Association of Personal Characteristics and Effectiveness of Immunotherapy in Late-Stage Non-Small Cell Lung Cancer: A Systematic Review

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Abstract

Background: Although immunotherapy can increase survival in non-small cell lung cancer (NSCLC), response rates are low. It is unclear which characteristics contribute to variability in immunotherapy efficacy and survival. Research is needed to identify reasons for heterogeneity in response rates to better tailor treatments. Methods: Web of Science, Ovid EMBASE, and MEDLINE were queried from 2013 to January 2021, and all studies reporting overall or progression-free survival for patients treated with immunotherapy for NSCLC of at least stage IIIb were screened. Results: Included were 18 randomized controlled trials (RCTs; 6534 immunotherapy RCTs; 11 192 nonimmunotherapy RCTs) and 16 observational studies (n = 9073 immunotherapy patients). Among RCTs, there was improved survival with the addition of immunotherapy in patients aged younger than 65 years in 10 of 17 studies; smokers in 8 of 15 studies; and males in 10 of 17 studies and 6 of 17 females. Only 5 studies reported outcomes by race. Among observational studies, younger patients (aged younger than 60, younger than 65, or younger than 70 years in most studies) had better survival than older patients (aged 60 years and older, 65 years and older, or 70 years and older) in 4 of 13 studies, ever-smokers in 7 of 13, and females in 2 of 14. Three studies reported race with mixed results. Conclusion: Although evidence is mixed, younger patients, smokers, and males may derive more benefit from immunotherapy. Evidence on racial differences is limited. Physicians should be mindful of personal characteristics when formulating treatment plans. Further research is needed to understand underlying mechanisms and to identify the best immunotherapy candidates and alternative treatments for those unlikely to benefit.

Immunotherapy is now the standard of care for many of the approximately 200 000 non-small cell lung cancer (NSCLC) patients diagnosed annually in the United States (1). For some late-stage, unresectable cancers, immunotherapies can be less toxic and more targeted than chemotherapy. Multiple approaches combining immune checkpoint inhibitors with chemotherapy and radiotherapy continue to be tested (2). Compared with other cancers, NSCLC is relatively amenable to immunotherapy, but many patients still do not benefit. Reported response rates for pembrolizumab and nivolumab for patients with Programmed death—ligand 1 (PD-L1) of more than 50% are 41% and 19%, respectively, and as low as 15% for atezolizumab (3). Research is ongoing to identify personal characteristics, biomarkers, and clinical or histological features that may explain heterogeneity in immunotherapy response and predict which patients may benefit most.

However, much remains poorly understood about how various prognostic factors contribute to differences in efficacy and disparities in survival among those receiving immunotherapy, especially in the presence of clinical characteristics that can act as confounders. There is substantial heterogeneity of clinical characteristics, tumor mutation expression, and line of therapy between existing studies, which heightens the need for synthesis across experimental and observational studies. Patients enrolled in clinical trials tend to be White, younger, healthier, and more tolerant of treatment-related toxicities (4). Women have long been underrepresented in clinical trials (4), as have minority groups, and there has not been a systematic attempt to...
aggregate evidence on metastatic NSCLC with respect to race (5). Concurrently, increased use of immunotherapy globally has enabled publication of multiple observational studies with more diverse patients and more representative, real-world outcomes. This systematic review aims to synthesize evidence across experimental and observational studies to assess the effects of age, smoking status, sex, and race on survival among those receiving immunotherapy.

**Methods**

**Search Strategy**

Ovid EMBASE, MEDLINE (including PubMed), and Web of Science were queried using MeSH and free-text terms identified using the Population-Intervention-Comparator-Outcome—Timing—Setting framework (6). Search logic was [(immuno* OR CHECK* OR PD-1 OR PD-L1 OR *mab OR cyramza) AND Ti=(NSCLC OR "non-small cell lung cancer" OR "non-small cell lung cancer") AND Ts=("sex" OR "gender" OR "smok*" OR "rac*" OR "ethnic*" OR "age" OR "Comorb*" OR "soci*" OR "socioeco")], as a topic (title, abstract, keyword search) search in Web of Science, and a title-only search in Ovid. Food and Drug Administration approval was granted for immunotherapy in NSCLC in 2015; studies from 2013 to January 2021 were included to provide a 2-year buffer. Bibliographies of all review articles returned by the searches were hand searched and evaluated for inclusion.

**Inclusion and Exclusion Criteria and Selection of Studies**

All clinical trials, observational studies, and secondary analyses studying patients diagnosed with late-stage NSCLC, regardless of histology, that reported hazard ratios (HRs) for either overall or progression-free survival were eligible for inclusion. Studies were also eligible for inclusion if they reported hazard ratios for overall survival (OS) or progression-free survival (PFS) (or data that allowed for calculation of these values) and had immunotherapy and nonimmunotherapy treatment arms. Ongoing trials as of January 31, 2021, trial protocols, case reports, and data on patient samples were excluded.

**Data Collection and Extraction**

Search results were exported into EndNote X9 (Clarivate, Endnote X9) (7), and all duplicates were removed. Titles and abstracts were screened. The full texts of 65 studies were assessed along all inclusion and exclusion criteria; 18 experimental studies (all randomized controlled trials [RCTs]) and 16 observational studies met all inclusion criteria (Tables 1 and 2). All 18 included experimental studies fulfilled at least 10 of 14 checklist items; all were randomized, had groups comparable across all covariates at baseline, and used reliable outcome measures (9). Although many of the included studies were retrospective analyses, lack of sample size justifications, and sparse reporting around whether hypotheses were specified a priori (Supplementary Table 2, available online). Areas of potential bias included retrospective analyses, lack of sample size justifications, and sparse reporting around whether hypotheses were specified a priori (Supplementary Table 2, available online).

**Quality Assessment**

All 18 included experimental studies fulfilled at least 10 of 14 checklist items; all were randomized, had groups comparable across all covariates at baseline, and used reliable outcome measures (9). Although many of the included studies were retrospective analyses, lack of sample size justifications, and sparse reporting around whether hypotheses were specified a priori (Supplementary Table 2, available online).

**Narrative Synthesis of Experimental Studies**

The 18 included experimental studies had immunotherapy treatment regimens of pembrolizumab (n = 5), atezolizumab (n = 6), nivolumab (n = 4), durvalumab (n = 1), avelumab (n = 1), and ipilimumab (n = 1) (Table 1). Two studies reported hazard ratios based on PFS, and 16 studies reported hazard ratios for OS. Nine studies tested chemotherapy–immunotherapy combinations, and the other 9 compared single-agent immunotherapy with chemotherapy. All control groups consisted of 1 or more chemotherapy drugs including docetaxel, paclitaxel, and various platinum chemotherapies. Patients were enrolled in first (n = 11), second (n = 4), or second and/or third (n = 3) lines of treatment (23,26,27). Of the 18 included experimental studies, 13 reported statistically significant improvements in OS or PFS with immunotherapy across all patients (Table 3).

**Age**

Of the experimental studies, 17 reported data across age groups (Table 3). Of the 11 that defined age as binary, 8 studies showed statistically significant improvements in OS or PFS with
| Clinical trial | Author, year | Prognostic factors | Histology | Line of therapy | Stage | Immunotherapy | Control | No. immunotherapy/total | Male, % | Female, % | NIH rating (out of 14) |
|----------------|--------------|--------------------|-----------|----------------|-------|---------------|---------|-----------------------|--------|-------------|----------------------|
| KEYNOTE-010    | Herbst et al., 2016 (10) | Age, sex | NSCLC (22% squamous) | Second | Advanced | Pembrolizumab [10 mg/kg or 2 mg/kg—pooled] | Docetaxel (75 mg/m²) | 690/1033 | 62 | 38 | 12 |
| KEYNOTE-024¹   | Reck et al., 2016 (11) | Age, smoking, sex | NSCLC (19% squamous) | First | IV | Pembrolizumab (200 mg) | Platinum | 154/305 | 60 | 40 | 13 |
| KEYNOTE-042    | Mok et al., 2019 (12) | Age, smoking, sex | NSCLC (38% squamous) | First | Locally advanced or metastatic | Pembrolizumab (200 mg) | Platinum | 637/1274 | 71 | 29 | 12 |
| KEYNOTE-047    | Gandhi et al., 2018 (13) | Age, smoking, sex | Nonsquamous | First | Locally advanced or metastatic | Pembrolizumab (200 mg) + pemetrexed + platinum | Platinum | 410/616 | 62 | 38 | 14 |
| KEYNOTE-189    | Paz-Ares et al., 2018 (14) | Age, sex | Squamous | First | IV | Pembrolizumab (200 mg) | Platinum | 278/559 | 79 | 21 | 14 |
| IMpower130     | West et al., 2019 (15) | Age, smoking, sex | Nonsquamous | First | IV | Atezolizumab [200mg] + carboplatin + nab-paclitaxel | Carboplatin + nab-paclitaxel | 451/723 | 59 | 41 | 10 |
| IMpower131     | Jotte et al., 2020 (16) | Age, smoking, sex | Squamous | First | IV | Atezolizumab [200mg] + carboplatin + nab-paclitaxel | Carboplatin + nab-paclitaxel | 343/683 | 82 | 18 | 10 |
| IMpower132     | Nishio et al., 2020 (17) | Age, smoking, sex, race | Nonsquamous | First | IV | Atezolizumab [200mg] + cisplatin/carboplatin + nab-paclitaxel | Carboplatin/cisplatin + nab-paclitaxel | 292/578 | 66 | 34 | 12 |
| IMpower150²    | Socinski et al., 2018 (18) | Age, smoking, sex | Nonsquamous | First | IV or recurrent | Atezolizumab + carboplatin + nab-paclitaxel | Carboplatin + nab-paclitaxel | 356/692 | 60 | 40 | 11 |
| CheckMate 017  | Brahmer et al., 2015 (19) | Age, smoking, sex | Squamous | Second | IIIB: 21%; IV: 79% | Nivolumab (3mg/kg) | Docetaxel (75 mg/m²) | 135/272 | 82 | 18 | 12 |
| CheckMate 026  | Carbone et al., 2017 (20) | Age, smoking, sex | NSCLC | First | IV or recurrent | Nivolumab (3mg/kg) | Platinum | 271/541 | 68 | 32 | 10 |
| CheckMate 227  | Bonghein et al., 2015 (21) | Age, smoking, sex, race | Nonsquamous | Second | IIIB: 8%; IV: 92% | Nivolumab (3mg/kg) | Docetaxel (75 mg/m²) | 292/582 | 52 | 48 | 11 |
| OAK            | Rittmeier et al., 2017 (22) | Age, smoking, sex | NSCLC | First | IV/Recurrent | Nivolumab (3mg/kg) + ipilimumab (1mg/kg) | Platinum doublet chemotherapy | 396/793 | 64 | 36 | 12 |
| JAVELIN Lung 200 | Barlesi et al., 2017 (23) | Age, smoking, sex | NSCLC (30.5% squamous) | Second | IIIB-IV | Atezolizumab [200mg] | Docetaxel (75 mg/m²) | 425/850 | 61 | 39 | 11 |
| CA184-104      | Govin dan et al., 2017 (24) | Age, sex, race | NSCLC | First | IV/Recurrent | Avelumab (10mg/kg) | Docetaxel (75 mg/m²) | 396/792 | 69 | 31 | 11 |
| PACIFIC        | Antonia et al., 2018 (25) | Age, smoking, sex, race | NSCLC | Second and further | Stage III unresectable | Durvalumab + chemo-radiotherapy | Placebo + chemo-radiotherapy | 476/713 | 70 | 30 | 14 |
| POPLAR         | Fehrenbacher et al., 2016 (26) | Smoking | NSCLC (34% squamous) | Second-third | All comers | Atezolizumab (1200mg) | Docetaxel (75 mg/m²) | 144/287 | 65 | 35 | 12 |

¹Studies reporting outcomes as progression-free survival. The remaining studies reported overall survival. NIH = National Institutes Health; NSCLC = non-small cell lung cancer.
| Study                  | Study population                                      | Prognostic factors                  | Histology                        | Line of therapy                          | Stage         | Immunotherapy                                                                 | No. of patients | Male, % | Female, % | NIH rating |
|------------------------|------------------------------------------------------|-------------------------------------|-----------------------------------|-----------------------------------------|---------------|-------------------------------------------------------------------------------|----------------|---------|-----------|------------|
| Chen et al., 2020      | Peking Union Medical College Hospital (China)         | Age, smoking, sex                   | Nonsquamous: 59.8%; squamous: 40.2% | Second (74%); Third (26%)              | IIIB: 22.68%; IV: 77.32%              | Pembrolizumab (35/97) or nivolumab (62/97) | 97             | 67      | 33        | 10/14      |
| Smit et al., 2020      | Netherlands NVALT Registry                           | Age, smoking                        | ADC: 66.1%; SCC: 26.6%; NOS: 6.3% | All                                      | IV: 100%      | Nivolumab and pembrolizumab for second line; durvalumab, atezolizumab       | 2302            | 57      | 43        | 10/14      |
| Lichtenstein et al., 2019 | Massachusetts General Hospital                       | Age, sex                            | ADC: 65.3%; SCC: 25.7%; LCC: 1.6%; other: 7.3% | All                                      | I: 10.6%; II: 7.8%; III: 16.3%; IV: 62.9%; Unknown: 2.5% | PD-1/PD-L1 inhibitors | 141            | 54      | 46        | 10/14      |
| Yang et al., 2020      | Shandong Cancer Hospital                             | Age, smoking, sex                   | ADC: 46.5%; SCC: 53.5%            | Third-anlotinib (RTK-inhibitor targeting VEGF2/3) + immunotherapy; ECOG PS 0-2 | III: 43.5%; IV: 56.5%| Anlotinib + immunotherapy combination (pembrolizumab [41], sintilimab [32], 15 nivolumab [15], tislelizumab [13]) | 101             | 58      | 42        | 10/14      |
| Huang et al., 2020     | Harbin Medical University Cancer Hospital (China)     | Age, smoking, sex                   | ADC: 73.2%; SCC: 26.8%            | All (first [28%]; second and later [72%]), patients receiving at least 1 cycle ICI and wild-type EGFR, ALK, ROS | III: 9.8%; IV: 90.2% | Anti-PD-1 (nivolumab and pembrolizumab); anti-PD-1 (Atezolizumab); CTLA4 antibody (ipilimumab) | 61              | 62      | 38        | 10/14      |
| Nazha et al., 2020     | Winship Cancer Institute, Emory University           | Sex, race                           | ADC: 65.2%; SCC: 17.8%; large cell lung cancer: 2%; NOS: 6.7%; SCLC: 7.1% | All (first [19.9%], second [62.9%], third [12.9%], fourth [4.3%]) | III: 19.8%; IV: 67.8%; nonadvanced: 13.4% | Single agent (nivolumab [49%], pembrolizumab [25.3%], atezolizumab [21.4%], nivolumab + ipilimumab [4.3%]) | 257             | 49      | 51        | 10/14      |
| Prelaj et al., 2019    | National Cancer Institute of Milan                   | Age, smoking, sex                   | ADC: 73%; SCC 24%; other: 3%      | Second [61%] or further (39%)           | IIIB-C: 3%; IV: 97%                   | Anti-PD 1/anti PD-L1 (single agent) | 193             | 62      | 38        | 10/14      |
| Elkrief et al., 2020   | Dijon Cancer Center (n = 177); University of Montreal University Hospital (n = 106); Quebec Heart and Lung Institute (n = 98) | Age, smoking, sex                   | Nonsquamous: 73%; SCC: 22%, other: 5% | First (12%); second or further (88%) | III: 7%; IV: 93%                      | Nivolumab (67%), pembrolizumab (28%), other (5%) | 381             | 57      | 43        | 10/14      |

(continued)
| Study                          | Study population                        | Prognostic factors | Histology | Line of therapy | Stage | Immunotherapy | No. of patients | Male, % | Female, % | NIH rating |
|-------------------------------|-----------------------------------------|--------------------|-----------|-----------------|-------|---------------|----------------|---------|-----------|------------|
| Kano et al., 2020 (35)        | Okayama Lung Cancer Database (Japan)    | Smoking, sex       | ADC: 63.9%; SCC: 28.3%; other: 7.7% | First (17%); second (35%); third or further (48%) | IIIB-IV: 71.7%; recurrence: 28.3% | Anti-PD-1/Anti-PD-L1 monotherapy (nivolumab [69.8%]; pembrolizumab [29.6%]; atezolizumab 0.6%) | 527     | 79        | 21        | 10/14      |
| Anouti et al., 2020 (36)      | Hoosier Cancer Research Network (LUN 14-19 trial) | Age, smoking, sex  | Nonsquamous: 55%; squamous: 45% | Previous chemotherapy | IIA: 60%, IIIB: 40% | Pembrolizumab | 92      | 64        | 36        | 10/14      |
| Adachi et al., 2019 (37)      | Kinki-Chuo Chest Medical Center (Japan) | Age, smoking, sex  | ADC: 62.5%; SCC: 27.4%; other: 10.1% | All | NR | Nivolumab | 296     | 70        | 30        | 10/14      |
| Ahn et al., 2019 (38)         | Yonsei Cancer Center, Korea             | Age, smoking, sex  | ADC: 67.7%; SCC: 30.3%; other: 2% | All (first [10.3%], second: [39.4%], third or further [50.3%]) | 100% advanced NSCLC | Nivolumab, pembrolizumab | 155     | 73        | 27        | 10/14      |
| Lin et al., 2018 (39)         | National Taiwan University Hospital     | Age, smoking, sex  | ADC: 64.9%; SCC: 18.9%; other: 16.2% | All (69% Third-or further-) | IIIB: 2.7%, IV: 97.3% | Nivolumab or pembrolizumab | 74      | 58        | 42        | 10/14      |
| Ng et al., 2018 (40)          | University of Colorado Hospital and Shanghai Pulmonary Hospital, Tongji University | Age, smoking, sex, race | NR | All | 100% locally advanced or metastatic NSCLC | Anti-PD-1/PD-L1 monotherapy—nivolumab, pembrolizumab, atezolizumab | 91      | NR        | NR        | 10/14      |
| Foster et al., 2019 (41)      | US National Cancer Database             | Age, sex, race     | ADC: 79.1%; non-ADC: 20.9% | First commission on cancer-accredited programs | IV: 100% | Unspecified (most likely pembrolizumab) | 5807    | 52        | 48        | 10/14      |
| Song et al., 2020 (42)        | Peking Union Medical College            | Smoking            | ADC: 42.86%; SCC: 57.14% | All (first [32%]; second [22%]; third and further [9]) | IIIB: 6.35%; IIIC: 9.52%; IVA: 61.9%; IVB: 22.2% | Pembrolizumab (42), nivolumab (8), sintilizumab (17) | 63      | 84        | 16        | 10/14      |

*Studies reporting outcomes as progression-free survival. The remaining studies reported overall survival. ADC = adenocarcinoma; ALK = Anaplastic lymphoma kinase; anti PD-L1 = anti Programmed death-ligand 1; CTLA4 = Cytotoxic T-lymphocyte-associated antigen 4; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; ICI = immune checkpoint inhibitor; LCC = large cell carcinoma; NIH = National Institutes of Health; NOS = not otherwise specified; NVALT = Nederlandse Vereniging voor Artsen Longziekten en Tuberculose; ROS = Reactive oxygen species; RTK = Receptor tyrosine kinase; SCC = squamous cell carcinoma; VEGF = Vascular endothelial growth factor.
immunotherapy for patients aged younger than 65 years, compared with 3 studies for patients aged 65 years and older.

Six studies reported age as a trinomial variable (16,18,19,21,22,25); 2 of which reported statistically significantly improved survival with immunotherapy for those aged younger than 65 years and those 65-75 years (Table 3 (19,21)). One study reported improved survival only in patients aged younger than 65 years (22), and 1 did not report confidence intervals by age (18). No study reported statistically significant OS or PFS improvements with immunotherapy for patients aged older than 75 years.

Smoking Status

Of the experimental studies, 15 reported hazard ratios stratified by smoking status (Table 4). Of the 12 studies that dichotomized smoking status, 6 had statistically significantly improved survival with immunotherapy for ever-smokers (13,19,21-23,26). Of these 6 studies, 2 also showed statistically significantly improved survival for never-smokers (13,26). Three RCTs grouped smoking as trinomial (11,12,20); 2 (KEYNOTE-042 and KEYNOTE-024) showed statistically significant OS or PFS improvements with immunotherapy for those aged younger than 65 years, compared with 3 studies for patients aged 65 years and older.

Race

Of the 5 RCTs that reported OS hazard ratios by race (16,17,24-26), only the PACIFIC study (durvalumab and chemoradiotherapy combination) (26) reported statistically significant improvement with immunotherapy. Asian and White patients derived similar benefit from immunotherapy, but the improvement was statistically significant only for White patients (26).

Two of the remaining studies reported hazard ratios for Asian, Black, and White patients (16,25), and 1 reported this data for only Asian and White patients (17). Distinctly, Barlesi et al. (24) reported race either as Hispanic or Latino, Japanese living in Japan, non-Hispanic or non-Latino, or Other. There were no statistically significant differences in OS in any of these studies (Supplementary Table 3, available online).

Narrative Synthesis of Observational Studies

Of the observational studies where all patients received immunotherapy, 16 assessed at least one of age, smoking status, sex, or race. Six studies reported hazard ratios based on PFS, and 10 studies reported hazard ratios for OS (Table 2). Pembrolizumab and nivolumab (PD-1 inhibitors) were the most frequently studied immunotherapy agents. Both were used in all lines of treatment as monotherapies (5,33,39) and as part of combination therapy (31). Atezolizumab, ipilimumab, durvalumab, sintilimab, and tislelizumab were the other evaluated immunotherapy regimens.

### Table 3. Association between survival and immunotherapy, stratified by age in experimental studies (n = 17)

| Clinical Trial   | Study                  | Immunotherapy vs no immunotherapy by age | HR (95% CI) |
|------------------|------------------------|------------------------------------------|-------------|
|                  |                        | All patients                             | Younger than 65 years | 65 years and older | 65-75 years | Older than 75 years |
| KEYNOTE-024      | Reck et al., 2016 (11)* | 0.50 (0.37 to 0.68)                      | 0.61 (0.40 to 0.92) | 0.45 (0.29 to 0.70) | N/A         | N/A         |
| KEYNOTE-042      | Mok et al., 2019 (12)   | 0.81 (0.71 to 0.93)                      | 0.81 (0.67 to 0.98) | 0.82 (0.66 to 1.02) | N/A         | N/A         |
| KEYNOTE-189      | Gandhi et al., 2018 (13)| 0.49 (0.38 to 0.64)                      | 0.43 (0.31 to 0.61) | 0.64 (0.43 to 0.95) | N/A         | N/A         |
| KEYNOTE-407      | Paz-Ares et al., 2018 (14)| 0.64 (0.49 to 0.85) | 0.52 (0.34 to 0.80) | 0.74 (0.51 to 1.07) | N/A         | N/A         |
| IMpower130       | West et al., 2019 (15)  | 0.79 (0.64 to 0.98)                      | 0.79 (0.58 to 1.08) | 0.78 (0.58 to 1.05) | N/A         | N/A         |
| IMpower131       | Jotte et al., 2020 (16) | 0.88 (0.73 to 1.05)                      | 0.89 (0.68 to 1.15) | N/A | 0.84 (0.63 to 1.13) | 0.74 (0.45 to 1.23) |
| IMpower132       | Nishio et al., 2020 (17) | 0.86 (0.71 to 1.06)                      | 0.88 (0.67 to 1.16) | 0.84 (0.63 to 1.13) | N/A         | N/A         |
| IMpower150       | Socinski et al., 2018 (19)* | 0.62 (0.52 to 0.74) | 0.65 | N/A | 0.52 | 0.78 |
| CheckMate 017    | Brahmer et al., 2015 (19) | 0.59 (0.44 to 0.79)                      | 0.52 (0.35 to 0.75) | N/A | 0.56 (0.34 to 0.91) | 1.85 (0.76 to 4.51) |
| CheckMate 026    | Carbone et al., 2017 (20) | 1.08 (0.87 to 1.34)                      | 1.13 (0.83 to 1.54) | 1.04 (0.77 to 1.41) | N/A         | N/A         |
| CheckMate 057    | Borghaei et al., 2015 (21) | 0.75 (0.62 to 0.91)                      | 0.81 (0.62 to 1.04) | N/A | 0.63 (0.45 to 0.89) | 0.90 (0.43 to 1.87) |
| KEYNOTE-010      | Herbst et al., 2016 (10) | 0.67 (0.56 to 0.80)                      | 0.63 (0.50 to 0.79) | 0.76 (0.57 to 1.02) | N/A         | N/A         |
| OAK              | Rittmeyer et al., 2017 (23) | 0.73 (0.62 to 0.87)                      | 0.80 (0.64 to 1.00) | 0.66 (0.52 to 0.83) | N/A         | N/A         |
| JAVELIN Lung 200 | Barlesi et al., 2018 (24) | 0.90 (0.73 to 1.12)                      | 0.84 (0.65 to 1.13) | 0.98 (0.71 to 1.34) | N/A         | N/A         |
| CA184-104        | Govindan et al., 2017 (25) | 0.91 (0.77 to 1.07)                      | 0.82 (0.64 to 1.04) | N/A | 1.06 (0.81 to 1.37) | 0.85 (0.51 to 1.43) |
| PACIFIC          | Antonia et al., 2018 (26) | 0.68 (0.47 to 1.00)                      | 0.62 (0.44 to 0.86) | 0.76 (0.55 to 1.06) | N/A         | N/A         |
| CheckMate227     | Hellmann et al., 2019 (22) | 0.79 (0.65 to 0.96)                      | 0.70 (0.55 to 0.89) | N/A | 0.91 (0.70 to 1.19) | 0.92 (0.57 to 1.48) |

*Progression-free survival. CI = confidence interval; HR = hazard ratio; N/A = not applicable.
of stage IV NSCLC patients who received first-line immunotherapy treatment, those aged 18-59 years had longer overall survival than older patients (41).

A study of 61 hospitalized patients in China treated with pembrolizumab, nivolumab, atezolizumab, or ipilimumab (28% first-line; 72% second-line and later) showed statistically significantly worse survival for patients aged 65 years or older compared with those aged younger than 65 years, before and after adjustments for metastasis, adverse effects, line of therapy, and other biomarkers (32). In a multivariate model, Lichtenstein et al. (30) found immunotherapy patients aged older than 80 years had worse OS than those aged younger than 80 years. However, no statistically significant differences in OS were observed for patients in other age groups.

**Table 4.** Association between survival and immunotherapy, stratified by smoking status in experimental studies (n = 15)

| Clinical trial | Author, year | Immunotherapy vs no immunotherapy by smoking status | HR (95% CI) |
|----------------|--------------|---------------------------------------------|--------------|
| CheckMate 017  | Brahmer et al., 2015 (19) | 0.59 (0.44 to 0.79) | 0.57 (0.41 to 0.78) | 0.67 (0.36 to 1.25) |
| CheckMate 026  | Carbone et al., 2017 (20) | 1.08 (0.87 to 1.34) | 1.02 (0.54 to 1.93) | N/A | 1.09 (0.84 to 1.42) | 1.05 (0.63 to 1.74) |
| CheckMate 057  | Borghaei et al., 2015 (21) | 0.75 (0.62 to 0.91) | 1.02 (0.64 to 1.61) | 0.69 (0.56 to 0.86) | N/A | N/A |
| KEYNOTE-024a   | Reck et al., 2016 (11) | 0.50 (0.37 to 0.68) | 0.90 (0.11 to 7.48) | N/A | 0.47 (0.33 to 0.67) | 0.68 (0.36 to 1.30) |
| KEYNOTE-042    | Mok et al., 2019 (12) | 0.81 (0.71 to 0.93) | 1.00 (0.73 to 1.37) | N/A | 0.71 (0.59 to 0.86) | 0.95 (0.70 to 1.29) |
| KEYNOTE-189    | Gandhi et al., 2018 (13) | 0.49 (0.38 to 0.64) | 0.23 (0.10 to 0.54) | 0.54 (0.41 to 0.71) | N/A | N/A |
| POPLAR         | Fehrenbacher et al., 2016 (27) | 0.73 (0.53 to 0.99) | 0.55 (0.24 to 1.25) | 0.75 (0.54 to 1.04) | N/A | N/A |
| IMpower130     | West et al., 2019 (15) | 0.79 (0.64 to 0.98) | 0.87 (0.66 to 1.15) | 0.66 (0.46 to 0.93) | N/A | N/A |
| IMpower131     | Jotte et al., 2020 (16) | 0.88 (0.73 to 1.05) | 0.91 (0.75 to 1.12) | 0.75 (0.72 to 1.09) | N/A | N/A |
| IMpower150b    | Socinski et al., 2018 (18) | 0.62 (0.52 to 0.74) | 0.78 (0.42 to 1.43) | 0.89 (0.72 to 1.09) | N/A | N/A |

**Table 5.** Association between survival and immunotherapy, stratified by sex in experimental studies (n = 18)

| Clinical trial | Author, Year | Immunotherapy vs no immunotherapy by sex | HR (95% CI) |
|----------------|--------------|---------------------------------------------|--------------|
| CheckMate 017  | Brahmer et al., 2015 (19) | 0.59 (0.44 to 0.79) | 0.57 (0.41 to 0.78) | 0.67 (0.36 to 1.25) |
| CheckMate 057  | Borghaei et al., 2015 (21) | 0.75 (0.62 to 0.91) | 0.73 (0.56 to 0.96) | 0.78 (0.58 to 1.04) |
| KEYNOTE-010    | Herbst et al., 2016 (10) | 0.67 (0.56 to 0.80) | 0.65 (0.52 to 0.81) | 0.69 (0.51 to 0.94) |
| KEYNOTE-024a   | Reck et al., 2016 (11) | 0.50 (0.37 to 0.68) | 0.39 (0.26 to 0.58) | 0.75 (0.46 to 1.21) |
| CheckMate 026  | Carbone et al., 2017 (20) | 1.08 (0.87 to 1.34) | 0.97 (0.74 to 1.26) | 1.15 (0.79 to 1.66) |
| OAK, 2017      | Rittmeyer et al., 2017 (23) | 0.73 (0.62 to 0.87) | 0.71 (0.47 to 1.08) | 0.73 (0.61 to 0.88) | N/A | N/A |
| JAVELIN Lung 200 | Barlesi et al., 2018 (24) | 0.90 (0.73 to 1.12) | 1.69 (0.97 to 2.95) | 0.83 (0.66 to 1.04) | N/A | N/A |
| CheckMate227   | Hellmann et al., 2019 (22) | 0.79 (0.65 to 0.96) | 1.23 (0.76 to 1.98) | 0.77 (0.64 to 0.92) | N/A | N/A |
| PACIFIC        | Antonia et al., 2018 (26) | 0.68 (0.47 to 1.00) | 0.35 (0.16 to 0.76) | 0.72 (0.56 to 0.92) | N/A | N/A |
| IMpower130     | West et al., 2019 (15) | 0.79 (0.64 to 0.98) | 0.55 (0.26 to 1.19) | 0.81 (0.65 to 1.02) | N/A | N/A |
| IMpower131     | Jotte et al., 2020 (16) | 0.88 (0.73 to 1.05) | 0.85 (0.43 to 1.68) | 0.87 (0.72 to 1.05) | N/A | N/A |
| IMpower132     | Nishio et al., 2020 (17) | 0.86 (0.71 to 1.06) | 0.84 (0.42 to 1.43) | 0.89 (0.72 to 1.09) | N/A | N/A |
| IMpower150b    | Socinski et al., 2018 (18) | 0.62 (0.52 to 0.74) | 0.80 (0.42 to 1.43) | 0.89 (0.72 to 1.09) | N/A | N/A |

**Table 6.** Association between survival and immunotherapy, stratified by smoking status in experimental studies (n = 15)

**Table 7.** Association between survival and immunotherapy, stratified by smoking status in experimental studies (n = 15)

**Table 8.** Association between survival and immunotherapy, stratified by smoking status in experimental studies (n = 15)

**Table 9.** Association between survival and immunotherapy, stratified by smoking status in experimental studies (n = 15)

Age

Of the 13 studies reporting hazard ratios for age, 4 reported statistically significantly better OS or PFS for younger patients compared with older patients (Table 6) (30-32,41). A Dutch national database study (n = 2302) of patients with stage IV NSCLC in all lines of treatment found no statistically significant difference in OS by age (29). However, in a US-based study (n = 5807) of stage IV NSCLC patients who received first-line immunotherapy treatment, those aged 18-59 years had longer overall survival than older patients (41).

A study of 61 hospitalized patients in China treated with pembrolizumab, nivolumab, atezolizumab, or ipilimumab (28% first-line; 72% second-line and later) showed statistically significantly worse survival for patients aged 65 years or older compared with those aged younger than 65 years, before and after adjustments for metastasis, adverse effects, line of therapy, and other biomarkers (32). In a multivariate model, Lichtenstein et al. (30) found immunotherapy patients aged older than 80 years had worse OS than those aged younger than 60 years. However, no statistically significant differences in OS were observed for patients in other age groups.

**Smoking Status**

Of 13 studies, 8 reported statistically significant OS or PFS differences (either univariate or multivariate) for smoking status.
Seven showed that among immunotherapy recipients, former and current smokers had statistically significantly better OS and PFS than never-smokers (29,33,35,37,39,40,42). Distinctly, only 1 study (n = 101) of stage III-IV NSCLC patients receiving third-line, immunotherapy with anlotinib combination therapy showed statistically better PFS for never-smokers relative to ever-smokers (Table 7) (31).

The 2 largest studies examining multiple immunotherapy agents showed statistically significantly better survival for smokers than nonsmokers (29,35). In Smit and colleagues’ (29) analysis of Dutch patients (n = 2302), nonsmokers had statistically significantly worse survival than smokers. In the Japanese Okayama Lung Cancer Study of NSCLC patients in all lines of treatment with metastatic or recurrent disease, univariate analysis of patients in Colorado and Shanghai with targetable driver mutations in all treatment lines showed better OS than White patients.

Race

Only 3 observational studies assessed the association between survival and race, among immunotherapy patients (Supplementary Table 4, available online) (5,40,41). Foster et al. (41) found non-White patients had statistically significantly better OS than White patients.

Nazha et al. (5) observed no differences in OS by race. A univariate analysis of patients in Colorado and Shanghai with targetable driver mutations in all treatment lines showed better survival for non-Asian compared with Asian patients, but the difference was not statistically significant in the multivariate analysis (40).

Discussion

This systematic review was performed to evaluate whether age, smoking status, sex, and race modify the effectiveness of immunotherapy in late-stage NSCLC and to assess variability in survival among patients who received immunotherapy. We reviewed 18 experimental studies comparing immunotherapy and nonimmunotherapy groups (n = 6534 and 11 192, respectively) and 16 observational studies of 9073 patients who received immunotherapy. Because of study design differences, results from experimental and observational studies are complementary, rather than comparable. Experimental hazard ratios reflect benefit from the addition of immunotherapy (compared with those without) and allow us to assess factors that may modify immunotherapy efficacy. Immunotherapy was universal across patients in observational studies, which focus

Table 6. Association between survival after immunotherapy and age in observational studies (n = 13)

| Study                  | Reference | Comparison | Univariate HR (95% CI) | Multivariate HR (95% CI) | Adjustments |
|------------------------|-----------|------------|------------------------|--------------------------|-------------|
| Chen et al., 2020 (28)* | < 65      | ≥ 65       | 1.20 (0.73 to 1.95)    | N/A                      | N/A         |
| Smit et al., 2020 (29)  | 28-74     | 75-88      | 0.84 (0.66 to 1.08)    | N/A                      | N/A         |
| Lichtenstein et al., 2019 (30) | < 60 | 60-69      | N/A                    | 0.76 (0.46-1.25)         | CCI, initial stage, sex, ECOG PS |
|                       | 70-79     | N/A        | 0.93 (0.57-1.51)       | N/A                      | N/A         |
|                       | ≥ 80      | N/A        | 2.74 (1.42-5.25)       | N/A                      | N/A         |
| Huang et al., 2020 (32) | < 65      | ≥ 5        | 3.88 (1.69 to 8.92)    | 5.45 (1.98-14.98)        | Metastasis, NLR C4, CEA, irAE, line of therapy, response to therapy |
| Prelaj et al., 2019 (33)* | < 70     | ≥ 70       | N/A                    | 1.20 (0.85-1.69)         | Sex, smoking, ECOG PS, histology, metastasis |
| Elkrief et al., 2020 (34) | < 70     | ≥ 70       | N/A                    | 0.78 (0.56 to 1.08)      | Sex, smoking, ECOG PS, histology, stage, line of treatment, anti-PD-1 agent |
| Anouti et al., 2020 (36) | < 65      | ≥ 65       | 1.00 (0.97 to 1.03)    | N/A                      | N/A         |
| Adachi et al., 2019 (37)* | < 70     | ≥ 70       | 1.09 (0.85 to 1.39)    | N/A                      | N/A         |
| Ahn et al., 2019 (38)   | < 75      | ≥ 75       | 0.95 (0.54 to 1.69)    | 0.71 (0.34 to 1.50)     | Sex, smoking, prior treatment lines, mutations, brain and liver metastasis, PD-L1 expression level |
| Lin et al., 2018 (39)   | < 65      | ≥ 65       | 1.32 (0.70 to 2.49)    | 0.70 (0.35 to 1.42)     | Sex, smoking, ECOG PS, brain metastasis, EGFR |
| Ng et al., 2018 (40)*   | < 65      | ≥ 65       | 0.75 (0.47 to 1.21)    | N/A                      | N/A         |
| Foster et al., 2019 (41) | 18-59    | 60-69      | N/A                    | 1.08 (1.01 to 1.17)      | NR          |
|                       | 70-79     | N/A        | 1.14 (1.05 to 1.24)    | N/A                      | N/A         |
|                       | ≥ 80      | N/A        | 1.26 (1.09 to 1.46)    | N/A                      | N/A         |
| Yang et al., 2020 (31)* | < 60      | ≥ 60       | N/A                    | 2.02 (1.30 to 3.14)      | NR          |

*Progression-free survival. CCI = Charlson comorbidity index; CEA = carotid endarterectomy; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGFR = epidermal growth factor receptor; HR = hazard ratio, irAE = immune-related adverse events; N/A = not applicable; NLR = neutrophil-to-lymphocyte ratio; NR = not reported.

Sex

Of 14 studies reporting on sex, 12 found no statistically significant differences in OS or PFS in males compared with females treated with immunotherapy (Table 8). However, the largest study (n = 5807) of patients receiving first-line immunotherapy found females had better survival than males (41). Another retrospective analysis of patients (n = 257) treated with single-agent pembrolizumab, nivolumab, or atezolizumab showed statistically significantly better OS for females than males only in the adjusted model (5).
on directly comparing survival among patient subgroups. As such, observational studies may provide insight into whether differential efficacy of immunotherapy contributes to survival disparities.

Experimental studies generally suggested that younger patients derive more benefit from immunotherapy than their older counterparts. In particular, survival outcomes of patients aged 75 years and older tended to be less favorable, and trends were less consistent than for patients aged younger than 75 years. For subgroups of patients aged younger than 65 years, all experimental studies except CheckMate 026 (20) showed a trend toward improved survival with receipt of immunotherapy, even if the improvement in survival was not statistically significant. Likewise, with the exception of the CA184-104 trial (25), all subgroups of patients aged 65-75 years trended toward receiving benefit from immunotherapy. This is consistent with research showing older adults are more susceptible to the onset of immunosenescence and reduced intrinsic immunity (43). Increased age is also linked to a longer period of carcinogenesis as well as increased vulnerability and sensitization of cells to environmental carcinogens (44,45).

However, when directly comparing survival by age group, the majority of observational studies found no statistically significant difference. This is somewhat paradoxical, as younger lung cancer patients generally survive longer (44,46). The 2 largest observational studies had inconsistent findings, although they assessed different treatment lines. This may suggest that the marginal benefit of immunotherapy by age may differ across treatment lines. More uniform reporting of outcomes would be needed to address this hypothesis.

For smoking status, experimental studies more frequently showed increased survival benefit in smokers compared with nonsmokers. Likewise, most observational studies reported improved survival for current or former smokers but not never-smokers. These results are consistent with previous reviews and may reflect the fact that smokers tend to have more tumor mutations, corresponding to greater immunogenicity and a higher likelihood of immune cell recognition of tumor cells (47). For instance, whole-genome sequencing revealed smokers had a tenfold higher mutation frequency than never-smokers (48). Considering nonsmokers tend to have fewer comorbidities and are generally healthier than smokers (49), this suggests nonsmokers may not be ideal candidates for immunotherapy, especially in the absence of a high tumor mutational burden.

Two clinical trials—KEYNOTE-189 (13) and PACIFIC (26)—yielded statistically significant improvement in OS for never-smokers, and more so than in ever-smokers. These findings differ from the majority of included studies and may be partially

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**Table 7. Association between survival after immunotherapy and smoking status in observational studies (n = 13)**

| Smoking status | Author, year | Comparison | Univariate HR (95% CI) | Multivariate HR (95% CI) | Adjustments |
|----------------|-------------|------------|------------------------|--------------------------|-------------|
| Smoker Nonsmoker | Chen et al., 2020 (28)* | 1.23 (0.76 to 1.96) | N/A | N/A | N/A |
| Smoker Nonsmoker | Smit et al., 2020 (29) | 1.28 (1.00 to 1.63) | N/A | N/A | N/A |
| Smoker Nonsmoker | Yang et al., 2020 (31)* | N/A | 0.35 (0.21 to 0.59) | 2.7 (1.37 to 5.26) | PD-L1 expression, NLR |
| Smoking index ≥ 400 Smoking Index <400 | Song et al., 2020 (42)* | 0.94 (0.47 to 1.86) | N/A | 1.39 (1.02 to 1.92) | Age, sex, ECOG PS, histology, metastasis |
| Smoker Nonsmoker | Huang et al., 2020 (32) | N/A | 0.84 (0.51 to 1.38) | Sex, ECOG PS, histology, stage, line of treatment, anti-PD-1 agent |
| ≥ 40 packs/year <40 packs/year | Prelaj et al., 2019 (33)* | N/A | 2.7 (1.37 to 5.26) | PD-L1 expression, NLR |
| Smoker Nonsmoker | Elkrief et al., 2020 (34) | N/A | 1.82 (1.03 to 3.09) | Age, sex, ECOG PS, histology, metastasis |
| Former/Current smoker Never smoker | Kano et al., 2020 (35) | 1.28 (0.94 to 1.73) | 1.68 (1.16 to 2.43) | Age, sex, prior treatment lines, mutational status, brain and liver metastasis, pleural effusion, steroid use |
| Current smoker Former/Current smoker | Anouti et al., 2020 (36) | 0.59 (0.12 to 2.78) | 0.88 (0.26 to 2.99) | Age, sex, ECOG PS, driver mutation, LDH, CRP, ALB, NLR, ALL liver and brain metastasis, pleural effusion, steroid use |
| Smoker Nonsmoker | Adachi et al., 2019 (37)* | 1.42 (1.05 to 1.93) | 2.27 (1.10 to 4.67) | Age, sex, ECOG PS ≥ 2, brain metastasis, EGFR |
| Former/Current smoker Never smoker | Ahn et al., 2019 (38) | 1.02 (0.65 to 1.62) | Age, sex, ECOG PS ≥ 2, brain metastasis, EGFR |
| smoker Nonsmoker | Lin et al., 2018 (39) | 1.39 (0.73 to 2.63) | N/A | N/A | N/A |

*Progression-free survival. ALB — albumin blood; ALI — acute lung injury; CI — confidence interval; CRP — C-reactive protein; ECOG PS — Eastern Cooperative Oncology Group Performance Status; EGFR — epidermal growth factor receptor; HR — hazard ratio; LDH — lactate dehydrogenase; N/A — not applicable; NLR — neutrophil-to-lymphocyte ratio; NR — not reported.
attributable to the unique characteristics of the trials. KEYNOTE-189 was the only trial to have an immunotherapy intervention arm with both pembrolizumab and pemetrexed (13). The PACIFIC trial, which enrolled patients in second-line and later treatment lines, was the only included trial to enroll patients with unresectable stage III NSCLC or to assess either durvalumab or chemoradiotherapy (26). As such, combination therapies like pembrolizumab and pemetrexed as well as durvalumab and chemoradiotherapy ought to be further examined as potential options for immunotherapy treatment of patients who may otherwise be poor responders.

Findings around sex were mixed, reflecting the ongoing debate in the current literature (50). Among the 17 experimental studies reporting data stratified by sex, 10 reported statistically significant improvements with the addition of immunotherapy for males, compared with only 6 for females. However, every experimental study trended toward survival improvement for males with the addition of immunotherapy, even when results did not rise to the level of statistical significance. Results for female patients were less consistent, although trends from most studies did suggest some potential benefit. Notably, the KEYNOTE-189 trial, which uniquely evaluated pembrolizumab–pemetrexed combination therapy, reported especially high survival gains for females (HR = 0.29) that exceeded those seen in male patients (HR = 0.70) (13). Given the different trends for KEYNOTE-189 with regard to both smoking status and sex, this combination may warrant future examination. Most observational studies found no statistically significant difference in survival by sex, although the largest found statistically significantly better survival for females, compared with males, consistent with previous research (51). Although there is uncertainty, one interpretation of these findings is that even if males derive more benefit from immunotherapy than females, the increased benefit is insufficient to overcome the existing female survival advantage (41,51,52). Although a specific mechanism for NSCLC is still unclear, sex hormones such as estrogen and testosterone, which have immunogenic and immunosuppressive properties, respectively, are known to modulate gene expression, immune system agents, and treatment-related adverse effects (53,54). Additional research is needed to further examine moderating factors that may favor positive prognoses by sex. Moreover, only 1 clinical trial had approximately equal enrollment of males and females (21): the rest were at least 59% male, with 6 trials enrolling 70% males or more. Therefore, these results reinforce the need for proper representation of females in clinical trials to better evaluate how sex may affect survival and response to immunotherapy.

Only 5 experimental studies and 3 observational studies provided race information. More data is needed on outcomes according to race in clinical trials, considering recent evidence of differential tumor mutation burden (55,56). Trials reporting outcomes by race were severely underpowered because of their disproportionate underenrollment of non-White patients. Despite representing 13% of the US population, Black patients comprised no more than 4% of any clinical trial. Although in Foster and colleagues’ study (41), non-White patients survived longer than White patients, the classification of non-White makes interpretation difficult and further highlights the need for more diverse, inclusive clinical trials with details on patients’ ethnic and racial backgrounds.

This review highlights several gaps in current research on immunotherapy efficacy. There was uneven reporting of univariate and multivariate hazard ratios among the included observational studies. Even when multivariate hazard ratios were reported, not all studies specified adjustment variables, and no 2 studies used the same set of covariate adjustments. To minimize some of this variation, specific covariates that will be adjusted for in multivariate hazard ratios or adjusted risk

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**Table 8. Association between survival after immunotherapy and sex in observational studies (n = 14)**

| Author, year | Reference | Comparison | Univariate HR (95% CI) | Multivariate HR (95% CI) | Adjustments |
|--------------|-----------|------------|------------------------|--------------------------|-------------|
| Chen et al., 2020 (28)* | Female | Male | 1.05 (0.63 to 1.75) | N/A | N/A |
| Yang et al., 2020 (31)* | Female | Male | 0.71 (0.37 to 1.34) | N/A | N/A |
| Huang et al., 2020 (32) | Female | Male | 1.12 (0.57 to 2.23) | N/A | N/A |
| Nazha et al., 2020 (5) | Female | Male | 1.43 (0.97 to 2.08) | 8.33 (2.5 to 25) | NR |
| Prelaj et al., 2019 (33)* | Female | Male | N/A | 1.06 (0.76 to 1.47) | NR |
| Eltkrief et al., 2020 (34) | Female | Male | N/A | 0.81 (0.58 to 1.12) | Age, smoking, ECOG PS, histology, metastasis |
| Kano et al., 2020 (35) | Female | Male | 0.95 (0.71 to 1.27) | 1.57 (0.94 to 2.60) | N/A |
| Anouti et al., 2020 (36) | Female | Male | 1.12 (0.58 to 2.13) | N/A | N/A |
| Adachi et al., 2019 (37)* | Female | Male | 0.96 (0.74 to 1.27) | N/A | N/A |
| Ahn et al., 2019 (38) | Female | Male | 1.17 (0.75 to 1.82) | 0.527 (0.15 to 1.85) | Age, smoking, prior treatment, mutational status, brain and liver metastasis, PD-L1 expression |
| Lin et al., 2018 (39) | Female | Male | 0.71 (0.37 to 1.34) | N/A | N/A |
| Ng et al., 2018 (40)* | Female | Male | 1.36 (0.86 to 2.16) | N/A | N/A |
| Foster et al., 2019 (41) | Female | Male | N/A | 1.26 (1.19 to 1.33) | NR |
| Lichtenstein et al., 2019 (30) | Female | Male | N/A | 1.13 (0.83 to 1.54) | CCI, initial cancer stage, ECOG PS |

*Progression-free survival. CCI = Charlson comorbidity index; CI = confidence interval; HR = hazard ratio; N/A = not applicable; NR = not reported; ECOG PS = Eastern Cooperative Oncology Group Performance Status.
calculations should be chosen and reported a priori. Establishing a consensus around adjustments will facilitate comparisons between different studies. Lastly, more frequent reporting of interaction terms (i.e., age/sex/smoking status/race*-immunotherapy) in observational studies may allow for more direct comparison with experimental studies and provide more information about effectiveness outside of a clinical trial setting, where male, younger, and healthier patients are frequently overenrolled (57). As such, greater consistency in methodology and reporting of risk calculations can further the understanding of clinical confounders that may contribute to differential survival outcomes, and ultimately, help tailor patient therapies.

To our knowledge, this systematic review is the first to aggregate evidence across both experimental and observational studies and analyze outcomes with respect to multiple personal characteristics, including race. Although head-to-head comparisons with previous reviews are difficult because of differences in inclusion and exclusion criteria and patient populations, many of our findings from observational studies pertaining to age and smoking status align with those in previous reviews of experimental studies (47,58-60).

This review is not without limitations. Because of the heterogeneity in patient populations, immunotherapies administered, and uneven reporting of outcomes, meta-analysis was not possible. Moreover, although there were a couple of national database studies that met all inclusion criteria, most observational studies were retrospective analyses of patient cohorts at individual hospitals. Therefore, some studies may have limited generalizability to the broader patient population receiving immunotherapy. Publication bias toward negative findings is also a concern as both observational studies and clinical trials that fail to identify statistically significant differences or associations are less likely to be published.

Overall, evidence is mixed around which personal characteristics may be associated with increased benefit from immunotherapy treatment in advanced NSCLC. In aggregate, the findings from this review confirm those of previous reviews and individual studies, which suggest immunotherapy may increase survival in younger patients, smokers, and males.

We also highlight gaps in the literature, as very few experimental and observational studies have reported outcomes by race and those which have are severely underpowered. Further research into the moderating effects of race on immunotherapy efficacy can fill this gap while potentially creating more opportunities for treatment of self-identified Black patients with advanced non-small-cell lung cancer. Cancer 2020;126(23):5040-5049.

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