Review Article

Oncogene-addicted non-small-cell lung cancer in women: a narrative review of the importance of gender-related differences in treatment outcome

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Background and Objective: The objectives are to identify potential differences in outcomes between males and females patients with oncogene-addicted non-small-cell lung cancer (NSCLC) treated with targeted agents. The discovery of driver oncogene alterations and the identification of their targeted inhibitors have dramatically improved the outcomes of patients with oncogene-addicted advanced NSCLC and the use of this class of drugs, in clinical practice, became the gold standard. Although gender is considered an independent prognostic factor and several studies showed some differences in terms of activation of metabolic pathways between sex, few data are available regarding potential differences in outcomes between males and females patients with oncogene-addicted NSCLC treated with targeted agents.

Methods: Available data regarding potential differences in outcomes between males and females affected by oncogene-addicted NSCLC and treated with targeted agents are reported. The study was limited to published manuscripts in the English language using extended literature data collection starting from 2009 and was focused on phase 3 trials.

Key Content and Findings: In most of the trials carried out in patients with oncogene-addicted NSCLC, women reported a better progression-free-survival than men.

Conclusions: The existence of a targetable driver alteration is significantly more frequent in women than in men. The majority of trials evaluating activity and efficacy of target agents demonstrated that both men and women with addicted-NSCLC benefited from the use of these treatments, whatever the treatment line. Most of the trials reported a hazard ratio (HR) for progression-free survival (PFS) consistently in favour of female patients over male. Unfortunately, a few studies used sex as a stratification factor, although this might impact the final results. Prospective studies are warranted to draw definitive conclusions about this topic.

Keywords: Oncogene-addicted; women; non-small-cell lung cancer (NSCLC)

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Introduction

Lung cancer is the leading cause of cancer-related deaths in Western countries. Non-small-cell lung cancer (NSCLC) accounts for more than 85% of primary lung cancers and approximately two-thirds of NSCLC patients are diagnosed at an advanced stage and their prognosis remains poor (1).

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	1 Jun 2021
Databases and other sources searched	Extended literature data collection
Search terms used (including MeSH and free text search terms and filters). Note: please use an independent supplement table to present detailed search strategy of one database as an example	Oncogene addicted, EGFR tyrosine-kinase inhibitors, ALK tyrosine-kinase inhibitors
Timeframe	Since 2009
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Phase 3 studies, English language
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The authors conducted independently the selection
Any additional considerations, if applicable	–

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

The discovery of driver oncogene alterations such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements, among others, and the identification of their targeted inhibitors, have significantly improved the outcomes in highly selected patients (2,3).

Gender difference can affect cancer prognosis, but also efficacy, activity and adverse events of systemic anticancer therapy. Some studies showed, in fact, important differences in terms of genetic polymorphisms of drug metabolizing enzymes (4), sex hormone levels (5), and immune system function (6). Differences are also reported regarding the gender-related susceptibility to smoke exposure (the risk of developing a lung cancer seems to be higher in women) (7), an aspect that, together with the delayed onset of smoking in women in comparison with men, may partly explain the epidemiological changes that have occurred in recent decades in terms of increased incidence of lung cancer in women. In NSCLC, gender has an established independent prognostic value regardless of stage, therapeutic modalities, or histology, with a risk of death which is 1.6 times higher in male than in female (8). This evidence should have implications in the design and interpretation of clinical trials, where females are more and more represented. Nevertheless, few data are available regarding potential differences in outcomes between males and females affected by oncogene-addicted NSCLC and treated with targeted agents. This paper summarizes the current evidence on the topic.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-31/rc).

Methods

The information regarding treatment of oncogene-addicted NSCLC extended over 2 decades. The study was limited to published manuscripts in the English language using extended literature data collection and was focused on phase 3 trials (*Table 1*).

EGFR tyrosine-kinase inhibitors (TKIs)

Four pivotal randomized trials comparing front-line chemotherapy combination with or without gefitinib (INTACT 1 and 2) or erlotinib (TALENT and TRIBUTE) showed no benefit in adding TKIs to standard platinum-based chemotherapy in patients with advanced NSCLC (9-12). It should be emphasized that the population of patients included was unselected. In a post hoc analysis, however, some clinical features emerged that correlated with a benefit from the addition of TKI to chemotherapy: adenocarcinoma histology, female sex, non-smoking status and ethnicity. In NSCLC, at the same time, clinical research led to the identification of mutations in a member of the human epidermal receptor (HER) receptor family and more precisely the presence of EGFR mutations. Patients with activating EGFR mutations were those who benefited most from adding TKI to chemotherapy (13). The EGFR mutation frequency was found to be higher in the clinical subgroups of patients identified from the retrospective studies indicated above: never smokers/smokers (51% *vs.* 10%), in adenocarcinomas *vs.* other histologies (40% *vs.* 3%), East Asian/other ethnicities (30% *vs.* 8%), females/

males (42% *vs.* 14%). All of these factors were independent predictors of benefit from TKIs on multivariate analysis (14). Sex emerged as a factor of clinical enrichment, correlation with the presence of EGFR mutations and, therefore, benefit from the use of TKIs. Some reports also suggested a gender difference in the presence of common mutation subtypes: the deletions in exon 19 were more frequently associated with male gender while exon 21 point mutations were with female gender (15). The exact mechanism by which each mutation subtype occurs still needs to be clarified; however some authors speculated that chromosomal recombination, that involves DNA double strand breaks and repairs, is likely to be involved in exon 19 deletions. It is well known that the meiotic recombination rate shows a clear gender difference (16).

To date we have three different generations of TKIs available in clinical practice: in patients with EGFR-mutated NSCLC all have demonstrated greater efficacy than chemotherapy in front- and subsequent lines of treatments.

Most of the initial phase 3 trials, that compared EGFR-TKIs with chemotherapy, also describe the results by gender; however, sex is not always a stratification factor in the randomization processes.

The IPASS was the first study comparing Gefitinib with chemotherapy (carboplatin plus paclitaxel) in an Asian clinically enriched patient population selected on the basis of smoking habits and histology. However women enrolled into the study were 965 and men were 252 only; therefore also the gender, although not declared, represented an important factor of clinical selection. The TKI showed a progression-free survival (PFS) statistically not inferior to chemotherapy in the intention-to treat analysis: hazard ratio (HR) for PFS or death (0.74; 95% CI: 0.65–0.85; P<0.01). However it demonstrated, at a planned exploratory analysis, a significantly longer PFS in EGFR-mutated patients (17).

On the contrary, the North-East Japan Study Group (18) comparing gefitinib with chemotherapy in treatment-naïve patients selected for the presence of activating EGFR mutations, used gender as stratification factor. The median PFS for gefitinib and chemotherapy was 10.8 *vs.* 5.4 months, respectively (HR 0.30; 95% CI: 0.22–0.41; P<0.001), while the response rate was 73.7% for the TKI and 30.7% for the carboplatin + paclitaxel combination (P<0.001). The analysis based on pre-randomization stratification factors showed that women had significantly longer PFS than men (HR 0.68; 95% CI: 0.51–0.92; P=0.01) (see *Table 2*). The overall survival did not differ significantly between the two treatment groups and, in particular, sex did not affect overall survival. However, in the present trial, 95% of the patients who have failed chemotherapy received second-line gefitinib.

In the same year the West Japan Oncology Group (WJOG) (19) carried out a randomized trial in EGFR-mutated Japanese patients comparing gefitinib with cisplatin/docetaxel in the front-line setting. The study randomized 117 patients and provided a pre-randomization stratification by sex like the previous study. Overall, the median PFS time was 9.2 months (95% CI: 8.0–13.9 months) in the gefitinib *vs.* 6.3 months (95% CI: 5.8–7.8 months) in the chemotherapy arm (HR 0.49, 95% CI: 0.33–0.71, log-rank P<0.0001). Although women treated with gefitinib had a longer PFS than men [HR for PFS was 0.42 (95% CI: 0.26–0.65) for women and 0.67 (95% CI: 0.33–1.33) for men] sex did not have a statistically significant relationship with PFS neither to univariate analysis (HR 0.93; 95% CI: 0.62–1.39; P=0.742) nor to multivariate (HR 0.63; 95% CI: 0.36–1.09; P=0.099).

Erlotinib, the other first-generation TKI inhibitor, was studied in the same setting in two pivotal phase 3 randomized studies.

The OPTIMAL-CTONG-0802 (20) was performed in 22 centers in China and recruited 154 NSCLC patients who randomly received either oral erlotinib or carboplatin/gemcitabine. This study did not include any stratification by sex. Patients in the experimental arm had a significantly longer median PFS [13.1 months (95% CI: 10.58–16.53 months) *vs.* 4.6 months (95% CI: 4.21–5.42 months)] in comparison with patients in the standard one (HR 0.16; 95% CI: 0.10–0.26; P<0.0001). The benefit in PFS seemed to be consistent across all clinical subgroups, including sex; in this regard the HR was 0.13 for women and 0.26 for men, without any statistically significant difference (*Table 2*). However, we must remember that the study was not sufficiently powered to identify significant differences in subgroups.

The EURTAC trial (21), randomised Caucasian patients to receive erlotinib or standard chemotherapy (cisplatin plus docetaxel or cisplatin/gemcitabine). The median PFS was 9.7 months (95% CI: 8.4–12.3 months) in the erlotinib arm *vs.* 5.2 months (95% CI: 4.5–5.8 months) in the chemotherapy group (HR 0.37; 95% CI: 0.25–0.54; P<0.0001). At the multivariable analysis sex was not significantly associated with PFS: HR was 0.35 for women and 0.38 for men. EURTAC was the first prospective head to-head phase 3 study carried out in non-Asian EGFR mutated NSCLC patients only. The Spanish Lung Cancer Group (27) conducted a population

Table 2 EGFR tyrosine-kinase inhibitors in first-line treatment

Author/study	Treatment arms	PFS (HR) in overall population	Male/female (n)	PFS (HR) by gender
Maemondo (18), NEJSG; Phase 3	Gefitinib, carboplatin/paclitaxel	0.30 (0.22–0.41)	83	NR
			145	0.68 (0.51–0.92)
Mitsudomi (19), WJOG; Phase 3	Gefitinib, platinum/docetaxel	0.48 (0.33–0.71)	53	0.67 (0.33–1.33)
			119	0.42 (0.26–0.65)
Zhou (20), OPTIMAL-CTONG-0802; Phase 3	Erlotinib, carboplatin/gemcitabine	0.34 (0.17–0.31)	63	0.26 (0.14–0.50)
			91	0.13 (0.07–0.24)
Rosell (21), EURTAC; Phase 3	Erlotinib/cisplatin + docetaxel or gemcitabine	0.37 (0.25–0.54)	47	0.38 (0.17–0.84)
			126	0.35 (0.22–0.55)
Wu (22), ENSURE; Phase 3	Erlotinib, cisplatin/gemcitabine	0.34 (0.22–0.51)	84	0.43 (0.22–0.83)
			133	0.29 (0.17–0.50)
Sequist (23), LUX-LUNG 3; Phase 3	Afatinib, cisplatin/pemetrexed	0.58 (0.43–0.78)	121	0.61 (0.37–1.01)
			224	0.54 (0.38–0.78)
Wu (24), LUX-LUNG 6; Phase 3	Afatinib, cisplatin/gemcitabine	0.28 (0.20–0.39)	126	0.36 (0.21–0.63)
			238	0.24 (0.16–0.35)
Wu (25), ARCHER 1050; Phase 3	Daconitinib, gefitinib	0.59 (0.47–0.74)	54	0.72 (0.51–1.02)
			82	0.50 (0.37–0.67)
Soria (26), FLAURA; Phase 3	Osimertinib, gefitinib or erlotinib	0.46 (0.37–0.57)	206	0.58 (0.41–0.82)
				0.40 (0.30–0.52)

EGFR, epidermal-growth factor receptor; PFS, progression-free survival; HR, hazard ratio; NR, not reported.

screening in Spanish NSCLC patients to establish the EGFR mutation frequency in that country. This job produced interesting results: it showed that in a European population of patients the frequency of EGFR activating mutation was 16.6% (far less than in the Asian ethnicity) and confirmed that EGFR mutations were more frequent in women (69.7%) than in men (30.3%). Patients with EGFR mutated NSCLC received erlotinib in first or further lines of therapy as standard treatment. Interestingly clinical results vary significantly according to sex: the adjusted HR for the duration of PFS and OS were 2.94 (95% CI: 1.72–5.03) and 3.48 (95% CI: 1.76–6.91) for men, respectively (P<0.001). This means that men were about 3 times more likely to progress from EGFR mutated lung cancer than women and 3 and a half times more likely to die. A difference in PFS and OS was also observed between type of EGFR rearrangement: considering exon 19 deletions *vs.* L858R point mutation the PFS HR was 1.92 (95% CI: 1.19–3.10); P=0.02 and OS HR was 2.98 (95% CI: 1.48–6.04); P=0.002. Overall, patients with exon 19 deletion treated with erlotinib fared better than patients with exon 21 point mutation receiving the same drug. This observation was confirmed by subsequent data strongly supporting the hypothesis that lung adenocarcinoma driven by exon 19 deletion is distinct from that led by exon 21 point mutation and has a different prognosis. In addition, the paper by Rosell *et al.* showed that in the group of patients carrying L858R mutation, the PFS was of 6 months (95% CI: 3.2–8.8 months) in men and 16 months (95% CI: 10.3–21.7 months) in women (P=0.004); in particular, in the present study, the benefit that men with L858R mutated adenocarcinoma obtained from erlotinib appears to be the same as with chemotherapy. These very interesting data would need prospective confirmation: in this case we would have been able to choose the therapeutic approach not only on the basis of the type of EGFR mutation but, for the same mutation, on the basis of gender.

A meta-analysis, published in 2015, and including seven randomized trials comparing EGFR TKIs with

chemotherapy in the first-line setting, was aimed at evaluating the impact of different EGFR mutations and clinical characteristics on PFS. Although the meta-analysis showed lack of association between the type of EGFR mutation and gender (P=0.81), EGFR TKI treatment provided a 27% greater benefit in women than in men in terms of PFS compared with chemotherapy (P=0.02) and the predictive effect of gender was independent of smoking status and EGFR mutation type (28).

The phase III ENSURE study evaluated first-line erlotinib *vs.* gemcitabine/cisplatin in advanced EGFR mutated NSCLC patients from China, Malaysia, and Philippines. The primary endpoint of the study was PFS and the patients were stratified by gender. Overall the median PFS was 11.0 months for erlotinib and 5.5 months for chemotherapy (HR 0.34, 95% CI: 0.22–0.51; P<0.0001) while the response rate was 62.7% for erlotinib and 33.6% for chemotherapy. Considering gender as stratification factors the HR for PFS in women was 0.29 (95% CI: 0.17–0.50) and 0.43 (95% CI: 0.22–0.83) in men. Although erlotinib significantly reduces the risk of lung cancer progression in both sexes, the risk reduction is, again, greater in women than in men (22).

The LUX-Lung 3 (23) randomized phase 3 study compared first line Afatinib with the combination of Cisplatin/Pemetrexed. Primary end-point was PFS and median PFS was 11.1 months for the second-generation EGFR TKI *vs.* 6.9 months for chemotherapy (HR 0.58; 95% CI: 0.43 to 0.78; P=0.001). Subgroup analyses showed that the benefit in PFS persisted among all clinically relevant characteristics including sex: the HR for women and men was 0.54 and 0.61 respectively (not statistically significant, but, once again different). Similar findings were reported by the LUX-LUNG 6 (24) study that evaluated afatinib *vs.* gemcitabine/cisplatin in 364 advanced EGFR mutated NSCLC patients from China, Thailand, and South Korea. Median PFS was significantly longer in the Afatinib group (11.0 months; 95% CI: 9.7–13.7 months) than in the chemotherapy one (5.6 months; 95% CI: 5.1–6.7 months) (HR 0.28; 95% CI: 0.20 to 0.39; P<0.0001). The PFS HR was 0.24 for women and 0.36 for male respectively.

The phase 3 ARCHER 1050 (25) trial was the second trial which compared first generation (gefitinib) to second generation EGFR TKIs (dacomitinib). Although this study was designed and carried out later, when interesting data of a gender-oriented activity of EGFR TKIs were already available, it does not foresee gender as a clinical stratification factor. However, there was a slight difference in baseline demographic characteristics since women were 64% in the experimental arm *vs.* 56% in the control arm. The median PFS was 14.7 months (95% CI: 11.1–16.6 months) in the dacomitinib group and 9.2 months (95% CI: 9.1–11.0 months) in the gefitinib group (HR 0.59; 95% CI: 0.47–0.74; P<0.0001). A subgroup analysis of PFS, according to pre-specified baseline characteristics, confirmed the significant improvement in PFS provided by Dacomitinib with a HR of 0.50 for women and 0.72 for male respectively. The difference was not statistically significant but, in line with all the previously exposed studies, women obtain a greater reduction in the risk of disease recurrence than men.

The FLAURA study (26) compared osimertinib *vs.* gefitinib or erlotinib in untreated EGFR-mutated NSCLC. The primary endpoint of the study was PFS, and, again, the study was not stratified according to sex. The results were impressive: the median PFS was significantly longer with osimertinib than with first-generation TKIs (18.9 *vs.* 10.2 months) (HR 0.46; 95% CI: 0.37–0.57; P<0.001). The objective response rate was similar in the two groups: 80% with osimertinib and 76% with standards ITKs but the median duration of responses were 17.2 and 8.5 months, respectively. Osimertinib favoured both sexes over standard TKIs with PFS HR of 0.58 in men and 0.40 in women.

Moreover, osimertinib was the first TKI which demonstrated a survival advantage over control arm; in fact, the overall survival analysis of FLAURA study (29) reported a median OS of 38.6 months in the osimertinib group and 31.8 months in the comparator group. The survival advantage was similar in both men and women: HR 0.79 (95% CI: 0.55–1.14) in men and HR 0.79 (95% CI: 0.60–1.04) in women.

The BR.21 (30) trial compared erlotinib *vs.* placebo in heavily pre-treated molecularly unselected advanced NSCLC patients. The study met its primary end-point of OS which was 6.7 months in the erlotinib arm *vs.* 4.7 months in the placebo one. No significant difference in OS emerged between sexes but the response rate was 14.4% in female *vs.* 6% in males (P=0.006) underlining the importance of gender as a clinical enrichment factor of benefit. Same considerations could be made for the INTEREST study (31) were 1.446 pre-treated molecularly unselected NSCLC patients randomly received gefitinib or docetaxel. The study met its primary endpoint of non-inferiority in OS between the two treatments, but again, at subgroup analysis by gender the survival with gefitinib was higher in women than in men (median 11.2 *vs.* 6.1 months respectively) while no differences emerged for docetaxel.

In an attempt to improve the efficacy of EGFR-TKIs

therapy a dual blockade strategy (EGFR and VEGF pathways) was tested in untreated EGFR-mutated patients. The RELAY trial randomised 449 patients to receive erlotinib or erlotinib plus ramucirumab. Randomization was stratified by sex. The median PFS was 19.4 months (95% CI: 15.4–21.6 months) in the combination arm and 12.4 months (95% CI: 11.0–13.5 months) in the erlotinib one with a HR 0.50 (95% CI: 0.46–0.76; P<0.001). The benefit of combination was observed in both sexes but with a different HR: 0.51 (95% CI: 0.34–0.75) in men and 0.73 (95% CI: 0.54–0.99) in women (32). The NEJ026 trial (33) by using a similar approach, compared erlotinib plus bevacizumab with erlotinib alone and further stressed this finding. Also, in this study randomization was stratified by sex. The median PFS for patients in the experimental group was 16.9 months (95% CI: 14.2–21.60 months) and 13.3 months (95% CI: 11.1–15.3 months) in the erlotinib group with a HR 0.60 (95% CI: 0.41–0.87; P=0.016). In the subgroup analysis, women seemed to be the ones who benefited the most from the combination with a HR of 0.45 (95% CI: 0.28–0.73) *vs.* 1.06 (95% CI: 0.58–1.94) in men. Unfortunately, no subsequent prospective studies have been conducted to confirm this finding which could have led to gender-based differential treatment.

In conclusion, all studies showed a consistent advantage in PFS of EGFR-TKIs over chemotherapy in first or subsequent lines, regardless of gender. Again, the two studies that compared second/third generation of EGFR-ITKs *vs.* first generation EGFR-ITKs showed advantage in PFS of new generation of EGFR-ITKs regardless of gender. Notably, in all but one studies reported above, the risk reduction for PFS was greater in women than in men. EURTAC was the only study that reported a similar HR for PFS between gender.

In two phase 3 trials, anti-antiangiogenetic antibody (ramucirumab or bevacizumab) were associated with an EGFR TKI and compared to EGFR TKI alone. Although both studies showed a greater benefit from the combination arm, the HRs for PFS by sex resulted contradictory.

ALK TKIs

EML4-ALK rearrangements occurred in about 5% of NSCLC patients and it is more frequent in never/light smokers, adenocarcinoma subtype and younger patients. The frequencies of ALK rearrangements ranged from 0% to 30.65% in male and from 2.63% to 37.04% in female NSCLC patients, respectively. Some authors showed that the odds ratio of carrying an ALK rearrangements was reduced by 28% in males, especially among Asian patients (34), while opposite results have been reported among European populations (35).

Crizotinib was the first drug which demonstrated an advantage over standard chemotherapy when used up-front. In the pivotal phase III PROFILE 1014 study, 343 patients with advanced ALK-positive NSCLC were randomized to receive crizotinib or combination chemotherapy (36). The primary endpoint of the study was PFS and the study was not stratified according to sex. The median PFS was longer in the crizotinib arm than in chemotherapy arm [10.9 *vs.* 7.0 months (HR for progression or death: 0.45; 95% CI: 0.35 to 0.60; P<0.001)] and the benefit was observed in both sex; however the hazard ratio for PFS was different between genders and equal to 0.54 (95% CI: 0.36 to 0.82) and 0.45 (95% CI: 0.32 to 0.63) for men and women respectively (see *Table 3*). Furthermore, in both randomised phase III trials comparing crizotinib with chemotherapy (PROFILE 1014 and PROFILE 1007), higher numbers of female patients have been included with a trend toward differences in the efficacy of this drug according to gender-subgroup analysis (36,42).

The second- generation ALK-inhibitor ceritinib was compared with chemotherapy in untreated ALK positive patients. In the phase III ASCEND 4 study (37), 376 patients were randomized to receive ceritinib 750 mg/die or platinum-based chemotherapy. The median PFS was 16.6 months in the ceritinib group and 8.1 months in the chemotherapy group (HR for progression or death: 0.55; 95% CI: 0.42 to 0.73; P<0.0001); no differences in OS were reported. Although the study was not stratified according to sex, the HRs for PFS of ceritinib *vs.* chemotherapy was 0.41 (95% CI: 0.27 to 0.63) in men and 0.63 (95% CI: 0.43 to 0.93) in women (*Table 3*). Unfortunately, OS data according to sex were not reported.

Two phase 3 trials compared alectinib to crizotinib: the J-ALEX study performed in the Japanese population only (38) and the ALEX trial carried out in different ethnicities (39). In both trials alectinib showed significantly superior activity and efficacy than crizotinib in terms of PFS. Although neither study was stratified by gender, in the ALEX trial women had a HR for PFS of 0.39, (95% CI: 0.25 to 0.60) while it was 0.61 (95% CI: 0.38 to 0.98) in men. In the J-ALEX study, instead, the HR for PFS was similar in both genders: 0.31 in women (95% CI: 0.17 to 0.57) and 0.35 in men (95% CI: 0.17 to 0.57).

Un update analysis of the ALEX trial demonstrated an overall survival advantage of alectinib over crizotinib with a HR 0.67 (95% CI: 0.46 to 0.98); interestingly the figures

Table 3 ALK tyrosine-kinase inhibitors in first-line treatment

Author/study	Treatment arms	PFS (HR) in overall population	Male/female (n)	PFS (HR) by gender
Solomon BJ (36), PROFILE 1014; Phase 3	Crizotinib, platinum/ pemetrexed	0.45 (0.35–0.60)	131	0.54 (0.36–0.82)
			212	0.45 (0.32–0.63)
Soria JC (37), ASCEND 4; Phase 3	Ceritinib, platinum/ pemetrexed	0.55 (0.42–0.73)	160	0.41 (0.27–0.63)
			216	0.63 (0.43–0.93)
Hida T (38), J-ALEX; Phase 3	Alectinib, crizotinib	0.34 (0.17–0.31)	82	0.35 (0.16–0.77)
			125	0.31 (0.17–0.57)
Peters S (39); ALEX; Phase 3	Alectinib, crizotinib	0.47 (0.34–0.65)	132	0.61 (0.36–0.91)
			171	0.39 (0.25–0.60)
Camidge DR (40), ALTA-1L; Phase 3	Brigatinib, crizotinib	0.49 (0.33–0.74)	150	0.49 (0.28–0.85)
			125	0.44 (0.24–0.84)
Shaw AT (41), CROWN; Phase 3	Lorlatinib, crizotinib	0.28 (0.19–0.41)	175	0.31 (0.18–0.34)
			121	0.26 (0.16–0.44)

ALK, anaplastic lymphoma kinase; PFS, progression-free survival; HR, hazard ratio.

were 0.76 for female (95% CI: 0.45 to 1.28) and 0.66 for male (95% CI: 0.39 to 1.11; P=0.69) (43). The discrepancy between the initial outcome of the ALEX trial and the outcome from the updated analysis is unclear. However, the difference in OS HR according to sex was not significant.

Brigatinib was the second next generation ALK-inhibitor compared to crizotinib in the ALTA-1L phase 3 study. The median PFS, primary endpoint of the study, was not reach for brigatinib and was 9.9 months (95% CI: 9.0–12.9 months) for crizotinib with an HR for progression or death 0.49 (95% CI: 0.33 to 0.74); P<0.001. No gender difference was reported (40,44).

The CROWN randomized trial compared lorlatinib with crizotinib in first-line therapy (41). The percentage of patients who were alive without disease progression at 12 months was 78% (95% CI: 70 to 84) in the lorlatinib group and 39% (95% CI: 30 to 48) in the crizotinib group (HR 0.28; 95% CI: 0.19 to 0.41; P<0.001). The HR for PFS was 0.31 for male (95% CI: 0.18 to 0.34) and 0.26 for female (95% CI: 0.16 to 0.44). No survival data have been published to date (*Table 3*).

Two phase II studies tested alectinib and one study brigatinib in patients who experienced disease progression during crizotinib (45-47), but unfortunately, data regarding gender outcomes were not reported. In the Japanese phase I–II study (AF-001JP), patients received alectinib after disease progression during chemotherapy (48). In it important to note that in the group of 24 women enrolled into the study the 3-year PFS rate was 77% whereas the same figures for the group of 22 men was 47%.

In the ASCEND-5 phase III trial, 231 patients previously treated with chemotherapy and crizotinib were randomised to receive ceritinib or chemotherapy (49). After a median follow-up of 16.5 months ceritinib showed a significant improvement of median PFS compared to chemotherapy (5.5 *vs.* 1.6 months, HR 0.49; 95% CI: 0.36 to 0.67; P<0.0001). The median PFS was 1.4 months (95% CI: 1.2–2.1 months) in men and 1.8 months (95% CI: 1.5–3.2 months) in women; the HR was 0.41 (95% CI: 0.27 to 0.63) and 0.63 (95% CI: 0.43–0.93), in men and women, respectively.

In conclusion, all studies that compared ALK inhibitors *vs.* chemotherapy or that compared new generation ALK inhibitors *vs.* crizotinib showed a PFS advantage for experimental arms compared to standard arms regardless of gender. Similarly to the studies with EGFR TKIs also in those with ALK inhibitors the risk reduction for PFS was greater in women than in men. The ASCEND-4 study, that compared ceritinib to chemotherapy in untreated patients, was the only study that reported a better HR in PFS for men than for women.

Conclusions

There is a consistent literature documenting the presence

of substantial differences in the onset and characteristics of lung cancer between men and women (50): women are more susceptible to the carcinogens contained in cigarette smoke, and to the carcinogenic effects of second-hand and environmental smoking. In addition among non-smokers the percentage of women who develop lung cancer is significantly higher than among men: in fact, never-smoking females are more likely to develop lung cancer than men who have never smoked. Female sex represents a prognostic factor: a meta-analysis, which included more than 32,000 women and 54,000 men, reported that survival of women was significantly better than the survival of men regardless of stage, treatment, smoking habit or age at diagnosis. Sex may be regarded not only as a prognostic factor, but as a predictive factor of benefit and/or toxicity although, in no case, to date, the choice of treatment is influenced by the patient's sex.

Interesting data have emerged regarding a gender-related differential benefit in non-addicted NSCLC patient treated with chemotherapy, immunotherapy or both. Also in molecularly-driven NSCLC some considerations can be made. First of all the existence of a targetable driver alteration is significantly more frequent in women than in men. To date most of the available data correlating gender and treatment benefit, in this setting, are on EGFR activating mutations. The majority of trials evaluating activity and efficacy of EGFR TKIs clearly demonstrated that both men and women with addicted-NSCLC benefited from the use of these molecules, whatever the treatment line. Despite this, looking in detail the retrospective subgroup analyses, most of them reported a HR for PFS consistently in favour of female patients over male. The ASCEND-4 trial was the only one that reported a HR for PFS that favoured male patients over female. The data from these studies were confirmed by a meta-analysis that included randomized trials comparing EGFR TKIs *vs.* chemotherapy in the first-line setting: this meta-analysis showed that female patients derived a 27% greater benefit from TKI therapy than male (27).

In order to boost up inhibition of EGFR receptor and clinical results, an anti-antiangiogenetic antibody (ramucirumab or bevacizumab) were associated with an EGFR TKI. Although both studies were stratified by sex, only the NEJ026 showed a greater benefit from the combination in favour of women. On the contrary, the RELAY trial gave opposite results. The reasons of these opposite results are unclear and should be clarified.

Unfortunately, despite the intriguing and consistent results previously reported a few studies used sex as a stratification factor, although this might impact the final results. Moreover no prospective trials are gender-driven precluding the possibility of carrying out, in clinical practice, a treatment more tailored to the biological and metabolic peculiarities of women. In addition, the limited number of patients included in some of the databases and the very preliminary clinical data available do not allow to drawn conclusion about gender predominance in some molecular alterations or whether smoking pattern might be a confounding factor in the interaction between gender and the molecular profile. Moreover, it is important to evaluate whether the toxicity profile of these TKIs are different according to gender. Despite the previous mentioned data, which are consistent in suggesting a potential prognostic and predictive role of sex in oncogene-addicted NSCLC, in the absence of prospective studies it takes a lot of caution in drawing definitive conclusions.

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