ORIGINAL ARTICLE

Sex differences in the pharmacokinetics of anticancer drugs: a systematic review

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Background: In addition to the effect of body weight, a patient's sex can influence the pharmacokinetics (PK) of anticancer agents, and thereby their activity and safety. The magnitude and relevance of sex differences, however, are currently unclear.

Methods: We carried out a systematic review of published studies (clinical, $n \geq 10$) on Food and Drug Administration (FDA)-approved (on 31 January 2022) anticancer drugs (excluding hormonal agents), aiming to identify significant PK differences between male and female patients. A difference of $\geq 20\%$ on PK parameters (clearance or trough concentration) was considered significant. The methodological quality was assessed using the National Institutes of Health study quality assessment tool. This systematic review was conducted according to the PRISMA2020 guidelines and a previously published protocol, which was registered in the PROSPERO database (number 291008).

Results: Data on 99 anticancer agents (for a total of 1643 abstracts and European Medicines Agency/FDA documents) were screened. The final dataset included 112 articles and 8 European Medicines Agency/FDA documents. The median size of a study cohort was 445 patients (range: 12-6468 patients). Significant PK differences ($>+20\%$ in clearance or apparent clearance in women) were identified for 14 drugs, and potentially significant PK differences (due to conflicting reports) for another 8 drugs. None of the studies included sex-based summaries to assess whether the observed differences in PK may impact the efficacy or safety profile.

Conclusions: Significant sex differences in PK have been identified including commonly used drugs of different classes, such as 5-fluorouracil, doxorubicin, paclitaxel, regorafenib, atezolizumab, and temozolomide. The risk−benefit ratio for such anticancer drugs is likely to be improved by the development of sex-specific dosing strategies. Additional sex-based PK-pharmacodynamic analyses are recommended during dose optimisation and are to be conducted in line with the FDA Project Optimus guidance. They should be reported even if no association between the patients' sex and the activity and/or toxicity of an anticancer drug has been identified.

Key words: antineoplastic agents, pharmacokinetics, population pharmacokinetics, gender medicine, sex

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BACKGROUND

Many anticancer drugs are characterised by a narrow therapeutic window: a small change in pharmacokinetics (PK) can thus lead to altered pharmacodynamic (PD) effects, in terms of the safety, toxicity or antitumour activity.[1] Furthermore, even the population exposure-response function may differ for activity and toxicity, and may even be different for different types of toxicity.

Despite increasing evidence that a patient's sex can influence disease incidence and prognosis,[2,3] sex is not routinely taken into account when assessing the risk—benefit ratio of anticancer treatments. This may be due to the common understanding that differences in PK between male and female subjects are mostly explained by differences in body weight. Female patients are more prone to experience adverse effects of several anticancer drugs,[4,5] however, including both acute haematological and/or non-haematological toxicity (mucositis, nausea and emesis, and alopecia). Higher rates of adverse events are also observed in females receiving immunotherapy agents.[6] PK differences (disposition profiles, including distribution and tissue to plasma ratio between female and male patients) and individual (sex-dependent) PD could account for such differences in safety, but also, and ultimately, may result in different efficacy outcomes.[7,8]

Physiological differences exist between males and females in terms of cardiac output, liver blood flow, muscle mass, adipose tissue, and total body water,[9] which go beyond the known differences in body weight, height, and body surface area (BSA). Of note, dose selection based on BSA is customary to adjust the dose of conventional chemotherapy drugs (with the exception of carboplatin), but BSA is not a measure that can be used reliably to individualise treatment since it is poorly correlated with drug clearance (CL) for the majority of compounds.[1] Body composition (and especially skeletal muscle mass) can also significantly affect the PK of several anticancer agents (e.g. capecitabine, epirubicin, sorafenib or sunitinib) and their PD effects, and differs between males and females.[10-13]

The aforementioned physiological differences between males and females (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.104002)[14,15] can affect all the processes (i.e. absorption distribution, metabolism, and elimination) associated with the PK of anticancer drugs.

The present review was designed and conducted by the ESMO Gender Medicine Task Force,[16] created to raise awareness of the presence of potential sex differences in biology and treatment outcomes of non-sex-related cancers. The aim of this study was to gather evidence on PK differences that could be used as a basis for further personalisation of treatment of male and female patients.

MATERIALS AND METHODS

We carried out a systematic review of the published English literature on the investigated topic using PubMed (https://pubmed.ncbi.nlm.nih.gov/) including all publications until 31 January 2022. We used the following search terms: 'drug name AND pharmaco* AND [sex OR gender]', 'drug name AND population pharmaco* AND [sex OR gender]', and 'drug name AND [body composition OR lean body mass]', where drug names were the international non-proprietary names (INN) of Food and Drug Administration (FDA)-approved (www.fda.gov/drugs, accessed on 31 January 2022) anticancer drugs (chemotherapy, molecular targeted agents, and immunotherapy agents, excluding hormonotherapy agents,

see Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.104002). Preclinical studies were excluded, as well as paediatric studies and clinical studies in adults with a sample size <10 patients. Only studies approved by an ethics committee [or an institutional review board (IRB) for retrospective studies] were included.

References from the identified publications and related FDA package inserts (https://www.accessdata.fda.gov/) and European Medicines Agency (EMA) summary of products information (https://www.ema.europa.eu/en/homepage) were reviewed as well when appropriate.

The publications were separately reviewed by two investigators (JD and OM), and each drug was assigned to one of the following categories: (A) evidence of significant differences in PK between males and females; (B) conflicting data from one study to another; (C) lack of significant differences in PK between males and females. The criteria for establishing differences are outlined below.

The PK parameters examined for each study were: CL or apparent clearance (CL/F) and area under the concentration-time curve (AUC), for each drug and its active metabolites (when applicable), or trough concentrations at steady state ($C_{sstrough}$) when other parameters were not provided. A difference of $\geq$20% between males and females was considered significant, corresponding to the customary threshold used in population PK studies.[17-19] Population PK studies also allow for evaluation of the respective contribution of each covariate (including sex, but also weight and/or BSA), which was captured for each study.

Data were collected from the identified studies by the two separate investigators (JD and OM), implemented in separate MS Excel files, and reconciled at the end of the collection with a third investigator (AP) in order to identify and mitigate discrepancies. The resulting manuscript was reviewed by all members of the ESMO Gender Medicine Task Force and their comments were included.

For each study, the sample size and sex ratio were collected, as well as the difference in PK parameters. The methodological quality of each included analysis was assessed using the National Institutes of Health (NIH) study quality assessment tool, as previously used in systematic reviews that include observational studies.[20]

This systematic review was conducted according to the PRISMA2020 guidelines,[21] and registered in the PROSPERO database (https://www.crd.york.ac.uk/prospero/) under the number 291008.

RESULTS

Overall, data on 99 anticancer agents (for a total of 1643 abstracts and EMA/FDA documents) were screened, and 143 articles and documents meeting the inclusion criteria were identified. A total of 2 articles were excluded due to small sample size ($n < 10$), 15 because only preclinical data were included, 4 due to the study population, which was exclusively paediatric (aged <18 years), and 2 because the manuscript did not mention the approval of the study by an ethics committee and/or an IRB (see PRISMA diagram in Figure 1).
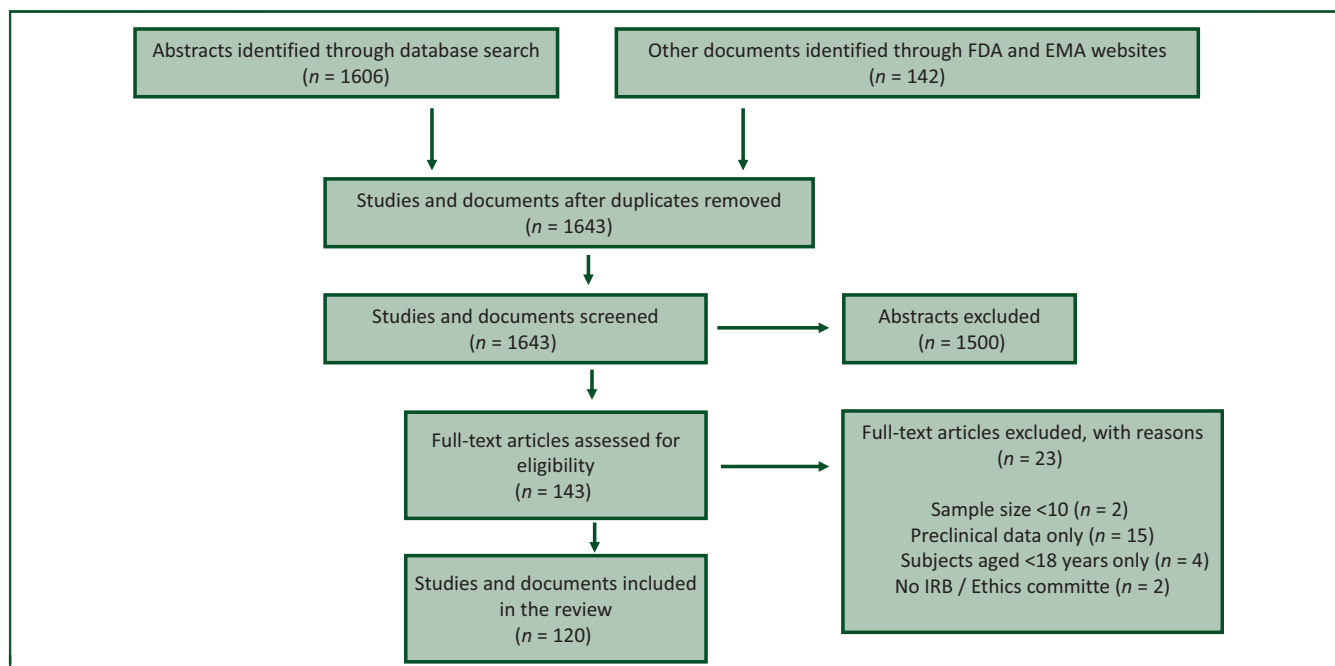
Figure 1. PRISMA diagram.
EMA, European Medicines Agency; FDA, Food and Drug Administration; IRB, institutional review board.

Three disagreements between investigators were noticed and solved by checking the inclusion criteria (two were preclinical studies, and one had a sample size = 9). The final dataset included 112 articles[18-121] and 8 EMA/FDA documents[122-129] reporting on 99 anticancer agents: 46 on chemotherapy, 62 on molecular targeted agents, and 12 on immunotherapy agents. A total of 72 articles were population PK studies derived from phase 1-III trials, 38 were prospective pharmacological studies, and 2 were retrospective studies. The median size of a study cohort was 445 patients (range: 12-6468 patients), and the mean was 484 patients ($\pm$410).

The categories were allocated as follows (Table 1). (A) Evidence of significant differences in PK between males and females: 21 articles[22-37,39-42] (on 14 drugs, 13% of the approved drugs, namely: 5-fluorouracil (5-FU), atezolizumab, axitinib, cabozantinib, carboplatin, doxorubicin, epirubicin, imatinib, paclitaxel, panitumumab, pegylated liposomal doxorubicin, regorafenib, temozolomide and topotecan) reported evidence of significant differences in PK between males and females (Table 2); a significant difference in active metabolites in the clinical setting was also reported for sunitinib and regorafenib[37,38] (for other agents,

Category	Drugs
Table 1. Anticancer drugs (n = 99) categorised according to the available data on pharmacokinetic (PK) differences between males and females	
A: evidence of significant differences ($\geq$20%) in PK parameters[a]	Chemotherapy: 5-fluorouracil, carboplatin, doxorubicin, epirubicin, paclitaxel, pegylated liposomal doxorubicin, temozolomide, topotecan Small molecules: axitinib, cabozantinib, imatinib, regorafenib (parent drug and active metabolites), sunitinib (active metabolite) Monoclonal antibodies: atezolizumab, panitumumab
B: conflicting data from one study to another	Chemotherapy: docetaxel, irinotecan, oxaliplatin, pemetrexed, raltitrexed Small molecules: everolimus, trametinib Monoclonal antibodies: nivolumab
C: evidence of a lack of significant differences in PK parameters	Chemotherapy: cabazitaxel, capecitabine, cisplatin, dacarbazine, dactinomycin, etoposide, fotemustine, gemcitabine, ifosfamide, melphalan, methotrexate, Nab-paclitaxel, thiotepa, trabectedin, trifluridine tipiracil, vincristine, vinorelbine, vinflunine Small molecules: abemaciclib, afatinib, alectinib, binimetinib, brigatinib, ceritinib, cobimetinib, crizotinib, dabrafenib, encorafenib, erlotinib, erdafitinib, gefitinib, lenvatinib, lorlatinib, nintedanib, olaparib, osimertinib, palbociclib, ribociclib, sonidegib, sorafenib, sotorasib, sunitinib (parent drug), talazoparib, tivozanib, veliparib, vismodegib Monoclonal antibodies and antibody—drug conjugates: aflibercept, avelumab, bevacizumab, cemiplimab, denosumab, durvalumab, enfortumab vedotin, ipilimumab, pembrolizumab, pertuzumab, ramucirumab, trastuzumab, trastuzumab emtansine, trastuzumab deruxtecan
No data available	Chemotherapy: bleomycin, cyclophosphamide, eribulin, lomustine, procarbazine, vinblastine Small molecules: lapatinib, neratinib, niraparib, pazopanib, vandetanib Antibody—drug conjugate: sacituzumab govitecan

[a]Differences of 15%-19% were reported for avelumab (15%), erdafitinib (17%), pembrolizumab (15%), sunitinib (19%), trastuzumab deruxtecan (17%), and vemurafenib (17%); in all cases, clearance (or apparent clearance) was higher in men.

Table 2. Anticancer drugs with documented pharmacokinetic differences between males and females

Drug	Population PK parameter	Reported effect	IIV	n (% M)	Ref.
5-Fluorouracil	CL 158 L/h	CL slower in F (−26%) CL faster in M (+26%)	22	26 (NR) 32 (32)	[22] [23]
Atezolizumab	CL 0.235 L/d	CL slower in F (−20%)	29%	1519 (65)	[24]
Axitinib	CL/F 20.1 L/h	CL/F slower in F (−35%)	39%-94%	237 (NR)	[25]
Cabozantinib	CL/F 106 L/day	CL/F slower in F (−22%)	35%	289 (70)	[26]
Carboplatin	CL 107 ml/min	CL slower in F (−31%)	NR	70 (66)	[27]
Doxorubicin	CL 19.9 L/h/1.8 m^2 for doxorubicinol CL 113.2 L/h in M	CL faster in M ($P = 0.04$) CL slower in F (−50%)	23%	66 (59) 27 (22)	[28] [29]
Epirubicin	CL 95.2 L/h in M	CL slower in F (−23%)	27%	36 (36)	[30]
Imatinib	CL/F 14.3 L/h $C_{sstrough}$ 1353 ng/ml in M CL/F 11.95 L/h	CL/F slower in F $C_{sstrough}$ lower in M (−25%) CL/F slower in F (−50%)	45%	59 (55) 190 (NR) 43 (63)	[31] [32] [33]
Paclitaxel	VM$_{EL}$ 37.4 µmol/h	VM$_{EL}$ maximal elimination capacity higher in M (+20%)	16%	168 (51)	[34]
Panitumumab	CL 0.273 L/day	CL slower in F (−23%)	NR	1200 (64)	[35]
Pegylated liposomal doxorubicin	CL 54.6 ml/h/m^2	CL slower in F (−43%)	NR	70 (70)	[36]
Regorafenib	CL/F 4.02 L/h	CL/F slower in F (−27% for regorafenib and −25% for active metabolites)	NR	62 (61-88)	[37]
Sunitinib	CL/F 34.1 L/h	CL/F slower in F (−35%) for the active metabolite SU12662	25% for sunitinib and 36% for SU12662	395 (66)	[38]
Temozolomide	CL/F 10 L/h CL/F 8.8 to 13.9 L/h	CL/F slower in F (−22%)	80.5%	35 (69) 445 (63)	[39] [40]
Topotecan	CL/F 237 L/h in M	CL slower in F (−33%) CL slower in F (−33%)	31%-62%	92 (60) 82 (49)	[41,42]

$C_{sstrough}$, trough concentration at steady state; CL, clearance; CL/F, apparent clearance; F, females; IIV, inter-individual variability; M, males; NR, not reported; PK, pharmacokinetics; Ref. reference, VM$_{EL}$, maximal elimination capacity.

only preclinical data were available). (B) Conflicting data from one study to another: 21 articles[43-63] (on eight drugs, 7% of the approved drugs, namely: docetaxel, everolimus, irinotecan, nivolumab, oxaliplatin, pemetrexed, raltitrexed, and trametinib) reported conflicting data from one study to another (Table 3). (C) The remaining 63 articles[38,63-124] (on 61 drugs, 61% of the approved drugs) reported no significant differences in PK between males and females.

All but two of the studies reporting effects on $C_{sstrough}$ ($n = 1$) and volume of distribution ($n = 1$) reported effects on CL or CL/F. In category A, the median effect on CL (or CL/F) was −26% (range: −20% to −50%). In all cases, CL was slower in females, indicating potentially excessive exposure compared with males, which could result in increased toxicity and/or efficacy (Table 3).

Table 3. Anticancer drugs with possible (conflicting results from one study to another) pharmacokinetic differences between males and females

Drug	Population PK parameter	Reported effect	n (% M)	Ref.
Docetaxel	CL 35.6 L/h CL 42 L/h	NSD NSD if normalised on BSA, otherwise CL higher in M (+20%)	26 (35) 243 (28)	[43] [44]
Everolimus	$C_{sstrough}$ 19.4 ng/ml in M CL/F 20.3 L/h	$C_{sstrough}$ higher in M (+34%) NSD	467 (69) 42 (52)	[45] [46]
Irinotecan	AUC 255.5 ng/ml × h in M for SN38 (active metabolite)	AUC lower in F for SN38 NSD	36 (78) 107 (58)	[47] [48]
Nivolumab	CL 0.185-0.237 L/day	CL slower in F (−10% to −22%)[a]	221 (62) 1895 (67) 1074 (NR) 1302 (NR) 1200 (68) 6468 (NR)	[49] [50] [51] [52] [53] [54]
Oxaliplatin	CL 18.7 L/h	CL slower in F (−15%) CL slower in F (-40%)	40 (55) 56 (52)	[55,56]
Pemetrexed	CL 91.6 ml/min	CL slower in F (−32%) NSD	103 (52) 287 (38)	[57] [58]
Raltitrexed	CL 2.82 L/h	CL slower in F (−23%) NSD	37 (65) 112 (66)	[59] [60]
Trametinib	CL/F 4.91 L/h	CL/F slower in F (−26%) C_{trough} higher in F (+31%) NSD	493 (59) 34 (53) 60 (55)	[61] [62] [63]

AUC, area under the concentration-time curve; BSA, body surface area; C_{max}, peak concentration; $C_{sstrough}$, trough concentration at steady state; CL, clearance; CL/F, apparent clearance; F, females; M, males; NSD, no significant difference; PK, pharmacokinetics; Ref. reference.
[a]Some studies on nivolumab report on populations derived from the same clinical trials.

For eight anticancer agents (binimetinib, encorafenib, enfortumab vedotin, olaparib, sotorasib, tivozanib, trifluridine tipiracil, and vemurafenib), the impact of sex on PK data was available from FDA or EMA websites only,[125-132] and no related peer-reviewed publication was found. For another 12 agents (12% of the approved drugs: bleomycin, cyclophosphamide, eribulin, lapatinib, lomustine, neratinib, niraparib, pazopanib, procarbazine, sacituzumab govitecan, vandetanib, and vinblastine), no data were found.

Importantly, none of the studies included sex-based summaries to assess whether the observed differences in PK correlate with the efficacy or safety profile of the anticancer drug.

DISCUSSION

In this systematic review, we identified that comparative PK data between males and females were available for 88% of the 99 approved anticancer agents we investigated (hormonotherapy was excluded). The existing data indicated significant PK differences ($>\pm 20\%$ in CL or CL/F in women) for 15 drugs (category A), including 8 chemotherapies, 6 targeted drugs, and 1 immunotherapy. At least potentially different PK due to conflicting reports were identified for another eight drugs (category B). As CL appears to be lower relative to male subjects, higher exposure in females may contribute to the observed differences in anticancer drug outcomes (efficacy and toxicity).[133] Interestingly, the differences were seen for drugs dosed according to BSA (including paclitaxel and temozolomide, two of the five drugs for which BSA is known to significantly impact CL[1]) or fixed dosing, for drugs with various routes of administration or different metabolic pathways (including chemotherapy agents, small molecules, and monoclonal antibodies).

With regard to tolerability, retrospective analyses of prospective trials indicate significantly increased toxicity in females with colorectal cancer receiving 5-FU-based chemotherapy in the adjuvant[134,135] and metastatic setting.[136] Importantly, the increased toxicity in females has been observed not only for 5-FU-based combinations, but also for 5-FU as a single-agent.[23,134,136-138] In this context, it is interesting to note that 5-FU, which was included in all aforementioned trials,[134,135] was categorised as A in the present analysis, meaning that its CL is expected to be lower in females. Thus, these differences in PK are likely to contribute to the higher toxicity profile in these patients.

As far as efficacy is concerned, females seem to derive a higher benefit of adjuvant imatinib in GIST[139] in the context of a lower CL compared with males (Table 2), suggesting that PK differences may also impact efficacy outcomes. This observation also suggests that different (higher) doses of adjuvant imatinib could be considered for men. It should be mentioned that for selected anticancer drugs, and imatinib is an example of such a drug, therapeutic drug monitoring (TDM) is certainly another, and probably more precise way, to improve the benefit/risk ratio of these treatments. The widespread use of TDM is limited, however, by the lack of

specialised laboratories and pharmacologists with the necessary expertise.

In contrast, although no difference in capecitabine PK is observed between males and females, significant sex differences in efficacy were seen in the BILCAP study, which compared adjuvant treatment with capecitabine after curatively resected biliary cancer to observation alone,[140] illustrating that PK differences do not necessarily account for all sex differences in treatment outcomes. Although dose-response evaluation is recommended to occur early in clinical development, cancer has adopted its own dosing paradigm in which a thorough evaluation of dose response is not generally included before moving to phase III trials, preventing the exploration and mitigation of complexity. The need to improve dose-optimisation processes used in oncology drug development to minimise toxicity and maximise patient benefit has been recognised by the FDA.[141-143] To the best of our knowledge, however, the evaluation of different dosages for male and female patients has not yet been discussed in this context. In fact, in addition to randomised dose trials, which evaluate different dosages in the same group of patients, the development of individualised dosing strategies may further improve the benefit—risk ratio of selected anticancer treatments. For selected drugs, sex-dependent dosing may help to achieve that goal. As an illustration, the SEXIE-R-CHOP-trial[144] assessed a sex-specific dosing strategy based on the fact that the approved dose of rituximab (defined at the beginning of the biologics era, and contingent to manufacturing complexity) leads to sub-optimal exposure in men.

Such approaches are supported by the results of this systematic review. A higher drug exposure in one sex, however, does not necessarily translate into a higher drug response. This is illustrated in metastatic colorectal cancer,[145] where higher drug levels of 5-FU and a higher toxicity in females is not associated with a higher efficacy.[145] Thus, potential sex differences in the relationship between PK and PD, which may be due to sex differences in tumour biology, should be considered. In fact, sex differences in cancer biology are supported by rapidly increasing evidence.[146-149] Such differences are important not only as they may impact treatment efficacy, but also because novel cancer mechanisms may emerge when accounting for sex as a biological variable.[150] Although no sex differences in PK profile were reported for the majority of the 99 approved drugs considered for the present analysis, further studies examining sex differences in toxicity and efficacy are clearly warranted for the 22 others (categories A and B). For the 12 agents (bleomycin, cyclophosphamide, eribulin, lapatinib, lomustine, neratinib, niraparib, pazopanib, procarbazine, sacituzumab govitecan, vandetanib and vinblastine) for which no data were found, disclosure of additional pharmaco-clinical data (for the most recent drugs) or dedicated studies are needed to assess whether sex differences could exist. Sex-specific dosing strategies should be encouraged in clinical trials where evidence for sex differences in PK exist.

In this context, there are two practical and methodological aspects that ought to be considered. First, the importance of evidence generation during the development of anticancer drugs that provide insight into the exposure-response relationship, as well as into the determinants of variability in PK and PD. This requirement has been overlooked due to clinical views on the role of maximum tolerated dose in phase I and II trials. A second aspect is the somewhat limited use of model-based approaches for the analysis of PK/PD relationships, and in particular on the effect of covariates on exposure and treatment outcome.[151-153] In addition to providing insight into the sources of variation in PK and PD, it also allows characterisation of interindividual differences in safety and efficacy profile of anticancer drugs. Consequently, dose optimisation could take patient's sex into account, resulting in less interpatient variability in exposure and outcomes, similarly to how the maximum tolerated dose of irinotecan was identified depending on the *UGT1A1* genotype.[154] Conversely, fixed dosing could be considered when sex, body weight, BSA, and pharmacogenetic background have limited impact on pharmacological parameters, as seen for most conventional chemotherapy agents[1] and monoclonal antibodies.[155]

Our findings suggest the need to assess potential sex differences in PK and/or PD for other drugs commonly used in oncology: e.g. drugs used for supportive care may also exhibit sex-dependent PK profiles.[14] In fact, higher rates of nausea and vomiting in women have been observed not only for treatments with an established difference in PK and higher plasma levels in females, such as 5-FU,[23,134,145] but also cisplatin and gemcitabine,[156] for which no such difference has been described. This may be explained by the effects of sex hormones which could affect the transport and metabolism of a broad spectrum of drugs. Testosterone has minimal effects on CYP3A4 activity, but its effects on other drug-metabolising enzymes (CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and UGT1A1) are poorly documented.[157] Conversely, estrogens increase the activity of CYP3A4, CYP2B6, and UGT1A1 and decrease the activity of CYP1A2, with potential consequences on the metabolism of a broad spectrum of drugs.

Given their major importance in modern oncology, immune checkpoint inhibitors (ICIs) deserve a separate discussion in this context: as described in the results, amongst the included immunotherapeutic agents, a consistently significant difference in PK between sexes was only found for atezolizumab, with females having a lower CL and therefore an increased risk of higher than expected PK exposure,[24] while for other ICIs there are conflicting results on PK parameters or lack of significance between sexes. Apart from PK,[158] the sexual dimorphism of immunity could also result in differences in efficacy of immunotherapy between sexes. In general, females exhibit stronger innate and adaptive immune responses to antigenic stimulation, vaccination, and infection than males, which is illustrated by greater vaccine efficacy and lower rates of infections in females.[149,150] This sex-based difference in immunity may be explained by a complex interplay between genes, hormones, behaviour, tumour-intrinsic factors, and the microbiome.[133,146,159] One hypothesis suggests that this stronger immune response in females contributes to their decreased lifetime risk of most cancer types and a nearly twofold lower risk of cancer mortality compared with males.[160,161] If a tumour in females manages to escape an anticancer immune response, however, this may be due to more immune editing of the tumour, meaning tumours in females may become more easily resistant to immunotherapy. In meta-analyses of randomised controlled trials of ICIs for treatment of various cancer types, some studies showed that male patients derive a greater benefit from ICIs.[162-164] This finding, however, was not confirmed in other studies.[165-168] This heterogeneity amongst meta-analyses on this subject is likely the result of the inclusion of clinical trials involving patients with a large diversity of tumour types, types of ICI, treatment in the control arm, and tumour characteristics. Known factors correlated with response to ICI, such as high tumour mutational burden and neoantigen burden, proportion of cancer cells versus non-cancer cells, cytolytic activity, and CD8+ T-cell infiltration have been more prevalent in tumours coming from male patients compared with those coming from females, but this may also be cancer specific.[168,169] Apart from tumour characteristics, lifestyle-related factors such as smoking and UV light exposure increase the number of cancer-specific mutations and may enhance recognition by the immune system and response to ICIs.[170,171] Regarding immune-related toxicities, the higher prevalence of autoimmune diseases in females may also contribute to a higher risk of adverse effects from ICIs.[172] Also here, contradictory results are seen in the literature, with the incidence of immune-related adverse events per sex varying across tumour types.[6,173] In summary, since the results on the association between sex and ICI efficacy or toxicity are conflicting, potential sex-dependent differences should be studied per cancer type and treatment, but may still be dependent on multiple immune-related, host-related, and cancer-specific factors.

One other finding of major importance of this review is the fact that no PK/PD population study was identified. In fact, sex differences in PD are studied less than sex differences in PK and, in addition to sex differences in PK, sex differences in systems level and cellular biology have the potential to impact PD and therapeutic responses.[7] In addition, only three studies assessed the impact of body composition on PK (for sunitinib, sorafenib, and epirubicin[11,13,174]), which pinpoints another area where further research is needed and opportunities to improve drug dosing could be identified. An individual patients' body composition can easily be estimated with a single abdominal cross-sectional image by computed tomography (CT),[175] and this information may inform drug dosing. Lastly, the difference in available data might also be explained by a 'lead-time bias', with older anticancer drugs (particularly chemotherapeutics) having undergone more post-marketing academic research looking at extensive

covariate matrices including sex to explain interindividual PK variability.

Overall, this review emphasises the need for more studies and attention to sex differences in anticancer treatments (as highlighted during a previous ESMO workshop[176]), and stresses the need to consider a patients' sex as one of several critical sources of variability in PK and consequently in drug response,[177] along with other factors such as age, body weight, body composition, polymorphisms in drug metabolism, distribution and transport, as well as renal and liver function, as illustrated in Figure 2. Importantly, the patient's sex intersects with several of these factors, such as body weight and renal function, while the patient's gender potentially intersects with other factors, such as drug adherence,[178,179] comorbidities, and comedications, which is beyond the scope of this review but should be considered. Thus, sex and gender are much more than just additions to the list of factors which influence drug responses, but instead play an overarching role, with an impact on multiple parameters. Furthermore, it should be mentioned that sex differences in long-term toxicity, the impact on fertility, and whether these drugs can be safely given in pregnant women needs active investigation and reporting. As a community, we need to collectively improve our understanding of sex differences in drug exposure and its potential consequences in terms of efficacy, activity, and toxicity and consider sex-specific dosing strategies for selected drugs and regimens.[180] In this context, additional PK—PD analyses appear to be mandatory.[181,182] The recent implementation of FDA guidance for dose optimisation (known as Project Optimus, https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus, last accessed 6 February 2023) with a randomised exploration of PK and PD parameters could represent an appropriate setting for these analyses. In addition to dose optimisation, differences in tumour biology
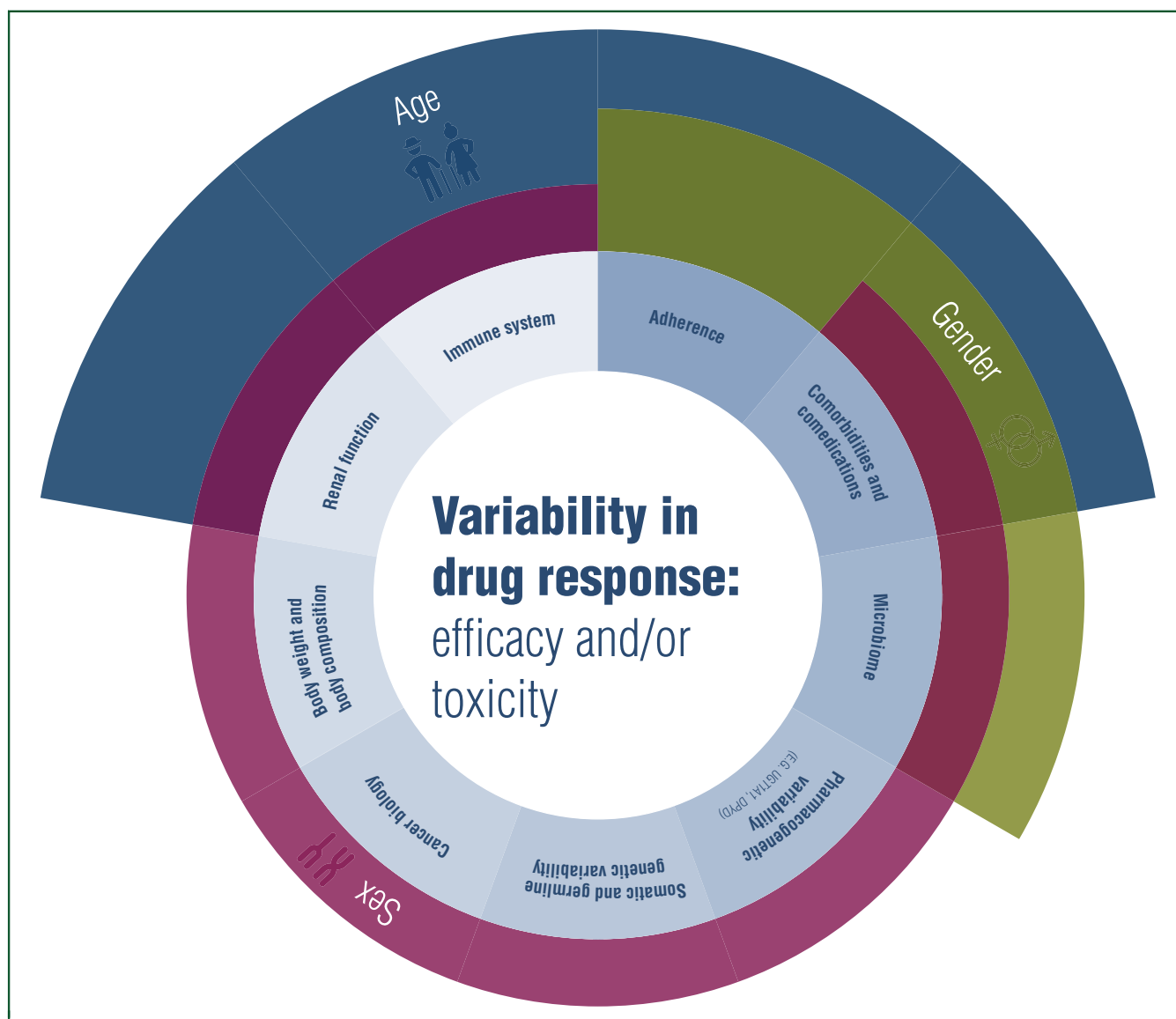

Figure 2. Examples of factors potentially influencing the variability in drug responses. Both biological sex and gender, as well as age are overarching factors, with potential influence on drug responses on different levels.

call for a separate evaluation of the risk—benefit ratio of anticancer treatments in female and male patients.

DISCLOSURE

AP is an employee of Servier since 1 June 2022. OM is a shareholder and employee of Amgen, Inc. since 1 February 2022. SB is founder and shareholder of Liqomics, consultant for Galapagos and has received speaker fees and travel support from Takeda and speaker fees from Diaceutics. None of these potential conflicts of interest are related to the work presented here. BCO reports honoraria paid to her institution for lectures and advisory boards from Bristol Myers Squibb (BMS), Merck Sharpe & Dohme (MSD), Merck, Ipsen, Roche, Pfizer, Novartis, Janssen, and Sanofi. RHAV reports research funding from BMS and consultancy for Daiichi Sankyo, all paid to the institute. ADW reports travel support for congress participation from AbbVie, Ipsen, Merck, Sanofi, advisory roles for Astellas, BMS, Daiichi Sankyo, Lilly, Merck, MSD, Pierre-Fabre, Sanofi, Servier. She is coordinating investigator of EORTC 1203, the 'INNOVATION'-trial, which is supported by an educational grant from Roche to EORTC. She is co-chair of the EORTC gastric cancer task force and chair of the ESMO gender medicine task force. ODP is also an employee of GlaxoSmithKline since 8 August 1998. JH serves on advisory board for Achilles Therapeutics, AstraZeneca, BioNTech, BMS, CureVac, Eisai, Imcyse, Immunocore, Instil Bio, Iovance Biotherapeutics, Ipsen, Merck Serono, MSD, Molecular Partners, Neogene Therapeutics, Novartis, Pfizer, PokeAcel, Roche, Sanofi, Scenic, T-Third Rock Venture, Knife. Research grants from Amgen, Asher Bio, BioNTech US, BMS, MSD, Novartis, Sastra Cell Therapy. Stocks/shares by Neogene Therapeutics and Sastra Cell Therapy. All other authors have declared no conflicts of interest.

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