Review Article

Sex dimorphism in response to targeted therapy and immunotherapy in non-small cell lung cancer patients: a narrative review

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Background and Objective: Multiple agents have been developed for treating non-small cell lung cancer (NSCLC). However, patients' response to these therapies vary drastically, which indicates a need to tailor therapy. Sex is a readily usable clinical characteristic that has been shown to impact patients' response to drugs. The main objective of this narrative review is to summarize the current state of knowledge, compiled from meta-analyses, on sex differences in treatment efficacy for targeted therapy and immunotherapy in NSCLC. We discuss the interplay of patient characteristics, both molecular and demographic, with sex on how they impact therapeutic response.

Methods: PubMed search was performed with the term "sex/gender differences" with currently FDA approved targeting therapy and immunotherapy agents in treating NSCLC.

Key Content and Findings: For targeted therapy, women tend to benefit more in terms of progression-free survival upon receiving first-generation anti-epidermal growth factor receptor (EGFR) treatment than men. On the other hand, there is an ongoing debate on sex differences in response to immunotherapy. Although preliminary, whether sex differences were observed depends on treatment settings, patient characteristics, and molecular features. Importantly, incorporating sex as a biological component in the biomarker discovery seems to reveal novel insights in immunotherapy response.

Conclusions: Taken together, sex differences in responding to standard care have been observed in clinical settings for NSCLC patients. A better understanding of sex-associated treatment response and the underlying biology will improve cancer prognosis and eliminate these sex differences.

Keywords: Sex dimorphism; non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); immunotherapy; immune checkpoint blockade (ICB)

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Introduction

The American cancer statistics for the year 2021 ranks lung cancer as the second most common (number of new cases) in men and women and attributes it to one-quarter of all cancer death (1). The majority (85%) of lung cancer patients have non-small cell lung cancer (NSCLC) (2). Despite the alarming statistics, the arrival of targeted therapy and immunotherapy has each been a major breakthrough in improving the NSCLC survival rates. For instance, annual decrease in NSCLC incidence-based mortality has markedly dropped after 2013, the year erlotinib was approved by the U.S. FDA as a first-line therapy for metastatic NSCLC with exon 19 deletion or exon 21 L858R substitution (3). The latest evolution in the NSCLC treatment landscape has been immunotherapy, and the research and development efforts surrounding this treatment strategy are currently ongoing.

A major challenge for these new classes of treatment is the large inter-patient variability in therapeutic response, which highlights the need for better biologic or clinical markers that can improve the ability of clinicians to predict patient response. Among various potential patient factors, sex stands out as an easy-to-use clinical characteristic that can reflect the genetic, epigenetic, and environmental effects influencing the patient (4). Additionally, response to drugs have been reported to differ based on sex (5,6). Therefore, we survey the knowledge in sex difference in NSCLC treatment response. Differences in tumoral features have been found between men and women alongside the difference of incidence, prognosis, and mortality in NSCLC. For instance, women are more likely than men to develop adenocarcinoma while men have higher rates of squamous cell carcinoma and large-cell lung cancer (7-10). Similarly, studies have found sex-based differences in common driver mutations of NSCLC (11,12). The underlying causes of these differences can generally be attributed to internal factors such as genetics, hormone, and immune system, as well as environmental factors such as social behaviors (e.g., smoking) (*Figure 1*). Given that NSCLC is not entirely the same disease between men and women, a better understanding of differences in response to treatment based on patient sex has high potential to improve patient outcome in the future (13). Regulatory authorities' recent efforts to encourage sex-based assessments in clinical trials have produced limited results so far (14). In order to better orient future studies of newer anticancer agents to sex-based personalization of therapies, it is worthwhile to review the existing literature on sex-based difference in the effectiveness of the existing targeting and immunotherapy agents against NSCLC.

In this review, we summarize and discuss reported sex differences in treatment effects (focusing on survival outcomes) in NSCLC patients. We focus on targeted therapy and immunotherapy and outline the evidence on sex differences in response to these treatments in clinical trials. We describe the current knowledge on sex dimorphism in genetic, immunologic, and behavioral factors that may impact the treatment outcomes. With this review, we aim to stimulate further research on the impact of sex as a biological variable on treatment response, with the goal of improving clinical understanding and decision making, We present the following article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-1013/rc).

Methods

We searched published meta-analysis/systematic reviews in PubMed for the following approved targeting therapy and immune checkpoint blockade (ICB) agents in NSCLC. For targeting therapy, we focused on agents that are targeting epidermal growth factor receptor (EGFR), angiogenesis, Kirsten rat sarcoma virus (KRAS), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), B-Raf Proto-Oncogene (BRAF), Ret Proto-Oncogene (RET), MET Proto-Oncogene (MET), Neurotrophic tyrosine receptor kinase (NTRK) (The name of each agent was retrieved from https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell/targeted-therapies.html); for ICB, we focused on agents that target "Programmed cell death protein 1 (PD1)", "Programmed death-ligand 1 (PD-L1)", and "Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA4)". Subsequently, we manually screened the resulting articles for "sex difference", "sex differences", "gender differences" in the title/abstract area to narrow down the articles to be included in our review (*Table 1*).

Sex differences in response to targeted therapy in NSCLC

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs)

The epidermal growth factor receptor (EGFR) is a transmembrane receptor whose activation of downstream signal pathways is involved in several key cellular functions including proliferation, differentiation, and survival (15).

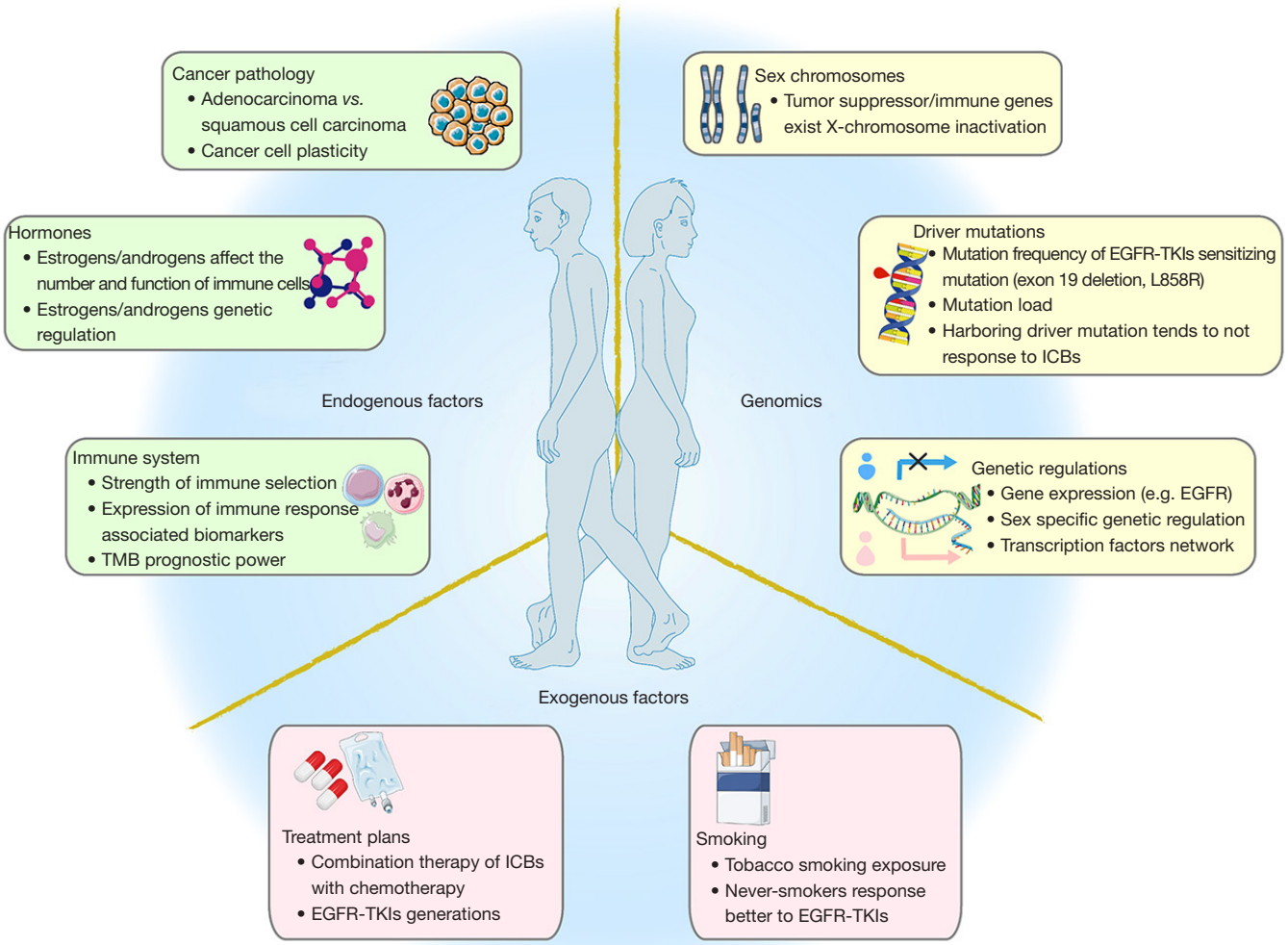

Figure 1 Factors contributing to sex differences in therapeutic response in NSCLC (Acknowledgement: smart.servier.com). Sex differences in drug response are shaped by the shared effect of cancer genomic, endogenous, and exogenous factors. The genetic effects that contribute to observed phenotypic differences between males and females include: Sex chromosomes. For example, tumor suppressor genes and immune-related genes have been reported to exit the X-chromosomal inactivation process, which results in unbalanced gene expression between sexes. Driver mutations. For example, clinically actionable gene mutations, such as *EGFR* exon 19 deletions, have been reported with sex differences in mutation frequency. Sex-specific genetic regulations. For example, the differences in transcription factor (TF) binding, which results in differences of gene expression patterns. Endogenous factors such as disease pathology, hormone, and immune system can influence the clinical drug response. For example, lung squamous cell carcinoma is less responsive to targeted therapy, whereas lung adenocarcinoma, which has more female cases, tends to respond to targeted therapy. Hormones are known to affect immune composition and can contribute to sex-biased gene expression and sex-specific regulatory networks. The strength of the immune system is generally higher in females than males, which can lead to an early selection of the cancer cell population. Exogenous factors such as treatment strategy and smoking history have been associated with sex differences. For example, combination therapies of immune checkpoint blockades (ICBs) and chemotherapy have been reported with female favored response, whereas males respond better when treated with ICBs alone. Females show a better response to the first-generation EGFR-TKIs than males, but the evidence is insufficient for second- and third-generation EGFR-TKIs specifically. Tobacco smoking rate is higher in males compared to females. Never-smokers are reported with better response with EGFR-TKIs than ever-smokers, although worse outcome was reported in these never smokers when treated with ICBs alone. EGFR, epidermal growth factor receptor; TMB, tumor mutation burden; TKI, tyrosine kinase inhibitor.

Table 1 The search strategy summary

Items	Specification
Date of search	No time restriction
Databases and other sources searched	the PubMed website
Search terms used (including MeSH and free text search terms and filters)	Searching terms were described above. A complete searching terms is listed in Table S1
Timeframe	No time restriction
Inclusion and exclusion criteria	Meta-analysis/systematic reviews; no language restriction
Selection process	The co-first authors conducted the conducted the selection independently.
Any additional considerations, if applicable	N/A

NSCLC, non-small cell lung cancer; MeSH, Medical Subject Headings.

Driver mutations that activate or overexpress *EGFR* have been associated with NSCLC as major therapeutic targets (16,17). Among these, exon 19 deletion and L858R substitution in exon 21 are some of the most common examples.

Gefitinib and erlotinib are the first-generation small molecule EGFR tyrosine kinase inhibitors (TKIs) that block EGFR's signaling pathway by competitively binding at the ATP site of its tyrosine kinase domain (18). Both have been approved by the FDA for metastatic NSCLC positive for exon 19 deletion or exon 21 substitution.

Afatinib and dacomitinib are the second-generation EGFR TKIs. Afatinib inhibits the tyrosine kinase domain of ErbB family of receptors (*EGFR 1*, *ErbB2*, and *ErbB4*), and therefore has a wider range of target receptors compared to the first-generation agents (19). Dacomitinib likewise has shown to have inhibitory activity against *EGFR*, *ErbB2*, and *ErbB4* (20). These irreversible covalent inhibitors of EGFR are active against cancers resistant to erlotinib or gefitinib except those with T790M substitution, a major resistance mutation for first and second generation EGFR-TKIs (21).

Osimertinib, a third-generation EGFR-TKI, has been FDA-approved for metastatic NSCLC positive for T790M substitution as well as exon 19 deletion or exon 21 L858R. It is also currently the only preferred agent for treating *EGFR* mutation positive NSCLC in the National Comprehensive Cancer Network (NCCN) guidelines (22). The third generation EGFR TKI has been developed largely to target T790M substitution positive cancers.

Females tend to have better PFS than males in receiving first/second generation EGFR TKIs

Sex differences in response to first generation EGFR-TKIs have been noted in the literature. Chen *et al.* performed a meta-analysis using five randomized controlled trials of first-generation EGFR TKIs as maintenance therapy in comparison with placebo control for stage IIIB/IV NSCLC (two studies with gefitinib and three with erlotinib; a total of 2,436 patients included) (23). The analysis showed that maintenance using first generation EGFR-TKIs provided benefit to both sexes in progression free survival [male: hazard ratio (HR) of progression free survival (PFS) =0.68, 95% CI: 0.55–0.82; female: HR of PFS =0.52, 95% CI: 0.37–0.68] while only females showed statistically significant overall survival (OS) benefits (male: HR of OS =0.91, 95% CI: 0.79–1.03; female: HR of OS =0.73, 95% CI: 0.58–0.89).

Pinto *et al.* performed another meta-analysis on six phase III trials that compared gefitinib, erlotinib, or afatinib to chemotherapy in order to assess any sex-based difference in response to these agents (total 1,425 patients; 931 females and 494 males) (24). While patients of both sexes had statistically significant PFS benefit from EGFR-TKI therapies, the investigators evaluated the size of PFS benefit for each sex and reported that females showed greater PFS benefit (HR of PFS =0.34, 95% CI: 0.28–0.40) than males did (HR of PFS =0.44, 95% CI: 0.34–0.56). However, no interaction test was reported to determine the statistical significance of this observed difference. Another meta-analysis with seven trials (six of which were included in the abovementioned meta-analysis) conducted by Hasegawa *et al.* demonstrated a female-bias in benefits from EGFR-TKI treatments (female: HR of PFS =0.31, 95% CI: 0.23–0.40; male: HR of PFS =0.43, 95% CI: 0.32–0.57) (25). However, a meta-regression analysis conducted by the investigators showed that the observed difference in PFS benefit between the two sexes was not significant (P=0.09).

More recently, a meta-analysis performed by Xiao *et al.*

assessed the efficacy differences of EGFR-TKIs (6 studies on gefitinib, 12 on erlotinib, 2 on afatinib, 1 on dacomitinib, and 1 on icotinib) in OS by sex and smoking status (26). The primary analysis of pooled interaction HRs of sex did not find any significant differences in OS between males and females. However, in the subgroup analysis, women showed significantly greater OS benefit compared to men when EGFR-TKIs were compared to placebo (HR of interaction =0.86, 95% CI: 0.75–1.00). No significant OS difference was observed between sexes when EGFR-TKIs were compared to chemotherapy. Similarly, no sex differences in OS were observed in any other subgroups (e.g., subgroups of specific agents, different lines of therapy, and different *EGFR* mutation statuses). The investigators have attributed this difference to previous findings that suggest better OS response of women to chemotherapy compared to men (27). This suggests that placebo-controlled results should be free of the sex-related confounding effect of chemotherapy. In other words, the subgroup analysis of placebo-controlled results may be considered more representative of the actual sex-based difference in OS response to EGFR-TKIs.

While two of the meta-analyses discussed above include afatinib trials, no meta-analysis has been found to the best of our abilities that specifically looks at sex-based difference in response to any one or both of the second-generation agents. One small retrospective study by Wang *et al.* evaluated 60 Chinese patients with advanced NSCLC with sensitive *EGFR* mutations who received afatinib treatments (28). The investigators found using multivariate cox proportional regression analyses that sex did not significantly affect the PFS of the studied patients regardless of the line of therapy.

Table 2 provides a summary of the meta-analyses included in this review. Overall, a female-favoring trend of sex difference has been observed in NSCLC patients receiving first and second-generation EGFR-TKIs when the treatment effectiveness is evaluated by PFS. Although the significance of the difference has not been evaluated in most of the included studies, the trend appears to be consistent. PFS is more likely to reflect the immediate response to treatment. Therefore, it would be reasonable to suggest that female tend to have a better response to the EGFR-TKIs than male. This trend in benefit difference has not been consistently observed in terms of OS, which reflects a combination of all treatment effects and patient characteristics.

No sex differences in response to third generation EGFR TKIs

Current existing literature does not support sex-based differences in patient response to the third generation EGFR TKIs. Huang *et al.* performed a meta-analysis assessing the efficacy of osimertinib on *EGFR* mutation-positive advanced NSCLC against that of previous generation EGFR TKIs or chemotherapy (32). Analyzing 975 patients over two trials, the investigators showed that, while women (HR of PFS =0.37, 95% CI: 0.30–0.46) had a trend of better response compared to men (HR of PFS =0.51, 95% CI: 0.39–0.67), there was no statistically significant difference (male *vs.* female; P=0.063).

Female sex is associated with higher frequency of EGFR alterations but this observation is confounded by other factors

Sex differences of *EGFR* alterations have been observed in NSCLC patients. Comprehensive analyses from The Cancer Genome Atlas (TCGA) on the molecular level reveal higher mutation frequency and gene expression of *EGFR* in female lung adenocarcinoma (LUAD) patients after controlling for other clinical features (40). This may lead to a higher response rate to the first-generation EGFR-TKIs in female patients. Moreover, there have been several studies showing the potential interplay between patient characteristics and *EGFR* mutations. Midha *et al.* conducted a comprehensive review of the frequency of *EGFR* mutations in patients with LUAD across 14 countries and found that the frequency of *EGFR* mutations was higher in women in all regions analyzed except Bangladesh (11). However, the investigators did not report on individual frequencies of specific mutations for *EGFR*. Similarly, Zhang *et al.* conducted a meta-analysis which revealed higher prevalence of *EGFR* mutations (mostly in exon 19 or 21) in female Caucasian (OR is 2.7, 95% CI: 2.3–3.3) and Asian (OR is 2.8, 95% CI: 2.6–3.1) populations (12). However, no sex-based estimation of the prevalence of specific mutations was provided. A similar observation has been reported in East Asian patients: females show higher frequencies of *EGFR* mutations while males show higher frequencies of *KRAS* and tumor protein P53 (*TP53*) mutations (41).

In addition to ethnicity, Sugio *et al.* showed that, in patients with LUAD, female sex and never-smoker status were associated with higher incidence of *EGFR* mutations (exon 19 deletion or exon 21 L858R substitution) (42). Additionally, exon 21 L858R was significantly more frequent in females and never-smokers. Tanaka *et al.* showed that female sex, smoking history of less than 20 pack-per-year (including never-smokers), and adenocarcinoma or

Table 2 Summary of meta-analyses of sex differences in responding to EGFR-TKIs and ICBs in NSCLC

Study	Total patients	Treatment	Control	Overall pooled HR of PFS (95% CI)	Overall pooled HR of OS (95% CI)	Sex of pooled HR of PFS (95% CI)		Sex of pooled HR of OS (95% CI)		Interaction HR of sex (PFS, 95% CI)	Interaction HR of sex (OS, 95% CI)
						Female	Male	Female	Male		
EGFR-TKIs											
(29)	1,942	Erlotinib	Standard chemotherapy	0.76 (0.70, 0.83)	0.87 (0.80, 0.95)	0.65 (0.55, 0.77)	0.80 (0.73, 0.88)	NR	NR	NR	NR
(23)	2,436	Erlotinib or gefitinib	Placebo	0.63 (0.50, 0.76)	0.84 (0.76, 0.93)	0.52 (0.37, 0.68)	0.68 (0.55, 0.82)	0.73 (0.58, 0.89)	0.91 (0.79, 1.03)	NR	NR
(30)	1,649	Erlotinib or gefitinib or afatinib	Standard chemotherapy	0.37 (0.32, 0.42)	NR	0.33 (0.28, 0.38)	0.45 (0.36, 0.55)	NR	NR	P=0.03	NR
(31)	1,231	Erlotinib or gefitinib	Standard chemotherapy	0.37 (0.32, 0.42)	1.01 (0.88, 1.17)	0.34 (0.29, 0.41)	0.42 (0.33, 0.54)	1.02 (0.86, 1.21)	0.98 (0.76, 1.27)	NR	NR
(32)	975	Osimertinib	Erlotinib or gefitinib/standard chemotherapy	0.38 (0.29, 0.50)	0.66 (0.48, 0.89)	0.37 (0.30, 0.46)	0.51 (0.39, 0.67)	NR	NR	NR	NR
(26)	11,154	Erlotinib or gefitinib or afatinib or icotinib	Placebo or chemotherapy	NR	0.94 (0.89, 1.00)	NR	NR	NR	NR	NR	0.95 (0.87, 1.04)
(24)	1,425	Erlotinib or gefitinib or afatinib	chemotherapy	NR	NR	0.34 (0.28, 0.40)	0.44 (0.34, 0.56)	NR	NR	NR	NR
(25)	1,649	Erlotinib or gefitinib or afatinib	Platinum-doublet chemotherapy	NR	NR	0.31 (0.23, 0.40)	0.43 (0.32, 0.57)	NR	NR	Meta-regression of HRs: P=0.090	NR
ICBs											
(33)	3,144	PD-1/PD-L1 inhibitor plus chemotherapy	Standard chemotherapy	0.62 (0.57, 0.67)	0.68 (0.53, 0.87)	0.60 (0.44, 0.81)	0.65 (0.58, 0.74)	0.32 (0.23, 0.46)	0.69 (0.55, 0.87)	P=0.365	P<0.001
(34)	6,964	PD-1/PD-L1 inhibitor/ CTLA-4 inhibitors plus chemotherapy	Standard chemotherapy	NR	NR	NR	NR	0.89 (0.71, 1.11)	0.72 (0.61, 0.86)	NR	P=0.72
(35)	6,645	PD-1/PD-L1 inhibitor/ CTLA-4 inhibitors plus chemotherapy	Standard chemotherapy	NR	NR	NR	NR	0.72 (0.56, 0.93)	0.79 (0.71, 0.88)	NR	P=0.79
(36)	4,923 (PFS)	PD-1/PD-L1 inhibitor plus chemotherapy	Standard chemotherapy	NR	NR	0.56 (0.49, 0.65)	0.64 (0.56, 0.71)	0.48 (0.35, 0.67)	0.76 (0.66, 0.87)	1.15 (0.96, 1.38)	1.56 (1.21, 2.01)
	2,970 (OS)									Favors greater effect of treatment in women	Favors greater effect of treatment in women
(36)	2,120	PD-1 inhibitors	Standard chemotherapy	NR	NR	NR	NR	0.78 (0.60, 1.01)	0.97 (0.79, 1.19)	NR	0.83 (0.65, 1.06) Favors greater effect of treatment in men
(37)	3,867	PD-1/PD-L1 inhibitors	Standard chemotherapy	0.84 (0.72, 0.97)	0.72 (0.63, 0.82)	1.02 (0.84, 1.23)	0.72 (0.55, 0.93)	0.76 (0.62, 0.93)	0.74 (0.63, 0.87)	NR	NR
(38)	3,025	PD-1/PD-L1 inhibitors	Docetaxel	NR	0.69 (0.63, 0.75)	NR	NR	0.70 (0.60, 0.82)	0.69 (0.61, 0.77)	NR	P=0.82
(39)	1,672	PD-1/PD-L1 inhibitors	Platinum-based chemotherapy	NR	NR	NR	NR	0.84 (0.64, 1.10)	0.59 (0.50, 0.69)	NR	P=0.04

HR, hazard ratio; NR, not reported; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; OS, overall survival; PFS, progression free survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ICB, immune checkpoint blockade; NSCLC, non-small cell lung cancer.

adeno-squamous cell carcinoma histology subgroup were associated with higher frequency of *EGFR* mutations (mainly exon 19 deletion and exon 21 L858R) (43). However, when the confounders were accounted for using logistic regression, the investigators found that histology (adenocarcinoma or adeno-squamous cell carcinoma) and smoking history (less than 20 packs per year), but not female sex, were associated with frequency of *EGFR* mutations. Hsiao *et al.* found similar results when they conducted a logistic regression to analyze age, sex, smoking status, histology, and cancer stage as predictors of *EGFR* mutations (exon 19 deletion or exon 21 L858R) (44). Univariate analysis showed higher OR for *EGFR* mutation with female sex, never smoker, and adenocarcinoma. However, only never smoker and adenocarcinoma (but not sex) were shown to be predictors of *EGFR* mutation frequency in multivariate analysis. Collectively, even though female sex has been reported to be associated with higher EGFR mutation frequency, this association may be the results of the interaction between sex and other confounding clinical characteristics such as smoking status and disease pathology. T790M substitution is a biomarker of resistance to the first and second-generation EGFR-TKIs. Several retrospective studies that analyzed biopsy samples from NSCLC patients revealed no significant sex differences in the frequency of T790M substitution (45-49). Aside from T790M mutation, other genetic alterations, such as $EGFR^{C797X}$, are reasons for drug resistance against EGFR-TKIs (50). However, relevant analysis on any potential sex differences in the frequencies of these alterations is lacking.

Smoking status and sex are independent predictors to the treatment effectiveness of EGFR TKIs

Since current literature supports association of never-smoker status and higher frequency of mutations in exons 18–21 among NSCLC patients, we sought to assess any interplay between smoking status and sex on their impact on EGFR-TKIs efficacy (51,52). Independent of sex, never smokers have been shown to derive significantly greater PFS benefits from EGFR-TKIs compared to smokers (P=0.007), although this difference has not been observed in OS (25,26). Lee *et al.* performed multivariable analyses on four clinical trials to investigate the potential interplay among three patient characteristics (sex, smoking status, and *EGFR* mutation) on their effects on PFS benefit from EGFR TKI therapy (30). Patients with each of the following characteristics had greater PFS benefit from EGFR TKIs compared to those with counterpart characteristics: exon 19 deletion (compared to exon 21 L858R), never-smoker (compared to ever-smoker), and female sex (compared to male sex). The differences in PFS HRs were statistically significant for all three subgroup pairs with or without adjustment for the other two variables, suggesting no significant interplay among them (adjusted P=0.004, P=0.01, P=0.03 for *EGFR* mutation types, smoking status, and sex, respectively; unadjusted P=0.004, 0.02, P=0.02 for *EGFR* mutation types, smoking status, and sex, respectively). In the same study, the investigators found no statistically significant association between *EGFR* mutation type and smoking status (P=0.81) or sex (P=0.81). These findings suggest that the potential mechanism of any PFS advantage in female is independently associated with the *EGFR* mutation, sex, and smoking status.

ALK and ROS1 inhibitors

Although not as prevalent as *EGFR* mutations, *ALK* and *ROS1* rearrangements represent targetable genetic alterations present in about 3% and less than 2% of NSCLC patients, respectively (53). Kinase inhibitors used to target ALK rearrangements, such as crizotinib, ceritinib, and lorlatinib, can also be used against ROS1 rearrangements and are included in both ALK-positive and ROS1-positive treatment algorithms of the NCCN guidelines (54). The current literature lacks evidence either supporting or refuting any sex-based differences in patient outcomes with ALK or ROS1 inhibitors, although one meta-analysis reports similar benefits from ALK-TKIs between males and females based on the results from four trials (two on crizotinib *vs.* chemotherapy and two on ceritinib *vs.* chemotherapy) (24). Additionally, a few studies provide conflicting results on any sex-based difference in *ALK* gene alteration (55-57). More studies are needed before a firm conclusion regarding sex differences to ALK and ROS1 inhibitors can be drawn.

Other targeting agents

For other targeted therapy agents, evidence of sex-based differences in drug response is limited due to their relatively recent entry to the drug development scene as well as the lower mutation frequencies of their target genes. Some sex differences have been reported at the molecular level of those clinical actionable genes. Alterations in the *MET* signaling pathway are able to bypass the inhibition from the *EGFR* pathway, which is a resistance mechanism leading

to disease progression in patients receiving EGFR-TKIs (50,58). Higher *c-MET* amplification has been detected in samples from lymph nodes of male NSCLC patients (28%) compared to female samples (8%), but this is not reflected in the primary tumor sample (59). Alterations on *ErbB2* genes also mediate resistance to EGFR-TKIs, and these mutations are enriched in female NSCLC patients. Out of 224 tumor biopsies, human epidermal growth factor receptor 2 (HER2) mutation was detected in 8 samples, all of which were from female patients (60). In addition, HER2/neu gene expression has been demonstrated as a prognostic factor in female NSCLC patients but not in males (higher HER2/neu expression is associated with worse survival profile) (61). Recently, inhibitors for $KRAS^{G12C}$ mutations, such as adagrasib, have been tested in clinical studies. Nearly half of patients with positive $KRAS^{G12C}$ mutations showed partial response when treated with adagrasib (62). Although the sex differences in response to KRAS-G12C inhibitor have not been reported, female sex (13.6%) is associated with a higher mutation frequency of $KRAS^{G12C}$ than male (10.4%) (63).

Sex differences in responding to immunotherapy in NSCLC

Immune checkpoint blockade

Overview

Since the approval of the first immune checkpoint blockade (ICB) agent, ipilimumab, by the FDA in 2011, immunotherapy has begun to revolutionize the treatment for cancers (64). ICBs are antibodies that can inhibit the interaction of cell surface ligands and modulate the immune response of T cells (65). Anti-cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA4) antibodies such as ipilimumab block the interaction between CTLA4 and CD80/86, which in turn prevents the immune inhibitory effect. Another type of ICB is the anti-programmed cell death protein 1 (anti-PD-1)/anti-PD ligand 1 (anti-PD-L1) antibody. PD-L1 is frequently expressed in immunosuppressive cancer cells, and cancer cells with high expression of PD-L1 exhibit ability to escape the immune surveillance. PD-1/PD-L1 antibodies such as pembrolizumab and nivolumab can block the interaction between PD-1 and PD-L1, thereby reactivating the cytotoxic effect of T cells at the tumor site (65-67).

ICBs, either combined with chemotherapy or as monotherapy agents, have been approved to treat advanced-stage NSCLC without targetable biomarkers (66). However, despite the approval of ICBs in NSCLC, results from phase III trials indicate divergent responses. Randomized controlled trials demonstrate an improved patient survival on pembrolizumab over chemotherapy in treating late-stage NSCLC, while nivolumab is not associated with prolonged PFS compared to chemotherapy (68,69). Such varied response between patients emphasizes the need for effective biomarkers for ICBs. Patient characteristics as well as immune parameters and components have all been investigated in predicting ICBs' efficacy in NSCLC. Among clinical characteristics, negative predictive values for ICBs' efficacy have been established in liver and brain metastases (66). Among many molecular features, positive response to ICB treatment has been associated with high tumor mutation burden (TMB), microsatellite instability (MSI), high PD-L1 expression and percentage of infiltrating CD8+ cytotoxic T cells, and low neutrophil-to-lymphocyte ratio (NLR) in NSCLC patients (70,71). In addition, certain signature mutations have been associated with response to ICBs. For example, *Kras/Lkb1* (*STK11*) mutation has been found to drive the resistance to anti-PD-1/PD-L1 therapy in lung adenocarcinoma (65,72). A combination of immune parameters and components have been reported to strongly predict the efficacy of pembrolizumab (73). By categorizing patients based on TMB and expression of signature genes for inflamed T cells, these new biomarkers reflect both tumor antigenicity and tumor microenvironment. Comprehensive overviews of predictive biomarkers for ICB treatment have been reported (65,70).

Female has better response in combination of ICBs with chemotherapy than male

The debates about sex differences in response to ICBs originated from the conflicting findings from several meta-analyses. In a pan-cancer study, Conforti *et al.* have reported a sex-dependent benefit (P=0.0019) of ICBs in patients with advanced cancers where male patients (HR of OS =0.72, 95% CI: 0.65–0.79) show a better response to ICBs compared to female patients (HR of OS =0.86, 95% CI: 0.79–0.93) (34). This sex difference has not been observed in the subgroup analysis of ICB categories and cancer types. In contrast, Wallis *et al.* have reported that there is no difference in the ICBs' efficacy between sexes; in this analysis, male (HR of OS =0.75, 95% CI: 0.69–0.81) and female (HR of OS =0.77, 95% CI: 0.67–0.88) patients benefitted from ICBs equally (35). The main difference between these two large-scale meta-analyses is the selection of published clinical trials. For example, in Wallis's report, four studies that have been included in Confonti's report

are removed. These four studies show male advantages in OS over females. In order to avoid the introduction of bias, Ye *et al.* have conducted an independent meta-analysis by including clinical trial results mentioned in both meta-analyses (74). No significant differences in the efficacy (HR women/men of OS =1.07, 95% CI: 0.95–1.19) of ICBs have been observed between the two sexes. Interestingly, among all cancers included in the meta-analysis, 6 of 11 NSCLC trials show male advantages in OS while one of the NSCLC trial results indicate a significant benefit of the intervention group in OS in female. In this trial, female patients (HR of OS =0.29, 95% CI: 0.19–0.44) responded significantly better to pembrolizumab plus chemotherapy compared to male patients (HR of OS =0.70, 95% CI: 0.50–0.99) (75).

The treatment design of the intervention group seems to significantly impact whether sex difference in response to ICBs is observed in NSCLC patients. A new meta-analysis conducted by Conforti *et al.* demonstrated a greater benefit from anti-PD-1/PD-L1 ICBs plus chemotherapy in female lung cancer patients than in males (HR men/women of OS =1.56, 95% CI: 1.21–2.01). Furthermore, they found that the sex differential benefits depended on the therapeutic strategy employed. Specifically, female patients saw greater efficacy from combining anti-PD-1/PD-L1 ICBs and chemotherapy compared to male patients (HR men/women of OS is 1.70, 95% CI: 1.16–2.49), whereas male patients tended to benefit more than female patients from anti-PD-1/PD-L1 ICBs alone (HR men/women of OS =0.83, 95% CI: 0.65–1.06) (36). These observations highlight the interaction of treatment setting and sex in the response of anti-PD-1/PD-L1 ICBs in NSCLC. These observations have also been confirmed by another meta-analysis that identifies sex, histology, age, and the type of ICBs as significant predictors of OS for patients who receive combination therapy of anti-PD-1/PD-L1 ICBs and chemotherapy. Female (HR of OS =0.32, 95% CI: 0.23–0.46), non-squamous (HR of OS =0.61, 95% CI: 0.44–0.84) patients who received anti-PD-1 ICBs (HR of OS =0.56, 95% CI: 0.47–0.67) plus chemotherapy tended to have better OS. Significant benefit differences (P<0.001) have been found between females and males (33).

The current clinical guideline suggests the use of anti-PD1/PD-L1 therapy in NSCLC patients with high expression of PD-L1. A Follow-up meta-analysis by Conforti *et al.* confirmed a male-favored response of anti-PD1/PD-L1 monotherapy verse platinum-based chemotherapy in NSCLC patients with higher expression of PD-L1 in cancer cells (HR men/women of OS =0.71, 95% CI: 0.52–0.98; P=0.04), which suggests a sex heterogeneous response even in patients selected for tumors highly responsive to ICBs (39). These findings suggest possible consideration of sex as a stratification variable when deciding a treatment plan involving ICBs.

Smoking status is associated with the ICBs response in NSCLC. Never smoker tends to have limited benefits from ICBs treatment than ever/current smoker. In our review, the Conforti meta-analyses (39) have included mostly smokers and the Empower-Lung trial (76) was conducted only in ever/current smokers. Both studies found sex differences in ICB responses and neither found smoking history to impact these observations. It is worth noting these conclusions may only be applicable in smokers and that smoking is attributed to a more inflamed tumor microenvironment, which might lead to a greater response of ICBs treatments. Moreover, a superior response to chemotherapy was observed in never-smokers (77). This might be in part explained the better response in females when ICBs are given along with chemotherapy.

Sex differences in ICBs biomarkers

The observed sex differences in patient response to ICBs are multifactorial. Indeed, differences between sexes such as immune system, disease types, genetics, and behavioral aspects, as well as the heterogeneity of treatment setting and dose regimen, complicated the consideration of sex as a determinant of ICBs' efficacy. This complication highlights the need to understand the underlying biology attributed to the observed sex differences, which in turn will help optimize treatment choice and utilization in NSCLC patients (78).

Currently, there are limited reports on sex differences in the predictive biomarkers of response to ICBs in the context of NSCLC. By using a combination of TMB and T cell inflamed gene expression profile (GEP), a strong predictor of pan-cancer pembrolizumab efficacy has been established (73). High TMB and GEP signature indicate an active immune response in the tumor microenvironment and are associated with better pembrolizumab response. Interestingly, a higher percentage male patients (42%, 81/191) are categorized in the high TMB and GEP group compared to female patients (26%, 29/111) (79). However, this analysis is not representative of NSCLC, since no NSCLC patients were included in this study. In another study, a slight benefit from anti-PD-1/PD-L1 ICBs has been observed in female NSCLC patients,

although this was not statistically significant. Moreover, APOBEC ("apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like"), which is associated with the immunotherapy response in NSCLC, shows a female-biased trend. No clear differences have been observed in TMB and PD-L1 expression level (74).

Although sex differences are not observed in biomarkers of ICBs, the predictability of those biomarkers may differ between sexes. A significantly better predictability of TMB in ICB efficacy has been observed in female NSCLC patients compared to males. Such sex differences were also observed in the prognostic power of TMB (80). The expression of PD-L1 is another biomarker of response to ICBs and is currently utilized in the NCCN guideline of NSCLC. However, the prediction power of PD-L1 expression shows no difference between sexes (81).

Methods, such as machine learning models, have been reported to forecast the ICBs response in cancer patients. A random forest model consists of 16 patient characteristics that achieved great sensitivity (pan-cancer area under the curve (AUC): 0.79; NSCLC AUC: 0.82) in predicting ICBs response. Sex is one of the input features but contributes less than others in the model. This might be due to the correlation between sex and other features, such as BMI (82). Therefore, it may be clinically inappropriate to only use a singular parameter to categorize patients. Prospective studies that are carefully designed to investigate the predictive power of each parameter as well as its interactions with other factors in determining responses to ICBs are needed to gain a better understanding of what has been clinically observed.

Sex differences in the molecular features of tumor

Sex differences in the immune features of tumor microenvironment have been comprehensively analyzed, and a disease-dependency has been reported (74). For example, more activated CD4 T cells have been observed in melanomas from male patients, whereas female-enrichment of CD4 T cells have been observed in lung squamous cell carcinoma [TCGA- Lung squamous cell carcinoma (LUSC)]. In NSCLC, more female-enriched immune features (such as T cell inflamed GEP, cytolytic activity, CD4 T cells, and CD8 T cells compositions) have been observed in LUSC but not in LUAD. In another study, Conforti *et al.* also observed a stronger structured immune response against NSCLC in females, such as a higher abundance of intratumor plasmacytoid and activated dendritic cells, CD4+, and CD8+ T cells. However, immune-suppressive regulators or cells have also been observed in female NSCLC tumor microenvironments (TME), such as cancer-associated fibroblasts (CAFs) and Myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs). Those negative regulators or cells potential lead to the dysfunction infiltrating T cells in TME, therefore, explained the less response of female NSCLC patients when treated with anti-PD1/PD-L1 monotherapy. On the other hand, lower infiltrating immune cells have been noted in the TME, which might be because of the less antigen presentation to the immune system, one of the potential explanations is that the higher degree of hypoxia in the male TME. Tumors characterized with higher glycolysis/OXPHOS ratio had lower expression of genes that related to the antigen-presenting process, including major histocompatibility complex (MHC) molecules (83). These observations indicate a combined effect of sex, cancer biology, and TME in patient response to ICB treatment. The interplay of these elements needs further elucidation.

Sex differences have been observed in the evolution of tumor immunity. Response to ICBs can be determined by the immune recognition of MHC-presented mutant peptides from cancer cells (67). A reduced presentation of immunogenic peptides can cause cancer cells to evade immune surveillance. In a pan-cancer setting, the tumors in female patients tend to have less visible driver mutations that are presented to the immune system than in male patients (84). This potentially is a consequence of a strong immune selection effect in females, in which cancer cells with visible driver mutations are eliminated by the immune system during the early tumorigenesis process.

TP53 is the most frequently mutated gene in NSCLC. A recent report demonstrated sex differences in immune features when patients were stratified by *TP53* mutation status (85). The tumor microenvironment of female LUAD patients with wild-type *TP53* is enriched with immune signatures of INF-gamma and lymphocyte infiltration as well as the dominant M1 macrophage population in comparison to male patients with wild-type *TP53*. Such differences are not observed in *TP53*-mutated LUAD patients. On the other hand, PD-L1 shows higher expression in the mutated *TP53* LUAD tumor. However, no significant difference is observed between sexes. These findings correspond with the survival advantage seen in female wild-type *TP53* LUAD patients. In contrast, different results are observed in LUSC patients. Mutated *TP53* is dominant in this pathological subtype. Immune

signatures (such as INF-gamma and lymphocyte infiltration) and better prognosis have been observed in female *TP53*-mutated LUSC patients compared to males. Although these observations do not necessarily correlate with therapeutic response to ICBs, this work emphasizes the importance of considering sex when stratifying patients using molecular markers and histological subtypes.

A crosstalk between sex chromosomes and *TP53* pathway genes has been reported in the pan-cancer setting (86). Non expressed mutations (NEMs) in X chromosomes emerge more frequently in females than in males, and a high incidence of NEMs belongs to the p53-network gene set, such as E3 Ubiquitin Protein Ligase 1 (*HUWE1*), ATP-dependent helicase ATRX (*ATRX*). This further indicates a female-biased protective effect that restricts the expression of somatic mutations.

Conclusions

Sex differences of cancers have been well documented in terms of both incidence and mortality through comprehensive epidemiological research (87). However, sex differences in treatment response, which heavily impact the survival outcomes of cancer patients, are reported sparsely. In NSCLC, the critical roles of targeted therapy and ICBs as first/second-line treatments have been well established (88). Despite reported sex-differences in drug response, such as female patients being more likely to benefit than males from EGFR-TKIs, the implementation of sex as a factor to stratify patients prior to treatment is rare in current practice. In this review, we summarized the existing clinical evidence of sex differences in therapeutic response of NSCLC patients to targeted therapy and ICBs. We observed a trend of better survival response from female NSCLC patients with first-generation EGFR-TKIs but no clear sex differences in response to second- or third-generation EGFR-TKIs specifically. Confounding effects from behaviors and ethnicity have also interplayed in the sex differences of response to EGFR-TKIs. In regard to ICBs, conflicting results have been observed among meta-analyses (34,35). Sex differences in response to ICBs are impacted by each patient's disease-context, clinical characteristics, and treatment options (33). Greater benefits have been observed in female patients when combining ICBs with platinum-doublets, whereas greater benefits have been observed in males when ICBs were given without chemotherapy (36,39). These results indicate that sex interplays with other patient characteristics and that singularly investigating each factor is not the best way to understand the underlying effects of this interplay. More robust evidence is needed to confirm sex as a clinical ICBs efficacy stratification factor/biomarker in treating NSCLC.

Overall, sex differences in therapeutic response have been recognized in clinical settings for NSCLC patients. Although differences in molecular features have been discovered and may explain at least partially the observed sex differences, the evidence only covers a handful of drugs. Careful and comprehensive genetic examination can provide insights on intrinsic biological interpretation for the role of sex in drug response.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-1013/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-1013/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Searching terms

Term 1	In		Term 2	In
Targeting Therapy				
Bevacizumab	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Ramucirumab	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Sotorasib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Adagrasib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Erlotinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Afatinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Gefitinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Osimertinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Dacomitinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Amivantamab	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Mobocertinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Crizotinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Ceritinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Alectinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Brigatinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Lorlatinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Entrectinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Dabrafenib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Trametinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Selpercatinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Pralsetinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Capmatinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Tepotinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Larotrectinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
Entrectinib	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
ICBs				
PD1	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
PDL1	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]
CTLA4	[Title/Abstract]	AND	Sex difference/Sex differences/Gender differences	[Title/Abstract]

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