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Heterogeneous tumor features and treatment outcome between males and females with lung cancer (LC): Do gender and sex matter?

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ABSTRACT

Lung cancer (LC) is the leading cause of cancer-related death worldwide, despite a decreasing incidence rate in recent years, especially in men. Most risk factors for LC could be linked to an individual's reproductive system and secondary sex characteristics ('sex-related') and/or to some physical, behavioral and personality traits ('gender-related') peculiar to males rather than females or vice versa. An imbalance of these etiologic factors could explain why some LC features may differ between sexes.

For this review, an extended literature data collection was performed, using keywords to identify 'sex/gender' and 'LC'.

Differences between genders in LC epidemiology, pathological and molecular characteristics, loco-regional and/or systemic treatments outcome and prognosis were systematically analyzed. The possible predictive role of physio-pathological factors in males and females paves the way for a personalized therapeutic approach, emphasizing the need to include gender as a stratification factor in future clinical trials design.

1. Introduction

Lung cancer (LC) is the leading cause of cancer-related death worldwide both in men and women, accounting for 1.8 million deaths in 2018 (Bray et al., 2018). Among all LC cases, about 85% are non-small cell lung cancer (NSCLC), with two main histological types: adenocarcinoma (ADC) and squamous cell carcinoma (SCC) (Bray et al., 2018; Herbst et al., 2018). While tobacco smoking is the most important risk factor for LC, a subset of NSCLC patients (approximately 10–40%) are never-smoker or light-smoker, and in this case the etiology is less clear (Özdemir et al., 2018; Siegel et al., 2019).

Over the last two decades, the therapeutic options for patients affected by LC have greatly expanded, mainly due to the increased use of anti-angiogenic agents, targeted therapies and immune checkpoints inhibitors (ICIs) (Herbst et al., 2018). A patient's sex was not normally used as a preplanned stratification factor in randomized control trials (RCTs) testing different anticancer agents and loco-regional approaches. Current assumptions about a patient's sex as a predictive and/or prognostic factor come from analysis of heterogeneous patient populations or meta-analysis of heterogeneous trials (Jemal et al., 2018). For these reasons, comprehensive knowledge about a possible predictive/prognostic role of gender in NSCLC is lacking.

In this review, we present data showing differences between men and women who develop LC in terms of epidemiology, risk factors, treatment outcome and prognosis.

2. Review methods

An extended literature data collection through the free search engine PubMed was performed, using keywords related to patient sex ('sex', 'gender', 'male/female', 'men/women') and LC epidemiological, etiological and clinical-pathological features. Data were systematically analyzed to outline putative differences between males and females, highlighting the available level of evidence, when necessary. In the second part of the review, we looked for potential heterogeneous efficacy of loco-regional (radiotherapy, surgery) and systemic treatments (chemotherapy, anti-angiogenic agents, targeted therapies, ICIs) in small cell lung cancer (SCLC) and NSCLC in males *versus* females. Data on limited/early disease stage were separately analyzed from those of extensive/metastatic stage to verify the impact of a patient's sex on outcome in both conditions. The review considered the results of more than 35 randomized controlled trials (RCTs) including patients affected

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by LC, across different tumor histologies, disease stages and treatment types; useful contributions coming from non-RCTs were also taken into account, and the meta-analytic and/or retrospective nature of these studies was specified in the text.

3. Epidemiology of LC in males and females

LC has been the most common diagnosed cancer in the world for several decades, and also the most common cause of death due to cancer. Worldwide, LC remains the leading cause of cancer incidence and mortality, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018, accounting for 18.4% of cancer deaths (Bray et al., 2018). LC is the most common cancer in men worldwide (1.3 million new cases/year), with the highest estimated age-standardized incidence rates in Eastern Europe (49.3 per 100,000/year) and Eastern Asia (47.2). Notably, low incidence rates are observed in Middle and Western Africa (3.8 and 2.4 respectively). In women, the incidence rates are generally lower and the geographical pattern is slightly different, mainly reflecting different historical exposure to tobacco smoke. Thus, the highest estimated rates are in Northern America (30.7 per 100,000/year) and Northern Europe (26.9) with a relatively high rate in Eastern Asia (19.2) and the lowest rates again in Western and Middle Africa (1.2 and 2.3 respectively) (Bray et al., 2018).

Over the last 40 years in the U.S., LC incidence rate has constantly declined in men (from 90 per 100,000 in 1975 to 71 per 100,000 in 2010–2015), while it had an increasing trend in women (from 25 per 100,000 in 1975 to 52.3 per 100,000 in 2010–2015), beginning to decline only since the mid-2000′s. The decline has been more consistent in the past decade, with rates decreasing from 2011 to 2015 by almost 3% per year in men, but only 1.5% per year in women (Siegel et al., 2019). In the U.S. LC incidence rates are now higher among young women than among young men, with the pattern confined to non-Hispanic whites and Hispanics born since the mid-1960s (Jemal et al., 2018). In contrast to men, most European countries are still observing a rising trend in LC incidence among women (Bray et al., 2018).

In the U.S. the LC death rate has declined by 48% since 1990 in men and by 23% since 2002 in women due to reductions in smoking, and from 2012 to 2016 the rate decreased by about 4% per year in men and 3% per year in women (Siegel et al., 2019). Anyway, among males, LC remains the leading cause of death in most countries in Eastern Europe, Western Asia, Northern Africa, and specific countries in Eastern Asia and South-Eastern Asia. Among females, LC is the leading cause of cancer death in 28 countries, with the highest incidence rates seen in North America, Northern and Western Europe (Bray et al., 2018).

4. Risk factors for LC in males and females

Males and females are possibly differently predisposed to develop LC, due to a series of distinct and/or unbalanced risk factors: those ascribable to male/female biological features, hereafter indicated as ‘sex-related’, and those indicated as ‘gender-related’, being more linked to male/female behavior.

4.1. Sex-related risk factors

4.1.1. Sex hormones

Sex hormones could have a key role considering that estrogen receptors (ERs) are often expressed in LC and that estrogens potentially influence tumor growth (Schwartz et al., 2005). In particular, hormone replacement therapy seems to increase incidence of, and mortality from lung cancer in women (Chakraborty et al., 2010).

On the contrary, anti-estrogen use in women was found to be correlated with a reduced risk of lung cancer incidence (Chu et al., 2017). Blood estrogen level is normally higher in females than males, but ERs are not exclusively expressed in lung cancer of women. However, data suggest that estrogens activate lung adenocarcinoma cell lines derived from women, but not from men (Dougherty et al., 2006; Ivanova et al., 2010). ER alpha (ERα) and ER beta (ERβ)are two types of classical ERs, with the latter appearing to be the predominant isoform in lung cancer (Hsu et al., 2017). The location on lung cancer cell (cytoplasm/nucleus) and the prognostic value of each ER have not been univocally reported in literature, and may vary according to a patient’s sex (Schwartz et al., 2005). On the contrary, few data exist on an eventual androgen role.

The effects of male sex steroids are mediated by the androgen receptor (AR), expressed in type II pneumocytes and in bronchial epithelium of murine lung model, after androgen stimulation (Mikkonen et al., 2010). In this model, androgens significantly altered lung gene expression profiles, by up-regulating transcripts involved in oxygen transport and down-regulating those responsible for DNA repair and recombination. The carcinogenic effect of androgens might reside in this cytotoxic effect, but it might also reside in the down-regulation of the systemic immune response, as seen in different immunological disorders where the immune-suppressive action of testosterone has been demonstrated (Trigunaite et al., 2015). A population-based cohort study on men aged 70–88 years (n = 3635) showed that a high testosterone level was associated with LC, even after exclusion of current smoker subjects (Hyde et al., 2012). Androgens might play a role in lung cancer pathophysiology, promoting both its origin and progression; androgen deprivation therapy has been found to have a benefic effect on survival after lung cancer diagnosis (HR 0.36; $p = 0.0007$), according to a retrospective analysis (n = 3018, APM treated = 339) (Harlos et al., 2015).

4.1.2. DNA adducts and DNA repair systems

Tobacco smoke contains a multitude of carcinogens, which exert their biologic effect through the formation of DNA adducts in lung tissue. Carcinogens are metabolized and detoxified within the lung by enzymes that 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 (Hemminki, 1993). It has been hypothesized that women are more susceptible to tobacco carcinogens than men. 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 polycyclic aromatic hydrocarbons (PAH)–related DNA adducts in female smokers compared to males (Berge et al., 2004). Inherited genetic polymorphisms affecting activating and detoxifying enzymes could explain a different susceptibility between sexes to tobacco carcinogens. The cytochrome P-4501A1 (CYP1A1) gene codes for an enzyme involved in DNA adduct formation and induced by cigarette smoke (Kawajiri et al., 1993). Despite substantially fewer pack-years and younger age, female smokers have been found to have significantly higher levels of CYP1A1 expression and of DNA adducts than men. Increased CYP1A1 expression might be a result of hormone induction, mostly estrogens. A cross-talk between ERs and the aryl hydrocarbon receptor, a regulator of CYP1A1, has been demonstrated in breast cancer cell lines (Thomsen et al., 1994).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 a reduced expression and in an increased risk for smoking-related cancers. Polymerase chain reaction analysis of peripheral blood indicated that women had a greater cancer risk than men (odds ratio [OR] 4.98 *versus* 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 GSTM1 null genotype are significantly more frequent in female cancer patients than female controls. The combined variant genotypes conferred an odds ratio of 6.54 for LC in women compared with 2.36 in men. This risk was not affected by age or by smoking history (Dresler et al., 2000; Seidegård et al., 1990).

DNA repair capacity (DRC) seems to be involved in LC pathogenesis and treatment outcome. Wei et al. looked at the impact of DRC in the pathogenesis of LC by measuring the ability of patients' lung tissue to identify and repair induced DNA adducts. Patients younger than 60 years, those with a family history of LC, and women had lower DRC and a higher risk for LC than the average population (Wei et al., 2000). These findings were confirmed in a similar case-control study by (Spitz et al. (2001).

4.2. Gender-related risk factors

4.2.1. Tobacco use

A smoking habit continues to be the primary risk factor for developing LC.

The World Health Organization (WHO) estimates that 20.2% of the world's population aged ≥ 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 (Anon., 2015). 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%).

Such differences may relate to a combination of physiological, cultural and behavioral factors. Despite the worldwide predominance of male smokers, female smoking is dominated by higher prevalence in the Americas and European regions. In these countries, the differences in smoking behavior between women and men have decreased over time, and currently 12.2% of American women smoke cigarettes compared with 15.8% of men (Wang et al., 2018). The prevalence of smoking in American women peaked in 1965 at 33% and remained elevated throughout the 70 s before beginning to slowly decrease in 1980. By contrast, more than half of American men smoked before 1965, but the prevalence dramatically decreased during the subsequent 20 years (Giovino, 2002). In last decades, the age-standardized prevalence of tobacco smoking has decreased more slowly in women *versus* men in Europe, with this trend expected to be confirmed also in the period 2010–2025 (Anon., 2018).

Second-hand smoke is another established risk factor for LC: approximately 20% of women with LC are non-smokers and women married to men who smoke have been shown to have a 25%–29% increased risk of developing LC (North C and Christiani, 2013).

Besides the difference in tobacco exposure between men and women, several behavioral lifestyles related to smoking habits as well as environmental and occupational exposures are found to be differently expressed, thus potentially representing other gender-related LC risk factors (Kiyohara and Ohno, 2010; Cote et al., 2009; Mollerup et al., 2006; Subramanian and Govindan, 2007).

4.2.2. Environmental exposures

Environmental exposures known to be carcinogenic to the lung include second hand smoke (SHS), asbestos, arsenic, radon, polycyclic aromatic hydrocarbons, cadmium, nickel, metal dusts and vinyl chloride (Kligerman and White, 2011). Moreover, indoor burning of cooking oil and other biomass fuels in poorly ventilated areas produce polycyclic aromatic hydrocarbons (PAHs), which are associated with LC. This effect is seen especially in East and South Asian women, but is significant in all developing countries (Sun et al., 2007). In LC attributed to household coal burning exposure, lung microbiota may play a potential etiopathogenetic role in females (Hosgood et al., 2014).

4.2.3. Other risk factors

Dietary patterns could influence LC risk differently in the two sexes. Among men, inverse relationships with vitamin C, folate, and carotenoids, and positive associations with total fat, monounsaturated and saturated fat were observed after adjusting for age, education, cigarettes/day, years smoking, and total energy intake(Bandera et al., 1997); diet did not appear to exert a major role on lung cancer risk among women. However, in LC of never-smokers of both gender, a protective effect was suggested for vegetables/carrots and a deleterious effect for cultured milk products (Nyberg et al., 1998); milk resulted a risk factor only among male high-consumers. According to a case-control study based on the results of community mass screening (LC = 363, control subjects = 1089), an inverse association between body mass index (BMI) and LC was observed in men after adjustment for age and smoking, while no association was found in women (Kanashiki et al., 2005). Some preclinical studies have shown that lung microbiome (LM) composition after exposure to external stimuli might differ by sex (Barfod et al., 2015), and recent studies have shown that certain respiratory microbes and microbiota dysbiosis are correlated with development of LC (Mao et al., 2018). However, the impact of LM in LC risk has not yet been described to differ between males and females.

5. Clinical-pathological and molecular features of LC in males and females

SCC, SCLC and large-cell carcinoma (LCC) rates declined since the 1990s for both gender, but less rapidly among females (Lewis et al., 2014).

Since then, the incidence of ADC rose worldwide, and nowadays ADC represents globally the most common type of LC both in men and women (Parkin et al., 2010; Cheng et al., 2016). In last decades in most countries ADC rates remained relatively constant in males, while it increased in females, thus representing an important medical issue (Weiderpass et al., 2014; Meza et al., 2015).

The subset of lung ADC once recognized as bronchoalveolar carcinoma (BAC) disproportionately affects women (Raz et al., 2016) but, since the latest WHO classification of LC discontinued the term BAC in favor of "lepidic" (Travis et al., 2015a), 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.

Some sex-oriented pathological LC features might depend on different co-etiological factors, such as tobacco exposure (Travis et al., 2015b), carcinogen-metabolizing enzymes expression and/or oncogenic virus prevalence. Moreover, important acquired molecular differences exist between males and females affected by LC.

NSCLC tumor samples of female smoker patients, rather than males, generally present higher frequency of mutations in critical driver genes, such as p53 and KRAS (Mollerup et al., 2006; Foeglé et al., 2007; Barrera and Morales Fuentes, 2012).

Nelson et al. reported a significant association between female sex and KRAS mutation in lung ADC tissue after adjustment for carcinogen exposures (OR 3.3; 95% CI 1.3–7.9), with mutations found only in smokers. They suggested a possible role of estrogen exposure in either the initiation or the selection of KRAS mutant clones in ADC (El Osta et al., 2019). In addition, a large study by Dogan et al. genotyped 3026 lung ADCs showing that KRAS G12C, the most common G > T transversion mutation in smokers, was more frequent in women ($p = 0.007$); these women were younger than men with the same mutation (median 65 years old *versus* 69 years old, $p = 0.0008$) and smoked less than men (Nelson et al., 1999). Regarding p53, 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 non-smokers (Dogan et al., 2012; Vähäkangas et al., 2001). Indeed, in smokers, 43% of the mutations were G to T transversions, but this number dropped to 13% in never-smokers (Hernandez-Boussard and Hainaut, 1998). Another analysis reported that the difference of p53 mutational spectrum between never-smokers and smokers was detectable only in women (Ding et al., 2008; Kure et al., 1996). p53 mutations in female never-smokers with ADC were predominantly transitions

(83%), while in smokers, they consisted predominantly in transversions (60%) and deletions (20%) (Toyooka et al., 2003).

Generally, the presence of most known driver mutations is more common in non-smokers and female patients. Often, the presence of one of these pathognomonic genetic alterations is recognized as the possible leading cause of cancer itself.

Female tumors more frequently harbor a wide set of targetable alterations, such as mutation of epidermal growth factor (EGFR) (Gealy et al., 1999), human epidermal growth factor receptor 2 (HER2) (Zhang et al., 2016) or serine/threonine-protein kinase B-RAF (Mazières et al., 2013), as well as rearrangement of proto-oncogene 1 receptor tyrosine kinase (ROS1) (Reddy et al., 2017; Rossi et al., 2017) and anaplastic lymphoma kinase (ALK) (Warth et al., 2014; Vidal et al., 2014), even though some discordant data are available on ALK prevalence in females. (Paik et al., 2012; Fallet et al., 2014).

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 (Shaw et al., 2009); however, no mutation among them is currently targeted by an available agent.

Two additional factors, programmed death-ligand 1 (PD-L1) and tumor mutation burden (TMB) are acquiring increasing relevance in NSCLC, because of their potential predictive value of response to immunotherapy. As known, the expression of PD-L1 on tumor cells promotes down-regulation and self-tolerance of the immune system from rejecting the tumor by suppressing T-cell inflammatory activity through binding to the regulatory T-cell receptor, PD-1 (Collisson et al., 2014).

According to a meta-analysis of nine studies in 1550 patients, gender resulted not correlated with PD-L1 expression (Sharpe et al., 2007). Despite some other experiences reporting no association of PD-L1 with gender (Pan et al., 2015; Lin et al., 2017; Chen et al., 2016), a more recent meta-analysis of fifty-two studies showed male gender as a factor associated with PD-L1 expression (odds ratio [OR] 4.8; 95% CI 3.2–7.2; $p < 0.001$) (Calles et al., 2015a).

Lung cancer has a very high rate of somatic mutations when compared to other tumors; 8.7 mutations per megabase in adenocarcinomas (ADCs) and 9.7 in squamous cell carcinomas (SCC) are reported (Petrelli et al., 2018). Even if TMB did not correlate with PD-L1 expression, they both emerged as key biomarkers of sensitivity to ICIs. Gender 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 (Lawrence et al., 2014; Govindan et al., 2012). 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 (Peters et al., 2017). Moreover, males and females own some differences in NSCLC immune-genes (Spigel et al., 2019) and micro-RNA (miRNA) expression (Araujo et al., 2016), but at the moment it is unknown whether these properties have a predictive/prognostic value.

6. LC treatment outcome by gender

6.1. Small cell-lung cancer (SCLC)

In SCLC, female gender is generally regarded as a positive prognostic factor (Guo et al., 2017; Osterlind et al., 1986; Videtic et al., 2005; Wolf et al., 1991; Albain et al., 1990; Paesmans et al., 2000), whereas it may be related to an increased toxicity from chemotherapy (Johnson et al., 1988; Singh et al., 2005). The role of a patient's sex on SCLC outcome has been fully explored for limited and advanced disease, across clinical trials and real-life evidence.

6.2. Limited-stage disease (LD)

Chemotherapy remains the main option in SCLC management, excluding T1,2 N0,1 M0 tumors where a surgical approach might be proposed (Wheatley-Price et al., 2010; Jett et al., 2013; Rudin et al., 2015). After curative-intent surgical resection, platinum-based adjuvant chemotherapy is recommended (Früh et al., 2013; Shepherd et al., 1988; Tsuchiya et al., 2005).

Two real-life experiences investigated the impact of sex in this setting. A retrospective study, including 1574 patients with pT1-2N0M0 SCLC undergoing surgery, showed that lobectomy followed by adjuvant chemotherapy was associated with improved survival at multivariate analysis, whereas higher age, tumor size, and presence of comorbidities were independently associated with worse survival; in this analysis, sex was not associated with survival (Tsuchiya et al., 2005).

In another retrospective study including stage I SCLCs patients (n = 2681) from the National Cancer Database, patient age, female gender, Charlson-Deyo comorbidity score < 2, tumor size ≤3 cm, surgery and chemotherapy were all associated with improved OS (C-FJ et al., 2016).

Recommended treatment in non-surgical limited stage disease is concurrent chemotherapy and thoracic radiotherapy (Paximadis et al., 2017; Saito et al., 2006; Kubota et al., 2014; Skarlos et al., 2001; Pignon et al., 1992; Warde and Payne, 1992). Cox multivariate models were applied to 1363 patients in six limited disease trials conducted by Southwest Oncology Group (SWOG): good performance status (PS), female sex, age less than 70 years, white race, and normal lactate dehydrogenase (LDH) were significant favorable independent predictors (Wolf et al., 1991).

A meta-analysis of 16 RCTs including 2140 patients and evaluating thoracic radiotherapy showed no statistically different treatment effects according to sex (pooled relative risk for women 0.79, 95% CI 0.66-0.94, and for men 0.88, 95% CI 0.78-0.98) (Skarlos et al., 2001).

A RCT comparing twice-daily with once-daily thoracic radiotherapy in 417 patients with limited SCLC treated concurrently with cisplatin and etoposide, showed that male sex and a PS of 2 were significantly associated with shorter failure-free survival at multivariate analysis (no hazard ratio was reported) (Warde and Payne, 1992).

As far as evidence from real-life experiences is concerned, a retrospective study including a cohort of 6271 limited stage SCLCs from the Surveillance, Epidemiology, and End Results (SEER) database reported in multivariate analysis female sex as a positive prognostic factor (HR = 0.91; 95% CI 0.87–0.96; $p = 0.0007$), whereas older age, African American race, and main bronchus location were all associated with a statistically significant increase in mortality hazard (Turrisi et al., 1999).

A retrospective study investigating the role of chemo-radiotherapy on 8637 elderly patients (aged ≥ 70 years) with limited SCLC included female sex among factors associated with improved OS on univariate and on multivariate analysis (HR = 0.83; 95% CI 0.79-0.87; $p = 0.001$) (Lally et al., 2009).

Another retrospective study on 179 limited SCLC treated with definitive chemo-radiotherapy in a real-life scenario showed that female gender was significantly associated with longer brain metastases free survival ($p = 0.023$) and a lower incidence of metachronous brain failure. In this study, males resulted to have an inferior median OS than females (14 months [95% CI, 10–18] *versus* 20 months [95% CI, 10–22],respectively; $p = 0.021$), and this correlation was also found at multivariate analysis (HR 1.38; 95% CI 1.08–1.92; $p = 0.04$) (Corso et al., 2015).

6.3. Extensive-stage disease (ED)

Palliative systemic treatment of metastatic disease is based on cisplatin-etoposide regimen up to 4–6 cycles (Roengvoraphoj et al., 2018; Pujol et al., 2000); cisplatin can be replaced by carboplatin with no

apparent lack of efficacy and a better tolerance (Mascaux et al., 2000). The combinations irinotecan-cisplatin (Rossi et al., 2012), topotecan-cisplatin (Zatloukal et al., 2010; Fink et al., 2012) and gemcitabine-carboplatin (in poor prognostic patients only) (Eckardt et al., 2006) could also be valid alternatives. Patients having a PFS less than 6 months can benefit in terms of improved symptoms control and survival from use of oral or intravenous topotecan (Lee et al., 2009; O'Brien et al., 2006) or cyclophosfamide *plus* doxorubicin and vincristine (CAV) (Eckardt et al., 2007). Patients having a late disease relapse instead could benefit from re-challenge with first-line therapy. Independent determinants of improved outcome in patients with ED are traceable in a normal LDH, an intensive multidrug regimen treatment, and a single metastatic lesion (Wolf et al., 1991).Regarding patients' sex, a meta-analysis that included 4 RCTs comparing cisplatin-etoposide *versus* carboplatin-etoposide showed no evidence of treatment difference between the two arms according to patients' sex (sex interaction for OS $p = 0.42$, for PFS $p = 0.57$) (Mascaux et al., 2000).

In the randomized non-inferiority study comparing gemcitabine-carboplatin with etoposide-cisplatin, no difference was observed in treatment effect on OS or PFS survival in subgroups defined by age, sex, performance status and stage (Eckardt et al., 2006).

Subgroup analyses of the phase III trial comparing oral topotecan to BSC showed a survival benefit in favor of the chemotherapy arm in females, but not so clearly in males (Lee et al., 2009).

A sex-based retrospective analysis of 4 trials including 1006 patients treated with CAV regimen and etoposide-cisplatin conducted by the National Cancer Institute of Canada Clinical Trials Group showed that anemia (55.9% *vs* 38.6%, $p < 0.0001$) and leukopenia (92.7% *vs* 84.7% $p = 0.0002$) were significantly higher in female patients (Johnson et al., 1988). Females also experienced stomatitis (16.8% *vs* 8.3%, $p < 0.0001$) and vomiting (76.8% *vs* 67.2%, $p = 0.0014$) more often; when logistic regression analysis was performed to adjust the comparisons between the sexes by other factors (age, body surface area, PS, LDH, trial), female sex was still a significant predictor for all these toxicities. Moreover, more females than males had treatment delays of 2 weeks or more (52% *vs* 43.4%, $p = 0.022$), which was likely due to increased toxicity. Females, compared to males, had a superior overall response rate (RR) and median OS (80.3% *vs* 55.9% and 1.31 years *vs* 0.71 years respectively, $p < 0.0001$) (Johnson et al., 1988).Pharmacokinetic differences have been suggested as the cause of this imbalance in toxicity (Von et al., 1999; Kaul et al., 1996).

A pooled analysis of six chemotherapy trials (n = 1707) from the Manchester Lung Group and the Medical Research Council Clinical Trials Unit was carried out to validate the results from the previous analysis. This confirmed a significantly longer median survival for women (10.2 *vs* 9.6 months, $p = 0.006$), and in multivariate analysis female sex remained a significant predictor of improved survival (HR 0.88, 95% CI 0.79-0.99, $p = 0.04$). No differences between the sexes were found for hematological toxicity, but women experienced more frequently grade 3 or 4 emesis (18% *vs* 9%, $p < 0.0001$) and mucositis (13% *vs* 8%, $p = 0.005$) (Singh et al., 2005).

Regarding immunotherapy application, nivolumab with or without ipilimumab – an anti Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) inhibitor – has shown antitumor activity in previously chemo-treated patients, leading to Food and Drug Administration (FDA) accelerated approval of nivolumab for third and further line treatment of ED SCLC (Dobbs et al., 1995). TMB was recognized as a predictive factor (Antonia et al., 2016), while it is unknown if males and females benefit equally from ICIs, as no subgroup analyses by gender was performed in Checkmate 032 trial. More recently, IMpower133 phase III randomized trial showed OS and PFS improvement with the addition of atezolizumab to chemotherapy in the first-line treatment of ED SCLC; OS benefit was consistent across patient sex subgroups (males 12.3 mo *vs* 10.9 mo, HR = 0.74, 95% CI, 0.54–1.00; females 12.5 mo *vs* 9.5 mo, HR = 0.65, 95% CI, 0.42–1.00) (Hellmann et al., 2018a).

6.4. Non-small cell lung cancer (NSCLC)

6.4.1. Early-locally advanced stage

The subgroup analyses performed during the development of the 7th edition UICC/AJCC/IASLC TNM staging system confirmed male sex as an independent poor prognostic factor in surgically managed patients (unadjusted HR = 1.17, $p < 0.001$; adjusted HR = 1.21, $p < 0.001$) (Horn et al., 2018). At each stage of disease, the relative survival in women was longer than in men, with the largest difference in earlier stages.

According to the national SEER database, which collected data of patients with primary bronchogenic carcinoma (diagnosed from 1975 to 1999), female patients who underwent surgery alone had 2-year and 5-year survival rates of 74.3% and 56.8%, both greater than those of males equal to 66.0% and 48.3%, respectively ($p < 0.0001$) (Chansky et al., 2009). Female gender exerts a significant positive effect on survival of NSCLC patients following lung resection by a prospective collected dataset (n = 883). This benefit was more pronounced in earlier stages (stage I, $p = 0.01$; stage II-III, $p = 0.3$) and persisted after adjusting for important differences in the clinical, histo-pathological features and extent of pulmonary resection between male and female patients (Minami et al., 2000). The reason for this advantage in females seems not to be related to a different efficacy of post-surgical treatment. Indeed, subgroup analysis of the main trials of adjuvant chemotherapy showed no different effect of CT on OS according to patient's sex (Alexiou et al., 2002; Group, 2010; Strauss et al., 2008; Artal Cortés et al., 2015; Pignon et al., 2008; Wakelee et al., 2016). Furthermore, a meta-analysis of 35 trials including individuals with histologically confirmed NSCLC who underwent a potentially curative resection and subsequent adjuvant chemotherapy, showed no significant effect of patient's sex on the absolute improvement in 5-year survival (Butts et al., 2010). Sex-based differences in the timing of postoperative recurrence are also reported. A retrospective study conducted on patients who underwent complete pulmonary resection with or without adjuvant chemotherapy found that the risk and the peak time of post-surgical recurrences differed considerably between men and women, with the latter having a longer disease free interval (DFI) at the same disease stage, histological type, and smoking status (Burdett et al., 2015).

The use of neoadjuvant CT appears beneficial in resectable locally advanced disease (Watanabe et al., 2018; Gilligan et al., 2007; Lim et al., 2009). Some trials suggest the effect might be greater in women and others in men, but it is not clear why. A meta-analysis of 15 RCTs (n = 2385) did not point out a different outcome by sex, despite a difference in the effect of treatment or treatment by covariate interactions across trials(HR = 1.08, 95% CI, 0.81–1.44; $p = 0.62$; heterogeneity $p = 0.04$) (Lim et al., 2009).

Radiotherapy benefit in localized/locally advanced NSCLC seems no to be so clearly sex-dependent. In patients undergoing radiotherapy within the above cited SEER database, the relative 2-year and 5-year survival rates in men and women were 15.5% *vs* 12.2% and 5.3% *vs* 3.4%, respectively ($p \leq 0.0001$) (Chansky et al., 2009). A different pooled prospective data on more than 1300 NSCLC inoperable patients treated within the Radiation Therapy Oncology Group (RTOG) non-operative trials showed that women treated with radiotherapy had longer overall survival (Burdett, 2014). For patients with stage IIIB or stage IIIA NSCLC not resectable, concurrent chemoradiotherapy (CRT) is considered the preferred treatment, when feasible. This option is also valid for patients who, after induction chemotherapy, are not eligible for surgery (Siddiqui et al., 2010). Subgroup analyses for sex reported on two meta-analyses comparing concurrent to sequential CRT did not report any difference of treatment outcome by sex (Stewart, 1995; Aupérin et al., 2006). For elderly or less fit patients, the sequential approach is preferred, regardless of patients' sex (Aupérin et al., 2010).

6.4.2. Advanced-metastatic stage

Platinum-based chemotherapy has been the only treatment available for patients affected by NSCLC for almost 30 years, and currently still plays a major role in advanced and metastatic setting. The realization of the first EGFR tyrosine kinase inhibitor (TKI) and the discovery of its great activity in patients with a sensitizing EGFR gene mutation, allowed the first big revolution in the treatment of this disease (Brunelli et al., 2009). The subsequent identification of other targetable NSCLC genetic alterations led to the development of efficacious drugs for patients harboring them, opening the era of personalized therapy. Nowadays different TKIs targeting a series of genes alterations (EGFR, ALK, ROS-1, BRAF) have already received approval for patients with no radically treatable NSCLC. Meanwhile, the introduction of anti-angiogenic agents led to survival improvements for non-SCC NSCLC when associated with chemotherapy (Bell et al., 2005), although without significant revolution in current clinical practice. Another big innovation for the treatment of NSCLC came with the advent of ICIs, especially those targeting the PD-1/PD-L1 axis. Initially approved only for chemotherapy-pretreated patients (Soria et al., 2013), more recently ICIs alone or combined with chemotherapy have also shown benefit in naïve patients (Ramos-Esquivel et al., 2017), and as consolidation treatment in patients pretreated with definitive chemo-radiotherapy for locally advanced disease (Martinez et al., 2019). The scientific community has tried over the years to detect potential predictive factors of response to these agents. The possible predictive/prognostic value of the variable gender is below that analyzed in NSCLC patients treated with the three main drugs categories described.

6.4.2.1. Chemotherapy with or without anti-angiogenic agents. In patients with advanced NSCLC, CT *plus* best BSC showed survival benefit *over* BSC alone irrespective of age, sex, histology and PS (Siddiqui et al., 2010; Antonia et al., 2017). Subsequent meta-analyses pointed out a greater benefit of two-agents *over* single-agent CT (Group, 2008) and for those patients treated with regimens containing a platinum compound (Delbaldo et al., 2004). Different platinum-doublets with third-generation cytotoxic agents showed comparable efficacy (Pujol et al., 2006), but a slight advantage in OS emerged for cisplatin-based *versus* carboplatin-based chemotherapy (Schiller et al., 2002).Later, a survival benefit was noticed when platinum was combined with the antifolate agent pemetrexed rather than with gemcitabine or docetaxel, in patients with non-SCC histology (Ardizzoni et al., 2007). In all these studies, no subgroup analyses for sex were performed.

Patients are usually treated with four cycles of platinum-based doublet, as adding more cycles does not further improve the outcome in either males or females (Li et al., 2012). In these patients however, RCTs showed a survival benefit for single agent pemetrexed *versus* placebo, both when used as switched maintenance (Rossi et al., 2014) or – limited to non SCC NSCLC – as continuous maintenance after an induction treatment with pemetrexed plus cisplatin (Ciuleanu et al., 2009; Paz-Ares et al., 2012); even if females sometimes resulted to have a much lower PFS HR than males, this did not translate to a different OS HR in subgroup analysis (Ciuleanu et al., 2009; Paz-Ares et al., 2012).

The addition of the anti-vascular growth factor receptor (VGFR) bevacizumab (Bev) to standard platinum-based CT doublets in the first-line setting led to a small but significantly improved OS, PFS and RR for patients with advanced non-SCC NSCLC (Bell et al., 2005; Paz-Ares et al., 2013). The subgroup analyses of the main approval trials of Bev led to conflicting findings about the predictive value of sex. In the Eastern Cooperative Oncology Group (ECOG) 4599 trial, the addition of Bev to paclitaxel-carboplatin was possibly not beneficial on survival among women, while of benefit for men (Lima et al., 2011); further analyses of this trial showed that females younger than 60 years treated with the experimental arm combination had an improved survival compared to females older than 60 years, with menopausal status possibly being a negative predictor of response to Bev (Sandler et al., 2006; Brahmer et al., 2011). In the AVAiL trial, evaluating the addition of 7.5 or 15 mg/Kg of Bev to cisplatin-gemcitabine, Reck et al. reported subset differences by means of Forest plots of HRs: females had a statistically improved PFS at 15 mg/kg of Bev, but males had a significantly better PFS at the 7.5 mg/kg Bev dose (Wakelee et al., 2012). Retrospective analysis of ECOG 4599 trial showed a possible benefit of maintenance Bev (Reck et al., 2009), while a following RCT failed to demonstrate a superiority of Bev *plus* pemetrexed maintenance *over* Bev alone after induction treatment (Lopez-chavez et al., 2018; Barlesi et al., 2013); no subgroup analysis by gender was reported for either study.

In ECOG PS 2 patients, CT has shown to improve survival and quality of life (QoL) compared with BSC alone (Barlesi et al., 2014). Single-agent CT (gemcitabine, vinorelbine, taxanes) could be the preferred option, although carboplatin-based or low-dose cisplatin-based doublets may represent alternative options in eligible patients (Gridelli et al., 2004; Lilenbaum et al., 2009; Morère et al., 2010; Zukin et al., 2013). No specific gender subgroup analyses were performed in this setting.

For patients 70 years of age or older, therapeutic options include single agent chemotherapy (Bronte et al., 2015; Kudoh et al., 2006) - especially for unfit patients - or combination with carboplatin (Gridelli et al., 2003), while two meta-analyses showed a worse tolerability and contrasting results of OS prolongation with the use of platinum-based regimens (Quoix et al., 2011; Des et al., 2012). The addition of cisplatin to single-agent chemotherapy does not improve OS or QoL in elderly patients, according to a joint analysis of MILES-3 and MILES-4 RCTs (Qi et al., 2012). When reported, subgroup analyses did not show differences in outcome among male and female patients (Kudoh et al., 2006; Gridelli et al., 2003; Qi et al., 2012).

Although prospective data are quite lacking, several retrospective evaluations of gender differences in survival in advanced-stage NSCLC chemo-treated patients have been performed. In an earlier ECOG data analysis of seven phase III RCTs (n = 893), the 1-year survival rate was significantly higher in women *versus* men (26% and 16% respectively), even at multivariate analysis ($p = 0.005$) (Gridelli et al., 2018). Female sex resulted a strong independent factor for improved survival ($p < 0.00005$) according to another huge joint analysis from 13 SWOG trials (n = 2531) between 1974 and 1988, but this significance was lost when other prognostic variables were considered (Finkelstein et al., 1986). The European Lung Cancer Working Party (ELCWP) evaluated patients receiving platinum-based chemotherapy for either locally advanced or advanced NSCLC from 1980 to 1991 (n = 1052) and found female sex to be one of several variables associated with improved survival with a relative risk of death of 0.7 ($p = 0.03$) in multivariate analysis (Albain et al., 1991). A single cancer center study including advanced-staged NCSLC patients chemo-treated from 1978 to 1986 (n = 378) further confirmed female sex as an independent predictor of improved survival (median OS of 12.4 months for women *versus* 8.8 months for men, $p = 0.001$) (Paesmans et al., 1995). The ECOG E1594 trial randomized patients with advanced NSCLC (n = 1157) to one of four platinum doublets and found that all four regimens had comparable efficacy. The effect of sex on survival was later examined in this population and, despite a similar response rate (19% in both sexes, $p = 0.15$), women had a 1.9-month statistically significant improvement in median OS compared with men and also greater toxicity (O'Connell et al., 1986). The reasons for this apparent major benefit for female sex after a platinum-based chemoregimen among LC patients are currently unknown. Platinum-based agents act through the formation of DNA adducts, which leads to cell cycle arrest; the repair of these adducts is one mechanism of resistance to platinum-based agents. A defective DNA repair and/or recombination function was found to correlate with prolonged survival after cisplatin-based chemotherapy, even in NSCLC patients (Wakelee et al., 2006). Thus, the above seen difference in DRC between sexes (Wei et al., 2000; Spitz et al., 2001) could partially explain why women could benefit more than men from chemotherapy.

Second line CT should be offered to patients progressing after first line CT and with specific contraindications to ICIs. In this setting, combination CT failed to improve OS compared with single-agent CT (Lord et al., 2002), with no evidence of heterogeneity among subgroups of treatment effect around the overall effect. Among single chemotherapeutic agents, docetaxel demonstrated a significant better survival compared to best supportive care (Gridelli et al., 2009). Moreover, treatment with pemetrexed resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects compared with docetaxel (Shepherd et al., 2000). No subgroup by sex were reported in those studies.

Despite a doubtful clinical relevance, the association of docetaxel with the anti-VEGFR inhibitor Ramucirumab gave a statistically significant outcome benefit over docetaxel alone, similarly between sexes (Hanna et al., 2004). The multi-targeted tyrosine kinase inhibitor Nintedanib in combination with docetaxel is an effective second-line option, especially for patients with adenocarcinoma. No differential efficacy of nintedanib was shown by subgroup analyses by sex (Garon et al., 2014). Prognosis of patients eligible for second-line treatment of advanced NSCLC is significantly conditioned by gender (worse in males), PS, histology, stage, previous use of platinum and response to first-line. A derived prognostic score that also includes a patient's sex could be useful to discriminate subjects with a relatively more favorable prognosis and those with a very short life expectancy (Reck et al., 2014).

6.4.2.2. Targeted therapies

6.4.2.2.1. EGFR inhibitors (EGFRi). The transmembrane protein with cytoplasmic kinase activity EGFR transduces, upon ligand binding, growth factor signaling to the cancer cell. In around 15%–30% of NSCLC, according to patient ethnicity, EGFR results aberrantly activated due to an acquired mutation (EGFRm). In case of EGFR sensitizing mutations, the best front line therapy consists on an EGFR TKI. EGFR mutation rate is found higher in never-smokers compared with ever-smokers, as well as in women compared to men [185].Results from pivotal phase III studies, including EGFRm NSCLC patients treated with an EGFRi, showed a reduction in the risk of progression in the female subgroup but not in the male counterpart (Table 1). In the same way, a recent exploratory study showed that women affected by EGFRm NSCLC had a greater benefit from EGFRi than men (HR = 0.34; 95% CI, 0.28-0.40; p < 0.00001 *vs* HR = 0.44; 95% CI, 0.34-0.56; $p < 0.00001$, respectively) (Remon et al., 2017). A possible explanation is that women could benefit more than men from TKI therapy due to their lower tobacco smoking exposure. In fact, a meta-analysis including advanced EGFRm NSCLC patients showed that non-smokers have longer PFS to EGFRi treatment compared to patients who have a smoking history (Pinto et al., 2018). Furthermore, sexual hormones were found to regulate the EGFR signaling pathway, thereby potentially determining different effects on tumor growth and response to TKIs in EGFRm NSCLC patients of different genders. Specifically, growing evidence shows that ERs are expressed in LC cells and are able to interact with the EGFR cascade. In NSCLC cell lines and xenografts, a functional interaction between ERs and the EGFR activity was documented, being the EGFR protein expression down-regulated in response to estrogen and up-regulated in response to estrogen receptor inhibitors (Zhang et al., 2015; Stabile et al., 2005). This suggests that the EGFR pathway is activated when estrogen is depleted. Similarly, ER-β protein expression may be down-regulated after the addition of EGF and up-regulated in response to EGFRi (Zhang et al., 2015). A recent retrospective study investigated the associations between ERα/ERβ expression and EGFR mutational status and response to TKI treatment in metastatic lung ADC, and concluded that cytoplasmic ERβ expression is a negative predictor of clinical response to EGFR-TKIs in patients with EGFR mutations (Márquez-Garbán et al., 2007a). This awareness suggests that the ER and EGFR pathways might contribute together to the progression of LC, providing the rationale to target both the ER and EGFR pathways (Ding et al., 2018). Anyway, despite the promising preliminary activity data of antiestrogen plus EGFR-TKI combination (Márquez-Garbán et al., 2007b), two phase II trials failed to show any further survival benefit from adding fulvestrant to EGFR-inhibitors as single agent in EGFR mutant patients (Traynor et al., 2009; Garon et al., 2010). On the other hand, the oncogenic role of androgens in LC development and/or progression was also found in the subset of LC harboring an EGFR mutation. In particular, the androgen receptor resulted over expressed among EGFRm NSCLC and in those acquiring the most common TKI resistance mutation (T790 M) (Mazieres et al., 2018).

Thus, despite their different spectrum of interaction with EGFR, both male and female hormonal mediators have a common pro-tumor effect even in EGFRm NSCLC. Further studies are needed to explain the mechanisms involved in a possible different efficacy of TKI therapy between genders, and also if sexual hormones might play a crucial role in this sense or not.

6.4.2.2.2. ALK inhibitors (ALKi). ALK rearrangements are found in about 5% of patients with NSCLC and are related to younger age, no history of smoking and distinct clinical-pathological features such as adenocarcinoma histology (Fallet et al., 2014). Crizotinib was the first agent approved for front-line therapy of ALK-rearranged NSCLC after its demonstrated superiority over chemotherapy. Next-generation ALKi have been developed to overcome crizotinib resistance. Currently, three second-generation ALKi, ceritinib, alectinib, and brigatinib, and the third-generation inhibitor lorlatinib are FDA approved for use in ALK-rearranged NSCLC following progression or intolerance to crizotinib. Later on, different second generation ALKi demonstrated a survival advantage when used upfront, thus leading FDA to broaden ceritinib and alectinib indication to untreated patients with ALK-rearrangement; more recently brigatinib showed a significantly longer PFS compared to crizotinib in ALKi naïve patients (Blakely et al., 2017).

Analyzing the registration studies of the ALKi, no difference between genders in terms of PFS has been observed (Table 1). This scenario is confirmed by the above mentioned meta-analysis by Pinto el al. (Remon et al., 2017), where ALKi gave a higher benefit over the standard of care independently of patients gender (male, HR = 0.48, 95% CI, 0.39-0.59; $p < 0.00001$; female, HR = 0.51; 95% CI, 0.45-0.61; $p < 0.00001$).

6.4.2.3. Immune check point inhibitors (ICIs). Recently, the advent of ICIs led to substantial and unprecedented changes in the therapeutic algorithms of NSCLC. Thanks to a better outcome and safety profile over previous standard of care chemotherapy regimens, different ICIs - especially those targeting the PD-1/PD-L1 axis - received rapid approval for the treatment of locally advanced/metastatic NSCLC. Subsequent developments led to validation of ICI-ICI and ICI-chemotherapy combinations in metastatic NSCLC (Camidge et al., 2018; Socinski et al., 2018), and to an optimization of chemo-radiotherapy in locally advanced NSCLC through anti-PD1 as consolidation approach (Martinez et al., 2019). Moreover, some neoadjuvant and adjuvant clinical ICI trials are currently ongoing in early-stage disease. Beyond a general benefit in median PFS and/or OS, some metastatic NSCLC patients treated with ICIs find, a major benefit, in terms of a more prolonged OS. Predictive criteria of ICI efficacy are not yet fully identified and the efforts of the scientific community are directed to their identification, in order to improve patient selection. Despite their increasing popularity integrated immunograms generally do not take into account a s sex. Usually, a patient's sex is considered as a stratification criterion in randomized clinical trials, and considerations about ICI efficacy in males and females mainly derive from post-hoc subgroup analysis (Table 1). A phase III study comparing nivolumab with docetaxel in patients with advanced non-SCCNSCLC showed that nivolumab did not improve overall survival in women (HR = 0.78, 95% CI, 0.58–1.04) (Gandhi et al., 2018). Similarly, lack of survival benefit for females was also found in the same setting for SCC

Table 1
Outcome by patients' sex according to NSCLC phase III randomized clinical trials. 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. Legend: BEV: bevacizumab; CBDCA: carboplatin; CDDP: cisplatin; ChT: chemotherapy; GEM: gemcitabine; (nab)TAX: nab-paclitaxel/paclitaxel; NA: not assessed; ND: not determinate; PEM: pemetrexed; Plt: platinum; SCC: squamous cell carcinoma; TAX: paclitaxel; TXT: docetaxel.

Drug class	Trial	Histology	Stage	Inclusion criteria	Treatment	Comparator	Line	Pts, n	M to F ratio	PFS, male HR (95% CI)	PFS, female HR (95% CI)	PFS, p interact	OS, male HR (95% CI)	OS, female HR (95% CI)	OS, p interact
ICI	KEYNOTE 189	nSCC NSCLC	IIIB, IV	No PD-L1 threshold	PEM-PltCht + Pembrolizumab	PEM-PltCht	1	616	1,4	0.70 (0.50-	0.29 (0.19-	ND	0.66	0.40	ND
	KEYNOTE 407	SCC NSCLC	IIIB, IV	No PD-L1 threshold	Pembrolizumab + CBDCA + (nab)TAX	CBDCA + (nab)TAX	1	559	4,9	0.99)	0.44)	ND	(0.50-	(0.29-	ND
	KEYNOTE-024	NSCLC	IIIB, IV	PD-L1 TPS ≥ 50%	Pembrolizumab	Plt-based ChT	1	305	1,6	0.58 (0.46-	0.49 (0.30-	ND	0.87)	0.54)	NA
	KEYNOTE-042	NSCLC	IIIB, IV	PD-L1 TPS ≥ 1%	Pembrolizumab	Plt-based ChT	1	1274	2,42	0.73)	0.81)	ND	0.69	042	ND
	CheckMate 057	nSCC NSCLC	IIIB, IV	No PD-L1 threshold	Nivolumab	TXT	≥ 2	582	1,2	0.39 (0.26-	0.75 (0.46-	ND	(0.51-	(0.22-	ND
										0.58)	1.21)		0.94)	0.81)	
										ND	ND		ND	ND	
										0.81 (0.63-	1.04 (0.80-		0.80	0.89	
										1.04)	1.37)		(0.68-	(0.68-	
													0.94)	1.17)	
													0.73	0.78	
													(0.56-	(0.58-	
													0.96)	1.04)	
	CheckMate 017	SCC NSCLC	IIIB, IV	No PD-L1 threshold	Nivolumab	TXT	2	272	3,3	0.63 (0.46-	0.71 (0.40-	ND	0.57	0.67	ND
										0.85)	1.26)		(0.44-	(0.36-	
													0.71)	1.25)	
	KEYNOTE-010	NSCLC	IIIB, IV	PD-L1 TPS ≥ 1%	Pembrolizumab 2 mg/kg	TXT	2	687	1,6	0.78 (0.64-	1.02 (0.78-	ND	0.65	0.69	ND
	KEYNOTE-010	NSCLC			Pembrolizumab 10 mg/kg			689		0.94)	1.32)		(0.52-	(0.52-	
													0.81)	0.81)	
	OAK	NSCLC	IIIB, IV	No PD-L1 threshold	Atezolizumab	TXT	≥ 2	850	1,6	ND	ND	NA	0.79	0.64	ND
													(0.64-	(0.49-	
													0.97)	0.85)	
	PACIFIC	NSCLC	IIIA, IIIB	No PD-L1 threshold	Durvalumab	placebo	cons.	713	2,3	0.56 (0.44-	0.54(0.37-	ND	NA	NA	NA
										0.71)	0.79)				
EGFRi	ISEL	NSCLC	IIIB-IV	No selection for EGFR	Gefitinib	placebo	≥ 1	1692	2,1	ND	ND	NA	0,9	0.75	ND
	INTEREST	NSCLC	IIIB-IV	No selection for EGFR	Gefitinib	TXT	≥2	1466	1,9	ND	ND	NA	1.15	0.89	0,27
	IPASS	NSCLC	IIIB-IV	No/former smokers	Gefitinib	CBDCA-TAX	1	1217	0,3	ND	ND	NA	ND	ND	NA
	NEJ002	NSCLC	IIIB-IV	EGFR del19, L858R, others, no T790M	Gefitinib	CBDCA-TAX	1	228	0,6	ND	ND	NA	ND	ND	0,883
	WJTOG3405	NSCLC	IIIB-IV	EGFR del19, L858R	Gefitinib	CDDP-TXT	1	172	0,4	0.67 (0.33-	0.41 (0.26-	ND	ND	ND	NA
										1.33)	0.65)				
	OPTIMAL, CTONG-0802	NSCLC	IIIB-IV	EGFR del19, L858R	Erlotinib	CBDCA-GEM	1	154	0,7	0.26 (0.14-	0.13 (0.07-	ND	1.31	1.2	NA
										0.50)	0.24)				
	EURTAC	NSCLC	IIIB-IV	EGFR del19, L858R	Erlotinib	Plt-based ChT	1	173	0,4	0.38 (0.17-	0.35 (0.22-	0.4721	ND	ND	ND
										0.84)	0.55)				
	LUX-Lung 3	ADC NSCLC	IIIB-IV	EGFR del19, L858R, others	Afatinib	CDDP-PEM	1	345	0,5	0.61 (0.37-	0.54 (0.38-	0,85	ND	ND	ND
										1.01)	0.76)				
	LUX-Lung 6	ADC NSCLC	IIIB-IV	EGFR del19, L858R, others	Afatinib	CDDP-GEM	1	364	0,5	0.36 (0.21-	0.24 (0.16-	ND	ND	ND	ND
										0.62)	0.35)				
	AURA3	NSCLC	IIIB-IV	EGFR T790M	Osimertinib	Plt-PEM	2	419	0,6	0.43 (0.28-	0.34 (0.25-	ND	NA	NA	NA
										0.65)	0.47)				
	FLAURA	NSCLC	IIIB-IV	EGFR del19, L858R	Osimertinib	Gefitinib or Erlotinib	1	556	0,6	0.58 (0.41-	0.4 (0.30-	ND	NA	NA	NA
										0.82)	0.52)				

(*continued on next page*)

Table 1 (*continued*)

Drug class	Trial	Histology	Stage	Inclusion criteria	Treatment	Comparator	Line	Pts, n	M to F ratio	PFS, male HR (95% CI)	PFS, female HR (95% CI)	PFS, p interact	OS, male HR (95% CI)	OS, female HR (95% CI)	OS, p interact
ALKi	PROFILE 1007	NSCLC	IIIB-IV	ALK positive	Crizotinib	PEM or TXT	2	347	0,8	0.52 (0.35-0.77)	0.48 (0.34-068)	ND	ND	ND	ND
	PROFILE 1014	NSCLC	IIIB-IV	ALK positive	Crizotinib	PEM-PltCht	1	343	0,6	0.54 (0.36-0.82)	0.45 (0.32-0.63)	ND	ND	ND	ND
	ASCEND-5	NSCLC	IIIB-IV	ALK positive	Ceritinib	PEM or TXT	2 or 3	231	0,8	0.43 (0.26-0.71)	0.51 (0.33-0.78)	ND	ND	ND	ND
	ASCEND-4	NSCLC	IIIB-IV	ALK positive	Ceritinib	PEM-PltCht	1	376	0,7	0.41 (0.27-0.63)	0.63 (0.43-0.93)	ND	ND	ND	ND
	J-ALEX	NSCLC	IIIB-IV	ALK positive	Alectinib	Crizotinib	1 or 2	207	0,7	0.35 (0.16-0.77)	0.31 (0.17-0.57)	ND	ND	ND	ND
	ALEX	NSCLC	IIIB-IV	ALK positive	Alectinib	Crizotinib	1	303	0,8	0.61 (0.38-0.98)	0.39 (0.25-0.60)	ND	ND	ND	ND
	ALUR	NSCLC	IIIB-IV	ALK positive	Alectinib	PEM or TXT	3	107	1,2	0.25 (0.10-0.60)	0.08 (0.02-0.30)	ND	ND	ND	ND
	ALTA-1 L	NSCLC	IIIB-IV	ALK-positive	Brigatinib	Crizotinib	1	275	0,83	0.49 (0.28-0.85)	0.44 (0.24-0.84)	ND	ND	ND	ND
ChT	Schiller JH et al.	NSCLC	IIIB-IV	See Schiller JH et al.	CDDP-GEM	CDDP-TAX	1	576	1,7	ND	ND	ND	ND	ND	ND
		NSCLC	IIIB-IV		CDDP-TXT	CDDP-TAX	1	577	1,7	ND	ND	ND	ND	ND	ND
	NEJM 2002	NSCLC	IIIB-IV	NEJM 2002	CBDCA-TAX	CDDP-TAX	1	578	1,7	ND	ND	ND	ND	ND	ND
	JMDB	NSCLC	IIIB-IV	See NCT000887711	CDDP-PEM	CDDP-GEM	1	1725	2,3	ND	ND	ND	0.98	0.84	ND
	PARAMOUNT	nSCC NSCLC	IIIB-IV	Induction CDDP-PEM	PEM maintenance	placebo	1	539	1,4	0.74(0.55-1.00)	0.49 (0.34-0.72)	ND	0.82	0.73	ND
	ECOG 4599	nSCC NSCLC	IIIB-IV	No brain metastases	CBDCA-TAX-BEV	CBDCA-TAX	1	850	1,2	ND	ND	ND	0.7	0.98	ND
	AVAiL	nSCC NSCLC	IIIB-IV	No brain metastases	CDDP-GEM-BEV 7.5 mg/kg	CDDP-GEM	1	692	1,8	0.76	0,8	ND	0.94	0.91	ND
	AVAiL	nSCC NSCLC	IIIB-IV	No brain metastases	CDDP-GEM-BEV 15 mg/kg	CDDP-GEM	1	698	1,7	0.98	0.57	ND	1.12	0.84	ND

(HR = 0.67; 95% CI, 0.36–1.25) (Borghaei et al., 2015). Likewise, the results of KEYNOTE-010 trial comparing pembrolizumab *versus* docetaxel in patients previously treated with platinum-doublet chemotherapy showed that pembrolizumab did not increase the progression free survival (PFS) in women (HR = 1.02, 95% CI:0.78–1.32); however, these women benefited in OS from the experimental treatment, just like the men (Brahmer et al., 2015). Pembrolizumab did not confer a PFS benefit in women (HR = 0.75; 95% CI,0.46–1.21) even when administered in naïve patients having a PD-L1 expression ≥50% (Herbst et al., 2016). Sex-subgroup analysis for the updated OS results of this latest trial has not been reported (Reck et al., 2016), but another first line study testing pembrolizumab in patients with PD-L1 expression ≥1% showed that women did not benefit in OS (HR = 0.89; 95% CI,0.68–1.17) (Brahmer et al., 2017a). Conversely, all these RCTs showed that ICIs improved the outcome in the male subgroup. Differently from the anti-PD-1 agents, the activity of ICIs targeting its ligand seems not to be influenced by a patient's sex (Martinez et al., 2019; Lopes et al., 2018).

Recently some systematic reviews and meta-analyses investigated the correlation between patient sex and survival benefit from ICI. According to a meta-analysis of five RCTs (N = 3025) comparing a PD-1/PD-L1 ICI with docetaxel as second line treatment, the immunotherapy benefit resulted similar in men [HR = 0.69] compared to women [HR = 0.70]; interaction, p = 0.82) (Rittmeyer et al., 2017). Willis et al. showed no statistically significant association of patient sex with the efficacy of ICIs in terms of OS in the treatment of advanced cancers, and even for NSCLC by subgroup analyses of eleven RCTs involving more than 6000 patients (male HR = 0.79; 95% CI,0.71-0.88; female HR = 0.72; 95% CI,0.56-0.93; p = 0.79) (Lee et al., 2018).

However, another meta-analysis showed a greater benefit from ICIs in men than in women across different advanced solid cancer types. This trend was also found for the six RCTs that enrolled NSCLC patients (N = 3482), with the pooled hazard ratio of these studies revealing a sex-dependent magnitude of benefit from ICI use (male pooled HR = 0.72; 95% CI,0.61–0.86; female pooled HR = 0.89; 95% CI,0.71–1.11; p heterogeneity = 0.72) (Wallis et al., 2019).

Data about ORR to PD-1/PD-L1-inhibitors as single agents in NSCLC patients included in the main clinical trials are generally unreported distinctly for patients' sex. As known, ICIs confer a variably defined long-term benefit in about a quarter of treated NSCLC patients. Based on data from the ICI trial with the current longest follow-up time, no difference was shown in 5-year survival rate between males and females (Conforti et al., 2018).

More recent, first line setting RCTs showed a benefit from the use of ICIs, when added to standard first line chemotherapy, even in patients with PD-L1 less than 1%. The addition of pembrolizumab to standard chemotherapy doublet of platinum-based drug *plus* pemetrexed resulted in significantly longer OS and PFS than chemotherapy alone in non-squamous NSCLC. Subgroup analysis for OS showed a relative greater benefit, although not significant, for female patients treated with immunotherapy (female HR = 0.44, CI 0.28–0.71; male HR = 0.70, CI 0.50–0.99) (Socinski et al., 2018). The addition of atezolizumab to Bev *plus* carboplatin and paclitaxel (BCP) significantly improved PFS compared to BCP alone among patients with metastatic non-squamous NSCLC regardless of PD-L1 expression and gender (female HR = 0.73, 8.2 mo *vs* 6.8 mo; male HR = 0.55, 8.4 mo *vs* 6.8 mo), showing also a OS benefit at the interim analysis (Camidge et al., 2018); similar results came from another first line atezolizumab-chemo combo regimen (Brahmer et al., 2017b). Even SCC-NSCLC patients seem to benefit from the use of upfront anti PD-L1 (Papadimitrakopoulou et al., 2019) or anti PD-1 *plus* chemo combinations; the addition of pembrolizumab to carboplatin *plus* paclitaxel or nab-paclitaxel resulted in a significantly longer OS and PFS than chemotherapy alone (Jotte et al., 2019), with no apparent discrepancy between sexes (Table 1). Combining different ICIs together is another emerging strategy: first-line nivolumab *plus* ipilimumab showed a significantly longer PFS compared with chemotherapy in naïve patients with NSCLC and a high TMB (≥ 10 mutations per megabase), with a greater survival benefit in males than females at the subgroup analysis (male HR = 0.52, 95% CI, 0.36-0.74; female HR = 0.70, 95% CI, 0.41–1.20) (Paz-Ares et al., 2018).

Thus, whether gender could be a factor impacting on ICI benefit remains unclear. Despite this unanswered question, speculations about the role of a patient's sex on immunotherapy efficacy are possible. With various degrees of evidence, an absence of common driver mutations, a positive PD-L1 expression and a high TMB smoking status is known to be associated with smoking status (Hellmann et al., 2018b; Keselman et al., 2017; Davis et al., 2017). Thus, the smoking-related genomic signature, more frequent in males, might be correlated with their major benefit of ICI use.

Furthermore, the physiological differences between male and female immune system responses may also play a role. Across all ages, males have a higher lymphocyteCD8+/CD4+ ratio than females. The functional expansion and activation of CD8+ cytotoxicity by PD-1/PD-1 ICIs could therefore be more powered in males, thus resulting in their better outcome secondary to immunotherapy use. An additional effect of ICIs seem to be a M1 macrophage polarization (Calles et al., 2015b), known to be correlated to an extended OS in lung cancer patients (Mediavilla-Varela et al., 2019). The classical activated M1-macrophages comprise immune effector cells with an acute inflammatory phenotype, while the alternatively activated M2-macrophages promote cell proliferation and tissue repair. Females, partly due to estrogen signaling (Hellmann et al., 2018b), have a greater M2-macrophage polarization than males, and this could contribute to the lesser benefit from ICIs therapy.

Multiple factors could be responsible for the discrepancies in immune responses observed between males and females (Fig.1), with sexual hormones apparently playing a major role.

For example, the 17β-estradiol(E2) pathway promotes a protumor microenvironment (TME) through a redundancy of mechanisms (Jackute et al., 2018), among which a PD-L1 increased expression (Rothenberger et al., 2018). Furthermore, under sex hormone stimulation, T cells of males were found to produce higher IFNγ+ Th1-type cytokines than those of women (Yang et al., 2017).

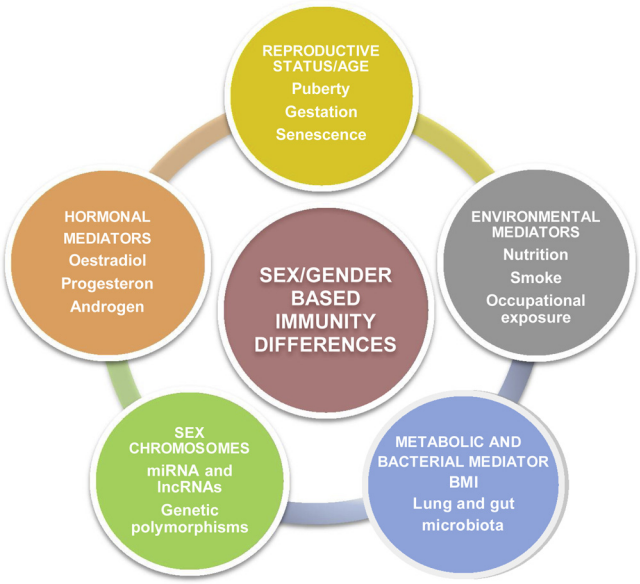

Fig. 1. Putative mediators differently expressed in M and F and influencing the immune-system. The differences in the immune system features existing between M and F could be a consequence of various kind of mediators differently expressed in the two sexes, mediators that resulted functionally connected to each other. Legend: BMI: body mass index; miRNA: micro RNA; lncRNAs: long-non-coding RNA; SHS: second hand smoke.

Sex/gender-based differences in lung cancer	♂	♀
Epidemiology	▪ Incidence: 70/100.000 in U.S. ▪ Decreasing incidence since mid-80's	▪ Incidence: 52/100.000 in U.S. ▪ Decreasing incidence since early 2000 ▪ Lower decreasing trend than M
Etiological concauses	▪ Higher smoking status ▪ Androgen carcinogenic effect	▪ Higher level of CYP1A1 ▪ Estrogen carcinogenic effect ▪ Domestic PAH exposure
Cancer histology	▪ Higher incidence of SCC-NSCLC	▪ Higher incidence of ADK-NSCLC ▪ Higher incidence of bronchioalveolar carcinoma
Cancer molecular features	▪ Higher incidence of STK11, RBM10, SMARCA4 mutation ▪ Higher TMB, PD-L1 expression	▪ Higher incidence of more common oncogene driver alterations (KRAS G12C, EGFR, ALK, ROS1, HER2, BRAF)
Immune system features	▪ Higher CD8+/CD4+ ratio* ▪ M1 oriented macrophages* ▪ Th1 oriented CD4+ helper T cells*	▪ Higher PD-L1 neg and TILs neg tumors ▪ Tumor immune gene sets enrichment (APOBEC3G-F, LAT, CD1D, CCL5)
Therapies efficacy	▪ Apparent greater benefit than F from ICIs	▪ Apparent greater benefit than M from loco-regional, chemo and targeted therapies

Fig. 2. Sex/gender-based differences in lung cancer patients. The known differences between males and females in etiological concauses, tumor histology and molecular features, as well as in immune-system characteristics might theoretically be responsible for a sex-based difference in therapy efficacy, especially for NSCLC histology. The asterisk (*) indicates those differences between the sexes evidenced in the general population, but not specifically in lung cancer patients. ADK: adenocarcinoma; APOBEC3 G: apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3 G; CCL5: Chemokine (C-C motif) ligand 5; CD1D: cluster of differentiation 1 D; CYP1A1: cytochrome P450, family 1, subfamily A, polypeptide 1. F: females; ICIs: immune checkpoint inhibitors; LAT: linker for activation T cell; M: males; PAH: polycyclic aromatic hydrocarbons; RCTs: randomized clinical trials; SCC: squamous cell carcinoma; TILs: tumour infiltrating lymphocytes.

The main limitation of this finding is that our knowledge about the male and female immune compartment mostly derives from healthy patients or from patients affected by non-oncological diseases. Noteworthy, the same M2-oriented macrophage differentiation of females has not been found in cancer patients, with tumor associated macrophages (TAM) features not differently represented by sex according to small NSCLC case series (Girón-González et al., 2000).

Finally, on the basis of results from clinical trials investigating ICI-chemo combinations, where similar survival benefit between genders is observed, it is tempting to speculate that the relative greater benefit of chemotherapy described in females (Albain et al., 1991) might balance the lower sensitivity to immunotherapy action, and vice versa in males.

7. Conclusion and perspectives

Available literature data suggest some different features in male and female lung cancer patients, from etiology to anatomo-pathology and treatment outcome (Fig. 2); even some differences between genders at gene-expression and miRNA levels are emerging.

Historically, women with NSCLC exhibit greater survival rates than men regardless of disease stage, histology, treatment modality, or smoking status, even after adjusting for gender-specific life expectancy (Girón-González et al., 2000; Fu et al., 2005; Thomas et al., 2005). With various levels of evidence, a survival advantage in favor of females was found in both NSCLC patients treated with radical aim (surgery, radiotherapy, chemo-radiotherapy) and those treated with a palliative platinum-based chemotherapy regimen or an EGFR TKI (O'Connell et al., 1986). Data on a patient's sex as a predictor of benefit of targeted therapies other than EGFR inhibitors are quite lacking. Also, in SCLC histology, female sex seems to be associated with improved survival.

These suggestions derived mainly from results of a retrospective study including a heterogeneous patient population (Nakamura et al., 2011) and a subgroup analysis of RCTs, in which a patient's sex was not considered as a stratification factor. Females are historically underrepresented in RTCs (Viñolas et al., 2007), despite some recent positive data about women enrollment (Murthy et al., 2004; Labots et al., 2018), and trials among uniform populations addressing the role of sex on survival in NSCLC are lacking.

Moreover, most of the available data on treatment outcome refers to patients submitted to cytotoxic, anti-angiogenic or targeted therapies. Whether female sex remains a positive prognostic factor with the incoming of immunotherapy has to be clarified. First analyses investigating the role of gender in ICIs treated NSCLC patients turned the tide, with males apparently experiencing greater benefit compared to females. Some clinical-pathological features might explain such outcome discrepancies, and these data strongly support the significance of gender as a separate prognostic factor in advanced NSCLC and emphasize its importance as a stratification factor in future phase III NSCLC trial design.

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