43 m	5.25 m	0.13
1-year PFS	36%	37%	0.94
1-year OS	70%	40%	0.03

Hispanics vs. 21.5 months for NHW) or median PFS (4.2 months for Hispanics vs. 3.7 months for NHW) as shown in Tables 2 and 3. Kaplan-Meier curves for OS and PFS by ethnicity are depicted in Figure 1.

The PFS at 12 and 24 months were 11% and 4% respectively in Hispanics, and 18%, and 2% in NHW. The OS at 12 and 24 months were 78% and 42% respectively in Hispanics and 71% and 43% in NHW. No major significant ($p < 0.05$) statistical differences were seen. One hundred twenty-seven patients were tested for STK11, KRAS, and PD-L1 (by IHC). Thirty-one patients were STK11 positive (STK11+), 14 were both STK11/KRAS double-positive [SKM group], and 10 were SKM plus PD-L1 negative [SKMP group]. The median age at diagnosis was 65 years [range 27-88y]; males made up 54% of the study population. Thirty patients (24%) were Hispanic, and the rest were NHW. The proportion of STK11 mutations were similar among Hispanics and NHW patients (26.7% vs. 23.7%; $p = 0.74$). STK11 negative (STK11-) group had increased median OS (12.1 vs. 8.6 months; $p < 0.05$) and 1-year survival (73% vs. 55%; $p < 0.05$) compared to the STK11+ group, which was statistically significant. No statistically significant differences in PFS between these groups were seen, though a trend towards increased PFS was observed in the STK11- group (Table 3). Patients in the SKM and SKMP groups had reduced OS and PFS compared with the STK11- group, although these differences were not significant. TP53 mutations were present in 44% of the patients who were tested and we tried to find a correlation with the presence of STK11 mutations comparing the major endpoints: ORR, PFS and OS. Patients who have the presence of both mutations at the same time (STK11 and TP53) have a worse OS than patients who were wild type for both mutations: OS: 10.7 m vs. 16 m but the difference was not statistically significant ($p = 0.47$) HR = 1.43 (0.54 - 3.84). We got similar results for PFS and ORR where patients with concomitant mutations have worse outcomes than patients with wild type genes but again the differences did not achieve statistical significance.



Log-Rank Test; p = 0.1891

Log-Rank Test; p = 0.8197

Figure 1. Kaplan-Meier survival curves by ethnicity.

Table 4. Adverse events.

Patients with AEs	n (%)	p-value
	31 (44.29%)	
AEs (H)	12 (39%)	0.052
AEs (NH)	19 (61%)	
# of AEs	42	
Hypothyroidism (NH)	10 (19.6%)	0.020
Hypothyroidism (H)	9 (47.4%)	0.023
Rash (NH)	8 (15.7%)	0.247
Rash (H)	1 (5.3%)	-
Pneumonitis (NH)	1 (1.9%)	0.472
Pneumonitis (H)	1 (5.3%)	
Other (NH)	8 (15.7%)	0.723
Other (H)	4 (21.1%)	-

An exploratory analysis of toxicity profiles and AEs was conducted in a subgroup of 70 patients. There were 19 Hispanic patients and 51 NHW patients. The group that experienced AEs had significantly increased median PFS (7.5 vs. 2.1 months; p = 0.001) and OS (14.7 vs. 4.7 months; p = 0.001) compared to the AEs negative group. At 12 months, OS was 58.1% in the AEs positive group compared to 20.5% in the AEs negative group (p = 0.001) (Table 4). There was a non-statistically significant trend towards improved patient outcomes with baseline NLR < 5 vs.> 5. The overall incidence of AEs was similar between Hispanics and NHWs; however, hypothyroidism was observed more frequently in Hispanics (45% vs. 20%; p-value 0.020). Baseline NLR < 5 vs.> 5 was similar between Hispanics and NHWs.

4. DISCUSSION

Hispanic patients come from over 25 Latin American countries and are not collectively considered a race but rather an ethnic group with several differences in their lung cancers' outcomes and presentations. Historically they have not been included in clinical trials developed in the US and Europe (where most trials are done) for several reasons. Primary studies for FDA-approved ICIs like nivolumab, pembrolizumab or atezolizumab did not include Hispanic patients in their cohorts [1, 15-18]. We have found after this analysis that the results of this study are comparable and consistent with recent literature on patients with metastatic NSCLC receiving immunotherapy [13, 15-19]. Despite expected genomic differences and lower lung cancer mortality, Hispanics appear to have similar responses to ICI and OS compared to their NHW counterparts. Patients harboring actionable mutations (including EGFR, which is thought to contribute to improving OS in Hispanics due to higher incidence in this population) were excluded from this study as the guidelines did not recommend the use of ICIs as single agents for patients who have tumors with EGFR or ALK genetic aberrations at that time; this might change now with the IMPOWER150 [20] and PROLUNG [21] studies providing results that suggest improvement of outcomes in patients with these genetic aberrations that have failed targeted therapy and are treated now with the combination of chemotherapy and immunotherapy. Excluding a selected population with EGFR mutations and ALK aberrations from the analysis probably contributes significantly to the equivalence of responses and survival after exposure to ICIs between Hispanics and NHW. Notably, Asian patients appeared to have better outcomes with ICIs despite multiple characteristics associated with lower immunogenicity, such as a more significant proportion of negative PD-L1 expression and lower bTMB, in addition to more nonsmokers and EGFR mutations. Qian *et al.* [22] recently reported differences in the characteristics and prognoses between Asian and white patients with NSCLC receiving atezolizumab in the POPLAR and OAK studies. Patients with mutations in KEAP1, TP53, EPHA5, CREBBP, RB1, and APC had significantly shorter OS than those without these gene mutations. In addition, KEAP1, EGFR, and STK11 mutations were linked to progressive disease, while patients with mutations in POLE, ATM, STAG2, and GRM3 had better responses [22].

STK11/LKB1 gene encodes for the serine/threonine kinase 11, which, when inactive, has been shown to limit the density of tumor-infiltrating lymphocytes and therefore prevent an effective response to immunotherapy, especially in KRAS mutant tumors [23]. Some clinical reports have suggested that the presence of KRAS or STK11/LKB1 mutations may act as negative predictive factors for response to ICIs [23, 24]. This finding is both valuable and

worrisome because KRAS and STK11/LKB1 are very frequent genetic aberrations in lung cancer, and until now, there is only one agent, not available in Latin America, that might be FDA-approved in the near future that can effectively target a sub-group of KRAS mutations, the KRASg12c (sotorasib). Recently, Carrot *et al.* [25] documented the genomic and ancestry analysis of 1,153 lung cancer tumors from Latin American patients that showed striking associations between Native American (NAT) ancestry and their somatic landscape, including tumor mutational burden (TMB), and specific driver mutations in EGFR, KRAS, and STK11. They found that a local Native American ancestry risk score predicted EGFR and KRAS mutation frequency more strongly than global ancestry, suggesting that germline genetics (rather than environmental exposure) underlie these disparities. The study also found a lower frequency of mutations in TP53 (32%), KRAS (12%), STK11 (5%), and KEAP1 (3%), versus the European Caucasian counterpart (TP53 62%, KRAS 33% and STK11 11%) [25]. These data were recently confirmed by Sepúlveda-Hermosilla *et al.* in a cohort of 1,732 NSCLC cases from Brazil, Chile, and Peru [26].

Although most of the patients included in the study received ICIs as second-line or beyond, it is essential to note that in the population using ICIs as the first line (when the PD-L1 ≥50%), there was a trend towards better clinical outcomes (ORR and OS), but these did not statistically differ between Hispanics and NHW. These results are compatible with pembrolizumab as a single agent in front-line therapy, as presented in Keynote 024 and 042 studies [17, 18]. The same was true for patients expressing PD-L1 compared to non-expressors. There were no differences according to sex or histology, either. This comparison did not include data of chemoimmunotherapy combinations that have now become the standard of care for the NSCLC front line therapy. In the same way, our study demonstrated that the presence of STK11+ mutations negatively affected PFS and OS. Similarly, the presence of mutations in KRAS/STK11 plus negativity in PD-L1 demonstrated an adverse prognosis, similar to that previously described. This observation raises the idea of developing a score based on a regression analysis and a random forest tree (RFT) evaluation to find factors associated with this positive outcome. This score could include various biomarkers and clinical criteria, especially when considering the cost of ICIs and the utility of PD-L1, mainly when combinations with chemoimmunotherapy or immuno-immunotherapy are used [13, 15, 16]. Controversy remains open, especially with findings such as that of Papillon-Cavanagh *et al.* [27] who found from the analysis of 2,276 patients exposed to ICIs (in 574 patients used as first-line) that STK11-KEAP1 mutations are prognostic, not predictive, biomarkers for anti-PD-1/L1 therapy. The study did not observe any interaction between STK11 mutations and anti-PD-1/L1 treatment on real-world PFS (HR, 1.05; 95% CI 0.76 to 1.44; p = 0.785) or OS (HR, 1.13; 95 % CI 0.76 to 1.67; p = 0.540). Similarly, there was no observable interaction between KEAP1 mutations and treatment on real-world PFS (HR, 0.93; 95% CI 0.67 to 1.28; p = 0.653) or OS (HR, 0.98; 95% CI 0.66 to 1.45; p = 0.913) [27].

Somatic TP53 gene alterations are frequent in human cancers and in patients with tobacco-associated NSCLC. Patients with TP53 mutations in NSCLC generally have more aggressive disease, increased rates of resistance to chemotherapy, and shorter survival; for these reasons we believe that the presence of TP53 genetic aberrations can be considered a negative predictor of response to ICI especially in the presence of concomitant STK11 mutations. Despite the fact that 44% of the tested patients had this genetic aberration we were unable to find a correlation with the clinical outcomes in our patients. There are many factors that can be responsible for the findings; one of them is that TP53 mutations might not be a homogeneous genetic aberration as we have demonstrated already with the KRAS gene: we know now that different subtypes of KRAS genes have different behaviors and responses to therapy.

The contribution of race-based differences in the innate and adaptive immune systems to outcome differences is well-recognized and such variability was shown to impact disease severity and outcomes. In the same dimension prior studies focusing on pharmaco-ethnic differences showed that ethnic background can impact toxicities from chemotherapy and targeted kinase inhibitors in addition to efficacy

outcome [28]. There are only limited data available on the potential impact of race or gender on the pharmacokinetics (PKs) of immune checkpoint inhibitors. Analysis of PK data for nivolumab (a PD-1 inhibitor) from 1,895 patients enrolled across 11 different clinical trials showed no clinically meaningful impact of race on the PK [29]. However, Asian ethnicity and male gender had significant impact that did not meet the threshold set for clinically meaningful (<20%) effect on nivolumab clearance. A similar analysis conducted for pembrolizumab using pooled data from 1,223 patients enrolled on the KEYNOTE-001 trial, 421 patients on KEYNOTE-002, and 551 patients on KEYNOTE-006 showed significant differences by gender, which were deemed not clinically meaningful [30]. This study did not analyze differences based on race. One critical mechanism that impacts PK of monoclonal antibodies is the development of anti-drug antibodies, limiting the efficacy of antibody-based immunotherapy, as witnessed with the shortened progression-free survival in patients with melanoma treated with ipilimumab [31]. It is very plausible that anti-drug antibodies' development to these therapeutic agents will vary by race or ethnicity as already observed with other biologic agents [32]. Addressing these questions will require a dedicated prospective study given the negligible number of minority background patients enrolled in clinical trials of immunotherapy to date.

Recent studies have shown that immune-related adverse events (irAEs) caused by ICIs were associated with clinical benefit in patients with melanoma, gastric and lung cancer [33, 34]. Patients who developed ≥2 irAEs during treatment (n = 37) had a significantly longer median PFS and OS than those with one or none AEs, and multivariable analysis revealed that AEs were positively associated with PFS and OS improvement [33]. Hence the occurrence of irAEs seems to be associated with improved clinical outcomes, which might be useful in identifying potential responders to ICI. This is a complicated issue as patients who develop irAEs often have their ICI therapy discontinued for safety reasons [34]. In our current study, our Hispanic patients have a similar toxicity profile with ICIs as other cited studies except that Hispanic population receiving ICIs may be at higher risk for developing hypothyroidism.

Racial and ethnic minority populations have a high burden of cancer incidence but low participation in clinical trials. Although immunotherapy has rapidly become a critical foundation for cancer therapy, there is limited understanding of race's impact on the efficacy of approved immunotherapy agents because of the disappointingly low number of ethnic minority patients enrolled in the pivotal trials that led to drug approval [35]. Therefore, it is imperative that deliberate and concerted effort be brought to bear on the challenge of minority patient participation in clinical trials. Race and ethnicity are complex and dynamic constructs that are often self-reported and are dependent on individual and collective experiences. However, race/ethnicity remains one of the critical determinants of how and why diseases such as cancer development and treatment selection achieve optimal outcomes in specific patient subsets. Whereas disparity analyses in the United States have focused mainly on a black/white and Hispanic/Non-Hispanic dichotomy, a more comprehensive approach is warranted given the increasing diversity in Latin American countries.

5. STUDY LIMITATIONS

There are some limitations to our study. Real-world data are retrospective and observational and may not offer the same robustness as prospective randomized clinical trials. Factors that influence clinical decision-making but are not explicitly captured by real-world data sets may exist and confound analyses. Other factors, such as tumor evolutionary dynamics between specimen collection, diagnosis, and time to start treatment or duration of treatment, may influence the associations. Moreover, although the cohort was considerable for previous Hispanics reports, it might not be sufficiently powered to capture a low-effect-size interaction between STK11 and KRAS or TP53 mutations.

6. CONCLUSIONS

This is the most extensive comparison of NSCLC immunotherapy outcomes in Hispanic patients vs. NHW patients. No significant differences were found in the clinical outcomes between these two ethnic groups despite expected genomic differences. These results are comparable to the ones seen in Checkmate and Keynote studies. As expected,

higher response rates were seen in first-line therapy, and patients with PD-L1 positive status. Interestingly, better clinical outcomes were seen in patients who experienced AEs, a phenomenon that has been described with immunotherapy. Further comparisons will be better addressed by a larger prospective study evaluating the new standard of care using upfront chemotherapy/immunotherapy combination as well as several biomarkers in different ethnic groups.

CONFLICT OF INTEREST STATEMENT

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