Sex and gender differences in anticancer treatment toxicity – a call for revisiting drug dosing in oncology

Berna C. Özdemir[1,2*] MD PhD, Camille L. Gerard[3,4] MD, Cristina Espinosa da Silva[5,6] MPH

[1] Department of Medical Oncology, Bern University Hospital and University of Bern, Switzerland

[2] International Cancer Prevention Institute, Epalinges, Switzerland

[3] Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

[4] The Francis Crick Institute, London, United Kingdom

[5] Herbert Wertheim School of Public Health & Human Longevity Science, University of California San Diego, USA

[6] Division of Epidemiology and Biostatistics, School of Public Health, San Diego State University, USA

*corresponding author

Berna C. Özdemir

Bern University Hospital

Department of Medical Oncology

Freiburgstrasse 111

3011 Bern

Switzerland

Berna.oezdemir@insel.ch

ORCID ID: https://orcid.org/0000-0002-7380-0055

Disclosures

CLG and CEDS declared to have nothing to disclose

BCÖ declared receiving institutional honoraria for lectures and advisory boards from BMS, MSD, Merck, Ipsen, Roche, Novartis, Pfizer and a contribution to registration fees for conferences from Janssen.

Abstract

The practice of oncology has dramatically changed in the last decade with the introduction of molecular tumor profiling into routine tumor diagnostics and the extraordinary progress in immunotherapies. However, there remains an unmet need to explore personalized dosing strategies that take into account the patient's sex to optimize the balance between efficacy and toxicity for each individual patient. In this mini-review, we summarize the evidence on sex differences in toxicity of anticancer therapies and present data on dose reduction and dose discontinuation rates for selected chemotherapies and targeted therapies. Finally, we propose the investigation of body composition (specifically fat free muscle mass) as a viable approach for personalized treatment dosage.

Keywords: sex differences, gender differences, body composition, fat free muscle mass, targeted therapies

Introduction

In the last decade, the practice of oncology has profoundly changed with the introduction of molecular tumor profiling in routine tumor diagnostics as well as the extraordinary progress in immunotherapies. Yet, largely missing in treatment decisions is the integration of a patient's sex and gender as a critical modulator of their cancer risk and potential treatment outcomes. Despite the significant progress in treatment options for most cancer types, there remains an unmet need to explore personalized dosing strategies that take into account the patient's sex and gender to subsequently optimize the balance between efficacy and toxicity for each individual patient.

In this mini-review, we discuss the evidence pertaining to observed sex differences in the toxicity of anticancer therapies, present data on dose reduction and dose discontinuation rates for selected drugs, and propose the investigation of body composition-based drug dosing as a viable approach to personalize cytotoxic agents and targeted therapies. To obtain information for this mini-review, we performed a literature search on PubMed in January 2022 using the terms "sex differences," "gender," "cancer," and "drug toxicity" and also manually searched the reference lists of several publications of interest.

Sex versus gender

The terms "sex" and "gender" are often used interchangeably in scientific literature (1) although this can be misleading as there are important distinctions between the terms. Sex refers to a person as female and male based on their biological features assigned by their gonads and sex chromosomes. As such, sex-related differences are the result of the interplay between genetic, hormonal, and physiological traits. Gender, on the other hand, is based on a person's cultural self-identification as a woman or man and also encapsulates

how that person may be perceived by society given their presentation (1). Gender-based differences arise in part from environmental factors related to the socio-cultural roles of women and men. Often these biological and environmental factors are entangled and interact with each other. In this mini-review, we use the terms “female,” “woman,” and “women” to refer to people who were assigned female sex at birth and socially self-identify as women. Likewise, we use the terms “male,” “man,” and “men” to refer to people who were assigned male sex at birth and socially self-identify as men. We acknowledge that there are likely important gender-based differences in anticancer treatment toxicity among transgender people that should be further examined in future work, as it is beyond the scope of this mini-review.

Women have a higher risk of experiencing adverse drug reactions

A patient’s sex is a key modulator of drug responses, (2,3) which is expected given the important biological differences between women and men that can affect many aspects of treatment. Multiple analyses from different countries have shown that women have a 1.5- to 2-fold greater risk for developing adverse drug reactions (ADRs) across all drug classes and are significantly more likely to be hospitalized because of ADRs compared to men (4,5). This increased ADR risk among women may be related to the fact that many Phase I and Phase II clinical drug trials are conducted predominately among men, (6) (7) and the optimal drug dosing that are subsequently derived from these trials are likely not generalizable to women. These underexamined sex differences in drug dosing can have serious implications. Of the ten drugs withdrawn from the US market between 1997 and 2000, 80% were found to represent a greater health risk for women than for men and 37% of the FDA-approved drugs between 2000-2002 were found to have sex differences in pharmacokinetics, efficacy, or adverse events (8). However, no recommendation on sex-based dose adaptation was made

(9), possibly based on the erroneous assumption that these differences are not clinically relevant.

Various sex- (biological) and gender-related (psychosocial and societal) factors might contribute to the disproportionately higher ADR susceptibility among women compared to men. These include sex differences in pharmacokinetics and pharmacodynamics, gut microbiota composition, (10) (11) sex-specific organizational (early life) and activational (peripubertal through adulthood) endogenous sex hormone exposure, sex differences in exogenous sex hormone supplementation (e.g., oral contraceptives, menopausal hormone replacement therapies), higher rates of polypharmacy in women with a consequently greater risk of potential drug-drug interactions, and gender differences in the reporting or recall of ADRs (with women being more frequent reporters) (12). Importantly, sex differences in pharmacokinetics predict ADR across multiple classes of drugs, including antineoplastic agents (5).

Women present significantly higher blood drug concentrations and longer drug elimination times compared to men when administered the same drug dose. This is possibly related to the greater plasma volume, organ perfusion, and the approximately 10% higher body fat in women (13). Given the binding of drugs to erythrocytes, the lower haematocrit levels in women might also contribute to this excess drug toxicity (14). Sex differences in the expression levels of drug-metabolizing enzymes resulting from genetic polymorphisms (e.g., cytochrome P450 isoforms; “pharmacogenetics”) may also play a role (15). While data on differential expression of various CYP450 isoforms provide either conflicting results or do not indicate moderation by sex, the isoform CYP3A (which accounts for the metabolism of about 50% of drugs) has been reported to have a 25% higher activity in women (16). In contrast, the expression levels of the drug efflux pump P-gp encoded by the *MDR1* gene are higher in

men and might partially explain the lower toxicity rate observed in men (17). Indeed, sex steroids were found to regulate P-gp expression and increase drug absorption through blocking of the P-gp activity in the small intestine of rats (18). A comprehensive review of sex differences in pharmacokinetics and pharmacodynamics can be found in (3)

Several pharmacokinetic analyses have found that women have a lower elimination capacity for various anticancer drugs, including cytotoxic agents (i.e., paclitaxel (19), 5-fluorouracil (20), doxorubicin (21)), tyrosine kinase inhibitors (i.e., imatinib (22), sunitinib (23)), and monoclonal antibodies (i.e., bevacizumab (24) and rituximab (25)) which results in higher plasma levels (**Table 1**). There are significant sex differences in renal function (which is taken into account in renal function calculators (26,27)), with men having an average of 20% greater renal function than women (28). Despite these well documented sex-related differences, most analyses of anticancer drug elimination and distribution do not even include sex as a covariate. In a literature survey of 256 population studies on anticancer agents, only 80 reported that sex was included as a covariate in the analytic models (29).

Flat doses and doses based on body surface area hamper personalized anticancer treatment

A recent study of over 23,000 patients (38% women) in Phase II and III clinical trials found that female sex was associated with a higher risk of experiencing toxicity from anticancer therapies (30). Unger and colleagues analysed individual patient data from 202 Phase II and III clinical trials testing systemic anticancer therapies and severe treatment-related adverse events (AEs). Their findings indicated that women had 34 times greater odds of severe toxicity compared to men (Odds Ratio [95% Confidence Interval]= 1.34 (1.27-1.42), $p<0.001$). Moreover, this increased odds of AEs among women persisted across treatment type (chemotherapies, targeted therapies, immunotherapies), AE type (symptomatic or

hematological), and treatment setting (advanced versus adjuvant) (30). Although it is possible that some of these AEs may be due to social gender differences in the reporting of symptomatic adverse events, the higher odds of objective hematological toxicity clearly point to the presence of biological sex differences in pharmacokinetics and/or pharmacodynamics which modulate the patient's sensitivity towards adverse effects. The sex-specific toxicities likely result from both an increased drug exposure through hormonal regulation of proteins involved in drug metabolism as well as via the direct effect of sex hormones on the drug target (13). Given the lack of a systematic collection of information on menopause status, the dose and type of hormonal contraception and the measurement of sex hormone levels in clinical trials, the magnitude of the hormonal effects remains unknown.

In addition, the individual genetic background/ethnicity as well as differences in gut microbiota diversity and composition and diet also potentially contribute to the observed sex differences (31). In fact, microbiome profiling in age-and diet-matched individuals indicates that the microbiota composition can be affected by gender in a body-mass dependent manner (32). Yet, given the complexity of the crosstalk between immune responses, microbiome and sex hormones, dissecting the individual contribution of each of these factors is challenging (11).

Despite the above mentioned sex differences and the basic paradigm of clinical pharmacology that drug effects are generated from the circulating concentration profile of a drug rather than directly by the dose itself, dosage recommendations for anticancer drugs are not sex-specific and most agents are administered either as flat doses (e.g., tyrosine kinase inhibitors and some antibodies) or according to body weight (e.g., some antibodies such as bevacizumab and ipilimumab) or body surface are (BSA, e.g., cytotoxic agents). The recommended chemotherapy doses are meant to represent the dosages with the best therapeutic window showing the highest efficacy at the maximum tolerable dose (MTD).

However, drug dose has been demonstrated to have a positive correlation with drug-related toxicity in Phase I trials (33). This phenomenon may be occurring given that the recommended anticancer drug dosages are often developed from clinical trial data among predominately male study populations and may have limited generalizability. Considering that women are consistently underrepresented in all phases of drug testing in clinical trials, (6,7) the MTD may actually be lower in women. As such, the administration of current standard doses may lead to increased blood drug concentrations and toxicity in women. Indeed, higher toxicity rates for most of the commonly applied cytotoxic agents have been reported among women compared to men (**Table 1**). In addition, there is an increasing population of old, obese or underweight cancer patients, who are often undertreated because of arbitrary reductions of the calculated doses based on body weight or BSA and the use of an idealized body weight or capping of the total dose, although it was shown that BSA based dosing is safe for obese patients (34) (35). However, obese patients can be sarcopenic and at risk of excess toxicity. Until the impact of sarcopenia and other measures of body composition on optimal antineoplastic dosing has been addressed, clinical guidelines recommend using the full, approved doses of anticancer treatments for obese adults with cancer (36) (37).

Interestingly, although obesity is a risk factor for cancer and treatment toxicity, recent analyses suggests that some degree of obesity (Body mass index >30 kg/m2) might be protective, with obese cancer patients showing better responses to treatment when compared to lean patients, in particular for immune checkpoint inhibitors and targeted therapies (38,39). This phenomenon is termed the “obesity paradox” and has been reported for different cancer types. The visceral adipose tissue (VAT) is in fact considered an endocrine organ, responsible for secreting various factors which regulate innate and adaptive immunity, hematopoiesis, and angiogenesis (40).

Calculations based on BSA do not provide an accurate optimal therapeutic window for both sexes because this approach does not take into account sex differences in body composition and pharmacokinetics. As a comparison of 25 BSA formulas has shown, the BSA value may differ by 0.5m^2 depending on the formula used for the calculation (41). Additionally, the Du Bois & Du Bois formula for the BSA calculation was developed solely from the data derived from nine male individuals (42) and may be a less effective measurement tool among females. Similarly, according to three BSA bands (i.e., 1.7 m^2, 1.7 -1.9 m^2, ≥1.9 m^2) the dosing of the cytotoxic drugs cisplatin, docetaxel, paclitaxel, doxorubicin, irinotecan, and topotecan yielded comparable target area of the curve (AUC) values as dosing according to the calculated individual BSA, highlighting the inexactitude of the BSA method (43).

Alternative chemotherapy dosing strategies have been studied (i.e. dose-dense regimens and toxicity- or response-guided regimens) and are successfully incorporated in the management of hematological malignancies (44,45). In contrast, pharmacokinetically-guided dose adaptation (therapeutic drug monitoring) or genotyping for drug-metabolizing enzymes with known genetic polymorphisms have not been adopted for routine clinical use. This is due to several factors, most importantly due to the lack of an established therapeutic range for the majority of cytotoxic drugs, the scarcity of genetic studies characterizing the expression of specific enzyme variants, and the insufficient progress that has been made in investigating the factors responsible for sex-related pharmacokinetic differences (46).

As compared to cytotoxic agents, the impact of sex on the type, frequency, and severity of the toxicity from tyrosine kinase inhibitors (TKI) is largely unknown for many recently approved targeted therapies (47). Depending on the targeted signaling pathway (e.g., EGFR, ALK, VEGFR, BRAF), TKIs show highly variable dose reduction (4-70%) and discontinuation rates for toxicity (6-24%, **Table 2**). According to a meta-analysis of Phase I

trials of TKIs, treatment with intermediate doses (40-80% of the MTD) is associated with better survival as compared to lower or higher doses (48). For instance, subgroup analysis by age in the METEOR trial investigating the TKI cabozanitinib in renal cell carcinoma showed that patients aged 65-74 years and 75 years or older had an average daily median dose of 41 mg and 33 mg, respectively, as compared to the recommended standard dose of 60mg daily. However, their response rate (21% vs 19%, respectively) was very similar to that of the total trial population receiving cabozantinib (17%) (49).

Fat free muscle mass could become a novel parameter for drug dosing in oncology

The high toxicity rate of anticancer treatments has a negative impact on the quality of life of cancer patients, and strategies to diminish adverse events without affecting efficacy need to be explored. One possible strategy to decrease toxicity rates could be personalized dosing according to the body composition of the patient.

Drug metabolism is affected by body composition, specifically the metabolically active fat-free body mass (FFM). A single abdominal CT scan without contrast enhancement of the L3-L4 region is sufficient to measure the FFM and body composition in an individual patient, as it shows a strong correlation with whole body adipose tissue, muscle, and lean tissue mass (50). The FFM is significantly higher in men; in a man and a woman of equal weight and height, the FFM accounts for 80% and 65% of the man's and woman's body mass, respectively (51). The FFM also decreases with increasing age (52), highlighting potentially significant differences in drug metabolism by age (younger versus older patients) in addition to sex (male versus female patients).

In a meta-analysis of 28 studies including over 6000 metastatic renal cell carcinoma patients, low muscle mass was associated with a significantly higher toxicity rate of the TKIs sunitinib and sorafenib as well as a higher mortality rate (53). In a retrospective analysis of 107 children, a higher skeletal muscle density at diagnosis was associated with lower odds of severe hematological toxicity of chemotherapies (54). Also, a prospective trial with 60 colon cancer patients receiving adjuvant 5-FU treatment found that 20mg 5-FU/kg lean body mass was the threshold for developing overall toxicity which shows the potential utility of body composition as a dosing parameter (55). Given this evidence, dosing of chemotherapies and targeted therapies based on the FFM would take into consideration important patient characteristics, such as sex, age and body composition. This proposed approach to anticancer drug dosages could lead to a valuable improvement in the quality of life of cancer patients, including protecting them from unnecessary toxicity without compromising the efficacy of their treatment.

Conclusions

Compared to the progress made in drug development, the optimization of drug dosing lags significantly behind in the field of oncology. Given the different body composition of women and men, the administration of recommended drug doses established from studies with predominantly male populations may lead to increased blood drug concentrations and toxicity in female patients. In the era of precision medicine, a patient's biological sex and gender needs to be taken into account for treatment decisions. As such, the representation of women needs to be increased in clinical trials and trials should be designed to allow meaningful subgroup analysis by sex for both drug response and drug toxicity. Prospective studies testing the dosing of cytotoxic agents and targeted therapies according to the FFM could represent a viable alternative to the current BSA-based or fixed dosing, and significantly improve the balance between the toxicity and efficacy of anticancer therapies.

Data availability Statement: Not applicable

References

1. King BM. Point: a call for proper usage of "gender" and "sex" in biomedical publications. Am J Physiol Regul Integr Comp Physiol 2010; 298:R1700-1701
2. Schmetzer O, Florcken A. Sex differences in the drug therapy for oncologic diseases. Handb Exp Pharmacol 2012:411-442
3. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2009; 48:143-157
4. Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol 2001; 2:349-351
5. Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. Biol Sex Differ 2020; 11:32
6. Jenei K, Meyers DE, Prasad V. The Inclusion of Women in Global Oncology Drug Trials Over the Past 20 Years. JAMA Oncol 2021; 7:1569-1570
7. Steinberg JR, Turner BE, Weeks BT, Magnani CJ, Wong BO, Rodriguez F, Yee LM, Cullen MR. Analysis of Female Enrollment and Participant Sex by Burden of Disease in US Clinical Trials Between 2000 and 2020. JAMA Netw Open 2021; 4:e2113749
8. http://www.gao.gov/new.items/d01286r.pdf. Drug safety: most drugs withdrawn in recent years had greater health risks for women. 2001;
9. Yang Y, Carlin AS, Faustino PJ, Motta MI, Hamad ML, He R, Watanuki Y, Pinnow EE, Khan MA. Participation of women in clinical trials for new drugs approved by the food and drug administration in 2000-2002. J Womens Health (Larchmt) 2009; 18:303-310
10. Garrett WS. Cancer and the microbiota. Science 2015; 348:80-86
11. Wagner AD, Ozdemir B, Csajka C. Reply to L. Pala et al. J Clin Oncol 2019; 37:439-440
12. Watson S, Caster O, Rochon PA, den Ruijter H. Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. EClinicalMedicine 2019; 17:100188
13. Nicolson TJ, Mellor HR, Roberts RR. Gender differences in drug toxicity. Trends Pharmacol Sci 2010; 31:108-114
14. Schrijvers D. Role of red blood cells in pharmacokinetics of chemotherapeutic agents. Clin Pharmacokinet 2003; 42:779-791
15. Maliepaard M, Nofziger C, Papaluca M, Zineh I, Uyama Y, Prasad K, Grimstein C, Pacanowski M, Ehmann F, Dossena S, Paulmichl M. Pharmacogenetics in the evaluation of new drugs: a multiregional regulatory perspective. Nat Rev Drug Discov 2013; 12:103-115
16. Hunt CM, Westerkam WR, Stave GM. Effect of age and gender on the activity of human hepatic CYP3A. Biochem Pharmacol 1992; 44:275-283
17. Meibohm B, Beierle I, Derendorf H. How important are gender differences in pharmacokinetics? Clin Pharmacokinet 2002; 41:329-342
18. Nakayama A, Eguchi O, Hatakeyama M, Saitoh H, Takada M. Different absorption behaviors among steroid hormones due to possible interaction with P-glycoprotein in the rat small intestine. Biol Pharm Bull 1999; 22:535-538

19. Joerger M, Huitema AD, van den Bongard DH, Schellens JH, Beijnen JH. Quantitative effect of gender, age, liver function, and body size on the population pharmacokinetics of Paclitaxel in patients with solid tumors. Clin Cancer Res 2006; 12:2150-2157

20. Gusella M, Crepaldi G, Barile C, Bononi A, Menon D, Toso S, Scapoli D, Stievano L, Ferrazzi E, Grigoletto F, Ferrari M, Padrini R. Pharmacokinetic and demographic markers of 5-fluorouracil toxicity in 181 patients on adjuvant therapy for colorectal cancer. Ann Oncol 2006; 17:1656-1660

21. Dobbs NA, Twelves CJ, Gillies H, James CA, Harper PG, Rubens RD. Gender affects doxorubicin pharmacokinetics in patients with normal liver biochemistry. Cancer Chemother Pharmacol 1995; 36:473-476

22. Gotta V, Bouchet S, Widmer N, Schuld P, Decosterd LA, Buclin T, Mahon FX, Csajka C, Molimard M. Large-scale imatinib dose-concentration-effect study in CML patients under routine care conditions. Leuk Res 2014; 38:764-772

23. Houk BE, Bello CL, Kang D, Amantea M. A population pharmacokinetic meta-analysis of sunitinib malate (SU11248) and its primary metabolite (SU12662) in healthy volunteers and oncology patients. Clin Cancer Res 2009; 15:2497-2506

24. Lu JF, Bruno R, Eppler S, Novotny W, Lum B, Gaudreault J. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. Cancer Chemother Pharmacol 2008; 62:779-786

25. Pfreundschuh M, Poeschel V, Zeynalova S, Hanel M, Held G, Schmitz N, Viardot A, Dreyling MH, Hallek M, Mueller C, Wiesen MH, Witzens-Harig M, Truemper L, Keller U, Rixecker T, Zwick C, Murawski N. Optimization of rituximab for the treatment of diffuse large B-cell lymphoma (II): extended rituximab exposure time in the SMARTE-R-CHOP-14 trial of the german high-grade non-Hodgkin lymphoma study group. J Clin Oncol 2014; 32:4127-4133

26. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41

27. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, Coresh J, Levey AS, Investigators C-E. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012; 367:20-29

28. Schwartz JB. The current state of knowledge on age, sex, and their interactions on clinical pharmacology. Clin Pharmacol Ther 2007; 82:87-96

29. Wagner AD, Oertelt-Prigione S, Adjei A, Buclin T, Cristina V, Csajka C, Coukos G, Dafni U, Dotto GP, Ducreux M, Fellay J, Haanen J, Hocquelet A, Klinge I, Lemmens V, Letsch A, Mauer M, Moehler M, Peters S, Ozdemir BC. Gender Medicine and Oncology: Report and consensus of an ESMO Workshop. Ann Oncol 2019;

30. Unger JM, Vaidya R, Albain KS, LeBlanc M, Minasian LM, Gotay CC, Henry NL, Fisch MJ, Lee SM, Blanke CD, Hershman DL. Sex Differences in Risk of Severe Adverse Events in Patients Receiving Immunotherapy, Targeted Therapy, or Chemotherapy in Cancer Clinical Trials. J Clin Oncol 2022:JCO2102377

31. Garcia-Gonzalez AP, Ritter AD, Shrestha S, Andersen EC, Yilmaz LS, Walhout AJM. Bacterial Metabolism Affects the C. elegans Response to Cancer Chemotherapeutics. Cell 2017; 169:431-441 e438

32. Haro C, Rangel-Zuniga OA, Alcala-Diaz JF, Gomez-Delgado F, Perez-Martinez P, Delgado-Lista J, Quintana-Navarro GM, Landa BB, Navas-Cortes JA, Tena-Sempere M,

Clemente JC, Lopez-Miranda J, Perez-Jimenez F, Camargo A. Intestinal Microbiota Is Influenced by Gender and Body Mass Index. PLoS One 2016; 11:e0154090

33. Eaton A, Iasonos A, Gounder MM, Pamer EG, Drilon A, Vulih D, Smith GL, Ivy SP, Spriggs DR, Hyman DM. Toxicity Attribution in Phase I Trials: Evaluating the Effect of Dose on the Frequency of Related and Unrelated Toxicities. Clin Cancer Res 2016; 22:553-559

34. Field KM, Kosmider S, Jefford M, Michael M, Jennens R, Green M, Gibbs P. Chemotherapy dosing strategies in the obese, elderly, and thin patient: results of a nationwide survey. J Oncol Pract 2008; 4:108-113

35. Hourdequin KC, Schpero WL, McKenna DR, Piazik BL, Larson RJ. Toxic effect of chemotherapy dosing using actual body weight in obese versus normal-weight patients: a systematic review and meta-analysis. Ann Oncol 2013; 24:2952-2962

36. Griggs JJ, Bohlke K, Balaban EP, Dignam JJ, Hall ET, Harvey RD, Hecht DP, Klute KA, Morrison VA, Pini TM, Rosner GL, Runowicz CD, Shayne M, Sparreboom A, Turner S, Zarwan C, Lyman GH. Appropriate Systemic Therapy Dosing for Obese Adult Patients With Cancer: ASCO Guideline Update. J Clin Oncol 2021; 39:2037-2048

37. Silvestris N, Argentiero A, Natalicchio A, D'Oronzo S, Beretta GD, Acquati S, Adinolfi V, Di Bartolo P, Danesi R, Faggiano A, Ferrari P, Gallo M, Gori S, Morviducci L, Russo A, Tuveri E, Zatelli MC, Montagnani M, Giorgino F. Antineoplastic dosing in overweight and obese cancer patients: an Associazione Italiana Oncologia Medica (AIOM)/Associazione Medici Diabetologi (AMD)/Societa Italiana Endocrinologia (SIE)/Societa Italiana Farmacologia (SIF) multidisciplinary consensus position paper. ESMO Open 2021; 6:100153

38. Wang Z, Aguilar EG, Luna JI, Dunai C, Khuat LT, Le CT, Mirsoian A, Minnar CM, Stoffel KM, Sturgill IR, Grossenbacher SK, Withers SS, Rebhun RB, Hartigan-O'Connor DJ, Mendez-Lagares G, Tarantal AF, Isseroff RR, Griffith TS, Schalper KA, Merleev A, Saha A, Maverakis E, Kelly K, Aljumaily R, Ibrahimi S, Mukherjee S, Machiorlatti M, Vesely SK, Longo DL, Blazar BR, Canter RJ, Murphy WJ, Monjazeb AM. Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. Nat Med 2019; 25:141-151

39. McQuade JL, Daniel CR, Hess KR, Mak C, Wang DY, Rai RR, Park JJ, Haydu LE, Spencer C, Wongchenko M, Lane S, Lee DY, Kaper M, McKean M, Beckermann KE, Rubinstein SM, Rooney I, Musib L, Budha N, Hsu J, Nowicki TS, Avila A, Haas T, Puligandla M, Lee S, Fang S, Wargo JA, Gershenwald JE, Lee JE, Hwu P, Chapman PB, Sosman JA, Schadendorf D, Grob JJ, Flaherty KT, Walker D, Yan Y, McKenna E, Legos JJ, Carlino MS, Ribas A, Kirkwood JM, Long GV, Johnson DB, Menzies AM, Davies MA. Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. Lancet Oncol 2018; 19:310-322

40. Assumpcao JAF, Pasquarelli-do-Nascimento G, Duarte MSV, Bonamino MH, Magalhaes KG. The ambiguous role of obesity in oncology by promoting cancer but boosting antitumor immunotherapy. J Biomed Sci 2022; 29:12

41. Redlarski G, Palkowski A, Krawczuk M. Body surface area formulae: an alarming ambiguity. Sci Rep 2016; 6:27966

42. Shuter B, Aslani A. Body surface area: Du Bois and Du Bois revisited. Eur J Appl Physiol 2000; 82:250-254

43. Chatelut E, White-Koning ML, Mathijssen RH, Puisset F, Baker SD, Sparreboom A. Dose banding as an alternative to body surface area-based dosing of chemotherapeutic agents. Br J Cancer 2012; 107:1100-1106

44. Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, Steinberg SM, Little RF, Janik J, Gutierrez M, Raffeld M, Staudt L, Cheson BD, Longo DL, Harris N, Jaffe ES, Chabner BA, Wittes R, Balis F. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood 2002; 99:2685-2693

45. Johnson P, Longley J. Should Response-Adapted Therapy Now Be the Standard of Care for Advanced Hodgkin's Lymphoma? Curr Treat Options Oncol 2017; 18:15

46. Bardin C, Veal G, Paci A, Chatelut E, Astier A, Leveque D, Widmer N, Beijnen J. Therapeutic drug monitoring in cancer--are we missing a trick? Eur J Cancer 2014; 50:2005-2009

47. Ozdemir BC, Coukos G, Wagner AD. Immune related adverse events of immune checkpoint inhibitors and the impact of sex - what we know and what we need to learne. Ann Oncol 2017;

48. Moreno Garcia V, Olmos D, Gomez-Roca C, Cassier PA, Morales-Barrera R, Del Conte G, Gallerani E, Brunetto AT, Schoffski P, Marsoni S, Schellens JH, Penel N, Voest E, Evans J, Plummer R, Wilson RH, Soria JC, Tabernero J, Verweij J, Kaye SB. Dose-response relationship in phase i clinical trials: a European Drug Development Network (EDDN) Collaboration Study. Clin Cancer Res 2014; 20:5663-5671

49. Donskov F, Motzer RJ, Voog E, Hovey E, Grullich C, Nott LM, Cuff K, Gil T, Jensen NV, Chevreau C, Negrier S, Depenbusch R, Bergmann L, Cornelio I, Champsaur A, Escudier B, Pal S, Powles T, Choueiri TK. Outcomes based on age in the phase III METEOR trial of cabozantinib versus everolimus in patients with advanced renal cell carcinoma. Eur J Cancer 2020; 126:1-10

50. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008; 33:997-1006

51. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet 2005; 44:1051-1065

52. Kyle UG, Genton L, Hans D, Karsegard L, Slosman DO, Pichard C. Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. Eur J Clin Nutr 2001; 55:663-672

53. Vrieling A, Kampman E, Knijnenburg NC, Mulders PF, Sedelaar JPM, Baracos VE, Kiemeney LA. Body Composition in Relation to Clinical Outcomes in Renal Cell Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus 2018; 4:420-434

54. Wadhwa A, Adams KM, Dai C, Richman JS, McDonald AM, Williams GR, Bhatia S. Association between body composition and chemotherapy-related toxicity in children with lymphoma and rhabdomyosarcoma. Cancer 2022; 128:1302-1311

55. Prado CM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, Butts CA, Scarfe AG, Sawyer MB. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin Cancer Res 2007; 13:3264-3268

56. Milano G, Etienne MC, Cassuto-Viguier E, Thyss A, Santini J, Frenay M, Renee N, Schneider M, Demard F. Influence of sex and age on fluorouracil clearance. J Clin Oncol 1992; 10:1171-1175

57. Stein BN, Petrelli NJ, Douglass HO, Driscoll DL, Arcangeli G, Meropol NJ. Age and sex are independent predictors of 5-fluorouracil toxicity. Analysis of a large scale phase III trial. Cancer 1995; 75:11-17

58. Sloan JA, Goldberg RM, Sargent DJ, Vargas-Chanes D, Nair S, Cha SS, Novotny PJ, Poon MA, O'Connell MJ, Loprinzi CL. Women experience greater toxicity with fluorouracil-based chemotherapy for colorectal cancer. J Clin Oncol 2002; 20:1491-1498

59. Cristina V, Mahachie J, Mauer M, Buclin T, Van Cutsem E, Roth A, Wagner AD. Association of Patient Sex With Chemotherapy-Related Toxic Effects: A Retrospective Analysis of the PETACC-3 Trial Conducted by the EORTC Gastrointestinal Group. JAMA Oncol 2018; 4:1003-1006

60. Wagner AD, Grothey A, Andre T, Dixon JG, Wolmark N, Haller DG, Allegra CJ, de Gramont A, VanCutsem E, Alberts SR, George TJ, O'Connell MJ, Twelves C, Taieb J, Saltz LB, Blanke CD, Francini E, Kerr R, Yothers G, Seitz JF, Marsoni S, Goldberg RM, Shi Q. Sex and Adverse Events of Adjuvant Chemotherapy in Colon Cancer: An Analysis of 34 640 Patients in the ACCENT Database. J Natl Cancer Inst 2021; 113:400-407

61. Wagner ADea. Sex differences in efficacy and toxicity of first-line treatment of metastatic colorectal cancer (CRC): An analysis of 18,399 patients in the ARCAD database. DOI: 101200/JCO20203815_suppl4029 Journal of Clinical Oncology 38, no 15_suppl (May 20, 2020) 4029-4029 2020;

62. Kim J, Ji E, Jung K, Jung IH, Park J, Lee JC, Kim JW, Hwang JH, Kim J. Gender Differences in Patients with Metastatic Pancreatic Cancer Who Received FOLFIRINOX. J Pers Med 2021; 11

63. Marmorino F, Rossini D, Lonardi S, Moretto R, Zucchelli G, Aprile G, Dell'Aquila E, Ratti M, Bergamo F, Masi G, Urbano F, Ronzoni M, Libertini M, Borelli B, Randon G, Buonadonna A, Allegrini G, Pella N, Ricci V, Boccaccino A, Latiano TP, Cordio S, Passardi A, Tamburini E, Boni L, Falcone A, Cremolini C. Impact of age and gender on the safety and efficacy of chemotherapy plus bevacizumab in metastatic colorectal cancer: a pooled analysis of TRIBE and TRIBE2 studies. Ann Oncol 2019; 30:1969-1977

64. Yamada Y, Muro K, Takahashi K, Baba H, Komatsu Y, Satoh T, Goto M, Mishima H, Watanabe M, Sakata Y, Morita S, Shimada Y, Takenaka N, Hirooka T, Sugihara K. Impact of sex and histology on the therapeutic effects of fluoropyrimidines and oxaliplatin plus bevacizumab for patients with metastatic colorectal cancer in the SOFT trial. Glob Health Med 2020; 2:240-246

65. Fox Rea. Impact of sex on toxicity and outcome in the BILCAP study. DOI: 101200/JCO20183615_supple16151 Journal of Clinical Oncology 36, no 15_suppl 2020;

66. Yamamoto H, Sekine I, Yamada K, Nokihara H, Yamamoto N, Kunitoh H, Ohe Y, Tamura T. Gender differences in treatment outcomes among patients with non-small cell lung cancer given a combination of carboplatin and paclitaxel. Oncology 2008; 75:169-174

67. Yamada Y, Koizumi W, Nishikawa K, Gotoh M, Fuse N, Sugimoto N, Nishina T, Amagai K, Chin K, Niwa Y, Tsuji A, Imamura H, Tsuda M, Yasui H, Fujii H, Yamaguchi K, Yasui H, Hironaka S, Shimada K, Hyodo I. Sex differences in the safety of S-1 plus oxaliplatin

and S-1 plus cisplatin for patients with metastatic gastric cancer. Cancer Sci 2019; 110:2875-2883

68. Liaw CC, Wang CH, Chang HK, Liau CT, Yeh KY, Huang JS, Lin YC. Gender discrepancy observed between chemotherapy-induced emesis and hiccups. Support Care Cancer 2001; 9:435-441

69. Davidson M, Wagner AD, Kouvelakis K, Nanji H, Starling N, Chau I, Watkins D, Rao S, Peckitt C, Cunningham D. Influence of sex on chemotherapy efficacy and toxicity in oesophagogastric cancer: A pooled analysis of four randomised trials. Eur J Cancer 2019; 121:40-47

70. Wakelee HA, Wang W, Schiller JH, Langer CJ, Sandler AB, Belani CP, Johnson DH, Eastern Cooperative Oncology G. Survival differences by sex for patients with advanced non-small cell lung cancer on Eastern Cooperative Oncology Group trial 1594. J Thorac Oncol 2006; 1:441-446

71. Lipshultz SE, Lipsitz SR, Mone SM, Goorin AM, Sallan SE, Sanders SP, Orav EJ, Gelber RD, Colan SD. Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. N Engl J Med 1995; 332:1738-1743

72. Krischer JP, Epstein S, Cuthbertson DD, Goorin AM, Epstein ML, Lipshultz SE. Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group experience. J Clin Oncol 1997; 15:1544-1552

73. Silber JH, Jakacki RI, Larsen RL, Goldwein JW, Barber G. Increased risk of cardiac dysfunction after anthracyclines in girls. Med Pediatr Oncol 1993; 21:477-479

74. Meiners B, Shenoy C, Zordoky BN. Clinical and preclinical evidence of sex-related differences in anthracycline-induced cardiotoxicity. Biol Sex Differ 2018; 9:38

75. Heinrich K, Modest DP, Ricard I, Fischer von Weikersthal L, Decker T, Kaiser F, Graeven U, Uhlig J, Schenk M, Freiberg-Richter J, Peuser B, Denzlinger C, Giessen-Jung C, Stahler A, Michl M, Held S, Jung A, Kirchner T, Stintzing S, Heinemann V. Gender-dependent survival benefit from first-line irinotecan in metastatic colorectal cancer. Subgroup analysis of a phase III trial (XELAVIRI-study, AIO-KRK-0110). Eur J Cancer 2021; 147:128-139

76. Yang W, Warrington NM, Taylor SJ, Whitmire P, Carrasco E, Singleton KW, Wu N, Lathia JD, Berens ME, Kim AH, Barnholtz-Sloan JS, Swanson KR, Luo J, Rubin JB. Sex differences in GBM revealed by analysis of patient imaging, transcriptome, and survival data. Sci Transl Med 2019; 11

77. Lorence Jea. SEX DIFFERENCES IN GLIOBLASTOMA PATIENT SURVIVAL AS A FUNCTION OF EXTENT OF SURGICAL RESECTION AND CYCLES OF ADJUVANT TEMOZOLOMIDE DURING STANDARD-OF-CARE REGIMENS. Neuro-Oncology, Volume 22, Issue Supplement_2, November 2020, Pages ii144–ii145, https://doiorg/101093/neuonc/noaa215607 2020;

78. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Perol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T, Investigators AT. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2017; 377:829-838

79. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, Garbe C, Jouary T, Hauschild A, Grob JJ, Chiarion Sileni V, Lebbe C, Mandala M, Millward M, Arance A, Bondarenko I, Haanen JB, Hansson J, Utikal J, Ferraresi V, Kovalenko N, Mohr P, Probachai V, Schadendorf D, Nathan P, Robert C, Ribas A, DeMarini DJ, Irani

JG, Casey M, Ouellet D, Martin AM, Le N, Patel K, Flaherty K. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014; 371:1877-1888

80. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, Garbe C, Schadendorf D, Krajsova I, Gutzmer R, Chiarion-Sileni V, Dutriaux C, de Groot JWB, Yamazaki N, Loquai C, Moutouh-de Parseval LA, Pickard MD, Sandor V, Robert C, Flaherty KT. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2018; 19:603-615

81. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, Orlov S, Tsai CM, Boyer M, Su WC, Bennouna J, Kato T, Gorbunova V, Lee KH, Shah R, Massey D, Zazulina V, Shahidi M, Schuler M. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013; 31:3327-3334

82. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno MA, Terrasa J, Munoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M, Paz-Ares L, Spanish Lung Cancer Group in collaboration with Groupe Francais de P-C, Associazione Italiana Oncologia T. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13:239-246

83. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y, Ramalingam SS, Investigators F. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018; 378:113-125

84. Schlumberger M, Tahara M, Wirth LJ. Lenvatinib in radioiodine-refractory thyroid cancer. N Engl J Med 2015; 372:1868

85. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, de Souza P, Merchan JR, Boleti E, Fife K, Jin J, Jones R, Uemura H, De Giorgi U, Harmenberg U, Wang J, Sternberg CN, Deen K, McCann L, Hackshaw MD, Crescenzo R, Pandite LN, Choueiri TK. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013; 369:722-731

86. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, Hammers H, Hutson TE, Lee JL, Peltola K, Roth BJ, Bjarnason GA, Geczi L, Keam B, Maroto P, Heng DY, Schmidinger M, Kantoff PW, Borgman-Hagey A, Hessel C, Scheffold C, Schwab GM, Tannir NM, Motzer RJ, Investigators M. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015; 373:1814-1823

87. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, Chi KN, Sartor O, Agarwal N, Olmos D, Thiery-Vuillemin A, Twardowski P, Mehra N, Goessl C, Kang J, Burgents J,

Wu W, Kohlmann A, Adelman CA, Hussain M. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med 2020; 382:2091-2102

88. Penson RT, Valencia RV, Cibula D, Colombo N, Leath CA, 3rd, Bidzinski M, Kim JW, Nam JH, Madry R, Hernandez C, Mora PAR, Ryu SY, Milenkova T, Lowe ES, Barker L, Scambia G. Olaparib Versus Nonplatinum Chemotherapy in Patients With Platinum-Sensitive Relapsed Ovarian Cancer and a Germline BRCA1/2 Mutation (SOLO3): A Randomized Phase III Trial. J Clin Oncol 2020; 38:1164-1174

Table 1. Sex-moderated elimination capacity, toxicity and efficacy of various anticancer drugs

Drug / Regimen	Pharmakokinetics		Toxicity		Efficacy	
	Male	Female	Male	Female	Male	Female
5-Fluorouracil	Higher clearance (56)					
5-FU + LV (57)				Higher		
5-FU + XX (6 NGCCT trials) (58)				Higher		
Adjuvant FOLFIRI (PETACC-3) (59)				Higher		
Adjuvant FOLFOX/CAPOX/FOLFIRI (ACCENT database) (60)				Higher		
1st line FOLFIRI/FOLFOX (ARCAD database) (61)				Higher		No difference in OS, PFS
1st line FOLFIRINOX (prospective trial) (62)				Higher		Higher OS
1st line FOLFIRI + Bevacizumab/FOLFOX + Bevacizumab /FOLFOXIRI + Bevacizumab (TRIBE trials) (63)				Higher		No difference in ORR, PFS
1st line FOLFOX + Bevacizumab (SOFT trial) (64)				Higher		No difference in OS, PFS
Capecitabine						
Adjuvant Capecitabine				Higher	Higher OS	

(BILCAP trial) (65)			
Paclitaxel	20% higher elimination (19)		
1st line Paclitaxel + Carboplatin (66)		Higher	Higher PFS
Oxaliplatin			
1st line S-1 + Oxaliplatin (G-SOX trial) (67)		Higher	No difference in OS, PFS
1st line (?) S-1+ Oxaliplatin + Bevacizumab (SOFT trial) (64)		Higher	No difference in OS, PFS
Cisplatin			
Cisplatin-based therapy (prospective) (68)		Higher	
1st line ECF, ECX, EOF, EOX (4 UKNCRI trials) (69)		Higher	Higher OS
1st line S-1+ Cisplatin (G-SOX trial) (67)			No difference in OS, PFS
1st line Cisplatine-based therapy (ECOG 1594 trial) (70)		Higher	Higher OS and PFS
Doxorubicin	Higher clearance (21)	Higher (71) (72-74)	
Irinotecan			
1st line FOLFIRI+ Bevacizumab (XELAVIRI		No difference	Higher OS and ORR

trial) (75)			
Temozolomide			
Retrospective data (76)			Higher ORR
Adjuvant Temozolomide (Repository data) (77)			Higher OS

Abbreviations: ORR=Overall response rate, OS=Overall Survival, PFS=Progression free survival

Table 2. Dose reduction and discontinuation rates for selected anticancer drugs

Drug Classification *Trial Name* (Indication)	n	Starting dose	Grade 3-4 AEs	Dose reduction rate	Discontinuation rate (for toxicity)	ORR	Sex Moderation	
							Male	Female
ALK- Inhibitors								
ALEX, Phase III (ALK-positive NSCLC; 1L) (78)	303							
Alectinib vs		600 mg bid	41%	16%	11%	83%	45%	55%
Crizotinib		600 mg bid	50%	21%	13%	76%	42%	58%
BRAF + MEK inhibitors								
COMBI-d, Phase III (BRAF V600- positive melanoma, 1L) (79)	423							
Dabrafenib + Placebo vs		150 mg bid	30%	NR	7%	53%	54%	46%
Dabrafenib + Trametinib		150 mg bid + 2mg qd	32%		11%	69%	53%	47%
COLUMBUS, Phase III (BRAF V600-positive melanoma, 1L) (80)								
Encorafenib + Binimetinib vs	577	450 mg qd +45 mg bid	34%	48%	6%	63%	60%	40%
Encorafenib vs		300 mg qd	34%	70%	10%	51%	56%	44%
Vemurafenib		960 bid	37%	61%	14%	40%	58%	42%
EGFR-inhibitors								
LUX-Lung 3, Phase III (EGFR mutant NSCLC; 1L) (81)								
Afatinib vs chemotherapy	345	40 mg qd	49%	NR	8%	56%	36%	63%
EURTAC, Phase III (EGFR mutant NSCLC; 1L) (82)								
Erlotinib vs chemotherapy	174	150 mg qd	45%	21%	13%	58%	33%	67%
FLAURA, Phase III (EGFR mutant NSCLC; 1L) (83)	556							
Osimertinib vs		80 mg qd	34%	4%	13%	80%	36%	63%
Erlotinib / Gefitinib		140 mg qd /250 mg qd	45%	5%	18%	76%	38%	62%
VEGFR-inhibitors								

SELECT, Phase III (Thyroid cancer; 1L) (84)	261	24 mg qd						
Lenvatinib vs placebo		24 mg qd	76%	68%	14%	69%	48%	52%
REFLECT, Phase III (HCC; 1L)								
Lenvatinib vs	954	12 mg qd for ≥60 kg or 8 mg qd for <60 kg	57%	37%	9%	24%	85%	15%
Sorafenib		400 mg bid	49%	38%	7%	9%	84%	16%
COMPARZ, Phase III (RCC; 1L) (85)								
Pazopanib vs	1110	800 mg qd	74%	44%	24%	31%	71%	29%
Sunitinib		50 mg qd, 4weeks on/2 weeks off	74%	51%	20%	25%	75%	25%
METEOR, Phase III (RCC; 2L) (86)								
Cabozantinib vs	658	60 mg qd	68%	60%	9%	21%	77%	23%
Everolimus		10 mg qd	58%	25%	10%	5%	74%	26%
PARP-inhibitors								
PROfound, Phase III (mCRPC with BRCA1, BRCA2, ATM mutation, ≥2L) (87)	387							
Olaparib		300 mg bid	51%	22%	18%	33%	100%	0%
SOLO-3, Phase 3 (Ovarian cancer with BRCA mutation, ≥3L) (88)								
Olaparib vs chemotherapy	266	300 mg bid	50%	27%	7%	72%	0%	100%

Abbreviations: AEs=adverse events, n=patient sample size, NSCLC= Non-small cell lung cancer, HCC= Hepatocellular carcinoma, RCC= Renal cell carcinoma, mCRPC= metastatic castration resistant prostate cancer, NR=not reported, ORR=Overall Response Rate