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Original Research

Sex differences on multikinase inhibitors toxicity in patients with advanced gastroenteropancreatic neuroendocrine tumours

Jorge Hernando [a,*,1], Maria Roca-Herrera [a], Alejandro García-Álvarez [a], Eric Raymond [b], Philippe Ruszniewski [c], Matthew H. Kulke [d], Enrique Grande [e], Rocío García-Carbonero [f], Daniel Castellano [g], Ramón Salazar [h], Toni Ibrahim [i], Alex Teule [j], Vicente Alonso [k], Nicola Fazio [l], Juan W. Valle [m], Salvatore Tafuto [n], Ana Carmona [a], Victor Navarro [o], Jaume Capdevila [a]

[a] *Gastrointestinal and Endocrine Tumor Unit, Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain*
[b] *Department of Oncology, Paris Saint-Joseph Hospital, 185 rue Raymond Losserand, 75014 Paris, France*
[c] *Université Paris Cité, and Dept of Pancreatology-Digestive Oncology, Beaujon Hospital, Clichy, France*
[d] *Hematology/Oncology Unit, Boston Medical Center, USA*
[e] *Medical Oncology Department, MD Anderson Cancer Center Madrid, Madrid, Spain*
[f] *Oncology Department, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (Imas12), Universidad Complutense de Madrid (UCM), CNIO, CIBERONC, Madrid, Spain*
[g] *Oncología Médica, Hospital Universitario 12 de Octubre, Madrid, Spain*
[h] *Medical Oncology Department – Institut Català d'Oncologia, Oncobell Program-IDIBELL, University of Barcelona, CIBERONC, Barcelona, Spain*
[i] *Osteoncology, Bone and Soft Tissue Sarcomas and Innovative Therapies Unit, IRCCS, Istituto Ortopedico Rizzoli, Bologna, Italy*
[j] *Department of Medical Oncology, Hereditary Cancer Program, Program in Molecular Mechanisms and Experimental Therapy in Oncology (Oncobell), IDIBELL, Catalan Institute of Oncology, l'Hospitalet del Llobregat, Spain*
[k] *Oncology Department, Hospital Universitario Miguel Servet, Instituto Investigación Sanitaria Aragón, CIBERONC, Zaragoza, Spain*
[l] *Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, Milan, Italy*
[m] *Division of Cancer Sciences, University of Manchester & Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK*
[n] *Sarcoma and Rare Tumors Unit, Istituto Nazionale Tumori I.R.C.C.S., Fondazione "G.Pascale", Naples, Italy*
[o] *Oncology Data Science Group (ODysSey). Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

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* *Corresponding author.*
E-mail address: jhernando@vhio.net (J. Hernando).
[1] Twitter: @JHernando3.

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Abstract ***Purpose:*** There is an increasing interest in the role of sex and gender in cancer patients. The impact of sex differences in oncological systemic therapies is still unknown, and there is a lack of evidence specially in uncommon neoplasms like neuroendocrine tumours (NET). In the present study, we combine the differential toxicities by sex in five published clinical trials with multikinase inhibitors (MKI) in gastroenteropancreatic (GEP) NET.
Methods: We performed a pooled univariate analysis of reported toxicity in patients treated in five phase 2 and phase 3 clinical trials with MKI in the GEP NET setting: sunitinib (SU11248, SUN1111), Pazopanib (PAZONET), sorafenib-bevacizumab (GETNE0801) and Lenvatinib (TALENT). Differential toxicities between male and female patients were evaluated considering relationship with study drug and different weights of each trial by random effect adjustment.
Results: We found nine toxicities which were more frequent in female patients (leukopenia, alopecia, vomiting, headache, bleeding, nausea, dysgeusia, neutrophil count decreased and dry mouth) and two toxicities being more frequent in male patients (Anal Symptoms and Insomnia). Asthenia and diarrhoea were the only severe (Grade 3–4) toxicities more frequent in female patients.
Conclusions: Sex-related differences in toxicity with the MKI treatment require targeted information and individualised management of patients with NET. Differential reporting of toxicity should be promoted when clinical trials are published.

1. Introduction

Clinical cancer research has begun in recent years to focus on the differences in efficacy and toxicity of the different cancer treatments between male and female patients. Even though many of these studies usually use the term gender, this concept includes social variables beyond biological sex, and it could be a challenge to analyse from an objective point of view [1].

Although the literature exploring gender differences in cancer is still scarce, especially concerning oncological systemic therapies, there is growing evidence showing that this aspect must be considered and sex/gender differences should be included in design of clinical trials [2]. In parallel, there are groups of researchers who are organised in cooperative groups (taskforces) to promote this type of research [1]. Regarding neuroendocrine tumours (NET), we lack robust evidence that sex is a determinant in the prognosis or the effectiveness of treatments. There are no specific prospective studies in this area, and the available information is based mainly on retrospective cohorts. Large datasets of clinical trials have been analysed to determine sex differences in adverse events (AE). Unger JM et al. reviewed more than 23,000 patients included in 202 oncology clinical trials with systemic treatments and found a 66% increased risk of symptomatic AE and 34% of severe AE, specially in those treated with immunotherapy [3].

Treatment with multikinase inhibitors (MKI) is an emerging therapy in the field of NET. Currently, only Sunitinib has a phase 3 randomised clinical trial in the Western population and is widely used in clinical practice [4]. Nevertheless, different molecules have been evaluated in phase 2 studies and in ongoing clinical trials, both as monotherapy and in combination [5]. The toxicity of MKI is one of the most important factors impacting their effectiveness, constituting a limiting factor related to therapeutic adherence and dose intensity [6]. We currently have limited evidence on the differential toxicity by sex with this type of targeted therapies. Several studies show that there may be differences between the sexes [3]. However, there is no specific literature on possible differential toxicities between male and female patients with NET treated with MKI.

In the present study, we combined the differential toxicities by sex in five published clinical trials with MKI in gastroenteropancreatic (GEP) NET. Additionally, we hypothesise about the reasons for these differences, and its interest for the development of future analysis in this field.

2. Material and methods

2.1. Study design

Patients with advanced GEP NET treated with sunitinib, pazopanib, lenvatinib, or sorafenib-bevacizumab in five multicenter open-label phase 2 and 3 studies, were included in the analysis. The SU11248 is the phase 2 study of sunitinib in carcinoid and pancreatic NET [7], followed by the SUN1111 trial [8]. This phase 3 study met its primary end-point of improving median progression-free survival (mPFS) for sunitinib versus placebo and led to the approval of this treatment [4]. The GETNE0801 trial is a phase 2 study evaluating the combination of sorafenib and bevacizumab in patients with advanced GEP NET [9]. The PAZONET trial is a phase 2 study evaluating pazopanib as a single agent in advanced NETs (pancreatic and extrapancreatic tumours) [10]. The TALENT trial is a phase 2

study demonstrating efficacy of lenvatinib in pretreated NET (gastrointestinal and pancreatic tumours) [11]. The academic trials (GETNE0801, PAZONET, TALENT) were performed by the Spanish Task Force Group for Neuroendocrine and Endocrine Tumors (GETNE).

Information about sex, primary tumour origin and treatment received was obtained from the respective publication of each study. Regarding toxicity information, original datasets with AE were consulted for every clinical trial, and then toxicity was selected and combined for statistical analysis.

2.2. Patient population

All patients included in the five clinical trials receiving at least one administration of the study drug were considered for toxicity analysis. The baseline characteristics and main outcomes of all trials included, already published, are listed in Table 1.

2.3. Toxicity analysis

All AE reported in the trials were considered for initial review. The coding of these AE was done following the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 or v5.0, depending on the latest version available at the moment of trials initiation. We performed an initial selection of only drug-related toxicities to develop the complete list of terms included in the statistical analysis. In the GETNE0801, only sorafenib-related toxicities were included, excluding AE attributed to bevacizumab by study investigators.

All toxicities regardless of CTCAE grades in any of the five trials were considered for initial univariate analysis. Additionally, all CTCAE grade 3 and 4 events were analysed separately. Due to heterogeneity in the toxicity terminology used, some events were grouped in aggregated terms (Supplementary Materials 1 and 2).

2.4. Statistical analysis

The main objective was to determine if there were differences between toxicities affecting male and female patients in each trial. Therefore, we applied a test for proportions comparing the prevalence of each toxicity by sex. The p-values and proportions with their 95% confidence intervals (CIs) by sex for each toxicity were reported.

Second, we analysed which toxicities were different by sex considering all the trials together. Thus, we performed a pooled analysis with the disaggregated toxicity data for all the trials. We applied a logistic generalised linear mixed model with sex as response variable, each toxicity as the explanatory variable, and each trial as the random effect variable. Odds ratios (ORs) with 95% CIs, standard deviations of the random effect, and p-values were reported.

Only toxicities with less than 2 standard deviations of the random effect were considered as relevant in the pooled analysis. The smaller the standard deviation of the random effect is, the smaller the bias of the trial differences will be. Therefore, a very large deviation of the random effect indicates a stronger correlation between the response and the random effect than with the explanatory variable; that is why, we considered that our estimates of the explanatory variable had no value beyond 5. Between 2 and 5 standard deviations, we considered that there is too much 'noise' from each trial but they would be candidates to be taken into account in other studies. The variables considered relevant in the pooled analysis also had to have a p-value of less than 0.05 and were related to MKI inhibitors.

A descriptive analysis of sex, tumour location, treatment and trial expressed in absolute values and percentages was performed.

No data imputation was performed, and data analyses were conducted using R statistical software version 4.1.1. Statistically significant results are considered if $p < 0.05$.

3. Results

Three hundred ninety-two patients from the five clinical trials were included. Baseline characteristics are included in Table 2.

3.1. Sex-related differences: individual MKI

Differences between toxicities affecting male and female patients in each trial were addressed. The toxicities that were statistically significant in the proportion tests are shown in Fig. 1. The most meaningful differential toxicities in each trial were as follows: liver toxicity with pazopanib (62% [95% CI 41–80] male versus 95% [95% CI 73–100] female, p 0.02), aphonia with sorafenib-bevacizumab (50% [95% CI 32–68] male versus 11% [95% CI 2–36] female, p 0.01), face oedema with sunitinib (10% [95% CI 5–22] male versus 41% [95% CI 27–58] female, p 0.0005) and bleeding with lenvatinib (0% [95% CI 0–13] male versus 21% [95% CI 8–44] female, p 0.0198) (Fig. 1).

3.2. Sex-related differences: pooled analysis

In the pooled patient analysis with all trials included, we found differences in the proportion of toxicities between male and female (Table 3). Considering random effect, the following toxicities were more common in female: leukopenia, alopecia, vomiting, headache, bleeding, nausea, dysgeusia, neutrophil count decreased and dry mouth. On the other hand, anal symptoms and insomnia were more frequent in males. Differences found in proteinuria, face oedema, aphonia and liver toxicity are related to differences between

Table 1
Characteristics of trials included in the present study.

Trial (number)	Drug	Location (patients)	Female (%)	Efficacy outcomes	Overall toxicity
SU11248 (1) (NCT00056693)	Sunitinib 50 mg/d 4 w on/2 w off	Carcinoid (41) Pancreatic (66)	19 (46.3%) 24 (36.4%)	ORR 2.4% mPFS 10.2 ORR 16.7% mPFS 7.7	Leukopenia (91.6%) Fatigue (88.8%) Anaemia (81.3%) Lymphopenia (81.3%) Neutropenia (79.5%) Thrombocytopenia (68.2%) Diarrhoea (65.4%) Nausea (53.2%) Dysgeusia (48.6%) Skin discoloration (36.5%)
SUN1111 (2) (NCT00428597)	Sunitinib 37.5 mg/d versus Placebo	Pancreatic (171)	44 (51%) SUN 45 (53%) PBO	ORR 9.3% mPFS 11.4 ORR 0% mPFS 5.5	Diarrhoea (59%) Nausea (45%) Asthenia (34%) Vomiting (34%) Fatigue (32%) Hair-colour changes (29%) Neutropenia (29%) Abdominal pain (28%) Hypertension (26%) PPE (23%)
GETNE0801 (3) (EudraCT 2008-000225-19)	Sorafenib 200 mg bid d1–5 + Bevacizumab 5 mg/kg/2 w	Pancreatic (13) Gastrointestinal (31)	18 (40.9%)	ORR 9.4% mPFS 12.4	Asthenia (65.9%) HFS (61.4%) Mucositis (52.3%) Diarrhoea (50%) Hypertension (50%) Dysphonia (40.9%) Anorexia (36.4%) Arthralgia (22.7%) Epistaxis (22.7%) Cutaneous rash (18.2%)
PAZONET (4) (NCT01280201)	Pazopanib 800 mg/d	Pancreatic (18) Gastrointestinal (15) Other (11)	20 (45.5%)	ORR 9% mPFS 9.5	Asthenia (84.1%) Diarrhoea (68.2%) Abdominal pain (52.3%) Pain (47.7%) Nausea (40.9%) Hypertension (40.9%) Hepatotoxicity (36.4%) Vomiting (34.1%) HFS (29.5%) Mucositis (29.5%)
TALENT (5) (NCT02678780)	Lenvatinib 24 mg/d	Pancreatic (55) Gastrointestinal (56)	31 (56.4%) 23 (41.1%)	ORR 44.2% mPFS 15.6 ORR 16.4% mPFS 15.7	Asthenia (74.8%) Diarrhoea (58.6%) Hypertension (55.9%) Abdominal pain (36.9%) Hypothyroidism (36%) Dysphonia (35.1%) Nausea (32.4%) Mucosal inflammation (27%) Headache (26.1%)

NCT: National Clinical Trial; w: weeks; ORR: overall response rate; mPFS: median progression-free survival; SUN: sunitinib; PBO: placebo; PPE: palmar-plantar erythrodysesthesia; HFS: hand-foot syndrome.

studies more than sex differences, according to random effect (Table 3, Fig. 2).

Regarding severe toxicities, classified as CTCAE grade 3 or grade 4, significant differences were found in favour of female patients in asthenia (21.8% versus 11.8%, OR 0.44 [0.25–0.77], p 0.0039, random effect 0.16) and diarrhoea (10.6% versus 5.2%, OR 0.45 [0.21–0.98], p 0.0435, random effect 0.24). Other trends in higher toxicity in female patients were not confirmed by random effect. We did not find severe toxicities being more common in male patients (Fig. 2).

4. Discussion

We collected sex-related toxicities in five clinical trials in NET patients treated with MKI. These trials collected and published combined toxicity data following usual practice in biomedical publications. We performed a

Table 2
Baseline characteristics of pooled trials included in the study.

Characteristics	Total (%) n = 392
Sex	
- Female	179 (45.7)
- Male	213 (54.3)
Tumour site	
- Pancreatic	238 (60.7)
- Gastrointestinal	143 (36.5)
- Other	11 (2.8)
Treatment	
- Sunitinib	193 (49.2)
- Pazopanib	44 (11.2)
- Sorafenib-Bevacizumab	44 (11.2)
- Lenvatinib	111 (28.3)
Trial	
- SU11248	107 (27.3)
- SUN1111 (only sunitinib arm)	86 (21.9)
- PAZONET	44 (11.2)
- GETNE0801	44 (11.2)
- TALENT	111 (28.3)

pooled analysis to identify differential toxicities between female and male patients. We found nine toxicities more frequent in female patients (leukopenia, alopecia, vomiting, headache, bleeding, nausea, dysgeusia, neutrophil count decreased and dry mouth) and two toxicities more frequent in male patients (anal symptoms, insomnia). Also, we found a trend for aphonia to be more frequent in men. Asthenia and neutrophil count decrease were the two toxicities Grade 3/4 more frequent in female patients.

The study of sex differences in medicine is a growing field and examines how diseases differ between males and females in terms of prevention, diagnosis, and treatment outcomes [12]. The effect of sex in health is part of a complex network of interactions between gene expression, immune system, hormones, body mass index, metabolism, behaviour, and social factors [1]. There is growing evidence that some sex-related factors, such as differences in body composition, have an impact in treatment outcomes, and constitute a way to personalise treatment dosage [12]. Nevertheless, these variables are not routinely included in cancer trials [2,3]. Some retrospective cohorts suggest that greater toxicity rates could be found in female patients [13,14] and specific studies have been addressed regarding fluoropyrimidines [15,16].

There are few approaches to sex or gender in the study of NET. In large retrospective series, we can find a trend towards different occurrence of NET in specific primary locations between sexes. In an analysis of The Surveillance, Epidemiology and End Results (SEER) database, female patients were more likely to have primary NET in lung, stomach, appendix, or caecum. Also, female patients were less likely to have metastasis at the onset [17] and better survival rates in lung [18] and GEP NET [19,20]. However, since these are population approaches, the impact of these findings into prevention and treatment remains unknown.

Most clinical trials in the NET field were not specifically designed to investigate sex-related differences. Usually, this item is explored as covariate, with the perception that a lack of sex-adjustment in clinical practice is necessary. Current data is too heterogeneous to address conclusions which will impact in the therapeutic schedule. In recent years, individual efforts in some centres are reviewing the impact of sex in treatment outcomes with NET, but literature is still scarce. Al-Toubah et al. explored efficacy and toxicity in a large cohort of retrospective patients treated with capecitabine-temozolomide combination. They concluded that the risk of cytopenia is higher in female patients and sex-based dosing should be considered [21]. Recently, Minczeles et al. analysed dose-limiting toxicities of the bone marrow in patients with NET treated with 177Lutetium-DOTATATE in a phase II study. Females experienced more often treatment-induced thrombocytopenia and anaemia [22].

In recent years, there has been a growing interest in incorporating new drugs from the MKI family into the NET management algorithm [5]. Although, to date, none of them have obtained favourable results or approval at a global level, a significant effort has been made in the design of clinical trials that continues today. In recent years, results from phase 2 and phase 3 studies with different MKIs have been reported, including axitinib [23], cabozantinib [24], and surufatinib [25]. Precisely because of this probability of MKIs progressively occupying a more relevant role in the NET treatment algorithm, it is essential to study not only their efficacy but also their toxicity. Patients often maintain these treatments for months or years, impacting their quality of life. It is essential to extrapolate the experience in managing toxicities in other neoplasms where MKIs are more widely used, such as thyroid cancer, to handle MKI toxicities in the NET setting correctly [26].

Our findings in the present study are aligned with previous works in the field of sex differences in toxicity in oncology, with female patients experiencing more toxicity [13–16]. The implication of our findings is that sex differences in MKI treatment of NET patients should be considered in further works in the NET field. Our study constitutes a hypothesis generator to continue exploring the origins of these sex differences and their impact on treatment adherence and outcomes. We can address the hypothesis about the causes of differential toxicities found in our analysis. Blood test-related toxicities (leukopenia, liver toxicity, neutrophil count decreased), asthenia, nausea, vomiting and bleeding could be directly related to pharmacokinetic or pharmacodynamics factors (MKI blood concentrations, body mass index, body mass composition, drug absorption, CYP3A4 metabolism, etc). Higher haematologic AE have been reported in previous works with systemic treatment. Interestingly,

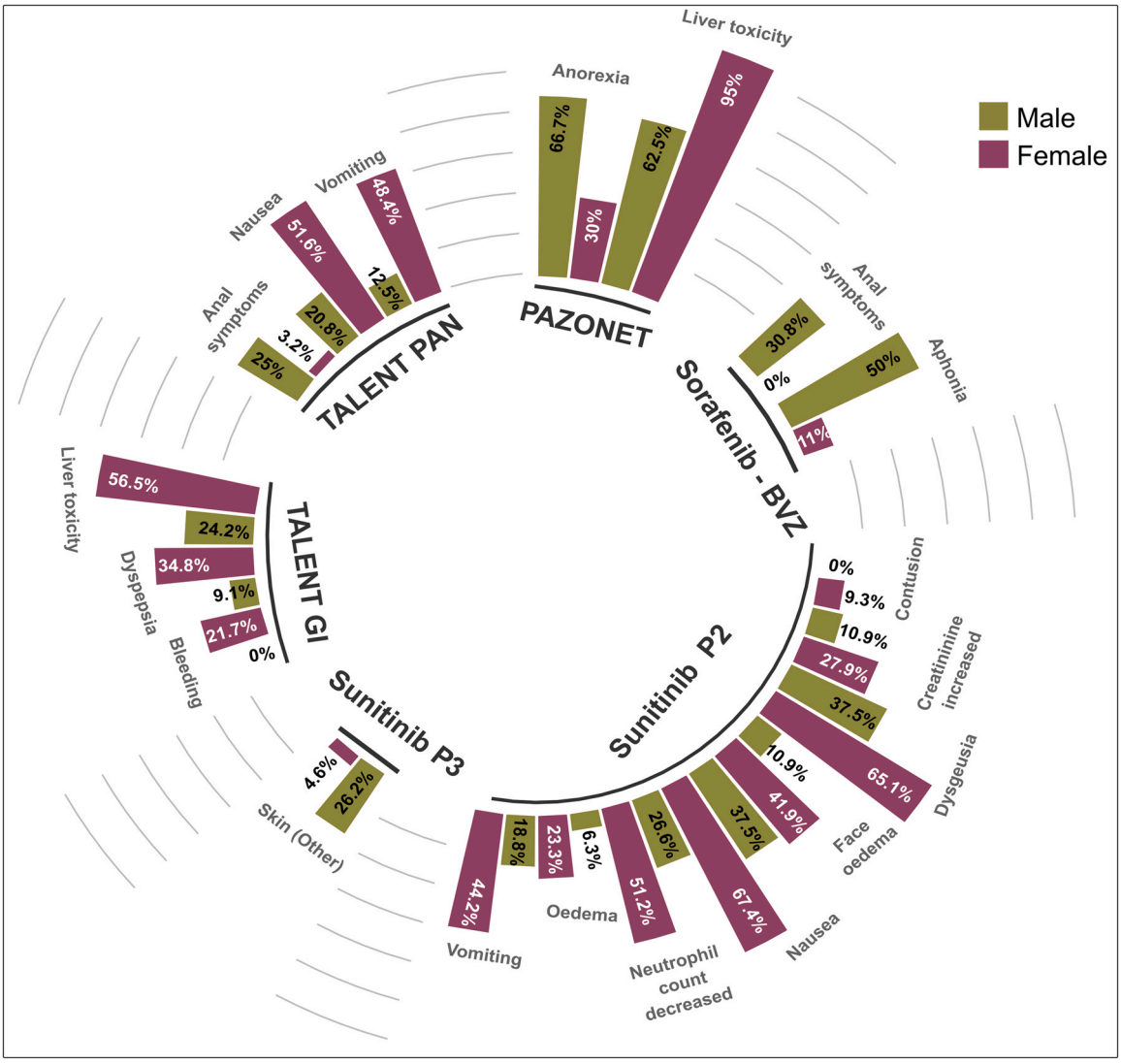

Fig. 1. Most common differential toxicities between male and female patients in each trial separately. BVZ: bevacizumab; P2: phase 2 trial; P3: phase 3 trial; GI: gastrointestinal cohort; PAN: pancreatic cohort.

other differential toxicities could be explained by social factors regarding what is considered 'uncommon' or 'abnormal' for each sex, such as haemorrhoids and insomnia for male and alopecia for females (also a higher rate of alopecia in male subjects in general population should be considered). These assumptions can distort the way patients report toxicity and investigators evaluate and register that information. Finally, some differences could be explained by intrinsic differences between male and female patients, for example, a deeper voice in males could be related with a higher rate of aphonia. All those implications potentially could impact the treatment compliance, drug doses and efficacy outcomes.

Plasma exposure of MKI is correlated with clinical response and toxicity [27–29], and current MKI dosage at flat dose could be potentially inappropriate for specific populations. Additional studies should be conducted to better understand the origin of these differences and address an individualised approach. Also, some individual differences between MKI included in this analysis should be highlighted and explored in further detail. Combination of bevacizumab with sorafenib potentially could increase rate of dysphonia in male patients. Dysphonia or voice changes have been reported in patients treated with anti-vascular endothelial growth factor therapies but there is a lack of data regarding differential toxicities in this population [30,31]. The role of sexual hormones in systemic treatment outcomes is another area of interest that should be explored. Interestingly, there is a sexual dimorphism in clinical evolution in small intestine NET that could be related to oestrogen receptor expression [32].

Limitations of the present study include the use of only biological sex to address differences in toxicity. The social aspects of the gender, usually self-reported and subjective, prevent a formal analysis from clinical trial data. The inclusion of gender information, beyond sex, in biomedical studies could help us determine the impact of this variable in future projects. Additionally, the

Table 3
Most frequent toxicities and differences in both sexes (all grades).

Category	Male n (%)	Female n (%)	Difference (%)	Odds ratio	p Value	Random effect
Proteinuria	15 (7.0)	24 (6.1)	0.9	1.27 (1.26–1.27)	< 0.0001	2.408
Leukopenia	15 (7.0)	16 (8.9)	1.9	0.69 (0.69–0.69)	< 0.0001	1.363
Face oedema	8 (3.8)	22 (12.3)	8.5	0.18 (0.07–0.45)	0.0002	20.926
Alopecia	5 (2.0)	19 (10.6)	8.3	0.2 (0.07–0.55)	0.0019	0.000
Vomiting	40 (18.8)	58 (32.4)	13.6	0.48 (0.3–0.77)	0.0024	0.144
Aphonia	40 (18.8)	20 (11.2)	7.6	2.69 (1.36–5.32)	0.0045	5.321
Anal Symptoms	25 (11.7)	8 (4.5)	7.2	3.1 (1.36–7.09)	0.0074	1.035
Liver Toxicity	53 (24.9)	67 (37.4)	12.5	0.48 (0.28–0.83)	0.0090	2.401
Headache	32 (15.0)	44 (24.6)	9.6	0.53 (0.31–0.88)	0.0145	0.201
Bleeding	8 (3.8)	18 (10.1)	6.3	0.35 (0.15–0.83)	0.0168	0.074
Nausea	68 (31.9)	77 (43.0)	11.1	0.61 (0.4–0.92)	0.0200	0.162
Insomnia	25 (11.7)	9 (5.0)	6.7	2.51 (1.14–5.53)	0.0222	0.000
Dysgeusia	38 (17.8)	43 (24.0)	6.2	0.53 (0.3–0.91)	0.0225	1.349
Neutrophil count decreased	35 (16.4)	43 (24.0)	7.6	0.57 (0.33–0.97)	0.0373	1.566
Dry mouth	8 (3.8)	17 (9.5)	5.7	0.42 (0.18–0.98)	0.0460	0.912

F: female; M: male.
Odds ratio values over 1.00 means the toxicity is higher in male versus female patients.

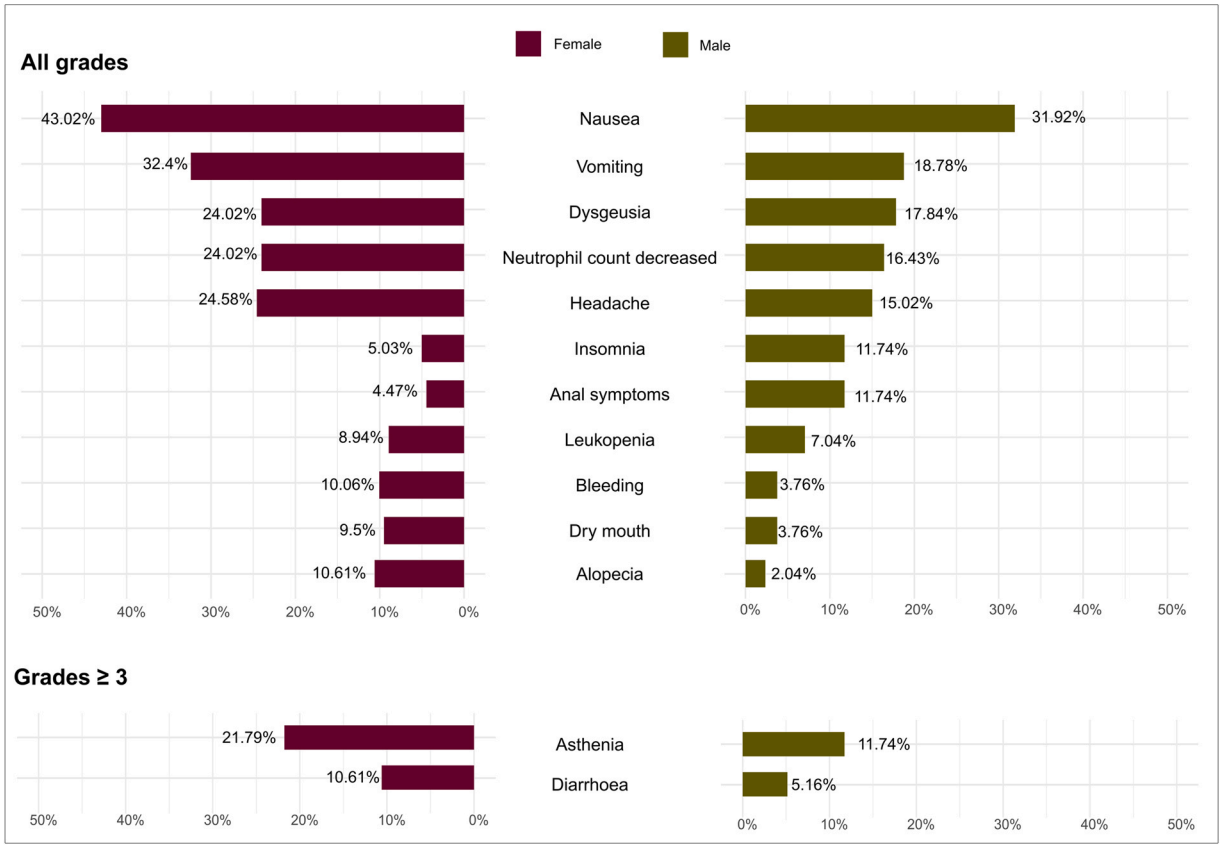

Fig. 2. Significant differential toxicities between male and female patients after random effect ponderation between trials.

heterogeneity in the report of adverse effects between trials increases the difficulty of exploring differential transversal toxicities according to sex. Another important limitation of the present study is the impossibility of accessing the complete datasets of all clinical trials that preclude a multivariate study and the impact of sex-related toxicities in efficacy outcomes. Although variability between trials was addressed by random effect, the impact of other characteristics such as body surface, comorbidities, general performance status, prior therapies, compliance and age, among others, must be considered. Some potential interesting variables in future studies should include dose reductions, dose interruptions and treatment discontinuation in male and female patients, and their impact on treatment outcomes.

Considering current evidence from our work and previous observations in the field of neuroendocrine neoplasms [21,22], a higher rate of haematological and non-haematological toxicities should be expected in female patients. Treatment doses should be individualised specially when other potential factors like comorbidities or older age concur. A closer follow-up during systemic treatment could be considered to monitor analytical parameters. Additionally, for non-haematological toxicities an individualised approach in should be followed when explaining the toxicities of each treatment. As an example, adequate information about alopecia or insomnia can help to prevent them with a great impact on the quality of life of patients.

5. Conclusions

Gender studies in oncology is an emerging field but still very limited in the context of NET. There are differences in toxicities in the MKI treatment that require individualisation in the information and management of patients. Additional studies will allow us to address the impact of the sex differences in efficacy outcomes of MKI treatments in NET patients. Differential reporting of toxicity should be promoted when clinical trials are published.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Jorge Hernando**: Speakers Bureau: Angelini, Leo, Eisai, Adacap, Novartis, Pfizer, Advanz, Ipsen. **Alejandro García-Alvarez:** Speakers Bureau: Angelini. Travel/Accommodation, Expenses: Pfizer, Ipsen, EISAI, Advanz, AAA. **Toni Ibrahim:** Advisory board (Amgen, Galxosmithkline and Pharmamar). Cover Participation at scientific meeting (Istituto gentili and Pharmamar). **Enrique Grande:** EG has received honoraria for speaker engagements, advisory roles or funding of continuous medical education from Adacap, AMGEN, Angelini, Astellas, AstraZeneca, Bayer, Blueprint, Bristol Myers Squibb, Caris Life Sciences, Celgene, Clovis-Oncology, Eisai, Eusa Pharma, Genetracer, Guardant Health, HRA-Pharma, IPSEN, ITM-Radiopharma, Janssen, Lexicon, Lilly, Merck KGaA, MSD, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi Genzyme, Servier, Taiho, and Thermo Fisher Scientific. EG has received research grants from Pfizer, AstraZeneca, Astellas, and Lexicon Pharmaceuticals. **Eric Raymond:** Consulting and Share holder for Genoscience Pharma, StromaCare, SCOR life science. Share Holder at Neuronax. Scientific and steering committee at Onward Therapeutics and BeiGen. Received travel grant for data presentation from BeiGen. **Rocio Garcia-Carbonero**: RGC has provided scientific advice and/or received honoraria or funding for continuous medical education from AAA-Novartis, Advanz Pharma, Amgen, Bayer, BMS, Boerhinger, Esteve, Hutchmed, Ipsen, Merck, Midatech Pharma, MSD, PharmaMar, Pierre Fabre, Roche, Servier and Sanofi, and has received research support from Pfizer, BMS and MSD. Ramon Salazar: Invited speaker: Advanced Accelerator Applications, Amgen, Astellas, Bayer, BMS, Eisai, GSK, Janssen Oncology, Lilly, Pierre Fabre, Roche, Sanofi Genzyme. Expert testimony: AstraZeneca, Celgene, Merck, MSD, Novartis, Pfizer. Advisory Board: Agendia, Amgen, Ferrer, Guardant Health, Ipsen, Lilly, Merck, MSD, Novartis, Pfizer, Roche Diagnostic, Roche Farma, Tayhoo, VCN-BCN. **Alex Teule**: Speakers Bureau: AAA, Pfizer, Ipsen, Novartis, AstraZeneca. Travel, Accommodation, Expenses: AAA, Pfizer, Ipsen, Novartis, AstraZeneca. **Salvatore Tafuto**: S.Tafuto has provided scientific advice and/or received honoraria or funding for continuous medical education from AAA-Novartis, Boerhinger, Ipsen, Merck, PharmaMar and has received research support from NOVARTIS, IPSEN. **Vicente Alonso**: VA has provided scientific advice and/or received honoraria or funding for continuous medical education from AAA-Novartis, Amgen, Ipsen, Merck, Pierre Fabre, Roche, Servier and Sanofi. **Daniel Castellano**: Advisory role

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Previous presentations

This study was not previously presented in any other journal.

Disclaimers

No disclaimers.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.04.013.

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