

# Sex-based heterogeneity in non-small cell lung cancer (NSCLC) and response to immune checkpoint inhibitors (ICIs): a narrative review

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**Objective:** The aim of our review is to analyse sex-based differences in advanced non-small cell lung cancer (aNSCLC) patients in terms of clinical-pathological and molecular features, focusing on their impact on immune response and outcome.

**Background:** Lung cancer (LC) remains the leading cause of cancer mortality both in men and women worldwide. In the era of precision oncology, the idea of unleashing the host immune system against cancer through the development of immune checkpoint inhibitors (ICIs) radically shaped the therapeutic approach in the setting of non-oncogene addicted aNSCLC. Despite durable remissions and prolonged survival in a subset of patients, potential markers for individual prediction of immunotherapy effectiveness lacked high sensitivity and specificity. The selection of patients who could most benefit from single ICIs remains an unmet need, as well as the improvement of combination strategies for those one unresponsive or refractory to immunotherapy. Sex is a known variable that affects both innate and adaptive immune responses, as well as possibly clinical-pathological and molecular basis of LC. Although smoking is the primary risk factor for LC development in both men and women, other variable such as genetic differences, sex hormones, environmental exposures and lifestyle habit, immune system and tumor microenvironment (TME) disparities, could play an important role in sex-biased carcinogenesis and development of immune responses.

**Methods:** An extended review of literature through PubMed was conducted, using the keywords related to patient sex (“sex”, “gender”, “male/female”, “men/women”) and NSCLC and LC epidemiological, etiological, clinical-pathological and molecular features.

**Conclusions:** Women *vs.* men differences in terms of response to ICIs remain to date only suggestive, so further research, including prospective clinical trials, is warranted to establish sex as a factor in the therapeutic decision-making process.

**Keywords:** Sex; non-small cell lung cancer (NSCLC); immune checkpoint inhibitors (ICIs); immune response; tumor microenvironment (TME)

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## Introduction

Lung cancer (LC) is still the leading cause of death by cancer worldwide for men and women, with over 2.2 million new cases diagnosed each year (11.4% of total cancer cases) and 1.8 million deaths (18% of total cancer deaths), confirming it the second most frequent cancer and first cause of cancer-related death in men and women combined in 2020 (*Figure 1*) (1). The 5-year survival of LC reported by the Surveillance, Epidemiology, and End Results (SEER) program in 2011 was 15.6% and in 2019 19.4% (2). Non-small cell lung cancer (NSCLC) accounts for about 85 percent of LCs, with nearly 60% of patients with NSCLC presenting in advanced stages of disease not eligible for radical-intent treatment (1). During the last few decades, management of patients affected by advanced NSCLC (aNSCLC) has dramatically improved mainly due to the introduction of targeted therapies and immune checkpoint inhibitors (ICIs) (3,4). In the setting of non-oncogene addicted aNSCLC, a deeper understanding of the immune cycle control and the discovery of anti-programmed death-1/anti-programmed death-ligand 1 (anti-PD-1/anti-PD-L1) antibodies led to clinically significant improvement in terms of survival, safety and quality of life (5,6). Currently, potential markers for individual prediction of immunotherapy effectiveness lacked high sensitivity and specificity. The selection of patients who could most benefit from ICIs remain crucial, as well as the development of combination strategies for those one unresponsive or refractory to immunotherapy. Furthermore, the optimal treatment duration of ICIs has yet to be clearly defined (7).

The aim of this review is to analyse sex-based differences

in aNSCLC patients in terms of clinical-pathological and molecular features focusing on their impact on immune response and outcome. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/pcm-21-7>).

## Review methods

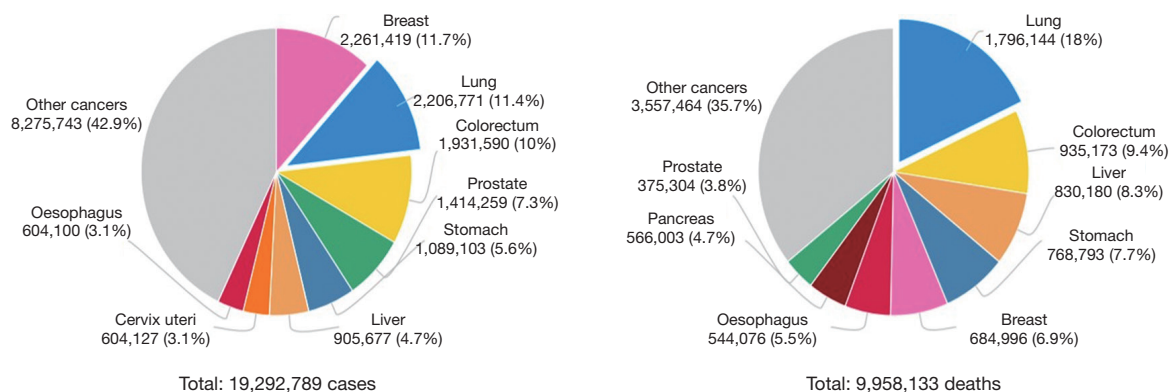
An extended review of literature through PubMed was conducted, using the keywords related to patient sex (“sex”, “gender”, “male/female”, “men/women”) and NSCLC and LC epidemiological, etiological, clinical-pathological and molecular features. Data collection has been evaluated in order to delineate differences between men and women, highlighting the available level of evidence, when necessary. In the second part of the review, we looked for potential heterogeneous efficacy of ICIs treatments in men *vs.* women patients diagnosed with aNSCLC.

## Sex-based heterogeneity in NSCLC patients

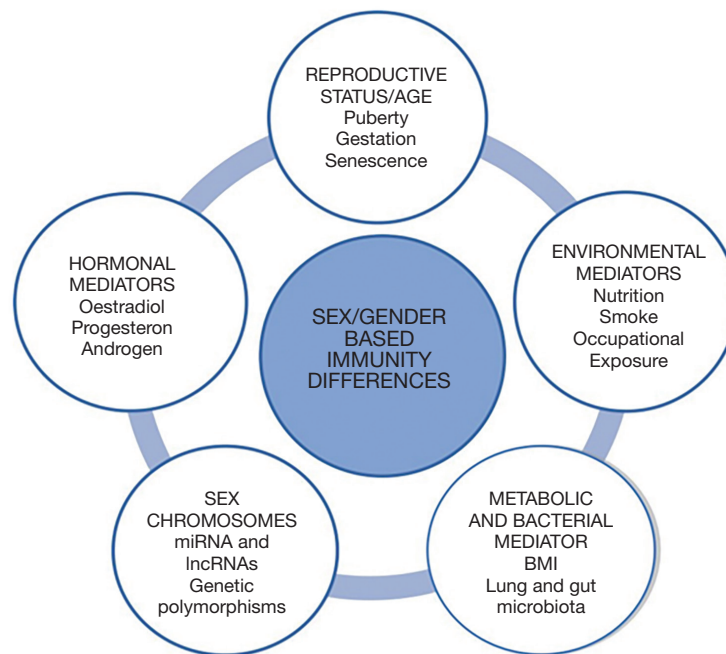
### Epidemiology

The lifetime probability of being diagnosed with malignancies is slightly higher for men (40.1%) than for women (38.7%). Overall, the chance that a man will develop LC in his lifetime is about 1 in 15, while for a woman the risk is about 1 in 17 (8).

Worldwide, female breast cancer is the most commonly diagnosed cancer (11.7% of total cases), closely followed by lung (11.4%). LC is the most common cancer in men with 14.3% of new cases, while the third most common cancer in women with 8.4%, behind breast and colorectal



**Figure 1** LC incidence and mortality statistics worldwide by GLOBOCAN 2020. (A) Number of new cases in 2020, both sexes, all ages; (B) number of deaths in 2020, both sexes, all ages. LC, lung cancer.



**Figure 2** Putative mediators differently expressed in M and F and influencing the immune-system. The differences in the immune system features existing between M and F could be a consequence of various kind of mediators differently expressed in the two sexes, mediators that resulted functionally connected to each other. BMI, body mass index; miRNA, microRNA; lncRNAs, long non-coding RNA; SHS, second-hand smoke.

cancers. LC remains the leading cancer killer considering all cancer-related deaths (18%), but among women breast cancer represents the principal cause of cancer death (15.5%) followed by LC (13.7%) (1). Incidence and mortality rates are roughly 2 times higher in men than in women, although the male-to-female ratio varies widely across regions, ranging from 1.2 in Northern America to 5.6 in Northern Africa. LC incidence and mortality rates are 3 to 4 times higher in transitioned countries than in transitioning countries, but this pattern may well change as the tobacco epidemic evolves given that 80% of smokers aged  $\geq 15$  years resided in low-income and middle-income countries in 2016 (9). Development of tobacco-control policies has led to a decline in the prevalence of smoke habit earlier in men *vs.* women, and thus to a continuous decreasing in LC mortality rate, but more pronounced in men *vs.* women (10,11).

According to the Italian Cancer Registry (AIRTUM), in Italy LC is much more frequent in men with one in 10 *vs.* one in 35 in women of risk of developing this specific cancer. Lung represents the second most frequent primary cancer site in male patients behind prostate (14.1% of new

cases), while the third one in female patients behind breast and colorectum (7.3% of new cases). Moreover, LC is the leading cause of cancer-related death in men (23,928 deaths, 23.9%), while among women it is breast cancer (16.1%), followed by LC (9,976 deaths, 12.5%). Interestingly, among women, the increase in LC incidence is confirmed, probably according to the greater smoking habit of women than in the past: specifically, it has been established a decrease in LC incidence in men (-6.5% compared to 2019) and an increase one in women (+2.5% compared to 2019) (12).

### **Risk factors**

Males and females are possibly differently predisposed to develop LC, due to a series of distinct and/or unbalanced risk factors (Figure 2) (13).

### **Smoking habit**

Tobacco smoke continues to be the primary risk factor for LC development: the chance in long-term smokers has been estimated as 10- to 30-fold compared with never-smokers, moreover risk is proportional to the quantity

of cigarette consumption, and important factors include the number of packs per day smoked, the age of onset of smoking, the degree of inhalation, the tar and nicotine content of cigarettes and use of unfiltered cigarettes (14). The World Health Organization (WHO) estimates that 20.2% of the world's population aged  $\geq 15$  years were current smokers in 2015, indicating that smoking rates have decreased by 6.7% globally since 2000 and by 4.1% since 2005. From 2000 onwards, this decreasing trend in smoking rate was registered for both sexes, being faster in men than in women, and equal to  $-0.22\%$  for year in women and  $-0.50\%$  for year in men in the period 2010–2015. Nevertheless, smoking remains globally far less common among adult females (6.4%) than among males (34.1%) (9).

A combination of physiological, but also behavioral and cultural factors may contribute to these differences. The counter-proof is represented by the spread of smoking depending on countries. Nowadays female smoking behavior in fact is dominated by higher prevalence in the Americas and European regions, where the differences with males have progressively decreased over time. The prevalence of smoking in American women peaked in 1965 at 33% and begins to slowly decrease only in 1980, while more than half of American men smoked before 1965 with a dramatically decreasing prevalence during the subsequent 20 years (15). Currently, 12.2% of American women smoke cigarettes compared with 15.8% of men (16). Similarly, in Europe the age-standardized prevalence of tobacco smoking has decreased more slowly in women *vs.* men in the last decades, and forecasts the period 2010–2025 confirm this trend (17).

Among non-smoker patients with LC, women are approximately 20% and seem to prevail over men, with second-hand smoke (SHS) possibly being one of the reasons why. Women living with a smoker partner have a 25–29% increased risk of developing LC (18).

### Environmental exposures and diet

Besides tobacco habit, smoking-related lifestyles as well as environmental or occupational exposures are differently expressed between men and women, thus representing possible risk factors for LC related to sex (19–22).

Asbestos, arsenic, radon, polycyclic aromatic hydrocarbons (PAHs), cadmium, nickel, metal dusts and vinyl chloride exposures are recognized as lung carcinogenic (23). PAHs produced by indoor burning of cooking oil and biomass fuels in poorly ventilated areas might be a relevant risk factor for

LC. This effect is common among East and South Asian women, but became progressively relevant in all developing countries (24), with lung microbiota (LM) being recognized as a potential etiopathogenetic factor in females LC attributed to household coal burning exposure (25).

Dietary patterns seem to influence LC risk differently by sex. Vitamin C, folate, and carotenoids appear to be protective, while total fat, monounsaturated and saturated fat are associated with LC in men after adjusting for age, education, cigarettes/day, years smoking, and total energy intake (26). Diet did not appear as a major risk factor for LC among women. Nevertheless, in the special subset of never-smoker patients with LC, a sex-independent protective effect was suggested for vegetables/carrots and a deleterious one for cultured milk products, while milk resulted a risk factor only among male high-consumers (27). An inverse association between body mass index (BMI) and LC was observed in men but not in women after adjustment for age and smoking, according to a case-control study based on the results of community mass screening (LC =363, control subjects =1,089) (28). Recent studies showed that certain respiratory microbes and microbiota dysbiosis could correlate with LC development (29), and that sex might influence LM composition after external stimuli exposure (30). However, the possible impact of sex-biased LM in LC risk has to be demonstrated.

### DNA adducts and DNA repair systems

Interestingly, sex differences on molecular/genetic levels also suggest a distinctive sensitivity of women toward tobacco-specific carcinogens as compared to men. Tobacco smoke contains a multitude of carcinogens belong to multiple chemical classes, which exert their biologic effect through the formation of DNA adducts in lung tissue. Most carcinogens require a metabolic activation process, generally catalysed by cytochrome P-450 enzymes (P-450s), to oxidize the hydrocarbons, producing reactive oxygen species or intermediates, later neutralized into water soluble conjugates. Reactive intermediates that are not detoxified bind DNA into DNA adducts, playing a role in lung carcinogenesis (31). The balance between metabolic activation and detoxification of carcinogens varies among men and women and may affects LC susceptibility: in particular, it has been hypothesized that women are more susceptible to tobacco carcinogens than men. Estrogen receptors (ERs) are present in both normal and neoplastic lung tissues and could accelerate the metabolism of tobacco carcinogens in a dose-dependent

way, as suggested by higher levels of PAH-related DNA adducts in female smokers compared to males (32). Inherited genetic polymorphisms affecting activating and detoxifying enzymes could explain a different susceptibility between sexes to tobacco carcinogens.

Female smokers have a higher expression of cytochrome P-4501A1 (CYP1A1) genes in the lungs than males, resulting in greater carcinogen activation, and this increased expression might be hormone induced (33). A cross-talk between ERs and the aryl hydrocarbon receptor, a regulator of CYP1A1, has been demonstrated in breast cancer cell lines (34). Additionally, several studies have shown that women have higher levels of DNA adducts than men (35). Ryberg *et al.* have described that among women the DNA adduct levels were higher than in men when adjusted for smoking dose: they found a highly significant difference in the distribution of men and women when smokers were divided into quartile groups according to adducts per pack year, indicating that women are at greater risk of tobacco-induced LC (36). This may confirm that women are at greater risk of tobacco-induced LC.

The most common gene involved in neutralizing adducts is glutathione S-transferase M1 (GTSM1). A GTSM1 homozygous deletion (GTSM1 null) genotype, which is present in 40–60% of the general population, results in the accumulation of free radicals and carcinogenic metabolites. Women exhibit a more prominent polymorphism in GTSM1 null genotype gene deletion induced, which increases the risk for smoking-related cancers (37). Polymerase chain reaction analysis of peripheral blood indicated that women had a greater cancer risk than men [odds ratio (OR), 4.98 *vs.* 1.37], if they harbor a mutant *CYP1A1* genotype. The absence of a functional GTSM1 enzyme alone was not associated with an increased risk of LC, but the *CYP1A1* mutation and the GTSM1 null genotype are significantly more frequent in female cancer patients than female controls. The combined variant genotypes conferred an OR of 6.54 for LC in women compared with 2.36 in men. This risk was not affected by age or by smoking history (38,39). Moreover, preclinical data suggest that women have lower DNA repair capacity than men, resulting in a deficit in the DNA repair systems which is associated with an increased risk of LC (40).

Furthermore, relevant mutations which may be caused by tobacco carcinogens were found more frequently in women than in men. Studies have shown that tumor protein p53 (*TP53*) is mutated in over two-thirds of LCs, and that genetic alteration is more frequently found in female patients (41–43).

Moreover, mutations in RAS family genes occur in 35% of patients with LC and in particular aNSCLCs show a mutation rate of 35–50%, that results higher in mucinous lung adenocarcinoma (ADC) (44). The mutations are significantly associated with smoking and the resulting DNA adduct formation. Interestingly, mutations are found more frequently in women and younger patients (45–47).

Several studies have focused on sex differences in LC risk for smoking subjects, but data are inconsistent. Risch *et al.* has been the first to hypothesize that women, dose for dose, are at higher risk sensitivity than men: it was found that the OR for women was almost three times greater than that for men (27.9 *vs.* 9.6), when smokers with a 40 pack-year smoking history were compared to non-smokers (48). Then, other case-control and absolute risk cohort studies about sex differences support the theory of higher female susceptibility to tobacco-related LC as well (49–53). On the contrary, other case-control and cohort studies have found either no sex difference or a higher rate ratio among men (54–60). Discrepancies among studies might be linked to variation in study design, the definition of smoking exposure, estimation of risks and the use of never smokers or light smokers as the reference category in the analysis.

### Sex hormones

Gubbels Bupp *et al.* analysed the age- and sex hormone-related changes to innate and adaptive immunity, highlighting their importance in the immune system and the subsequent impact on autoimmunity, cancers, and also on the efficacy of vaccination and cancer immunotherapy. The male higher cancer incidence and mortality before menopause has been at least partially attributed to the protective effect of estrogen, linked to enhanced immunosurveillance, as well as tissue-specific effects (61). The anticarcinogenic and pro-apoptotic effect of estrogen might be the results of the interaction with ER $\beta$  isoform and/or a consequence of the blood estrogenic level. Oestrogens modulate immune cell function following a threshold effect: physiologic doses of estrogen (approximately 0.5 nmol/L) stimulate inflammatory cytokine production, but supraphysiologic doses (above 50 nmol/L) can depress immune response. Thus estrogen interaction with anticancer surveillance depends on a series of variables, including patients' sex, age and their blood levels. Estrogens upregulate the inhibitor signal of PD-1 on effector T cells (Teffs) and CD4+CD25+Foxp3+ regulatory T cells (Tregs), thus contributing to repress antitumor immune responses. Findings from murine melanoma cell lines revealed that sex impacts on tumor immunopathogenesis and

immunotherapy responses through differential Treg function and B7-homologue 1 (B7-H1) signaling (62). B7-H1 is a co-signaling molecule abundantly expressed on APCs and other immune cells, that contributes to tumor immune evasion and to induced Treg function. As regard specifically LC, ERs are often expressed by LC cells, thus possibly influencing tumor growth (63). Hormone replacement therapy seems to increase incidence of, and mortality from LC (64), while anti-estrogen use was found to correlate with a reduced risk of LC incidence in women (65). Physiologically blood estrogen level is normally higher in females than males, but ERs are expressed on LC cells of both sexes. However, estrogens seem to activate lung ADC cell lines derived from women, but not from men (66,67). ER $\alpha$  and ER $\beta$  are two types of classical ERs, with the latter appearing to be commonest on LC cells (68). The prognostic value of ER $\alpha$  rather than ER $\beta$  and of their location on LC cell (cytoplasm/nucleus) remains unsolved, and possibly depending by patient's sex (63). The role of androgenic steroid on LC carcinogenesis is even more misunderstood.

In a murine lung model, androgens exert their effect by binding on androgen receptor (AR), expressed by type II pneumocytes and bronchial epithelium (69). Androgens altered lung gene expression profiles (GEP), by up-regulating transcripts involved in oxygen transport and down-regulating those responsible for DNA repair and recombination. This cytotoxic effect partially explains the carcinogenic effect of androgens, that might reside also in the immune-suppressive action of testosterone, already demonstrated in different immunological disorders (70). Testosterone level has been found to be associated with LC risk, according to a population-based cohort study on men aged 70–88 years (n=3,635), even after adjustment for smoking status (71). Thus, androgens might promote LC origin, but also be involved in LC progression. It is striking in this sense the finding coming from a retrospective analysis (n=3,018) by which androgen deprivation therapy resulted of benefit on survival after LC diagnosis [hazard ratio (HR), 0.36; P=0.0007] (72).

### ***Clinical-pathological and molecular features***

LCs are classified into two major classes: small cell lung carcinoma (SCLC) and NSCLC. The latter, which is the predominant type, includes histologic subtypes such as squamous cell carcinoma (SCC), large cell carcinoma (LCC) and ADC. SCC, SCLC and LCC rates declined since the 1990s for both sexes, but less rapidly among

females according to changes in smoking habit and cigarette manufacturing (73). Since then, ADC became the most common subtype of LC both in men and women worldwide (74,75). In last decades in most countries ADC rates remained relatively constant in males, while it increased in females (76,77). The subset of lung ADC once recognized as bronchoalveolar carcinoma (BAC) disproportionately affects women (78) but, since the latest WHO classification of LC discontinued the term BAC in favor of “lepidic” (79), no data is currently available about sex-difference incidence in lepidic ADC subtype; not even any valid information about men-women disparities in other ADC subtypes (acinar, solid, papillary, micropapillary) exists. SCLC and SCC histology are typically linked to a heavy smoke exposure, while approximately 10–15% of lung ADC is diagnosed in never-smokers. Near 50% of women diagnosed with LC are never-smokers compared with 15–20% of men, and this proportion is even higher in Asiatic female population (80–83).

As mentioned above, molecular characterization of LC from women reveals a higher mutational frequency in some driver genes, such as *TP53* and *KRAS* (21,84,85). *TP53* alterations are associated with increased cancer risk and earlier age at first-cancer diagnosis for females compared to males; female carriers have a 2.5- to 7-fold higher odds of having cancer than male carriers (86). Moreover, specifically in NSCLC, the frequency of G to T transversion mutation on *TP53* is higher among females than males (40% and 25% respectively) (42). LC from smokers shows a distinct *TP53* mutation spectrum, such as G to T transversions at codons 157, 158, 179, 248, and 273, which are uncommonly observed in never-smokers (87,88). Indeed, in smokers, 43% of the mutations were G to T transversions, but this number dropped to 13% in never-smokers (89). Another analysis reported that the difference of *TP53* mutational spectrum between never-smokers and smokers was detectable only in women (42,90). *TP53* mutations in female never-smokers with ADC were predominantly transitions (83%), while they consisted predominantly in transversions (60%) and deletions (20%) in smokers (43). As regard *KRAS* mutation, Nelson *et al.* reported a significant association between this genetic alteration and female sex in lung ADC tissue after adjustment for carcinogen exposures [OR, 3.3; 95% confidence interval (CI), 1.3–7.9], with mutations found only in smokers. Authors suggested a possible role of estrogen exposure in either the initiation or the selection of *KRAS* mutant clones in ADC (45). In addition, a large study by Dogan *et al.* genotyped 3,026 lung ADCs showing that *KRAS* G12C, typically associated with smoke habit,

was more frequent in women ( $P=0.007$ ). These women were younger than men with the same mutation (median 65 *vs.* 69 years old,  $P=0.0008$ ) and smoked less than men (87). The higher frequency of *KRAS* G12C in women, their younger age, and lesser smoking history support a higher susceptibility to tobacco carcinogens. More recently *KRAS* G12C mutation was found to occur more often in Caucasian females than in males with NSCLC (OR, 1.4; 95% CI, 1.3 to 1.6;  $Q<0.001$ ), and similarly in Asiatic population (OR, 5.2; 95% CI, 1.9 to 17.9;  $Q=0.01$ ) (91). The detection of *KRAS* G12C mutation have acquired a therapeutic implication, with encouraging results of targeted therapies against solid tumors harboring this one (92,93).

Generally, the presence of most relevant driver mutations in NSCLCs is more common in never or light smokers and female patients. Tumor molecular characterization and the subsequent identification of driver mutations allow the development of personalized molecular targeted therapies and improvement in NSCLC patients' outcome and prognosis. Female tumors more frequently carry out targetable alterations, such as mutation of epidermal growth factor receptor (EGFR) (94,95), human epidermal growth factor receptor 2 (HER2) (96) or serine/threonine-protein kinase B-RAF as well as rearrangement of proto-oncogene 1 receptor tyrosine kinase (ROS1) (97,98) and anaplastic lymphoma kinase (ALK) (99), even though some discordant data are available on ALK prevalence in females (100,101).

On the other hand, pathogenic mutations of serine/threonine kinase (STK11), RNA-binding protein 10 (RBM10) and SMARCA4 have been reported more frequently in lung ADC samples from males (102); however, none of these mutations is currently targetable by available drugs.

Tumor mutation burden (TMB) acquired increasing relevance in NSCLC, because of their potential predictive value of response to immunotherapy, being an indirect measure of tumor antigenicity generated by somatic tumor mutations (103). LC has a very high rate of somatic mutations when compared to other tumors; 8.7 mutations per megabase in ADCs and 9.7 in SCC are reported (104). Even if TMB do not correlate with PD-L1 expression, they both emerged as key biomarkers of sensitivity to ICIs.

Sex difference in TMB has already been reported in patients affected by cutaneous melanoma, and a more recent next-generation sequencing (NGS) analysis in NSCLC tumor samples confirmed a lower TMB in females than males. In particular, TMB resulted higher in males and 10-fold higher in smokers than in never-smokers (105,106). This correlates with the consistently lower TMB observed

in NSCLC harboring most oncogenic drivers such as alterations of EGFR, ALK, ROS1, BRAF-V600E and MET exon 14 genes, with the exception of BRAF non-V600E and *KRAS* mutant tumors (107). Wang *et al.* reported that the predictive value of TMB in LC treated with immunotherapy could be sex-oriented, being more significant in women *vs.* men (108).

Moreover, males and females own some differences in NSCLC immune-genes (109) and microRNA (miRNA) expression (110), but at the moment it is unknown whether these properties have a predictive/prognostic value.

### *Immune system and tumor microenvironment (TME)*

The immune system differs between males and females: women have stronger innate and adaptive (humoral and cellular) immune responses when compared to men, and this is the results of variety in genetic and epigenetic regulators (sex chromosome), sex hormones (androgens, estradiol and progesterone), microbiome and social factors (smoke and alcohol behaviors) (111).

Females have an immune system that acts predominantly by T helper (CD4+) response, specifically with a humoral response (112). Hormone receptors are present in many cells of immune system: especially ERs are expressed in macrophages, lymphocytes and dendritic cells, while progesterone receptors are also detected in the natural killer cells. On the other side, males' immune system mainly works through a cytotoxic action, with a higher number of T CD8+ lymphocytes and a lower CD4+/CD8+ ratio than females (113,114). The estrogenic signaling partly contributes to the female greater polarization of macrophages towards those called M2-like (115). These alternatively activated macrophages favor cell proliferation and tissue repair, while M1-like classical activated ones' express high levels of major histocompatibility complex and pro-inflammatory molecules, playing a central role in cellular death of cancer cells. This could become quite challenging in cancer patients, as macrophages orientation in the host could influence his benefit from a ICIs therapy. Some of the discrepancies in immune responses distinguishing males from females and vice versa may be secondarily to sexual hormones action. A pro-TME (116) may be promoted in females by the redundant pathway of 17 $\beta$ -estradiol (E2), even though a gain in PD-L1 increased expression (117). Th1-derived interferon gamma (IFN $\gamma$ ) cytokines response was found to be higher in males than in females, after T cells exposure to sex hormone stimulation (118).

These findings about male *vs.* female immune compartment do not translate in immediate therapeutic implications for cancer patients, the major limitation is that data derives mainly from healthy patients or from patients affected by non-oncological diseases.

The aforementioned M2-oriented macrophage differentiation tracked down in females has not been confirmed in cancer patients; according to a small experience investigating tumor associated macrophages (TAM) in NSCLC patients, TAM features do not differ by sex (119).

Nor studies about any sex-biased in tumor PD-L1 expression have been conclusive to date. By binding to the Treg receptor PD-1, PD-L1 play a key role in cancer immune cycle by promoting self-tolerance and down-regulation of T-cell inflammatory activity (120). Sex resulted to be not correlated with PD-L1 expression according to a meta-analysis of nine studies involving solid cancer patients (n=1,550) (121), and subsequent experiences agreed in this sense (122-124). A larger and more recent meta-analysis of 52 studies showed male sex as associated with PD-L1 expression (OR, 4.8; 95% CI, 3.2–7.2; P<0.001) (125). Discordant findings came from other studies, by which PD-L1 levels are significantly higher in women *vs.* men affected by solid tumors, including NSCLC (126-128).

Nevertheless, some experiences suggest possible sex-biased in tumor-infiltrating immune cells (TIICs) composition across solid cancers, including NSCLC (129). Recently, TIICs analyses of samples from advanced melanoma patients, partially exhausted cytotoxic T lymphocytes [i.e., tumor-infiltrating CD8+ T cells expressing high levels of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and PD-1] has been found much more in men *vs.* women (130).

The increasing interest on this topic led recently to comprehensive analyses from The Cancer Genome Atlas (TCGA), that revealed divergent patterns for sex bias in immune features across multiple cancer types. For example, women with SCC had higher than men levels of biomarkers, including cytolytic activity (CYT), GEP, relative richness of activated CD4+ and CD8+ T cells and T cells, 20 out of 34 immune checkpoints and T cell receptor (TCR) abundance. On the counterpart the aneuploidy scores appear lower than in SCC sample of male patients. Surprisingly, female-bias was observed for both inhibitory checkpoints [PD-1, lymphocyte activating 3 (LAG3), CTLA-4, adenosine A2a receptor (ADORA2A)] and stimulatory immune checkpoints [e.g., tumor necrosis factor receptor superfamily member 4 (TNFRSF4), TNF superfamily member 4

(TNFRSF4), inducible co-stimulator (ICOS), tumor necrosis factor receptor superfamily 7 (CD27)]. These findings were validated by the authors through independent dataset, that pointed out a female-biased pattern based on checkpoints [e.g., B and T lymphocyte attenuator (BTLA), cluster of differentiation 80 (CD80)] and immune cell populations (e.g., activated CD4+/CD8+ T cell) (130).

Similarly, a recent systematic review and meta-analysis of transcriptomic studies by Pérez-Díez *et al.* revealed that about 43% of detected functional alterations caused by lung ADC and associated to immune response are upregulated in females (131). These findings support other studies that showed more powerful innate and adaptive immune responses in women than men, with increased phagocytic activity of neutrophils and macrophages, more efficient antigen presenting cells, differences in lymphocyte subsets and cytokine production (111).

### Patients' sex and ICIs efficacy in NSCLC

Therapy with anti-PD-1/PD-L1 antibodies, which was first approved as second-line treatment in aNSCLC (132-135), was then extended to first-line treatment. ICI demonstrated its superiority over platinum-doublet chemotherapy (ChT) in untreated patients with aNSCLC and high PD-L1 expression (tumor proportion score  $\geq 50\%$ ) (136-138); moreover, the combination of pembrolizumab or atezolizumab with ChT showed better activity than ChT alone, regardless of PD-L1 status and histology (139-141).

Actually, the identification of predictive biomarkers for tumor response to immunotherapies is extensively studied in order to improve patient selection and ensure an effective personalized approach. Despite being a useful biomarker, PD-L1 expression by itself is not enough, as other immunologic or non-immunologic markers may influence ICIs efficacy (142). Sex differences could alter the mechanism of immune response modulation, but usually patient's sex is not considered as a stratification criterion in randomized clinical trials. Data about ICI efficacy in men and women in fact mainly derive from *post-hoc* subgroup analysis (Table 1).

Recently some oncologist groups specifically investigated the correlation between sex and survival benefit from ICI. According to a five RCTs meta-analysis (n=3,025) comparing a PD-1/PD-L1 agent with docetaxel in ChT-pretreated NSCLC patients, benefit from ICI resulted similar in men (HR, 0.69) compared to women (HR, 0.70); interaction, P=0.82) (143).



**Table 1** Outcome by patients' sex according to NSCLC phase III randomized clinical trials with ICI

Trial	Authors	Histology	Stage	Inclusion criteria	Treatment	Comparator	Line	M	F	M F ratio	PFS, ITT HR	PFS, male HR (95% CI)	PFS, female HR (95% CI)	OS, ITT HR	OS, male HR (95% CI)	OS, female HR (95% CI)
CheckMate 057	Borghaei <i>et al.</i>	nSCC, NSCLC	IIIB-IV	-	Nivolumab	Docetaxel	≥2	319263	121	0.91	0.81 (0.63-1.04)	1.04 (0.80-1.37)	0.73 (0.58-1.04)	0.73	0.73 (0.56-0.96)	0.78
CheckMate 017	Brahmer <i>et al.</i>	SCC, NSCLC	IIIB-IV	-	Nivolumab	Docetaxel	2	20864	325	0.62	0.63 (0.46-0.85)	0.71 (0.40-1.26)	0.59 (0.36-1.25)	0.67	0.57 (0.41-0.78)	0.67
KEYNOTE 024	Reck <i>et al.</i>	NSCLC	IIIB-IV	PD-L1 >50%	Pembrolizumab	Platinum-based ChT	1	187118	158	0.50	0.39 (0.26-0.58)	0.75 (0.46-1.21)	0.60 (0.36-1.64)	0.96	0.54 (0.36-0.80)	0.96
KEYNOTE 010	Herbst <i>et al.</i>	NSCLC	IIIB-IV	PD-L1 ≥1%	Pembrolizumab 2 mg/kg	Docetaxel	2	421266	158	0.88	0.78 (0.64-0.94)	1.02 (0.78-1.32)	0.71 (0.52-0.81)	0.69	0.65 (0.52-0.81)	0.69
KEYNOTE 010	Herbst <i>et al.</i>	NSCLC	IIIB-IV	PD-L1 ≥10 mg/kg	Pembrolizumab 10 mg/kg	Docetaxel	2	422267	158	0.79	0.78 (0.64-0.94)	1.02 (0.78-1.32)	0.61 (0.52-0.81)	0.69	0.65 (0.52-0.81)	0.69
OAK	Rittmeyer <i>et al.</i>	NSCLC	IIIB-IV	-	Atezolizumab	Docetaxel	≥2	520330	158	0.93	NA	NA	0.75 (0.66-0.99)	0.66	0.81 (0.66-0.99)	0.66
PACIFIC	Antonia <i>et al.</i>	NSCLC	III unresectable	-	Durvalumab	Placebo	Consolidation after CRT	500213	235	0.55	0.56 (0.44-0.71)	0.54 (0.37-0.79)	0.68 (0.59-1.03)	0.46	0.78 (0.59-1.03)	0.46
KEYNOTE 407	Paz-Ares <i>et al.</i>	SCC, NSCLC	IIIB-IV	-	ChT + pembrolizumab	Platinum-based ChT	1	455104	438	0.56	0.58 (0.66-0.73)	0.49 (0.3-0.81)	0.64 (0.51-0.94)	0.42	0.69 (0.51-0.94)	0.42
KEYNOTE 189	Gandhi <i>et al.</i>	nSCC, NSCLC	IIIB-IV	-	ChT + pembrolizumab	Platinum-based ChT + pemetrexed	1	363253	143	0.52	0.66 (0.5-0.87)	0.40 (0.29-0.54)	0.49 (0.50-0.99)	0.29	0.70 (0.50-0.99)	0.29
IMpower 130	Cappuzzo <i>et al.</i>	nSCC, NSCLC	IIIB-IV	-	ChT + atezolizumab	Platinum-based ChT	1	400279	143	0.64	0.67 (0.54-0.85)	0.59 (0.45-0.78)	0.79 (0.66-1.15)	0.66	0.87 (0.66-1.15)	0.66
IMpower 131	Jotte <i>et al.</i>	SCC, NSCLC	IIIB-IV	-	ChT + atezolizumab	Platinum-based ChT	1	557126	442	0.71	0.71 (0.59-0.85)	0.66 (0.45-0.97)	0.88 (0.75-1.12)	0.68	0.91 (0.75-1.12)	0.68
IMpower 132	Papadimitrakopoulou <i>et al.</i>	nSCC, NSCLC	IIIB-IV	-	ChT + atezolizumab	Platinum-based ChT + pemetrexed	1	384194	198	0.60	0.64 (0.51-0.79)	0.51 (0.36-0.71)	0.81 (0.51-0.79)	NA	NA	NA
IMpower 150	Socinski <i>et al.</i>	nSCC, NSCLC	IIIB-IV	Include also EGFR/ALK positive TKI pre-treated	ChT + atezolizumab	Platinum-based ChT + bevacizumab	1st ChT	425267	159	0.62	0.55 (0.44-0.67)	0.73 (0.54-0.96)	0.78 (0.44-0.96)	NA	NA	NA

**Table 1** (continued)

Table 1 (continued)

Trial	Authors	Histology	Stage	Inclusion criteria	Treatment	Comparator	Line	M	F	M F to F ratio	M PFS, IIT HR	PFS, IIT HR (95% CI)	PFS, female HR (95% CI)	OS, IIT HR	OS, male HR (95% CI)	OS, female HR (95% CI)
CheckMate 227	Hellmann <i>et al.</i>	NSCLC	IIIB–IV	PD-L1 ≥1%	Nivolumab + ipilimumab	Platinum-based ChT	1	515	278	1.85	0.82	NA	NA	0.79	0.75	0.91
CheckMate 227	Hellmann <i>et al.</i>	NSCLC	IIIB–IV	PD-L1 <1%	Nivolumab + ipilimumab	Platinum-based ChT	1	263	110	2.39	0.75	NA	NA	0.62	0.55	0.83

The table reports pivotal trials highlighting the difference between males and females in terms of number-rate of enrolled patients as well as of relative survival benefit. NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor; M, men; F, female; PFS, progression-free survival; OS, overall survival; IIT, intention-to-treat; HR, hazard ratio; CI, confidence interval; nSCLC, non-squamous cell carcinoma; SCC, squamous cell carcinoma; PD-L1, programmed death ligand-1; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; ChT, chemotherapy; CRT, chemo-radiotherapy; NA, not assessed.

Another meta-analysis (n=20 RCTs) showed a greater benefit from ICIs in men than in women across different forms of advanced solid cancers. Considering the pooled HR of the six RCTs that enrolled NSCLC patients (n=3,482), this sex-dependent magnitude of benefit from ICI seemed confirmed even for LC (male pooled HR, 0.72; 95% CI, 0.61–0.86; female pooled HR, 0.89; 95% CI, 0.71–1.11;  $P_{\text{heterogeneity}}=0.72$ ) (144).

According to a larger systematic review of advanced cancers studies (n=23), sex was found as not associated with efficacy in terms of OS, nor in the NSCLC subgroup analyses that involved eleven RCTs and more than 6,000 patients (male HR, 0.79; 95% CI, 0.71–0.88; female HR, 0.72; 95% CI, 0.56–0.93;  $P=0.79$ ) (145). Conforti *et al.* excluded anti-PD-L1 trials in their study, whereas trials with anti-PD-L1 agents were considered in the analysis by Wallis *et al.* and in a second larger one (n=34) by Yang *et al.*, which pointed out how sex is not associated with cancer immunotherapy survival benefit (146).

Other two meta-analyses performed by Conforti *et al.* assessed differences in terms of efficacy of the combination of an anti-PD-1/PD-L1 + ChT according to patients' sex, but focusing on LC patients (147).

The authors examined 8 RCTs reporting outcome of the association of ICI with ChT *vs.* ChT alone in patients with advanced LC. Results showed that men treated with the combination strategy had a statistically significant reduced risk of progression or death compared with men treated with ChT alone [pooled progression-free survival (PFS): HR, 0.64; 95% CI, 0.58 to 0.71]. While, in women the advantage obtained with immunotherapy + ChT compared with the control arm was larger (pooled PFS: HR, 0.56; 95% CI, 0.49 to 0.65). Interestingly, no statistically significant interaction was found between treatment efficacy and other relevant clinicopathological features, that were age (<65 *vs.* ≥65 y), smoking status (never *vs.* former or current smoker), performance status (PS 0 *vs.* PS 1) and tumor histology.

The second meta-analysis was conducted specifically on RCTs testing an anti-PD-1/PD-L1 given either alone or combined with ChT as front-line systemic treatment for patients with aNSCLC. Analysis considered 3,974 patients, of whom 66.4% were men and 68.9% patients had nonsquamous tumors. Results evidenced that men treated with anti-PD-1 alone had a statistically significantly reduced risk of death as compared with men treated with standard ChT [pooled overall survival (OS): HR, 0.78; 95% CI, 0.60 to 1.00]. On the other side, in women anti-PD-1 alone was not better than standard ChT (pooled OS: HR,

0.97; 95% CI, 0.79 to 1.19). Consistently with previous meta-analysis results, the combination strategy was associated with an OS advantage compared with ChT alone in women, while a statistically significantly smaller benefit was seen in men (female-pooled OS: HR, 0.44; 95% CI, 0.25 to 0.76; male-pooled OS: HR, 0.76; 95% CI, 0.64 to 0.91) (147).

Despite some small reports describing a greater ORR for women *vs.* men treated with PD-1/PD-L1-inhibitors (130), pivotal trials generally do not report distinctly response rate for patients' sex. It is not known either if sex could be associated with long-term survival, in the only one trial reporting the sex of patients who survived  $\geq 5$  y no apparent difference seems appreciable ( $M = 9$ ;  $F = 7$ ) (148).

Unfortunately, meta-analyses suffer from multiple confounding factors related to disease, treatment option and patient characteristics. RCTs were extremely heterogeneous in terms of included solid tumor types, class and line of ICI and non-ICI therapies. Analyses generally were not performed separately for studies with anti-PD-1 *vs.* anti-PD-L1 agents, whose action might be differently influenced by patient sexual hormones (149).

Trials allowed enrollment of both untreated and widely pretreated patients, some of the included trials had a ChT at investigator's choice inside at least one arm, thus amplifying treatments variety. Prognostically this is quite challenging, because antineoplastic agents use variably leads to tumor cellular selection, niche resistance creation and TME properties modulation (150). This heterogeneity compromises the direction and robustness of the results, which are limited also by the poor follow-up time of most considered RCTs. Therefore, the present evidence does not allow to draw any definitive conclusion about patient's sex and ICI efficacy.

Anyhow, latest research from Conforti *et al.* offers maybe more concrete insights, being focused on LC and naïve patients (147). As mentioned, women benefited less from single agent ICI *vs.* ChT, while the advantage of ICI + ChT *vs.* ChT was shown regardless of patient's sex, but much more in women. Explanations for this remain speculative, but findings by the same authors about NSCLC TME features help to (151). Tumor samples from women *vs.* men own greater T-cell dysfunction status, higher expression of inhibitory immune-checkpoint molecules and abundance of immune-suppressive cells thus potentially justifying the impaired efficacy of ICI when administered alone. ChT may subvert these blockades thus eliciting ICI action, more strongly in women *vs.* men possibly for a difference in neoantigens presentation and immune-evasion mechanisms.

## Perspectives and conclusion

Although smoking is the primary risk factor for LC in both men and women, other variable such as genetic differences, sex hormones, environmental exposures and lifestyle habit, immune system and TME disparities, could play an important role in sex-biased carcinogenesis and immune responses (112,152). NSCLC from women have a higher probability of harboring *KRAS G12C* mutation, that has a negative prognostic value (92).

Several tumor features and response to antineoplastic agents might be sex-dependent. In the latest years, clinicians have tried to find out any predictors of outcome in solid cancers treated with immunotherapy. Patients affected by advanced LC have been investigated too, with some emerging findings about sex differences in ICIs efficacy.

In our opinion, the most interesting finding having a potential impact on clinical practice is that men treated with ICIs alone have a statistically significantly better outcome than women, with these latest benefited more than men by adding ChT agents to ICIs ones instead (147). Associations between female sex and inferior immunotherapy outcomes have also been observed in a real-world retrospective cohort study conducted in the US on aNSCLC patients aged 66 to 89 years ( $n=19,529$ ) (153).

Results from treatment of cancers other than LC suggested the role of the combination strategy with chemo-immunotherapy that improved survival in female patients. Also in the setting of advanced breast cancer, benefit from immunotherapy alone have been disappointing (154), but, recently, the results of the IMpassion 130 study showed that the combination of atezolizumab + ChT improved outcome compared with ChT alone for women with advanced triple-negative breast cancer, especially in PD-L1 positive patients (155).

Unfortunately, these observations are only suggestive and even for LC patients, data about patients' sex impact on immunotherapy response remain to date not conclusive and sometimes even discordant. Future studies are warranted to assess the variables sex in an integrated way, taking of care of other known predictive/prognostic factors, in order to determinate the real impact of male and female gender in the field of cancer immunotherapy.

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