Review Article

New Oral Anti-Cancer Drugs and Medication Safety

Katja Schlichtig, Pauline Dürr, Frank Dörje, Martin F. Fromm

Summary

Background: Many oral anti-cancer drugs have come onto the market in the past 20 years. For example, kinase inhibitors, such as the BCR-ABL and BRAF inhibitors, have markedly improved the treatment of chronic myeloid leukemia and melanoma. In this review, we discuss the special challenges posed by poor adherence, drug–drug interactions with other substances, and side effects, among other problems, and the ways in which these challenges can be met.

Methods: A selective search was carried out in PubMed for original and review articles on the safety of new oral anti-cancer drugs. Guidelines and current Summaries of Product Characteristics (SmPC) were also considered in the analysis.

Results: Review articles have pointed out numerous safety concerns with oral anti-cancer drugs. One of these is adherence, on which highly variable figures are available (with mean non-adherence rates ranging from 0 to 54%). The absorption of approximately half of these drugs is influenced by the patient's diet, and that of approximately 20% by gastric pH (Caution: proton-pump inhibitors may influence bioavailability). 70% of the active substances are metabolized primarily by CYP3A4, which means that their pharmacokinetics can be altered by grapefruit juice and CYP3A4 modulators. The prevention, detection, and treatment of side effects (which can be gastrointestinal, cutaneous, cardiovascular, or other) is a highly important matter.

Conclusion: The increasing use of oral anti-cancer drugs confronts patients and treatment teams with special challenges. To optimize treatment outcomes, a multidisciplinary approach should be taken, involving physicians, pharmacists, and nurses. To improve medication safety, medication and side-effect management should be performed, and adherence should be regularly checked and systematically encouraged.

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More than 50 oral anti-cancer drugs have been licensed for use in Germany over the past 20 years. These agents are used for the treatment of a broad spectrum of solid tumors and hematological diseases (*Table 1a and b*). The anti-cancer properties of many substances are based on the inhibition of protein kinases, which are involved in cell growth and cell differentiation (*Table 1a*). In Germany, the protein kinase inhibitors have the second highest volume of sales among the group of oncological drugs (e1).

Apart from the convenience of oral intake for patients, the research data for the clinical benefit of protein kinase inhibitors are—at least in part—highly convincing (1–3). However, approaches involving oral administration of anti-cancer drugs can present considerable challenges to both patient and treatment team.

With intravenous chemotherapy, the entire dose reliably reaches the patient, but with oral intake this is less certain. Inadequate adherence must be assumed in a not inconsiderable proportion of patients: mean non-adherence rates of up to 54% have been described, which may endanger the success of treatment (4–6). About 50% of all oral anti-cancer drugs come with instructions regarding intake in relation to meal-times, as substance absorption can be increased or decreased by food (7, e2, *eTable 1*). The patient has a special responsibility to follow the instructions accurately.

Moreover, attention must be paid to a variety of potential drug–drug interactions. Many oral anti-cancer drugs are metabolized by CYP3A4. Inhibitors or inducers of CYP3A4 (see [8]) may reduce the therapeutic effect or elevate the risk of side effects. A retrospective study in the Netherlands found potential drug–drug interactions in 46% of around 900 patients treated with oral anti-cancer drugs; in 16% of patients these were classified as potentially major events (9). The potential consequences of interactions most frequently noted in this study were QT interval prolongation, gastrointestinal effects, or complications affecting the central nervous system (9). Medication errors therefore represent a serious problem in oral anti-cancer treatment (10–12).

Characteristic side effects (affecting, for example, the skin, the cardiovascular system, and the gastrointestinal system) must be anticipated whenever oral anti-cancer drugs are used. The wide variety of

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possible side effects means that the health care team must be experienced in their prevention and management; also, patients must be fully informed. The trend towards oral treatment often leads to less intensive contact between physician and patient and thus to fewer opportunities to observe potential side effects.

This review article summarizes the following data on new oral anti-cancer drugs licensed for use in Germany (starting from 2001, when capecitabine was approved): indications and target structures; influence of food intake and gastric pH; essential determinants of elimination (metabolism, transport, renal and hepatic function); drug–drug interactions; and typical side effects. Furthermore, we outline the areas of treatment with new orally administered anti-cancer substances where medication safety can be promoted successfully.

Methods

A selective survey of the PubMed database was carried out to identify original articles and review articles on the medication safety of new oral anti-cancer drugs (published in English or German between January 2001 and July 2019). The MeSH terms were: administration oral, protein kinase inhibitors, antineoplastic agents, neoplasms, patient safety, side effects, medication errors, drug interactions. In addition, we took account of pertinent guidelines and scrutinized the current German Summaries of Product Characteristics (SmPC) and American Prescribing Information Sheets (as of 8 July 2019).

Oral anti-cancer drugs

Table 1 provides an overview of the oral anti-cancer drugs currently licensed for use in Germany (*Table 1a*: kinase inhibitors; *Table 1b*: other oral anti-cancer drugs). The table specifies the tumor entities for which each drug is approved and the target structures via which the anti-tumor effects can be achieved (*Table 1a and b*). The essential mechanism of action of two thirds of the oral anti-cancer drugs is inhibition of protein kinases.

Too low exposure to the oral anti-cancer drug (due, for example, to CYP inducers or gastric acid suppressing substances) can endanger the success of treatment. Equally, factors leading to excessively high exposure (e.g., CYP inhibitors, grapefruit) should be avoided because they increase the risk of side effects.

Factors affecting absorption

The absorption of oral anti-cancer drugs is affected, sometimes greatly, by the timing of medication around food intake and also by changes in gastric pH (*eTable 1*). Around 50% of the substances have to be taken at particular times relative to meals. Consumption of food can reduce (e.g., afatinib) or increase exposure; for instance, plasma concentrations (area under the curve, AUC) are elevated up to tenfold for abiraterone and up to fivefold for venetoclax when they are taken with a meal (*eTable 1*). Attention should be paid to the

recommendations in the SmPC and patients should be informed about their relevance.

The absorption of some oral anti-cancer drugs is reduced by simultaneous administration of substances that inhibit gastric acid secretion. Proton pump inhibitors are particularly important in this regard, because they are very often prescribed and in some cases can be purchased in pharmacies without a prescription. For example, simultaneous intake of dasatinib (single dose) and omeprazole leads to a 43% reduction in the plasma concentration of dasatinib (*eTable 1*).

Pharmacokinetic interactions

Patients with cancer regularly take an average of around five different non-anti-cancer drugs (9, 13, 14). The accompanying medications may inhibit or induce metabolism of oral anti-cancer drugs. In such a case the oral anti-cancer drug is the “victim drug” (for oral anti-cancer drugs as “perpetrator drugs,” see next paragraph). Circa 70% of oral anti-cancer drugs are metabolized predominantly via CYP3A4. Simultaneous administration of CYP3A4 inhibitors (e.g., clarithromycin, azole antimycotics, HIV protease inhibitors) leads to elevated plasma concentrations of these oral anti-cancer drugs. Conversely, induction of CYP3A4 (e.g., by St. John’s wort, carbamazepine, or rifampicin) can result in reduced plasma concentrations and thus loss of anti-tumor effect (for information on further CYP3A4 inhibitors/inducers, please consult the reviews [8, 15]). The risk for drug–drug interactions is usually potentiated by the fact that oral anti-cancer drugs are often substrates of the efflux transporter P-glycoprotein and CYP3A4 inhibitors/inducers frequently inhibit/induce P-glycoprotein ([8]; *eTable 2*). Since substances contained in grapefruit juice strongly reduce the intestinal expression of CYP3A4, grapefruit products should be avoided by patients taking an oral anti-cancer drug that is metabolized predominantly via CYP3A4 (*eTable 2*).

An oral anti-cancer drug may also function as “perpetrator,” i.e., influence the plasma concentrations and effects of simultaneously administered medications. Examples are inhibition of CYP2D6 by abiraterone (CYP2D6 substrates: e.g., metoprolol, tricyclic antidepressants; see [8]) and inhibition of CYP3A4 by ribociclib. Marked induction of drug-metabolizing enzymes (e.g., CYP3A4) by apalutamide and enzalutamide can lead to loss of therapeutic effect of a variety of substances when these are administered simultaneously (*eTable 2*).

Side effects

Although these therapies are frequently referred to as “targeted”, most of the substances are not highly selective but also address so-called off-targets (16). Especially the multikinase inhibitors (e.g., pazopanib and sunitinib), which have a wide range of target structures, are associated with a broad spectrum of side effects. The inhibition of certain targets and off-targets often

TABLE 1a

Overview of the kinase inhibitors licensed for use in Germany, the tumor entities for which they have been approved, and the major target structures

Substance (INN)	Tumor entity* ¹	Pharmacological target structure(s): selection
Inhibitors of VEGFR-associated tyrosine kinases		
Axitinib	Renal cell carcinoma	VEGFR
Cabozantinib	Hepatic cell carcinoma, renal cell carcinoma, thyroid carcinoma	MET, VEGFR
Lenvatinib	Hepatic cell carcinoma, renal cell carcinoma, thyroid carcinoma	FGFR, PDGFR, VEGFR
Nintedanib	Non–small cell lung cancer	FGFR, PDGFR, VEGFR
Pazopanib	Renal cell carcinoma, soft-tissue sarcoma	VEGFR, PDGFR
Regorafenib* ²	GIST, colorectal cancer, hepatic cell carcinoma	PDGFR, RAF, VEGFR
Sorafenib	Hepatic cell carcinoma, renal cell carcinoma, thyroid carcinoma	PDGFR, RAF, VEGFR
Sunitinib	GIST, renal cell carcinoma, pancreatic neuroendocrine tumors	PDGFR, VEGFR
Tivozanib	Renal cell carcinoma	VEGFR
Vandetanib	Thyroid carcinoma	EGFR, RET, VEGFR
Inhibitors of EGFR-associated tyrosine kinases		
Afatinib	Non–small cell lung cancer	EGFR, HER2
Dacomitinib	Non–small cell lung cancer	EGFR
Erlotinib	Non–small cell lung cancer, pancreatic cancer	EGFR
Gefitinib	Non–small cell lung cancer	EGFR
Lapatinib	Breast cancer	EGFR, HER2
Osimertinib	Non–small cell lung cancer	EGFR
Inhibitors of BCR-ABL tyrosine kinase		
Bosutinib	Chronic myeloid leukemia	BCR-ABL, c-KIT, PDGFR
Dasatinib	Acute lymphoblastic leukemia, chronic myeloid leukemia	
Imatinib	E.g., acute lymphoblastic leukemia, chronic myeloid leukemia, GIST	
Nilotinib	Chronic myeloid leukemia	
Ponatinib	Acute lymphoblastic leukemia, chronic myeloid leukemia	
Inhibitors of ALK tyrosine kinase		
Alectinib	Non–small cell lung cancer	ALK, RET
Brigatinib	Non–small cell lung cancer	ALK, ROS1
Ceritinib	Non–small cell lung cancer	ALK
Crizotinib	Non–small cell lung cancer	ALK, ROS1
Lorlatinib	Non–small cell lung cancer	ALK, ROS1
Inhibitors of BRAF kinase		
Dabrafenib	Melanoma, non–small cell lung cancer	BRAF
Encorafenib	Melanoma	
Vemurafenib	Melanoma	
Inhibitors of MEK kinase		
Binimetinib	Melanoma	MEK
Cobimetinib	Melanoma	
Trametinib	Melanoma, non–small cell lung cancer	
Inhibitors of cyclin-dependent protein kinases (CDK)		
Abemaciclib	Breast cancer	CDK4/6
Palbociclib	Breast cancer	
Ribociclib	Breast cancer	

Substance (INN)	Tumor entity ^{*1}	Pharmacological target structure(s): selection
Other protein kinase inhibitors		
Everolimus	Breast cancer, neuroendocrine tumors, renal cell carcinoma	mTOR
Ibrutinib	E.g., chronic lymphocytic leukemia, mantle cell lymphoma	BTK
Midostaurin	E.g., acute myeloid leukemia, aggressive systemic mastocytosis	FLT3, c-KIT
Ruxolitinib	Myelofibrosis, polycythemia vera	JAK

Sources: Latest versions of Summaries of Product Characteristics for the kinase inhibitors licensed for use in Germany since 2001 (as of 8 July 2019)

^{*1} For details, e.g., on approval regarding genotype/phenotype of tumor or on necessary combination partners, see the individual Summary of Product Characteristics

^{*2} Removed from German market (available only as import)

ALK, anaplastic lymphoma kinase; BTK, bruton tyrosine kinase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor;

FLT3, FMS-like tyrosine kinase 3; GIST, gastrointestinal stromal tumor; HER2, human epidermal growth factor receptor 2; INN, international non-proprietary name; JAK, just another kinase; MEK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor

TABLE 1b

Overview of the other new oral anti-cancer drugs licensed for use in Germany, the tumor entities for which they have been approved, and the major target structures

Substance (INN)	Tumor entity ¹	Pharmacological target structure(s): selection
Anti-neoplastic drugs		
Anagrelide	Essential thrombocythemia	cAMP phosphodiesterase/inhibition of megakaryocyte maturation
Bexarotene	Cutaneous T-cell lymphoma	Retinoid X receptor (RXR)
Capecitabine	Breast cancer, gastric cancer, colorectal cancer	Antimetabolite
Idelalisib	Chronic lymphocytic leukemia, follicular lymphoma	Phosphatidylinositol-3-kinase p110δ (PI3Kδ)
Ixazomib	Multiple myeloma	Proteasome
Niraparib	Ovarian cancer, peritoneal cancer, fallopian tube cancer	Poly(ADP-ribose) polymerase (PARP)
Olaparib (as capsule)	Ovarian cancer, peritoneal cancer, fallopian tube cancer	Poly(ADP-ribose) polymerase (PARP)
Olaparib (as tablet)	Breast cancer, ovarian cancer, peritoneal cancer, fallopian tube cancer	Poly(ADP-ribose) polymerase (PARP)
Rucaparib	Ovarian cancer, peritoneal cancer, fallopian tube cancer	Poly(ADP-ribose) polymerase (PARP)
Panobinostat	Multiple myeloma	Histone deacetylase (HDAC)
Sonidegib	Basal cell carcinoma	Hedgehog signaling pathway
Tegafur/gimeracil/oteracil	Gastric cancer	Antimetabolite
Trifluridine/tipiracil	Colorectal cancer	Antimetabolite
Venetoclax	Chronic lymphocytic leukemia	B-cell lymphoma (BCL)-2 protein
Vinorelbine	Breast cancer, non–small cell lung cancer	Microtubules (vinca alkaloid)
Vismodegib	Basal cell carcinoma	Hedgehog signaling pathway
Immunomodulators		
Lenalidomide	Mantle cell lymphoma, multiple myeloma, myelodysplastic syndromes	Immunomodulatory action
Pomalidomide	Multiple myeloma	
Thalidomide	Multiple myeloma	
Hormone antagonists		
Abiraterone	Prostate cancer	CYP17
Apalutamide	Prostate cancer	Androgen receptor
Enzalutamide	Prostate cancer	Androgen receptor

Sources: Latest versions of Summaries of Product Characteristics for other new anti-cancer drugs licensed for use in Germany since 2001 (as of 8 July 2019)

^{*} For details, e.g., on approval regarding genotype/phenotype of tumor or on necessary combination partners, see the individual Summary of Product Characteristics.

cAMP, cyclic adenosine monophosphate; CYP17, cytochrome P450 17; INN, international non-proprietary name

gives rise to characteristic side effects and class effects (*eTable 3*). Some side effects, e.g., fatigue, are target independent and are listed in the Summaries of Product Characteristics of around 80% of oral anticancer agents as very commonly occurring side effects.

In general, the occurrence of side effects (depending on the substance involved and the type and severity of event) merits interruption of treatment until the symptoms resolve, and possibly dose reduction. Discontinuation of treatment may be necessary if the side effects are severe or if they persist despite reduction of the dose given. In each individual case, attention should be paid to the SmPC. A recent review investigated 74 pivot studies with regard to the frequency of dose reduction and showed that the dose was lowered in circa 20% to 70% of patients, mostly owing to toxicity (17). Subgroup analyses published for two substances (afatinib and palbociclib) demonstrated clinical efficacy despite dose reduction (17). Evidence of the efficacy of a decreased dose is often not available.

Gastrointestinal side effects

Diarrhea occurs commonly or very commonly with almost all oral anti-cancer drugs, but its severity is extremely variable. Patients receiving treatment with an oral anti-cancer drug that commonly causes diarrhea (*eTable 3*) should be prescribed loperamide in an initial dose of 4 mg followed by 2 mg every 2 to 4 h (off-label use, see [e3]).

Oral anti-cancer drugs classified as moderately emetogenic (e3–e6) may need to be accompanied by an prophylactic anti-emetic agent, e.g., 5-HT₃-receptor antagonists or either metoclopramide or domperidone. The current research data do not suffice for any evidence-based recommendations for anti-emetic prophylaxis in patients on oral anti-cancer treatment (e3).

Cutaneous side effects

Side effects affecting skin and mucous membranes are very common (>10%) (*eTable 3*). Serious cutaneous reactions (e.g., Stevens–Johnson syndrome) are sometimes described (*eTable 3*). EGFR inhibitors are known to cause an acneiform rash that may be a predictor of a good response to treatment and a favorable outcome (18, 19, e7). The EGF receptors of the epidermis are affected by the treatment, and this may lead to a typical sequence of rash, xerosis cutis, pruritus, rhagade formation, and alterations of hair and nails (20). BRAF and MEK inhibitors block the downstream signaling pathway and are associated with similar dermatological side effects (for the management of these lesions, see [20]). VEGFR inhibitors can cause hand–foot syndrome, the development and extent of which differ from the hand–foot syndrome triggered by classic cytostatic drugs. The procedures for prevention and treatment have to be adjusted correspondingly (21).

VEGFR inhibitors are known to cause wound healing disorders, so interruption of treatment is sometimes advisable when surgery is planned (*eTable 3*).

However, in most cases there are no concrete recommendations for the duration of the interruption or the timing of treatment resumption. In our opinion, decisions regarding the treatment break should take into account, in each individual case, the half-life of the oral anti-cancer drug, the type of surgical intervention/the risk of bleeding, the wound healing status, and any comorbidities. Disorders of thyroid function, usually in the form of hypothyroidism, occur with almost all VEGFR inhibitors (22) (*eTable 3*). Monitoring of thyroid-stimulating hormone (TSH) is then required, accompanied if necessary by initiation of treatment with levothyroxine. A patient who develops fatigue syndrome should be investigated not only for anemia, but also for hypothyroidism.

A further dermatological class effect, in the form of excessive keratinocyte proliferation, occurs with BRAF inhibitors (23). This can manifest as hyperkeratosis (especially hand–foot syndrome at sites exposed to friction and load) or as a secondary malignancy (e.g., cutaneous squamous cell carcinoma) (23).

Cardiovascular side effects

A meta-analysis has shown that VEGFR inhibitors increase the risk of hypertension (relative risk 3.43), bleeding (1.94), and cardiac dysfunction (5.87) (24). It is therefore essential to identify any pre-existing cardiovascular risk factors. The patient's blood pressure should be routinely measured and, if required, treated according to the pertinent guidelines (25). For some substances hypertension correlates with better response to treatment and is discussed as a potential biomarker (26–28).

Anti-cancer drugs directed against HER2, such as trastuzumab, are known for the occurrence of left ventricular dysfunction (29). Similar side effects have been described for lapatinib, which also acts against HER2. The left ventricular ejection fraction (LVEF) should therefore be determined before the commencement of treatment and at regular intervals during treatment. ABL kinase has a protective effect on cardiomyocytes, so BCR-ABL inhibitors may have cardiotoxic effects (29).

Many oral anti-cancer drugs have been described to cause arrhythmia and QT-interval prolongation. For some substances electrocardiography (ECG) must always be carried out before and during treatment, while for others this is recommended only in high-risk patients (*eTable 3*). Moreover, patients taking critical substances should have their electrolytes and thyroid function monitored and the QT-prolonging potential of their other medications should be observed.

Compared with healthy persons, cancer patients have a four- to sevenfold risk of thromboembolic events (30). In particular, it should be highlighted that the risk of thromboembolism is increased with immunomodulators (lenalidomide, pomalidomide, thalidomide). In such cases, risk-stratified prophylactic

BOX

Key points for patient management

● Recommendations for drug intake

The medication should always be taken at the same time of day, standardized in relation to meals. If substances intended to be taken on an empty stomach are incorrectly ingested with a meal, absorption may be decreased (e.g., afatinib, dabrafenib) or increased (e.g., abiraterone, nilotinib). The fat content of foodstuffs may also have a pronounced effect (e.g., lapatinib). Patients must therefore be informed about the reasons behind the intake recommendations they are given.

● Interactions

Patients should be informed about potential interaction partners such as grapefruit or prescription free medications (e.g., St. John's wort) and about the consequences of such interactions (i.e., intensified or reduced effect). Anti-cancer substances such as dasatinib, erlotinib, and pazopanib show considerably reduced absorption (AUC [area under the curve] up to -60%) if they are taken together with gastric acid suppressing substances.

● Side effects

Patients should especially be informed about the prevention and supportive treatment of gastrointestinal toxicity (e.g., antiemetic prophylaxis, use of loperamide in the event of diarrhea), cutaneous side effects (skin care, sun protection, avoidance of noxae), and stomatitis (oral hygiene including use of mouthwash). Patients should have access to the treatment team if they experience acute symptoms.

● Adherence

The vital importance of adherence must always be discussed with the patient, both before and during treatment. Risk factors for non-adherence should be minimized (e.g., make the treatment scheme as simple as possible, discuss anxiety regarding side effects) and offer ways of improving adherence (e.g., an alarm clock, apps, medication intake plans). The latest Onkopedia guideline on the treatment of chronic myeloid leukemia recommends measurement of plasma concentrations for, among other reasons, monitoring of adherence with the intake of imatinib.

● Storage and handling of oral anti-cancer drugs

Oral anti-cancer drugs are highly effective substances that may be harmful to healthy persons, and patients and their families must take precautions in the home environment. The medications must be kept in their original packaging, to avoid confusion with other drugs; they must not be crushed or divided into smaller pieces; and patients must wash their hands after intake to minimize the danger of contamination.

administration of low-dose acetylsalicylic acid (ASA) or low-molecular heparins is recommended (e8).

Myelosuppression and susceptibility to infection

The myelosuppression associated with most new oral anti-cancer drugs is less pronounced than with classic cytostatics. However, pancytopenia and febrile neutropenia can occur with oral anti-cancer drugs, e.g., with CDK4/6 inhibitors (eTable 3). This results in elevated susceptibility to infection. Infections with opportunistic pathogens such as *Pneumocystis jirovecii* pneumonia have been described in some instances, so

the appropriate preventive measures are indicated. The risk of hepatitis B virus (HBV) reactivation has also been reported for some oral anti-cancer drugs and has led to a number of Dear Doctor Letters (*Rote-Hand-Briefe*). These communications have particularly involved the BCR-ABL kinase inhibitors, but also the immunomodulators and ibrutinib. For the substances concerned, HBV serology testing must be conducted before treatment is initiated.

Effects on liver, kidneys, and lungs

Asymptomatic elevation of liver enzymes can occur with many different oral anti-cancer drugs and may make it necessary to interrupt the treatment or lower the dose. Severe elevation of liver enzymes (grade 3 or 4) is found in up to 12% of patients taking kinase inhibitors (31). Hepatotoxic effects to the point of acute liver failure and/or fulminant hepatitis, sometimes with a fatal outcome, have been described (for, among others, abiraterone, imatinib, lapatinib, pazopanib, and sunitinib) (31; Zytiga SmPC). This is not to be confused with the yellow coloration of the skin caused by sunitinib.

Impairment of renal function and renal failure may also occur. The inhibition of renal transporters may cause an elevated plasma creatinine concentration without worsening of filtration capacity. For the substances concerned (e.g., abemaciclib, bosutinib, imatinib, and vandetanib), determination of the glomerular filtration rate (GFR) by means of a creatinine-independent technique (e.g., cystatin C) is recommended in order to differentiate apparent worsening of the GFR from genuine renal toxicity (32).

Pulmonary toxicity, for instance the occurrence of pneumonitis or interstitial lung disease, has been described for many substances (eTable 3). This potentially life-threatening side effect displays wide inter-individual variability with regard to time of onset, severity, and clinical course (33). The occurrence of symptoms such as cough, fever, and dyspnea should therefore prompt consideration of the presence of interstitial lung disease.

Dose adjustment for patients with renal or hepatic insufficiency

There is often specific dosing advice for patients with impaired renal or hepatic function. Instructions extracted from the corresponding SmPC are presented in eTable 4.

Difficulties in oral anti-cancer drug treatment and published data on its optimization

The plasma concentrations of oral anti-cancer drugs vary considerably even in the relatively well controlled setting of clinical studies. Imatinib, for example, shows 60-fold variability of oral clearance (34). For quite a number of oral anti-cancer drugs an association has been shown between exposure and treatment response (e.g., crizotinib, imatinib, pazopanib, and vemurafenib)

or between exposure and toxicity (e.g., afatinib, gefitinib, imatinib, and sorafenib) (35, 36). Imatinib has been particularly closely investigated: several studies, for instance, have pointed to improved rates of molecular remission and complete cytogenetic response with higher exposure to the drug (target $C_{min} \geq 1000$ ng/mL) (35). Nevertheless, plasma concentrations of imatinib are not universally determined; measurement is recommended, for example, whenever unexplained side effects occur (e9). One major cause of variable exposure is treatment adherence (4–6, 37). A review showed high variability in rates of adherence (46% to 100%), depending on treatment regimen, patient characteristics, methods of adherence determination, and the definition of adherence (6). It can be assumed, however, that a not inconsiderable proportion of patients do not adhere to the intake recommendations in the long term: for instance, the average adherence rates for endocrine anti-cancer treatment were only around 50% after 5 years (6). Moreover, the authors of the article cited state that there are only a small number of intervention studies on the topic of improving adherence among patients being treated with oral anti-cancer drugs.

It is by no means easy for treating physicians to ensure medication safety in patients who are prescribed oral anti-cancer drugs (9, 10). These patients are taking an average of five other medications (9). It can be highly challenging to identify and avoid the myriad potential interactions among the various substances. There is a great deal of literature on the difficulty of maintaining medication safety for oral anti-cancer drugs (38), but unfortunately only a small number of high-quality randomized trials have been published that examine how medication safety can be enhanced (39, 40). Preliminary data from a randomized trial at the Comprehensive Cancer Center Erlangen–EMN, supported by German Cancer Aid and planned to continue until 2020, indicate that additional clinical pharmaceutical/pharmacological treatment support reduces the number of drug-related problems and increases patient satisfaction (e10). The data also indicate that severe side effects can be decreased by the intervention and that the number of treatment discontinuations goes down (e10).

The American Society for Clinical Oncology's guideline "Chemotherapy Administration Safety Standards" includes advised standards for safe prescription and management of oral anti-cancer drugs (e11). The essential recommendations relate to patient training, a physician–patient contact plan adapted to the individual course of treatment, and regular medication analyses (including OTC preparations and complementary medicine products) to identify potential interactions (e11).

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Key messages

- Variable absorption rates, associated with the time of intake relative to meals or with altered gastric pH, may endanger the success of treatment with oral anti-cancer drugs.
- Regular medication analyses, including an interaction check, should be performed routinely.
- Because they themselves are responsible for taking their medication, patients should be supervised by a multidisciplinary team of health professionals with regard to adherence as well as the prevention and treatment of side effects.
- To improve medication safety in treatment with oral anti-cancer drugs, standards of care and the pertinent guidelines should be further developed.

Conflict of interest statement

Pauline Dürr has received lecture fees and reimbursement of travel costs from Hoffmann-La Roche.

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eTABLE 1

Overview of factors that may affect the absorption of new oral anti-cancer drugs licensed for use in Germany

Substance (INN)	Influence of food intake		Influence of gastric pH	
	AUC change when taken with a meal (M)	Recommendation for intake relative to meals	AUC change caused by PPI	Recommendation/alternatives
Abemaciclib	↑ (+9% with a high-fat meal)	Independent of meals		
Abiraterone	↑ (+ up to 10-fold depending on fat content)	At least 1 h before/ no less than 2 h after		
Afatinib	↓ (−39% with a high-fat meal)	At least 1 h before/ no less than 3 h after		
Alectinib	↑ (+3-fold with a very high-fat meal)	With a meal	↔	
Anagrelide	↑ (+20%)	Independent of meals		
Apalutamide	↔	Independent of meals		
Axitinib	↓ (+10–19% depending on fat content)	Independent of meals		
Bexarotene	↑ (Prescribing Information USA: +35% with a high-fat meal)	With a meal		
Binimetinib	↔	Independent of meals	↔	
Bosutinib	↑ (+1.7-fold)	With a meal	↓ (−26%)	PPI with caution; alternative: antacids at different times (e.g., bosutinib in the morning—antacid in the evening) Prescribing Information USA: antacids or H ₂ -antagonists (−/+2 h) as alternative
Brigatinib	↔	Independent of meals		
Cabozantinib	↑ (+57% with a high-fat meal)	At least 1 h before/ no less than 2 h after	↔	
Capecitabine	↔	Within 30 min after		
Ceritinib	↑ (+58% with a low-fat, +73% with a high-fat meal)	With a meal	↓ (−76%)	Effect less pronounced with clinical use, PPI nevertheless with caution; alternatives: H ₂ -antagonists (−10 h/+2 h), antacids (−/+2 h) Prescribing Information USA: PPI possible, because in steady state AUC is reduced by only 30% (judged as clinically irrelevant)
Cobimetinib	↔	Independent of meals		
Crizotinib	↓ (−14% with a high-fat meal)	Independent of meals	↔	
Dabrafenib	↓ (−31%)	At least 1 h before/no less than 2 h after	↔	
Dacomitinib	↔	Independent of meals	↓ (−39%)	PPI not recommended; alternatives: H ₂ -antagonist (−10 h/+2 h), antacids
Dasatinib	↑ (+21% with a low-fat, +14% with a high-fat meal)	Independent of meals	↓ (−43% with PPI) ↓ (−61% with H ₂ -antagonist—despite intake at a different time)	PPI and H ₂ -antagonists not recommended; alternative: antacids (−/+2 h)
Encorafenib	↔	Independent of meals	↔	
Enzalutamide	↔	Independent of meals		
Erlotinib	↑ (Prescribing Information USA: +66%)	At least 1 h before/ no less than 2 h after	↓ (−46% with PPI) ↓ (−33% with H ₂ -antagonists)	PPI not recommended; alternative: H ₂ -antagonists (−10 h/+2 h), antacids (−4 h/+2 h)
Everolimus	↓ (−32% with a low-fat, −22% with a high-fat meal)	Independent of meals; standardize intake		

Substance (INN)	Influence of food intake		Influence of gastric pH	
	AUC change when taken with a meal (M)	Recommendation for intake relative to meals	AUC change caused by PPI	Recommendation/alternatives
Gefitinib	↔	Independent of meals	↓ (-47%)	No recommendations Prescribing Information USA: PPI if unavoidable (-/+12 h), H ₂ -antagonists (-/+6 h), antacids (+6 h)
Ibrutinib	↑ (Prescribing Information USA: +2-fold with a high-fat meal)	No explicit advice; avoid fish oil and vitamin-E-rich foods (elevated bleeding risk)	↔	
Idelalisib	↑ (+36% with a high-fat meal)	Independent of meals		
Imatinib	↓ (-7,4% with a high-fat meal)	With a meal (better gastro-intestinal tolerance)		
Ixazomib	↓ (-28% with a high-fat meal)	At least 1 h before/no less than 2 h after; loss of effect through complex formation in combination with green or black tea possible (Takeda: Ninlaro® treatment brochure, as of 2016)		
Lapatinib	↑ (+ up to 4-fold depending on fat content); high variability depending on time of intake	At least 1 h before/ no less than 1 h after; standardize intake	↓ (-27%)	Avoid PPI; Prescribing Information USA: PPI possible because the AUC reduction is not clinically relevant
Lenalidomide	↓ (-20% with a high-fat meal)	Independent of meals		
Lenvatinib	↔	Independent of meals		
Lorlatinib	↑ (+5% with a high-fat meal)	Independent of meals		
Midostaurin	↑ (+22% with a standard meal, +59% with a high-fat meal)	With a meal		
Nilotinib	↑ (+82%)	At least 1 h before/ no less than 2 h after	↓ (-34%)	PPI possible because, according to the manufacturer, the effect is clinically irrelevant; alternatives: H ₂ -antagonists (-10 h/+2 h), antacids (-/+2 h); Prescribing Information USA: avoid PPI
Nintedanib	↑ (+20%)	With a meal		
Niraparib	↔	Independent of meals		
Olaparib (as capsule)	↑ (+20%)	At least 2 h before/ no less than 1 h after		
Olaparib (as tablet)	↑ (+8%)	Independent of meals		
Osimertinib	↑ (+6%)	Independent of meals	↔	
Palbociclib	↑ (+12–21% depending on fat content)	With a meal	↓ (-62% when taken on an empty stomach)	Intake with a meal, then the interaction is clinically irrelevant
Panobinostat	↔	Independent of meals		
Pazopanib	↑ (+2-fold, independent of fat content)	At least 1 h before/ no less than 2 h after	↓ (-40%)	Avoid PPI; alternatives: intake of PPI in the evening on an empty stomach together with pazopanib, H ₂ -antagonists (-10 h/+2 h), antacids (-/+2 h); recommendations based on theoretical considerations! Prescribing Information USA: avoid PPI/ H ₂ -antagonists
Pomalidomide	↓ (-8% with a high-fat meal)	Independent of meals		
Ponatinib	↔	Independent of meals		
Regorafenib	↑ (+36% with a low-fat, +48% with a high-fat meal); concentration of active main metabolites ↓ with a high-fat meal	After a light (low-fat) meal		
Ribociclib	↔	Independent of meals	↔	

Substance (INN)	Influence of food intake		Influence of gastric pH	
	AUC change when taken with a meal (M)	Recommendation for intake relative to meals	AUC change caused by PPI	Recommendation/alternatives
Rucaparib	↑ (+38% with a high-fat meal)	Independent of meals	↔	
Ruxolitinib	↑ (+4% with a high-fat meal)	Independent of meals		
Sonidegib	↑ (+3.5-fold with a low-fat, +7.4-fold with a high-fat meal)	At least 1 h before/ no less than 2 h after	↓ (-32%)	Effect clinically irrelevant according to manufacturer
Sorafenib	↓ (-30% with a high-fat meal)	Independent of light to moderately fatty meals; at least 1 h before/no less than 2 h after a high-fat meal		
Sunitinib	↔	Independent of meals		
Tegafur/gimeracil/oteracil	↓ (tegafur unchanged, gimeracil -25%, oteracil -71%)	At least 1 h before/no less than 1 h after; more pronounced gastrointestinal side effects possible with a meal (oteracil improves gastrointestinal tolerance)	↔	
Thalidomide	↔	Independent of meals		
Tivozanib	↔	Independent of meals		
Trametinib	↓ (-10% with a high-fat meal, C _{max} : -70%)	At least 1 h before/ no less than 2 h after		
Trifluridine/tipiracil	↓ (AUC trifluridine unchanged, C _{max} trifluridine -40%, AUC tipiracil -40% with a high-fat meal)	Within 1 h after		
Vandetanib	↔	Independent of meals	↔	
Vemurafenib	↑ (+4.6 to +5.1-fold with a high-fat meal)	Independent of meals; avoid constant intake on an empty stomach (risk of lower "steady-state" exposure)		
Venetoclax	↑ (+3.4-fold with a low-fat, +5.1-bis 5.3-fold with a high-fat meal)	With a meal	↔	
Vinorelbine	↔	With a meal		
Vismodegib	↔	Independent of meals	↓ (-33%)	Effect clinically irrelevant according to manufacturer

Sources: If not otherwise stated, latest German Summary of Product Characteristics (as of 8 July 2019)

↓, AUC lowered; ↑, AUC elevated; ↔ AUC unchanged;
empty field, no data in German Summary of Product Characteristics;
-x h, take x hours before oral anti-cancer drug;
+x h, take x hours after oral anti-cancer drug
Independent of meals, intake with or without a meal is possible

AUC, Area under the curve; C_{max}, maximal concentration; h, hour; INN, international non-proprietary name; PPI, proton pump inhibitor

eTABLE 2

Influence of other medications and of grapefruit juice on the pharmacokinetics of the oral anti-cancer drugs licensed for use in Germany

Substance (INN)	Substrate of:		Pharmacokinetics of oral anti-cancer drug affected by:			Comments and selected further interactions
	CYP	P-gp	CYP3A4 inducers	CYP3A4 inhibitors	Grapefruit (products)	
Abemaciclib	3A4		!	! (DA: see SmPC)	!	
Abiraterone	3A4		!	✓		CYP2D6 inhibitor: DA of substrates as required
Afatinib	-	X				P-gp inhibitors to be taken as far apart as possible from afatinib
Alectinib	3A4		!	!	!	
Anagrelide	1A2					Combination with phosphodiesterase-III inhibitors (e.g., cilostazol, enoximone, milrinone) not recommended; DA as required in combination with CYP1A2 inducers/inhibitors
Apalutamide	2C8 3A4	X	✓	!	!*	Potent CYP2C9/2C19/3A4/P-gp inducer: DA of substrates as required; INR controls in coumarin anticoagulants
Axitinib	3A4 (1A2) (2C19)		! (DA: see SmPC)	! (DA: see SmPC)	!	
Bexarotene	3A4		!	!	!	PI USA: metabolism in vivo probably independent of CYP3A4
Binimetinib	(1A2) (2C19)	X				Metabolism predominantly via glucuronidation (UGT1A1): caution in combination with UGT1A1 inducers/inhibitors (e.g., atazanavir, indinavir, rifampicin); potent CYP1A2 inducer: caution with substrates (e.g., duloxetine, theophylline)
Bosutinib	3A4		!	! (DA: see SmPC)	!	
Brigatinib	2C8 3A4	X	!	! (DA: see SmPC)	!	CYP3A4 inducer: caution with substrates
Cabozantinib	3A4 (2C9)		!	!	!	
Capecitabine						CYP2C9 inhibitor: caution with substrates, INR controls in coumarin anticoagulants; Combination with inhibitors of dihydropyrimidine dehydrogenase (e.g., brivudine) contraindicated (accumulation of 5-fluorouracil through inhibition of metabolism—fatal outcome possible!)
Ceritinib	3A4	X	!	! (DA: see SmPC)	!	CYP2C9/3A4 inhibitor: caution with substrates
Cobimetinib	3A4	X	!	! (DA: see SmPC)	!	
Crizotinib	3A4	X	!	!	!	CYP3A4 inhibitor: avoid substrates with narrow therapeutic index
Dabrafenib	2C8 3A4	X	!	!	!*	Potent CYP2B6/2C9/3A4 inducer: caution with substrates; INR controls in coumarin anticoagulants
Dacomitinib	2D6 (3A4)	X				Potent CYP2D6 inhibitor: caution and DA as required with substrates
Dasatinib	3A4		!	! (DA: see SmPC)	!	CYP3A4 inhibitor: caution with substrates
Encorafenib	3A4 (2C19) (2D6)	X	!	!	!	
Enzalutamide	2C8 (3A4)		✓	✓		Avoid combination with CYP2C8 inhibitors, DA as required; potent CYP2B6/2C9/2C19/3A4 inducer: DA as required with substrates; INR controls in coumarin anticoagulants
Erlotinib	3A4 (1A2)	X	!	!	!*	Avoid combination with CYP1A2 inhibitors, DA as required; exposure lowered by cigarette smoke (CYP1A2 inducer)!
Everolimus	3A4	X	! (DA: see SmPC)	! (DA: see SmPC)	!	Avoid combination with P-gp inducers/inhibitors (DA as required on basis of AUC); avoid combination with ACE inhibitors (elevated risk of angioedema)

Substance (INN)	Substrate of:		Pharmacokinetics of oral anti-cancer drug affected by:			Comments and selected further interactions
	CYP	P-gp	CYP3A4 inducers	CYP3A4 inhibitors	Grapefruit (products)	
Gefitinib	3A4 (2D6)	X	!	!	!*	CYP2D6 polymorphisms: DA according to genotype necessary! <i>Potent CYP2D6 inhibitor: DA as required with substrates; INR controls in coumarin anticoagulants</i>
Ibrutinib	3A4 (2D6)		!	! (DA: see SmPC)	!	<i>P-gp inhibitor: substrates (p.o.) with narrow therapeutic index at least 6 h apart</i>
Idelalisib	(3A4)	X	!	!	!*	<i>Potent CYP3A4 inhibitor: caution in combination with substrates</i>
Imatinib	3A4 (among others)	X	!	!	!*	<i>CYP3A4/2D6 inhibitor: caution in combination with substrates</i>
Ixazomib	3A4 (1A2) among others	X	!	✓		
Lapatinib	3A4 (2C8) (2C19)	X	!	!	!	<i>CYP2C8/3A4 inhibitor: avoid substrates with narrow therapeutic index</i>
Lenalidomide	-	X				
Lenvatinib	(3A4)	X	✓	✓		Considerable proportion is metabolized with no contribution from CYP
Lorlatinib	3A4 (2C8) (2C19) (3A5)		CI	! (DA: see SmPC)	!	<i>CYP3A4 inducer: avoid substrates with narrow therapeutic spectrum</i>
Midostaurin	3A4		CI	!	!*	<i>CYP1A2/2B6/3A4 inducer: DA as required with substrates</i>
Nilotinib	3A4 (2C8)	X	!	!	!	<i>Potent CYP2C8/2C9/2D6/3A4 inhibitor: DA as required with substrates</i>
Nintedanib	(3A4)	X				CYP interactions not to be anticipated; DA as required in combination with P-gp inducers/inhibitors
Niraparib	(1A2) (3A4)	X	✓	✓		Metabolism via CYP enzymes minimal; combination with P-gp inducers/inhibitors unproblematic due to high permeability and bioavailability
Olaparib	3A4	X	!	! (DA: see SmPC)	!	
Osimertinib	3A4	X	!	✓		
Palbociclib	3A4		!	! (DA: see SmPC)	!	<i>CYP3A4 inhibitor: DA as required with substrates</i>
Panobinostat	3A4 (2C19) (2D6)	X	!	! (DA: see SmPC)	!	DA as required in combination with P-gp inhibitors; <i>CYP2D6 inhibitor: avoid substrates with narrow therapeutic index, DA as required</i>
Pazopanib	3A4 (1A2) (2C8)	X	!	! (DA: see SmPC)	!	Avoid combination with P-gp inducers/inhibitors, DA as required; combination with simvastatin with caution (increased rate of elevated liver enzymes)
Pomalidomide	(1A2) (3A4)	X	✓	✓		DA in combination with CYP1A2 inhibitors
Ponatinib	3A4	X	!	! (DA: see SmPC)	!	
Regorafenib	3A4	X	!	!	!	
Ribociclib	3A4	X	!	! (DA: see SmPC)	!	<i>Dose-dependent CYP3A4 inhibitor: caution with substrates (see SmPC for details)</i>
Rucaparib	2D6 (1A2) (3A4)	X	!	!	!*	<i>OCT1/OCT2 inhibitor: caution with substrates (e.g., metformin); CYP1A2/2C9/3A4 inhibitor: DA as required of substrates with narrow therapeutic index, INR controls in coumarin anticoagulants</i>
Ruxolitinib	3A4 (2C9)		!	! (DA: see SmPC)	!*	DA in combination with CYP2C9 inhibitors
Sonidegib	3A4		! (DA: see SmPC)	! (DA: see SmPC)	!*	

Substance (INN)	Substrate of:		Pharmacokinetics of oral anti-cancer drug affected by:			Comments and selected further interactions
	CYP	P-gp	CYP3A4 inducers	CYP3A4 inhibitors	Grapefruit (products)	
Sorafenib	(3A4)		!	✓		Combination with antibiotics (e.g., neomycin) may affect the entero-hepatic circulation and decrease exposure; <i>CYP2B6/2C8/2C9 inhibitor: caution with substrates, INR controls in coumarin anticoagulants</i>
Sunitinib	3A4		! (DA: see SmPC)	! (DA: see SmPC)	!	
Tegafur/gimeracil/oteracil	2A6					Avoid combination with CYP2A6 inhibitors, as CYP2A6 is the most important enzyme for conversion into the active form 5-fluorouracil; combination with inhibitors of dihydropyrimidine dehydrogenase (e.g., brivudine) contraindicated (accumulation of 5-fluorouracil through inhibition of metabolism—fatal outcome possible!)
Thalidomide	-					
Tivozanib	(1A1) (3A4)		!			
Trametinib	(3A4)	X				Oxidation via CYP3A4 is only a minor metabolism pathway; <i>BCRP inhibitor: substrates (e.g., cimetidine, lamivudine, rosuvastatin) 2 h apart</i>
Trifluridine/tipiracil	-					<i>Weakened antiviral action possible in combination with thymidine kinase substrates such as brivudine and zidovudine (competition with trifluridine for activation by thymidine kinase)</i>
Vandetanib	3A4		!	✓		<i>OCT2 inhibitor: DA of substrates as required (e.g., metformin); P-gp inhibitor: DA of substrates as required</i>
Vemurafenib	3A4	X	!	!	!*	<i>CYP1A2/P-gp inhibitor, CYP3A4 inducer: avoid substrates with narrow therapeutic index (DA as required)</i>
Venetoclax	3A4	X	!	CI (dose titration phase) DA (maintenance phase, see SmPC)	!	Avoid combination with P-gp inhibitors during the dose titration phase; <i>inhibitor of P-gp: substrates (p. o.) with narrow therapeutic index not to be taken at same time</i>
Vinorelbine	3A4	X	!	!	!*	Avoid combination with P-gp inducers
Vismodegib	(2C9) (3A4)	X	!	✓		Avoid combination with CYP inducers (recommendation from SmPC, of little importance from the pharmacokinetic viewpoint)

Summaries of Product Characteristics often differentiate between strong, moderate, and weak inducers/inhibitors. To aid comprehension we have not done so here.

Italic type indicates that the oral anti-cancer drug functions as a so-called perpetrator drug.

Sources: If not otherwise stated, latest German Summaries of Product Characteristics (as of 8 July 2019)

CI, Contraindication;

!, combination to be avoided/used with caution (for details, see individual SmPC);

!*, combination should be avoided; however, there is no explicit warning to this effect in the SmPC;

✓, combination unproblematic; empty field, no data in SmPC

CYP, Cytochrome P450; DA, dose adjustment; INN, international non-proprietary name; P-gp, P-glycoprotein; SmPC, German Summary of Product Information

eTABLE 3

Overview of selected side effects caused by new oral anti-cancer drugs licensed for use in Germany

Substance (INN)	Cardiovascular			Skin and mucous membranes			Emetogenic potential (e3–e6)	Remarks; further selected side effects
	QT	Hypertension	Other selected cardiovascular side effects	Hand–foot syndrome	Mucositis	Other cutaneous side effects		
Inhibitors of VEGFR-associated tyrosine kinases Class effects: Bleeding, gastrointestinal perforation/fistula, hypothyroidism, thromboembolic events, wound healings disorders (interruption of surgical interventions may be necessary – see column headed Remarks)								
Axitinib	–	+++	LVEF↓	+++	+++	+++	Low	At least 24 h interruption before surgical interventions; PRES
Cabozantinib	!!	+++		+++	+++	+++	Minimal to moderate	28 days' interruption before surgical interventions (also dental, due to osteonecrosis of jaw); change in hair color, diarrhea, pneumonitis, PRES
Lenvatinib	! DA	+++	LVEF ↓	+++	+++	+++	Minimal to moderate	Interruption before major surgical interventions; diarrhea, PRES
Nintedanib	–	++			+++	+++	Minimal	Interruption before major surgical interventions, at least 4 weeks' interruption after major surgery in gastrointestinal tract (perforations); diarrhea
Pazopanib	! TdP	+++	Bradycardia, LVEF ↓	+++	++	+++	Low	At least 7 days' interruption before major surgical interventions; change in skin and hair color, ILD/pneumonitis, ophthalmological SE (sometimes severe), PRES
Regorafenib	–	+++	Myocardial ischemia/infarction	+++	+++	+++	Low	Interruption before major surgical interventions; PRES, severe cutaneous reactions
Sorafenib	!!	+++	LVEF↓, myocardial ischemia/infarction	+++	++	+++	Minimal	Interruption before major surgical interventions, pneumonitis, severe cutaneous reactions
Sunitinib	! TdP	+++	LVEF↓	+++	+++	+++	Low	Interruption before surgical interventions (also dental, due to osteonecrosis of jaw); change in hair color/yellowing of skin, gastrointestinal SE (especially diarrhea), PRES, severe cutaneous reactions
Tivozanib	!	+++	LVEF↓, tachycardia	+++	+++	++	n.d.	Interruption before surgical interventions; PRES
Vandetanib	! TdP; DA black box warning	+++	Cerebrovascular ischemia	++	++	+++	Low	Wound healing disorders, but n.d. regarding interruption before surgical interventions; diarrhea, ILD/pneumonitis, PRES, severe cutaneous reactions
Inhibitors of EGFR-associated tyrosine kinases Class effects: very commonly occurring acneiform skin reactions, rare severe skin reactions (e.g., Stevens–Johnson syndrome), diarrhea (sometimes severe), ILD/pneumonitis, ophthalmological side effects (especially conjunctivitis, keratitis)								
Afatinib			Bleeding	++	+++	+++	Low	Hypothyroidism
Dacomitinib				+++	+++	+++	Minimal	
Erlotinib			Bleeding		+++	+++	Minimal	Gastrointestinal perforations
Gefitinib	!		Bleeding		+++	+++	Minimal	QT interval prolongation in vitro according to preclinical data, clinical relevance questionable! Gastrointestinal perforations, proteinuria
Lapatinib	! TdP		LVEF ↓			+++	Low	LVEF determination before and during treatment
Osimertinib	!! DA				+++	+++	Low	

Substance (INN)	Cardiovascular			Skin and mucous membranes			Emetogenic potential (e3–e6)	Remarks; further selected side effects
	QT	Hypertension	Other selected cardiovascular side effects	Hand–foot syndrome	Mucositis	Other cutaneous side effects		
Inhibitors of BCR-ABL tyrosine kinase								
Class effects: Bleeding, fluid retention, hepatitis-B reactivation described → HBV serology necessary before starting treatment! LVEF ↓ (exception: bosutinib), cardiac events, muscle cramps/myalgia, myelosuppression (sometimes pronounced), thromboembolic events (especially ponatinib), tumor lysis syndrome								
Bosutinib	!	++				+++	Moderate	Diarrhea, severe cutaneous reactions
Dasatinib	!!	++ (Hypotension +)		+	++	+++	Low	ILD/pneumonitis, proteinuria, severe cutaneous reactions, thyroid function disorders
Imatinib		+ (Hypotension +)			+	+++	Moderate	ILD, ophthalmological SE (sometimes severe), severe cutaneous reactions
Nilotinib	!!	++				+++	Low	Ophthalmological SE (sometimes severe)
Ponatinib	–	+++				+++	Low	Hypothyroidism, ophthalmological SE (sometimes severe), PRES
Inhibitors of ALK tyrosine kinase								
Class effects: Bradycardia, ILD/pneumonitis, visual disorders (sometimes severe ophthalmological side effects)								
Alectinib					++	+++	Low	Myalgia/CPK elevation
Brigatinib	–	+++	Palpitations		+++	+++	Low	Hyperglycemia, myalgia/CPK elevation, myelosuppression
Ceritinib	!! DA					+++	Moderate	Diarrhea, hyperglycemia
Crizotinib	!! DA		LVEF ↓			+++	Moderate	Gastrointestinal perforations, myelosuppression
Lorlatinib	! DA (see Remarks)		LVEF ↓ (clinical association?), PR interval prolongation/AV block			+++	Low	ECG and DA due not to QT but to PR interval prolongation (risk of AV block)! Hypercholesterolemia/hypertriglyceridemia, myalgia, psychiatric and neurological effects (incl. hallucinations, speech disorders)
Inhibitors of BRAF kinase								
Class effects: Occurrence of new cutaneous malignancies, visual disorders (also severe ophthalmological side effects, particularly in combination with MEK inhibitors), pyrexia, nephrotoxicity								
Dabrafenib	!	With trametinib +++	With trametinib: bleeding, LVEF ↓, thromboembolic events	+++	With trametinib ++	+++	Low	In combination with trametinib: ILD, pneumonitis, myalgia/muscle cramps, rhabdomyolysis
Encorafenib	! DA	With binimetinib +++	With binimetinib: bleeding, LVEF ↓, thromboembolic events	+++		+++	Low	
Vemurafenib	! DA			+++		+++	Minimal	Severe cutaneous reactions
Inhibitors of MEK kinases								
Class effects: Occurrence of new cutaneous malignancies, hemorrhage, CPK elevation/rhabdomyolysis, ILD/pneumonitis, LVEF ↓, pyrexia, visual disorders (also severe ophthalmological side effects), thromboembolic events (exception: cobimetinib)								
Binimetinib	–	+++		++		+++	Low	With regard to QT prolongation, see encorafenib!
Cobimetinib		+++				+++	Low	With regard to QT prolongation, see vemurafenib! Diarrhea
Trametinib		+++	Bradycardia	++	++	+++	Low	With regard to QT prolongation, see dabrafenib! Gastrointestinal perforations
Inhibitors of cyclin-dependent protein kinases (CDK)								
Class effects: Myelosuppression (sometimes pronounced), ophthalmological side effects								
Abemaciclib	–		Thromboembolic			+++	Low	Diarrhea
Palbociclib	–				+++	+++	Low	
Ribociclib	! DA				+++	+++	Low	

Substance (INN)	Cardiovascular			Skin and mucous membranes			Emetogenic potential (e3–e6)	Remarks; further selected side effects
	QT	Hypertension	Other selected cardiovascular side effects	Hand-foot syndrome	Mucositis	Other cutaneous side effects		
Other protein kinase inhibitors								
Everolimus		++	Bleeding, LVEF↓, thromboembolic events	++	+++	+++	Low	Hepatitis-B reactivation → HBV serology before beginning of treatment! Hyperglycemia/hypercholesterolemia/hyperlipidemia, ILD/pneumonitis, myelosuppression/susceptibility to infections, wound healing disorders→ if needed, interruption before major surgical interventions
Ibrutinib	–	++	Arrhythmias, bleeding		+++	+++	Low	Bleeding risk→ interruption before surgical interventions (3–7 days), hepatitis-B reactivation → HBV serology before beginning of treatment! ILD, cutaneous malignancies, myelosuppression/susceptibility to infections, severe cutaneous reactions, tumor lysis syndrome
Midostaurin	!! DA		Bleeding				Moderate	ILD/pneumonitis, myelosuppression
Ruxolitinib	–	+++	Bleeding				Minimal	Hepatitis-B reactivation → HBV serology before beginning of treatment! Hypercholesterolemia/hypertriglyceridemia, myelosuppression/susceptibility to infections
Antineoplastic drugs								
Anagrelide	! TdP	+	Bleeding, LVEF↓, palpitations, tachycardia			++	Minimal	ILD/pneumonitis
Bexarotene		+	Bleeding, tachycardia		+	+++	Low	Hypercholesterolemia/hypertriglyceridemia, hypo-/hyperthyroidism, risk of fetal malformation in pregnancy (vitamin A derivative), ophthalmological SE (sometimes severe)
Capecitabine	! TdP	+ (Hypotension +)	Myocardial infarction, palpitations, thromboembolic events	+++	+++	++	Low	Caution: Patients with dihydropyrimidine dehydrogenase (DPD) deficiency → greatly increased risk of severe SE; genotyping of certain alleles recommended in SmPC! Diarrhea, ophthalmological SE (sometimes severe), peripheral neuropathy/paresthesia, severe cutaneous reactions
Idelalisib	–					+++	Low	Cytomegaly virus reactivation → clinical/ laboratory monitoring, diarrhea/colitis, myelosuppression/susceptibility to infections, PJP prophylaxis mandatory (up to 2–6 months after the end of treatment), pneumonitis, severe cutaneous reactions
Ixazomib	–		See lenalidomide!			+++	Low	Peripheral neuropathy, severe cutaneous reactions
Niraparib		+++	Palpitations, tachycardia		++	++	Moderate	Elevated incidence of MDS and AML, myelosuppression
Olaparib					++	++	Low	Elevated incidence of MDS and AML, myelosuppression, pneumonitis
Rucaparib	–			++		+++	Moderate	Elevated incidence of MDS and AML, photosensitivity reactions, myelosuppression
Panobinostat	! DA black box warning USA	++ (Hypotension +++)	Arrhythmias, bleeding, palpitations			++	Low	Hypothyroidism, myelosuppression/ susceptibility to infections
Sonidegib	–					+++	Low	Myalgia, muscle cramps, rhabdomyolysis, contraception program (embryofetal death and birth defects possible)

Substance (INN)	Cardiovascular			Skin and mucous membranes			Emetogenic potential (e3–e6)	Remarks; further selected side effects
	QT	Hypertension	Other selected cardiovascular side effects	Hand–foot syndrome	Mucositis	Other cutaneous side effects		
Tegafur/gimeracil/oteracil	–	++ (Hypotension ++)	Arrhythmias, LVEF↓, palpitations, thromboembolic events	++	++	++	Low	Caution: high emetogenic potential of combination partner cisplatin! Diarrhea, ILD, myelosuppression, ophthalmological SE, severe cutaneous reactions
Trifluridine/tipiracil	–	+ (Hypotension +)	Angina pectoris, arrhythmias, embolism, palpitations	++	++	++	Moderate	Diarrhea, ILD, myelosuppression, proteinuria, severe cutaneous reactions
Venetoclax	–						Low	Tumor lysis prevention necessary! Myelosuppression
Vinorelbine	–	++ (Hypotension ++)	Arrhythmias, heart failure		+++	++	Moderate	Myelosuppression, neurosensory/neuromotor disorders, obstipation
Vismodegib	–					+++	Minimal	Contraception program (embryofetal death and birth defects possible)
Immunomodulators								
Class effects: Teratogenicity → contraception program (T-prescription)! Virus reactivations described (hepatitis-B, herpes zoster) → HBV serology before beginning of treatment, viral prophylaxis if needed! Thromboembolic events → thrombosis prophylaxis recommended, evening intake advised owing to somnolence, especially with lenalidomide and thalidomide, ILD, myelosuppression, peripheral neuropathy, second primary cancer, severe cutaneous reactions (e.g., Stevens–Johnson syndrome), tumor lysis syndrome								
Lenalidomide		++ (Hypotension ++)				+++	Low	Hypo-/hyperthyroidism
Pomalidomide			Bleeding, LVEF↓, AF			++	Minimal	
Thalidomide			Bradycardia, LVEF↓			++	Low	
Hormone antagonists								
Class effects: Elevated tendency towards falls and fractures, cramps (exception: abiraterone)								
Abiraterone	!!	+++	Angina pectoris, arrhythmias, fluid retention, LVEF↓			+++	Minimal	Cardiological SE and hypokalemia due to mineralocorticoid surplus → combination with prednisolone/prednisone
Apalutamide	!				+++	+++	n.d.	Hypothyroidism
Enzalutamide	!	+++	Ischemic heart disease			++	Minimal	PRES

Sources: If not otherwise stated, latest German Summaries of Product Characteristics (as of 8 July 2019)

- , No relevant prolongation of QT interval
- !, QT interval prolongation described; no data on ECG monitoring in SmPC
- !!, QT interval prolongation described; SmPC recommends ECG monitoring for high-risk patients
- !+, QT interval prolongation described; SmPC recommends ECG monitoring for all patients
- +++ , Occurs very frequently according to SmPC
- ++ , Occurs frequently according to SmPC
- + , Occurs occasionally according to SmPC

Empty field, Occurs rarely/frequency unknown according to SmPC or no data in SmPC

SE, side effects; AF, atrial fibrillation; AML, acute myeloid leukemia; CPK, creatinine phosphokinase; DA, dose adjustment; GFR, glomerular filtration rate; h, hour; HBV, hepatitis-B virus; ILD, interstitial lung disease; INN, international non-proprietary name; LVEF↓, lowered left ventricular ejection fraction; MDS, myelodysplastic syndrome; n.d., no data in literature; PJP, *Pneumocystis jirovecii* pneumonia; PRES, posterior reversible encephalopathy syndrome; SmPC, Summary of Product Characteristics; TdP, torsade de pointes

eTABLE 4

Overview of dose adjustments in the event of organ insufficiency for the new oral anti-cancer drugs licensed for use in Germany

Substance (INN)	Dose adjustment in renal insufficiency			Dose adjustment in hepatic insufficiency		
	Mild 89 –60 mL/min	Moderate 59 –30 mL/min	Severe 29 –15 mL/min	Mild Child–Pugh A	Moderate Child–Pugh B	Severe Child–Pugh C
Abemaciclib	–	–	Caution!	–	–	150 mg 1 ×/d
Abiraterone	–	–	Caution!	–	Benefit/risk	CI
Afatinib	–	–	Caution!	–	–	Not recommended
Alectinib	–	–	–	–	–	450 mg 2 ×/d
Anagrelide	Benefit/risk	< 50 mL/min: CI	CI	Benefit/risk	CI	CI
Apalutamide	–	–	Caution!	–	–	Not recommended
Axitinib	–	–	< 15 mL/min: no data	–	2 mg 2 ×/d	Not recommended
Bexarotene	Caution!	Caution!	Caution!	CI	CI	CI
Binimetinib	–	–	–	–	Not recommended	Not recommended
Bosutinib	–	<50 mL/min: DA depending on indication, see SmPC		CI	CI	CI
Brigatinib	–	–	60 mg 1 ×/d for 7 d, then 90 mg 1 ×/d	–	–	60 mg 1 ×/d for 7 d, then 120 mg 1 ×/d
Cabozantinib	Indications: renal cell carcinoma, hepatic cell carcinoma			Indications: renal cell carcinoma, hepatic cell carcinoma		
	Caution!	Caution!	Not recommended	–	Caution!	Not recommended
	Indication: thyroid carcinoma			Indication: thyroid carcinoma		
	Caution!	Caution!	Not recommended	60 mg 1 ×/d	60 mg 1 ×/d	Not recommended
Capecitabine	–	50–30 mL/min: 75 % with initial dose 1250 mg/m ²	CI	Caution!	Caution!	CI
Ceritinib	–	–	Caution!	–	–	Caution! Reduce dose by one third
Cobimetinib	–	–	Caution!	–	–	Caution!
Crizotinib	–	–	250 mg 1 ×/d, after no less than 4 weeks consider increase to 200 mg 2 ×/d	–	200 mg 2 ×/d	250 mg 1 ×/d
Dabrafenib	–	–	Caution!	–	Caution!	Caution!
Dacomitinib	–	–	n.d.	–	–	Not recommended
Dasatinib	–	–	–	Caution!	Caution!	Caution!
Encorafenib	–	–	Caution!	Caution! 300 mg 1 ×/d	Not recommended	Not recommended
Enzalutamide	–	–	Caution!	–	–	Caution!
Erlotinib	–	–	Not recommended	–	Caution!	Not recommended
Everolimus	–	–	–	7.5 mg 1 ×/d	5 mg 1 ×/d	Benefit/risk max. 2.5 mg 1 ×/d
Gefitinib	–	–	≤ 20 mL/min: Caution!	–	Caution!	Caution!
Ibrutinib	–	–	Benefit/risk	280 mg 1 ×/d	140 mg 1 ×/d	Not recommended
Idelalisib	–	–	–	–	–	Caution!
Imatinib	400 mg 1 ×/d	400 mg 1 ×/d	Caution! 400 mg 1 ×/d	400 mg 1 ×/d	400 mg 1 ×/d	400 mg 1 ×/d
Ixazomib	–	–	3 mg 1 ×/week (incl. dialysis)	–	3 mg 1 ×/week	3 mg 1 ×/week
Lapatinib	–	–	Caution!	–	Caution!	Caution!

Substance (INN)	Dose adjustment in renal insufficiency			Dose adjustment in hepatic insufficiency		
	Mild 89 –60 mL/min	Moderate 59 –30 mL/min	Severe 29 –15 mL/min	Mild Child–Pugh A	Moderate Child–Pugh B	Severe Child–Pugh C
Lenalidomide	–	<50 mL/min: DA depending on indication, see SmPC		–	n.d.	n.d.
Lenvatinib	Indication: renal cell carcinoma			Indication: renal cell carcinoma		
	–	–	10 mg 1 ×/d	–	–	Benefit/risk 10 mg 1 ×/d
	Indication: hepatic cell carcinoma			Indication: hepatic cell carcinoma		
	–	–	n.d.	–	Caution!	Not recommended
	Indication: thyroid carcinoma			Indication: thyroid carcinoma		
	–	–	14 mg 1 ×/d	–	–	14 mg 1 ×/d
Lorlatinib	–	–	Not recommended	–	Not recommended	Not recommended
Midostaurin	–	–	Caution!	–	–	Caution!
Nilotinib	–	–	–	Caution!	Caution!	Caution!
Nintedanib	–	–	n.d. (only 1% renal elimination)	–	Not recommended	Not recommended
Niraparib	–	–	Caution!	–	–	Caution!
Olaparib	As capsule			As capsule		
	–	50–31 mL/min: 300 mg 2 ×/d	≤ 30 mL/min: benefit/risk	–	–	Not recommended
	As tablet			As tablet		
	–	50–31 mL/min: 200 mg 2 ×/d	≤ 30 mL/min: benefit/risk	–	–	Not recommended
Osimertinib	–	–	–	–	–	Not recommended
Palbociclib	–	–	–	–	–	75 mg 1 ×/d
Panobinostat	–	–	–	First cycle 15 mg; second cycle consider 20 mg	First cycle 10 mg; second cycle consider 15 mg	Not recommended
Pazopanib	–	–	Caution!	Caution! 800 mg 1 ×/d	Caution! 200 mg 1 ×/d	Not recommended
Pomalidomide	–	–	– (incl. dialysis)	Caution!	Caution!	Caution!
Ponatinib	–	<50 mL/min: Caution!		Caution!	Caution!	Caution!
Regorafenib	–	–	–	–	Caution!	Not recommended
Ribociclib	–	–	Caution!	–	400 mg 1 ×/d	400 mg 1 ×/d
Rucaparib	–	–	Benefit/risk	–	Not recommended	Not recommended
Ruxolitinib	–	–	DA depending on indication, see SmPC	Reduce initial dose by 50%		
Sonidegib	–	–	n.d.	–	–	–
Sorafenib	–	–	–	–	–	n.d.
Sunitinib	–	–	–	–	–	Not recommended
Tegafur/gimeracil/oteracil	–	50–30 mL/min: 20 mg/m² 2 ×/d	Benefit/risk 20 mg/m² 2 ×/d	–	–	–
Thalidomide	–	–	Caution!	–	–	Caution!
Tivozanib	–	–	Caution!	Caution!	1340 µg every 2 d	Not recommended
Trametinib	–	–	Caution!	–	Caution!	Caution!
Trifluridine/	–	Not recommended	Not recommended	–	Not recommended	Not recommended

Substance (INN)	Dose adjustment in renal insufficiency			Dose adjustment in hepatic insufficiency		
	Mild 89 –60 mL/min	Moderate 59 –30 mL/min	Severe 29 –15 mL/min	Mild Child–Pugh A	Moderate Child–Pugh B	Severe Child–Pugh C
Vandetanib	–	Caution! 50–30 mL/ min: 200 mg 1 ×/d	Not recommended	Serum bilirubin >1.5 × ULN: Not recommended		
Vemurafenib	–	–	Caution!	–	Caution!	Caution!
Venetoclax	<80 mL/min: Caution! (tumor lysis syn- drome!)	Caution! (tumor lysis syn- drome!)	Benefit/risk (tumor lysis syndrome!)	–	Caution!	Reduce initial dose by at least 50%
Vinorelbine	–	–	–	Max. 60 mg/m ² /week	50 mg/m ² /week	Not recommended
Vismodegib	–	–	Caution!	–	–	–

Sources: If not otherwise stated, latest German Summaries of Product Characteristics (as of 8 July 2019)

–, No dose adjustment necessary; Caution!, use with care/under supervision; **Cl**, contraindication; DA, dose adjustment; INN, international non-proprietary name; n.d., no explicit statement in SmPC; SmPC, Summary of Product Characteristics; ULN, upper limit of normal