



Gender and outcomes in non-small cell lung cancer: an old prognostic variable comes back for targeted therapy and immunotherapy?

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ABSTRACT

Background There are well-known differences in gender outcome in non-small cell lung cancer (NSCLC) and other cancers. In this work, we evaluated several randomised clinical trials to explore the gender influence in the outcome of patients with NSCLC treated with targeted therapy and immunotherapy.

Methods We performed a series of meta-analysis to compare the gender outcome in the routine setting for overall survival and progression-free survival (PFS) in phase III randomised clinical trials comparing EGFR inhibitors versus chemotherapy (OPTIMAL, LUX-lung 3, LUX-lung 6, EURTAC, ENSURE and WTJOG); ALK inhibitors versus chemotherapy (ASCEND 4, ASCEND 5, PROFILE 1014 and NCT009323893) and anti-PD1 checkpoint inhibitors versus chemotherapy (CheckMate 017, CheckMate 026, CheckMate 057, KEYNOTE 010 and KEYNOTE 024).

Results Female patients with NSCLC have a reduced risk of death compared with men (HR=0.73; 95% CI 0.67 to 0.79; $p<0.00001$). Women had a better benefit from EGFR inhibitors than men (HR=0.34; 95% CI 0.28 to 0.40; $p<0.00001$ vs HR=0.44; 95% CI 0.34 to 0.56; $p<0.00001$, respectively). The benefit from ALK inhibitors was similar for both genders (HR=0.51; 95% CI 0.42 to 0.61; $p<0.00001$ vs HR=0.48; 95% CI 0.39 to 0.59; $p<0.00001$, for women and men, respectively). Anti-PD1 inhibitors significantly improved the PFS in male patients when compared with chemotherapy (HR=0.76; 95% CI 0.68 to 0.86; $p<0.00001$); in contrast, women showed no benefit in 5/5 randomised trials (HR=1.03; 95% CI 0.89 to 1.20; $p=0.69$).

Conclusions In this exploratory study, some targeted treatments were influenced by gender. Despite differences in outcomes that could be attributed to different histology, EGFR and smoking status, gender should be evaluated more deeply as prognostic variable in patients with NSCLC.

INTRODUCTION

Lung cancer is responsible for 1.6 million of deaths every year where tobacco smoking is the main risk factor.¹ While lung cancer has historically affected primarily men, the difference in the incidence of lung cancer between

Key questions

What is already known about this subject?

- Gender is an important prognostic variable in non-small cell lung cancers and other cancers.
- There is a different immune background between genders that could influence the response to therapy.
- Female patients have better outcomes than male patients in several cancer types.

What does this study add?

- Women have an improved benefit compared with men when they are treated with EGFR inhibitors versus chemotherapy.
- Women have a decreased benefit from anti-PD1 inhibitors compared with men.
- There is no difference in the benefit between genders when they are with ALK inhibitors versus chemotherapy.

How might this impact on clinical practice?

- Selection of female patients who will be treated with anti-PD1 immune checkpoint inhibitors should be improved.

genders has narrowed over the last years.² Differences are also observed in lung cancer susceptibility after tobacco smoke exposition (higher in women).^{3,4}

The difference in the clinical outcome between male and female patients with non-small cell lung cancer (NSCLC) is well known and has been addressed in several reports where women have a decreased risk to progression and death even when adjusting for age, histology and stage.^{5–8}

Because the cancer corresponds to a heterogeneous entity, differences in response to treatment and outcomes could be related also to a differential distribution of clinico-pathological features, for example, smoking status, histology, *EGFR* mutations, and so on.⁹

In a previous work we analysed gender-associated differences in immune gene sets enrichment in NSCLC where regardless of the smoking status or histology, women had higher expression of gene sets associated with immune processes.¹⁰ As gender influences innate and adaptive immune responses, immunological differences could be behind the differences in outcomes observed in some malignant diseases.¹¹

Some therapeutic strategies involve manipulating the immune system while the immune system per se helps to model cancer evolution determining differences in tumour aggressiveness and response to treatment.^{12–14}

In this paper we explore gender differences in outcomes and treatment effect in clinical trials evaluating targeted therapy.

METHODS

Meta-analysis

The meta-analysis was performed using the RevMan V.5 program (<http://community.cochrane.org/tools/review-production-tools/revman-5>). For overall survival (OS) and progression-free survival (PFS), we extracted the logarithm of HRs ($\ln(\text{HR})$) and the SE of $\ln(\text{HR})$ using the values of HRs and 95% CIs from the reports of interest. A random effects model was chosen for the meta-analysis of comparison between genders because of the heterogeneity of periods of time and treatment in the data sets. In contrast, we adopted fixed effects assumption for the evaluation of targeted therapy in clinical trials. I^2 statistic was used to estimate heterogeneity of results beyond chance. Publication bias was assessed by visual asymmetry on a funnel plot.

Meta-analysis for gender differences in OS

We retrieved information from 67 published records (from 1989 to 2016), of which 12 were eligible for data extraction. In total, only seven references were evaluable because they have data of HRs and 95% CI obtained from multivariate analysis of OS. One publication had HR data estimated in several periods of time. In this case, each period was included as a different group (online supplementary figure S1).^{15–21}

Gender-specific benefit from targeted therapy and immunotherapy in terms of PFS

Meta-analysis of EGFR tyrosine kinase inhibitors

In total, six phase III clinical trials testing EGFR tyrosine kinase inhibitor (TKI) versus chemotherapy in patients with NSCLC with EGFR mutations were identified (OPTIMAL, LUX-lung 3, LUX-lung 6, EURTAC, ENSURE and WTJOG) evaluating gefitinib or erlotinib or afatinib (table 1) (online supplementary figures S2–S4).^{22–27}

Meta-analysis of ALK inhibitors

In total, four phase III randomised trials comparing ALK inhibitors versus chemotherapy in patients with NSCLC whose tumours bared ALK rearrangements were identified and evaluated (ASCEND-4, ASCEND-5,

PROFILE-1014 and NCT009323893). Two trials evaluated ceritinib and two crizotinib.^{28–31} Two trials were in first-line treatment or metastatic or recurrent NSCLC (ASCEND-4 and PROFILE-1014), two trials in second-line treatment in patients who had received one prior platinum-based regimen (NCT00932893) or previously exposed to crizotinib and platinum-based doublet chemotherapy (ASCEND-5) (online supplementary figure S5).

Meta-analysis of anti-PD1 inhibitors

We evaluated five randomised phase III studies comparing anti-PD1 inhibitors versus chemotherapy, including two studies with pembrolizumab versus chemotherapy (KEYNOTE 010 and KEYNOTE 024) and two with nivolumab versus chemotherapy (CheckMate 017, CheckMate 026, CheckMate 057).^{32–36} The KEYNOTE 010, KEYNOTE 024 and CheckMate 026 trials included positivity to PD-L1 tumour expression as inclusion criteria while CheckMate 017 and CheckMate 057 trials included patients with NSCLC regardless of their PD-L1 status (online supplementary figure S6).

RESULTS

Improved OS in female patients in data from the routine setting

In total, seven studies for OS multivariate analysis were identified. Because one study included five periods of time, every period was evaluated independently. In the meta-analysis with the random effects methods, an HR=0.73 was obtained favouring female patients ($p<0.00001$; 95% CI 0.67 to 0.79), with high statistical heterogeneity between cohorts ($p=0.0005$; $I^2=68\%$) (figure 1).

Effect of gender in the benefit from targeted therapy and immunotherapy in terms of PFS

Anti-EGFR TKIs

In total, 931 female and 494 male patients were evaluated in six phase III trials. The meta-analysis in male patients showed an HR=0.44 (95% CI 0.34 to 0.56) favouring EGFR inhibitors. There was no observed significant heterogeneity between cohorts ($p=0.27$; $I^2=21\%$) (figure 2A). When women were evaluated, the meta-analysis showed an HR=0.34 (95% CI 0.28 to 0.40) with high heterogeneity between cohorts ($p=0.001$; $I^2=75\%$) (figure 2B). In the meta-analysis in the female cohort, there was observed a publication bias in the OPTIMAL study (figure 2C,D).

Anti-ALK inhibitors

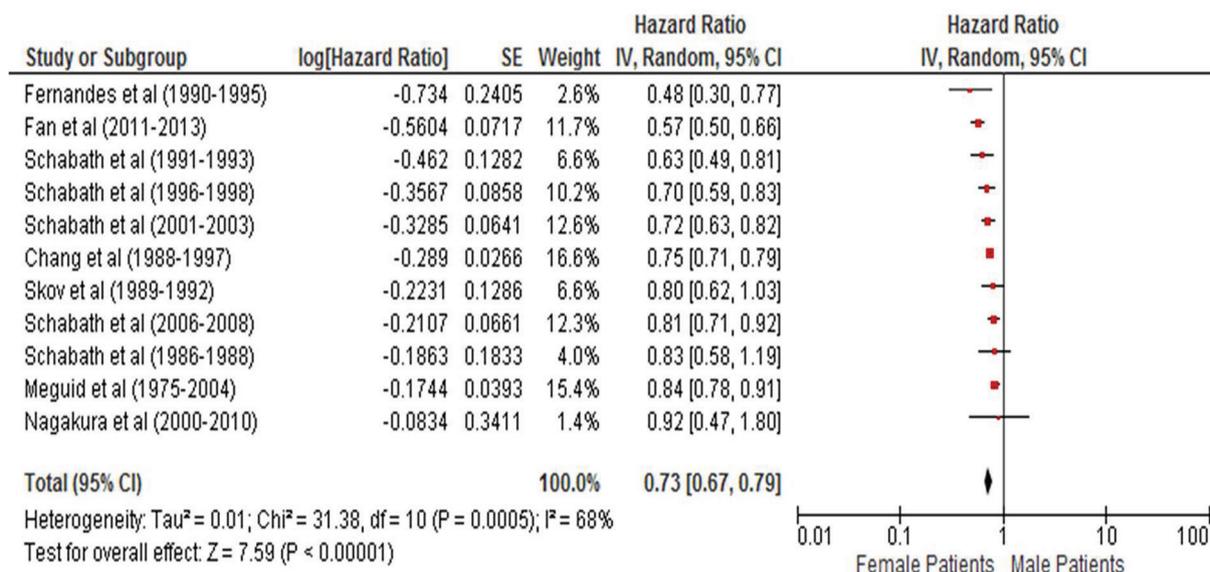
In four randomised phase III trials, 751 female and 536 male patients were evaluated. The meta-analysis resulted in an HR=0.48 (95% CI 0.39 to 0.59; $p<0.00001$) for men, favouring ALK inhibitors, without heterogeneity between trials ($p=0.76$; $I^2=0\%$) or publication bias (figure 3A,B). The analysis in the cohort of female patients showed an HR=0.51 (95% CI 0.45 to

Table 1 Randomised phase III trials comparing EGFR, ALK and anti-PD1 inhibitors versus chemotherapy in patients with NSCLC included in this study

Treatment	Study	Population	Arms (n)	Gender	HR (95% CI) for PFS
EGFR TKI	WTJOG	First line, stages IIIB–IV EGFR mutation	Gefitinib (n=86)	Female (n=119)	0.418 (0.267 to 0.654)
				Male (n=53)	0.67 (0.337 to 1.334)
	OPTIMAL	First line, stages IIIB–IV EGFR mutation	Cisplatin-docetaxel (n=86)		
			Erlotinib (n=82)	Female (n=91)	0.13 (0.07 to 0.24)
			Male (n=63)	0.26 (0.14 to 0.50)	
	EURTAC	First line, stages IIIA(1), IIIB, IV; EGFR mutation	Carboplatin-gemcitabine (n=72)		
			Erlotinib (n=86)	Female (n=126)	0.35 (0.22 to 0.55)
			Male (n=47)	0.38 (0.17 to 0.84)	
	LUX-lung 3	First line, stages IIIB–IV; EGFR mutation	Standard chemotherapy (n=87)		
			Afatinib (n=230)	Female (n=224)	0.54 (0.38 to 0.76)
		Male (n=121)	0.61 (0.37 to 1.01)		
LUX-lung 6	First line stages IIIB–IV EGFR mutation, Asian	Cisplatin-pemetrexed (n=115)			
		Afatinib (n=242)	Female (n=238)	0.24 (0.16 to 0.35)	
		Male (n=126)	0.36 (0.21 to 0.62)		
ENSURE	First line stages IIIB–IV EGFR mutation	Cisplatin-gemcitabine (n=122)			
		Erlotinib (n=110)	Female (n=133)	0.29 (0.17 to 0.50)	
		Male (n=84)	0.43 (0.22 to 0.83)		
ALK TKI	PROFILE-1014	ALK-rearranged recurrent, or first-line metastatic non-squamous NSCLC	Crizotinib (n=172)	Female (n=212)	0.45 (0.32 to 0.63)
				Male (n=131)	0.54 (0.36 to 0.82)
	ASCEND-4	ALK-rearranged recurrent, or first-line metastatic non-squamous NSCLC	Pemetrexed-carboplatin/cisplatin (n=171)		
			Ceritinib (n=189)	Female (n=216)	0.63 (0.43 to 0.93)
			Male (n=160)	0.41 (0.27 to 0.63)	
	ASCEND-5	ALK-rearranged stage IIIB or IV NSCLC previously exposed to at least a platinum-based chemotherapy and crizotinib	Pemetrexed-carboplatin/cisplatin (n=187)		
			Ceritinib (n=115)	Female (n=129)	0.51 (0.34 to 0.79)
			Male (n=102)	0.43 (0.26 to 0.71)	
	NCT00932893	ALK-rearranged stage locally advanced or metastatic NSCLC previously exposed to at least a platinum-based chemotherapy	Pemetrexed or docetaxel (n=116)		
			Crizotinib (n=173)	Female (n=194)	0.48 (0.34 to 0.68)
		Male (n=153)	0.52 (0.35 to 0.77)		
Anti-PD1	KEYNOTE 010	Patients with previously treated NSCLC with PD-L1 expression on at least 1%	Pemetrexed or docetaxel (n=174)		
			Pembrolizumab 2 mg/kg (n=344)	Female (n=399)	1.02 (0.78 to 1.32)
				Male (n=634)	0.78 (0.64 to 0.94)
	KEYNOTE 024	Patients with untreated advanced NSCLC, PD-L1 ≥50% of tumour cells, EGFR and ALK negative	Docetaxel (343)		
			Pembrolizumab (n=154)	Female (n=118)	0.75 (0.46 to 1.21)
			Male (n=187)	0.39 (0.26 to 0.58)	
	CheckMate 017	Patients with stage IIIB or IV squamous cell NSCLC who had disease recurrence after one prior platinum-containing chemotherapy regimen	Platinum-based chemotherapy (n=151)		
			Nivolumab (n=135)	Female (n=64)	0.71 (0.40 to 1.26)
			Male (n=208)	0.63 (0.46 to 0.85)	
	CheckMate 026	Patients with untreated stage IV or recurrent NSCLC and a PD-L1 tumour expression level ≥1%	Docetaxel (n=137)		
Nivolumab (n=271)			Female (n=332)	1.36 (0.98 to 1.90)	
		Male (n=209)	1.05 (0.81 to 1.37)		
CheckMate 057	Patients with non-squamous NSCLC that had progressed during or after platinum-based doublet chemotherapy	Platinum-based chemotherapy (n=270)			
		Nivolumab (n=292)	Female (n=263)	1.04 (0.80 to 1.37)	
		Male (n=319)	0.81 (0.63 to 1.04)		

NSCLC, non-small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

A



B

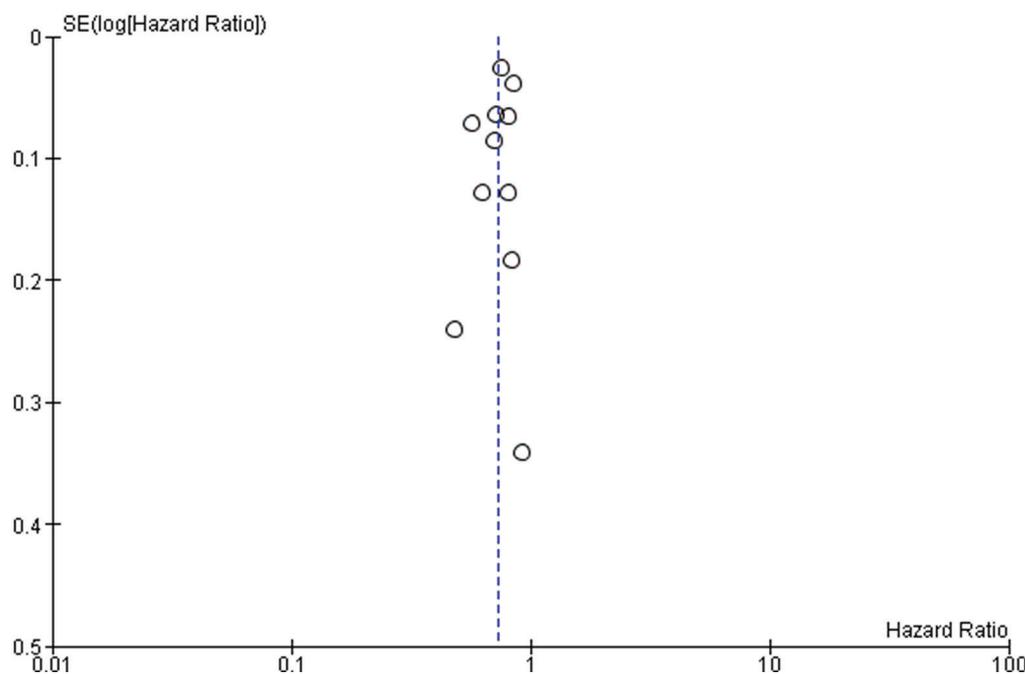


Figure 1 Meta-analysis of the effect of gender in the overall survival, comparing HRs and 95% CI obtained from multivariate analysis in hospital databases. Results show that gender is a prognostic factor favouring female patients (A). The funnel plot shows no publication bias among studies included in the analysis (B).

0.61; $p < 0.00001$) favouring ALK inhibitors (figure 3C). In this evaluation, there was no heterogeneity between trials ($p = 0.62$; $I^2 = 0\%$). In addition, there was no observed publication bias (figure 3D).

Anti-PD1 inhibitors

For all studies, 1028 female and 1435 male patients were evaluated. In male patients, it was observed an overall

HR=0.76 (95% CI 0.68 to 0.86; $p < 0.00001$) favouring anti-PD1 inhibitors with significant heterogeneity between studies ($p = 0.0001$; 95% CI 0.68 to 0.86). For female patients, there was no clear benefit seen from nivolumab or pembrolizumab when compared with chemotherapy (HR=1.03; 95% CI 0.89 to 1.03; $p = 0.69$). There was no significant heterogeneity between the cohorts ($p = 0.45$; $I^2 = 33\%$).

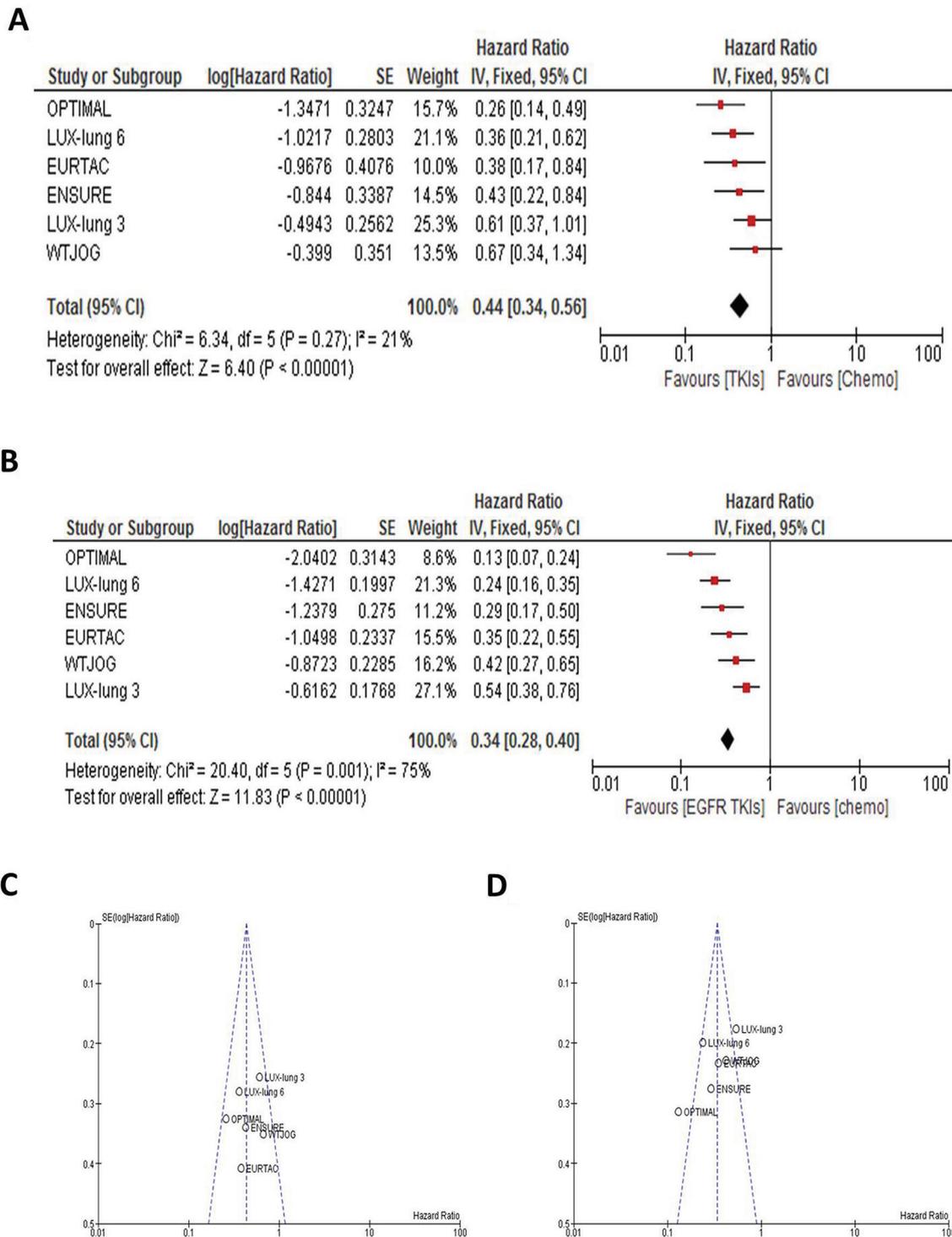


Figure 2 Meta-analysis of randomised phase III clinical trials comparing EGFR tyrosine kinase inhibitor (TKI) shows that male patients with non-small cell lung cancer (NSCLC) have a minor benefit from these drugs (A) compared with female patients who have a 10% additional reduction in progression risk (B). Funnel plots for the detection of publication bias in the meta-analysis of men (C) and women (D).

DISCUSSION

In this paper, we analysed different published studies to explore differences in gender outcomes in NSCLC. Although our study could have some limitations and biases properly from a retrospective review of data of other trials, we showed clear differences in gender

outcomes among some targeted therapies. There is a well-known fact that women have better outcomes than men in several cancers. The risk of death for cancer is 1.6 times higher in male than in female patients.¹⁴ In lung cancer, women present better outcomes and have been described in several studies. In our data, the meta-analysis

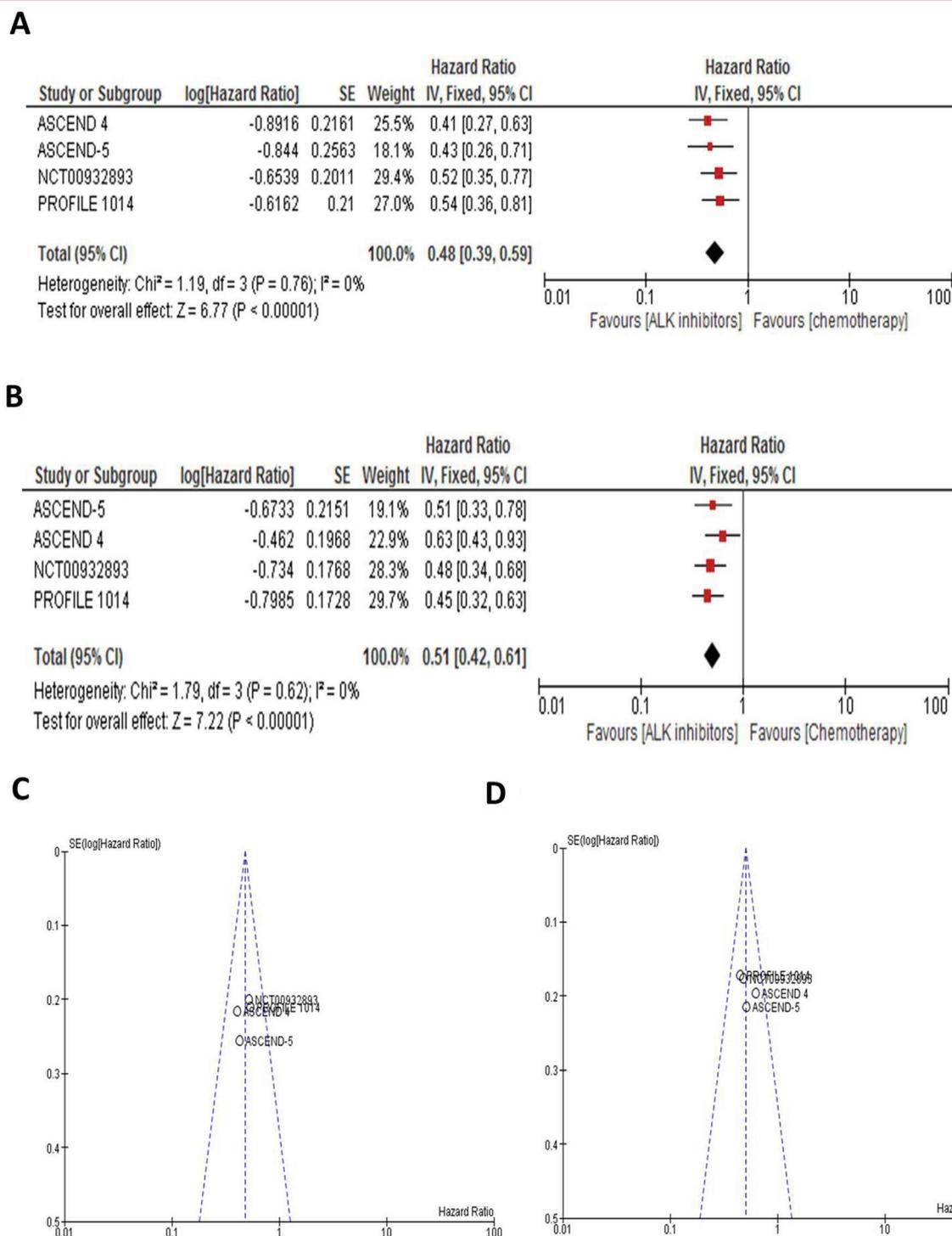


Figure 3 Meta-analysis of randomised phase III clinical trials with ALK inhibitors in non-small cell lung cancer (NSCLC) showing similar benefit in male patients (A) and female patients (B). There was no observed publication bias in the analysis of men (C) or women (D).

with random effects shows a 27% reduction in the risk of death in female patients (figure 1).

In six trials evaluating EGFR TKI we observed a 10% reduction in the risk of progression (HR=0.44 vs 0.34 for men and women, respectively) (figure 2). This improved benefit with EGFR inhibitors in female patients has been largely described in several clinical trials. In our analysis,

because all patients had sensitising mutations in EGFR, the treatment was given in first line and the comparison arm was chemotherapy, the results are less likely of being influenced by a cofounding variable, although our analysis does not consider ethnicity or smoking status. Despite the additional benefit from EGFR TKI seen in women, a meta-analysis by Pujol *et al*³⁷ did not show a difference in

benefit from cetuximab, an anti-EGFR antibody between genders in the subgroup analysis.³⁷

In the review of other biological agent, bevacizumab, the effect of gender has contradicting results. In the study ECOG 4599 of carboplatin and paclitaxel with or without bevacizumab (with 387 women and 463 men), women showed no benefit in terms of OS (HR=0.98, 95% CI 0.77 to 1.25) in contrast to men (HR=0.70, 95% CI 0.57 to 0.87).³⁸ In the AVAiL trial, comparing a phase III randomised study of cisplatin, gemcitabine plus low-dose bevacizumab or high-dose bevacizumab, or placebo until disease progression, showed distinct results for women in the PFS. In the arm of low-dose bevacizumab, women have no significant benefit in contrast to men; however, in the arm of high-dose bevacizumab, women have significant benefit from bevacizumab and men do not.³⁹ In the JO19907 trial, women have no benefit in terms of PFS (HR=0.59, 95% CI 0.30 to 1.13), although only 65 women were evaluated.⁴⁰ A meta-analysis by Soria *et al*⁴¹ showed no correlation between gender and treatment effect.⁴¹

In regard to the analysis of ALK inhibitors, crizotinib and ceritinib, a similar benefit was observed between genders. Although there was observed a high homogeneity in the analysis of both genders ($I^2=0%$ in both cases), the ASCEND-5 trial, evaluating ceritinib versus chemotherapy, included patients resistant to crizotinib (figure 3). In the ASCEND-5 trial the treatment effect of ceritinib was seen in all subgroups of patients, including previous response to crizotinib.²⁹

When we evaluated anti-PD1 inhibitors, the meta-analysis in female patients did not show a clear benefit from these agents when compared with chemotherapy. In contrast, male patients have a 24% reduction in the risk of progression (figure 4). Although this is an exploratory study, our finding raises the question about the value of gender itself as an independent prognostic factor for anti-PD1 or anti-PD-L1 blockade. A possible explanation of these differences is female patients could bear lung tumours with enriched intrinsic characteristics of resistance or mechanistically, immunity of women is more active than men producing a different effect to PD1 blockade.

The main bias is several risk factors could have a different distribution between genders. PD-L1 protein expression is the most widely marker used to predict response to checkpoint inhibitors, despite the heterogeneity of results seen in different immunohistochemical methods.⁴² A meta-analysis by Pan *et al*⁴³ resulted in no different PD-L1 expression between genders.⁴³

In contrast to PD-L1, *EGFR* alterations are more frequent in female patients. *EGFR* mutations confer lesser benefit from immune checkpoint inhibitors in NSCLC. A recent meta-analysis by Lee *et al*⁴⁴ evaluating three clinical trials of checkpoint inhibitors versus docetaxel showed that the subgroup of patients with tumours with *EGFR* has no benefit from these new agents.⁴⁴ In the subgroup analysis of the study KEYNOTE 024 that includes patients without

mutations in *EGFR* and *ALK* genes, there was no clear benefit seen in female contrasting to male patients.

On the other hand, tumour mutational burden (TMB) has raised as a new biomarker. Since a higher number of mutations in the cancer genome mean more neoantigens, it was shown that mutational load is predictive of response and outcome for immune checkpoint inhibitors in melanoma and NSCLC.⁴⁵⁻⁴⁷ A recent paper by Goodman *et al*⁴⁸ evaluating diverse cancers showed that only 15% of women have a higher mutational burden (9 out of 58 patients) in contrast to male patients with a 31.2% (29 out of 93 patients; $p=0.0349$), although only seven NSCLCs were included. In the univariate analysis gender was associated with the response and PFS; however, in the multivariate analysis, genders have no effect, in contrast to TMB.^{48 49}

Immunity fosters tumour evolution and since women have a different immune response than men it could also shape a distinctive biology among genders, for example, lower mutational burden.⁴⁸ In this case, we have to pay more attention to gender to redraw the investigation of biomarkers for anti-immune checkpoint activity. As previously stated by Klein,¹¹ journals should describe the gender of cell lines, animals and subjects because of the sex-biased immune responses.¹¹ There is a strong need to include the variable sex in the results of clinical trials, mainly in immunotherapy.

PD1 is expressed mainly in T lymphocytes where it is expected to be inhibited by drugs as nivolumab and pembrolizumab. The role of PD1 has been explored while several studies describe the influence of oestrogen and prolactin in the PD1 signalling.⁵⁰ It could produce different responses to inhibition. In a recent report evaluating melanoma patients, the female gender was significantly associated with a lower probability of response to anti-PD1 inhibitors.⁵¹

Interestingly, anti-PD-L1 inhibitors showed a different effect in the subgroup analysis of randomised phase III trials. The therapeutic effect of PD-L1 inhibitors is on tumour cells instead of T cells and could be less influenced by intrinsic factors of the host. In the subgroup analysis of the OAK study evaluating atezolizumab versus docetaxel shows benefit in favour of atezolizumab in terms of OS (HR=0.64, 95% CI 0.49 to 0.85).⁵² On the other hand, in the PACIFIC trial comparing the anti-PD-L1 durvalumab as consolidation therapy versus placebo in patients without disease progression after ≥ 2 cycles of platinum-based chemotherapy shows treatment effect in the PFS.⁵³

CONCLUSION

Results of our exploratory analysis suggest the need to re-evaluate the influence of gender in the treatment effect in retrospective and in a prospective controlled fashion in subsequent clinical trials of immunotherapy and targeted therapy. This is very important now that we are advocating for a personalised and a cost-effective medicine.

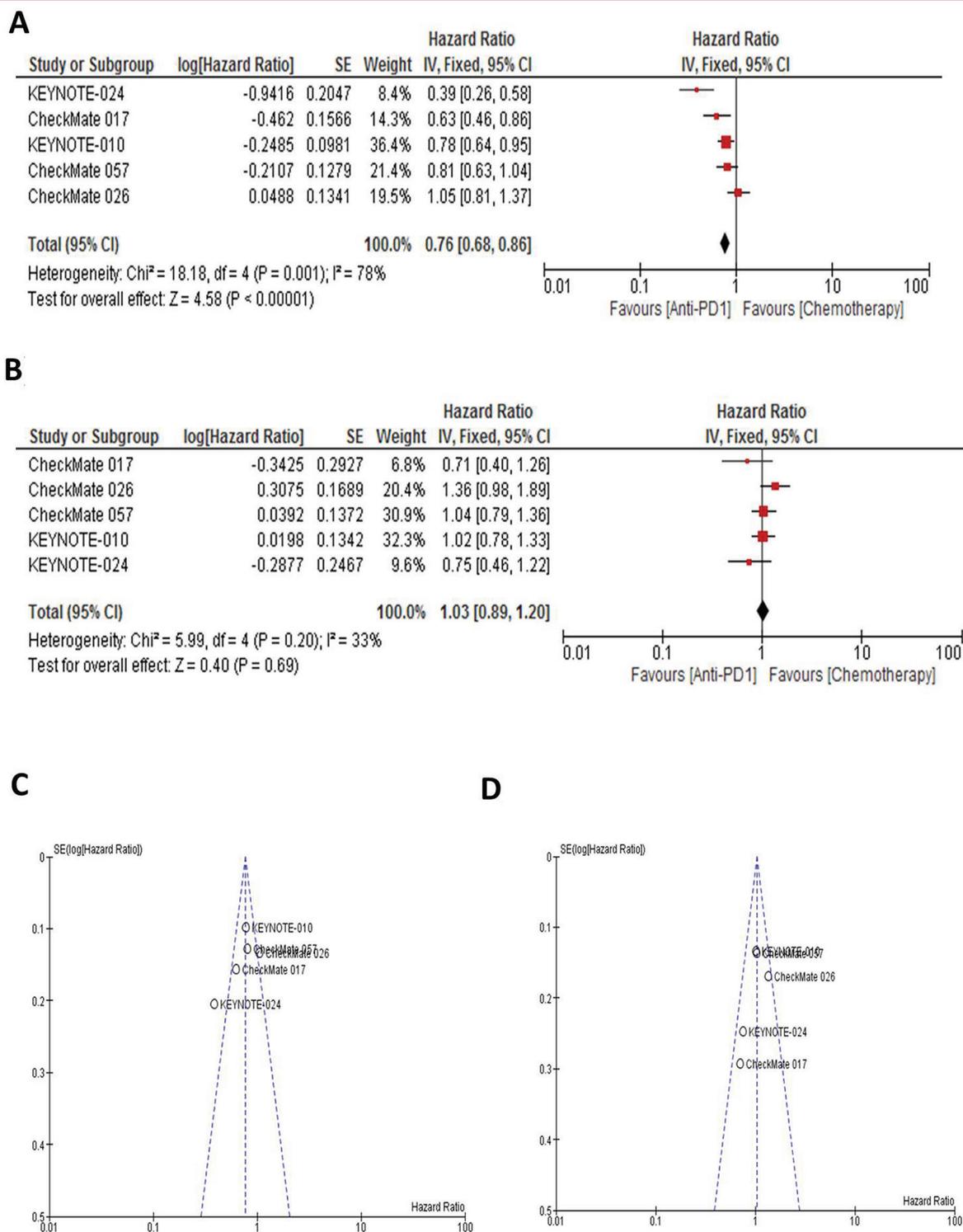


Figure 4 Male patients with non-small cell lung cancer (NSCLC) have a 24% reduction in the risk of disease progression (A). Women have a decreased benefit from anti-PD1 inhibitors nivolumab and pembrolizumab (B). Funnel plots showing publication bias in meta-analysis of male (C) or female patients (D).

CLINICAL PRACTICE POINTS

Since the beginning of the use of anti-TKIs in NSCLC, the female gender was associated to better drug activity to EGFR inhibitors, and then this variable was lost in the large amount of data involving genetic aberrations used in the current context of precision medicine in

NSCLC. Some differences in genders were attributed to different distribution of smoking status and histology; however, the gender per se was missed as variable. Anti-PD1 inhibitors were approved and are used in practice in both genders; our exploratory data suggest that there are some questions that should be addressed from the

biological point of view to improve the immune therapy in women. Precision medicine has put in the mind of oncologists to genomics as the axis of drugs prescription; however, there are classic prognostic variables that can be taken in consideration for precision medicine. Gender is one of the oldest prognostic variables in oncology that is being more and more time left behind in the current research. Gender should be analysed deeply in current trials because biological differences could compromise response to targeted drugs.

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