Optimized Dosing

Boosman, Rene J.; Burgers, Jacobus A.; Smit, Egbert F.; Steeghs, Neeltje; van der Wekken, Anthonie J.; Beijnen, Jos H.; Huitema, Alwin D. R.; ter Heine, Rob

Published in:
DRUGS

DOI:
10.1007/s40265-021-01654-3

Drugs (2022) 82:15–32
https://doi.org/10.1007/s40265-021-01654-3

REVIEW ARTICLE

Optimized Dosing: The Next Step in Precision Medicine in Non-Small-Cell Lung Cancer

René J. Boosman[1] · Jacobus A. Burgers[2] · Egbert F. Smit[2] · Neeltje Steeghs[3] · Anthonie J. van der Wekken[4] · Jos H. Beijnen[1,5] · Alwin D. R. Huitema[1,6,7] · Rob ter Heine[8]

Accepted: 22 November 2021 / Published online: 11 December 2021

Abstract

In oncology, and especially in the treatment of non-small-cell lung cancer (NSCLC), dose optimization is often a neglected part of precision medicine. Many drugs are still being administered in "one dose fits all" regimens or based on parameters that are often only minor determinants for systemic exposure. These dosing approaches often introduce additional pharmacokinetic variability and do not add to treatment outcomes. Fortunately, pharmacological knowledge is increasing, providing valuable information regarding the potential of, for example, therapeutic drug monitoring. This article focuses on the evidence for the most promising and easily implemented optimized dosing approaches for the small-molecule inhibitors, chemotherapeutic agents, and monoclonal antibodies as treatment options currently approved for NSCLC. Despite limitations such as investigations having been conducted in oncological diseases other than NSCLC or the retrospective origin of many analyses, an alternative dosing regimen could be beneficial for treatment outcomes, prescriber convenience, or financial burden on healthcare systems. This review of the literature provides recommendations on the implementation of dose optimization and advice regarding promising strategies that deserve further research in NSCLC.

Key Points

It is essential to optimize dosing of (expensive) treatments in oncology.

Implementation of optimized dosing of most treatment options in non-small-cell lung cancer is readily available.

Based on the recommendations in this review, further research can be initiated or dosing in clinical practice can be optimized.

✉ René J. Boosman
r.boosman@nki.nl

1 Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

2 Department of Thoracic Oncology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands

3 Department of Medical Oncology and Clinical Pharmacology, The Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands

4 Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

5 Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

6 Department of Pharmacology Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

7 Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

8 Department of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands

1 Introduction

In the current era of precision medicine in oncology, treatment is mainly tailored to the individual tumor characteristics to optimize therapy outcomes [1]. However, the dosing of these drugs has not yet entered this era. Special patient populations, such as patients with obesity or cachexia or with drug–drug interactions, are usually not studied in clinical trials. In addition, even in a clinical trial population, high

interindividual variability (IIV) in exposure, efficacy, tolerability, and safety of drugs is observed [2]. Consequently, it is unlikely that the approved dose for the population is the optimal dose for each individual. Moreover, assuming that toxicity is a biomarker for efficacy, the maximum tolerable dose (MTD) is targeted during clinical development of anticancer drugs. Although this may hold true for classic cytotoxic agents, whether it is the case for targeted therapies is debatable [3], creating opportunities for dose optimization in this class of drugs to reach optimal systemic and tumor exposure.

Implementation of dose optimization is already clinical practice for several drug classes, such as antibiotics, antiepileptics, antidepressants, and immunosuppressants [4–7]. However, its application in oncology is not commonplace [8], and this is best observed for lung cancer. Lung cancer is the leading cause of cancer-related deaths worldwide. In 2020, more than 2 million new cases of lung cancer arose and about 1.8 million patients with lung cancer died, accounting for 18% of the worldwide cancer-related deaths [9]. Therefore, even small benefits from optimized dosing will affect many patients. Over the past decade, several new treatment options for lung cancer have been approved and marketed, and more are to follow [10]. However, most therapeutics are still used in a "one dose fits all" approach. Altogether, dose optimization remains an important but forgotten part of precision medicine in lung cancer treatment.

In this review, we discuss opportunities for dose optimization of drugs currently approved by the European Medicines Agency (EMA) for treatment of non-small-cell lung cancer (NSCLC).

2 Methods of Literature Review

This article is not a systematic review, but a comprehensive search of the literature was performed. The Clinical Pharmacology and Biopharmaceutics Reviews of the US FDA, as well as the European Public Assessments Reports of the EMA were consulted for all of the drugs described in this review. In addition, terms related to pharmacokinetics, exposure–response analysis, and dose optimizations, in combination with the individual drugs or drug classes, were used in PubMed searches. Citation snowballing was used to find related articles.

3 General

Overall, dose optimization can be based a priori or a posteriori to the first administration of a drug. A priori dose optimizations include the implementation of covariate-specific dosing, such as organ function (e.g., renal function) or body size (e.g., weight or body surface area [BSA]). For some compounds, dosing based on covariates is included in the drug label, although evidence for this is lacking. In these cases, fixed dosing might be more appropriate. For a posteriori dose adaptations, doses can be based on laboratory tests such as neutrophil count for toxicity-guided dosing or drug concentrations for therapeutic drug monitoring (TDM). The latter might only be considered if (1) no easily measured biomarker for response to the drug is available, (2) therapy is given over a prolonged period to allow dose adaptions, (3) a sensitive and validated bioanalytic method is available, (4) there is high IIV and relatively low interoccasional variability in pharmacokinetic exposure, (5) the drug has a narrow therapeutic range, (6) exposure–response relationships are defined or expected, and (7) dose adaptation is feasible [11]. For all dose optimization strategies, information regarding dose–exposure–response relationships at both an individual and a population level is crucial to ensure sufficient exposure/pharmacodynamic effects during therapy [2, 12, 13]. Table 1 lists the characteristics of all drug-based therapeutic options and their optimized dosing strategies for the treatment of NSCLC.

4 Small-Molecule Inhibitors

4.1 Where Do We Stand?

In adenocarcinoma, epidermal growth factor receptor (*EGFR*) and $KRAS^{G12C}$ mutations are the most frequently detected driver mutations [14]. Other oncogenic drivers such as anaplastic lymphoma kinase (*ALK*) rearrangements, B-Raf proto-oncogene $(BRAF)^{v600}$ mutations, neurotrophic tyrosine receptor kinase (*NTRK*) fusion genes, hepatocyte growth factor receptor gene (*MET*), and exon skipping or transfection gene (*RET*) rearrangements are present in lower frequencies. In the last decade, several small-molecule inhibitors (SMIs) have been developed to target these driver mutations. Currently, all these SMIs have been developed according to the "one dose fits all" paradigm. However, since they are notoriously subject to high IIV, fixed doses might lead to under- and/or overexposure [15]. Several reviews have advocated the implementation of TDM as a tool to minimize toxicities while maintaining efficacy [11, 16], but this has not generally been accepted.

4.2 Epidermal Growth Factor Receptor (EGFR) Inhibitors

Erlotinib and gefitinib are first-generation EGFR SMIs [17]. Acquired resistance due to mutations has fueled the development of the second- and third-generation EGFR SMIs afatinib, dacomitinib, and osimertinib [18–20].

Table 1 Key characteristics and precision dosing strategies for the drug-based treatment options in NSCLC

Class/drug	Target	Currently approved dose	Exposure–efficacy[a]	Exposure–toxicity[a]	Precision dosing			References
					Directly implementable	On indication	Required additional research	
Small-molecule inhibitors								
Erlotinib	EGFR	150 mg QD	No	Yes		Fixed lower dose[b,c]		[23, 31, 34]
Gefitinib	EGFR	250 mg QD	No	Yes		Fixed lower dose (e.g., on alternating days)[b,c]		[21, 22]
Afatinib	EGFR/HER	40 mg QD	No	Yes		Fixed lower dose[b,c]		[40, 44]
Dacomitinib	EGFR/HER	45 mg QD	No	Yes		Fixed lower dose[b,c]		[42]
Osimertinib	EGFR	80 mg QD	No	Yes		Fixed lower dose[b,c]		[41, 45]
Crizotinib	ALK, ROS1, MET	250 mg BID	Yes	No	TDM-guided dosing			[56, 61, 180]
Alectinib	ALK	600 mg BID	Yes	No	TDM-guided dosing			[61, 181]
Ceritinib	ALK	450 mg QD (fed) 750 mg QD (fasted)	Positive trend	Yes	TDM-guided dosing		E–R analysis in NSCLC	[58, 182]
Brigatinib	ALK	90 mg QD for 7 days followed by 180 mg QD	Yes	Yes	TDM-guided dosing		E-R analysis in NSCLC	[59, 63, 183]
Lorlatinib	ALK, ROS1	100 mg QD	Yes	Yes	TDM-guided dosing		E–R analysis in NSCLC	[60, 184]
Dabrafenib	BRAF	150 mg BID	No[d]	Yes[d]			E–R analysis in NSCLC	[67, 185]
Trametinib	MEK	2 mg QD	Yes[d]	No[d]		TDM-guided dosing[b,c,e]	E–R analysis in NSCLC	[66, 67, 186]
Larotrectinib	NTRK	100 mg BID	Inconclusive	No		TDM-guided dosing[b,c,e]	TDM-guided dosing, lower fixed dose	[77, 187]
Entrectinib	NTRK, ALK, ROS1	600 mg QD	Inconclusive	Inconclusive		TDM-guided dosing[b,c,e]	TDM-guided dosing	[76, 188]
Cytotoxic agents								
Cisplatin	DNA bases	75 mg/m^2 Q3W	Yes	Yes			Neutrophil count	[79, 85–87]
Carboplatin	DNA bases	400 mg/m^2 Q3W	Yes	Yes	AUC-based dosing on renal function with inclusion of cystatin C. Fixed dosing of carboplatin in patients with CrCl >50 mL/min		TDM-guided dosing	[91–93]
Pemetrexed	Folate pathway	500 mg/m^2 Q3W	Weakly positive	Yes			AUC-based dosing on renal function	[107, 110, 116]
Docetaxel	Microtubules	75 mg/m^2 Q3W	Yes	Yes			Neutrophil count	[79, 117, 122–125]
Paclitaxel	Microtubules	175 mg/m^2 Q3W	Yes	Yes		TDM-guided dosing[b,c,e]		[128–130, 133, 134]

Table 1 (continued)

Class/drug	Target	Currently approved dose	Exposure–efficacy[a]	Exposure–toxicity[a]	Precision dosing			References
					Directly implementable	On indication	Required additional research	
Nab-paclitaxel	Microtubules	100 mg/m^2 Q1W	Yes[d]	Yes[d]			Neutrophil count TDM-guided dosing	[79, 118, 146, 189]
Gemcitabine	Cytidine analog	1250 mg/m^2 Q3W	Inconclusive	Inconclusive		Decreased infusion rate with low-dose gemcitabine[f]	Neutrophil count	[79, 125, 139, 146]
Vinorelbine	β-tubulin	25 mg/m^2	Inconclusive	Inconclusive			Neutrophil count, fixed dosing	[79, 144]
Monoclonal antibodies								
Nivolumab	PD-1	3 mg/kg Q2W	No	No	Fixed dose: 240 mg Q2W or 480 mg Q4W		Lower fixed dose	[155, 160, 190]
Pembrolizumab	PD-1	2 mg/kg Q3W	No	No	Fixed dose: 200 mg Q3W		Lower fixed dose	[154, 160, 191]
Durvalumab	PD-L1	10 mg/kg Q2W	No	No	Fixed dose: 750 mg Q2W or 1500 mg Q4W		Lower fixed dose	[160, 192, 193]
Atezolizumab	PD-L1	15 mg/kg Q3W	No	No	Fixed dose: 1200 mg Q3W		Lower fixed dose	[149, 160, 194]
Ipilimumab	CTLA-4	1 mg/kg Q6W	Yes	Yes	Weight group-based dosing		Tolerability-guided dosing	[160, 170, 172, 173]
Ramucirumab	VEGFR	10 mg/kg Q3W in combination with docetaxel 10 mg/kg Q2W in combination with erlotinib	Yes	Yes			Fixed dosing	[195, 196]
Bevacizumab	VEGFR	7.5–15 mg/kg Q3W	Yes	Yes	Fixed dose: 600–800 mg Q3W			[160, 177, 178, 197]

ALK anaplastic lymphoma kinase, *AUC* area under the plasma concentration–time curve , *BID* twice daily, *BRAF* B-Raf proto-oncogene, *CrCl* creatinine clearance, *CTLA-4* cytotoxic T-lymphocyte associated protein 4, *EGFR* epidermal growth factor receptor, *E–R* exposure-response, *HER* human epidermal growth factor receptor, *MEK* mitogen-activated extracellular signal-regulated kinase, *MET* mesenchymal epithelial transition factor, *NSCLC* non-small-cell lung cancer, *NTRK* neurotrophic tyrosine receptor kinase, *PD-1* programmed cell death protein 1, *PD-L1* programmed cell death-ligand 1, *QxW* every x weeks, *QD* once daily, *ROS1* c-ros oncogene 1, *TDM* therapeutic drug monitoring, *VEGFR* vascular endothelial growth factor receptor

[a]Found for the current dosing regimens

[b]In case of toxicity

[c]In case of pharmacokinetic-based drug–drug interactions which cannot be prevented

[d]In indications other than NSCLC

[e]In case of no efficacy

[f]Based on the preference of patient/prescriber

4.2.1 Dose Individualization of EGFR Small-Molecule Inhibitors (SMIs)

Overall, it has become evident that the approved doses (Table 1) of EGFR SMIs are higher than necessary for maximal efficacy. A lower dose of these drugs might minimize toxicities and increase tolerability while maintaining efficacy and making treatment available for a larger group, e.g., frail patients (under the condition that exposure–response relationships for both efficacy as toxicity are similar to those in the non-frail population).

4.2.1.1 First-Generation EGFR SMIs Erlotinib and gefitinib are both reversible inhibitors of EGFR. An exposure–response relationship might be expected, since the equilibrium of the bound and unbound drug will play a major role in the target occupancy. However, as shown in Table 1, in the current dosing regimens of both drugs, no relationship between plasma exposure and response has been found [21–24]. Interestingly, lower doses of erlotinib and gefitinib (25–100 mg once daily [QD] and 250 mg on alternating days, respectively) were noninferior to the approved dose of erlotinib 150 mg QD and gefitinib 250 mg QD [24–29]. Unfortunately, no exposure–response analyses were performed in these patients. However, these dose–response analyses showed that low doses of these first-generation SMIs were indeed as effective as and less toxic than the currently approved doses, indicating that extrapolation from non-frail to frail patients would be reasonable until new data arise [24–29]. Moreover, in lung cancer cell lines, half-maximal inhibition (IC_{50}) values for erlotinib have been reported to be in the order of 10–40 nM [30], which is a concentration approximately 1000-fold lower than the observed steady-state concentrations of erlotinib 150 mg QD [31]. Naturally, differences in target exposure between in vivo and in vitro experiments (e.g., the differences in partition coefficient) and additional factors such as protein binding, for which in vivo IC_{50} values are probably higher than those reported for in vitro experiments, should be considered. Still, these data together suggest that exposure is much higher at the approved doses than required for target inhibition and is at the plateau of the exposure–efficacy curve. Although data are scarce and conflicting [32], one preclinical study in mice advocated that lower doses (5–15 mg/kg) of at least gefitinib might result in a more rapid acquired resistance than higher doses (25–50 mg/kg) [33]. However, solid evidence in humans (with the equivalent doses) is missing.

At the approved dose, associations between systemic drug exposure and the development of rash and diarrhea have been reported [22, 34]. The development of these adverse events was observed to be far less for erlotinib 25–100 mg QD or gefitinib 250 mg on alternating days [24–29, 35]. Reported frequencies of 7–30% of patients discontinuing treatment because of side effects [36, 37] indicate that treatment may be optimized by the administration of lower doses.

4.2.1.2 Second- and Third-Generation EGFR SMIs For the irreversible inhibitors of EGFR (afatinib, dacomitinib, and osimertinib), the use of TDM is even more debatable. EGFRs have been found to be completely renewed every 1–5 days in vitro [38]. Afatinib, dacomitinib, and osimertinib all have elimination half-lives > 36 h, are dosed daily, and display low IC_{50} values for binding to mutated EGFR (steady-state trough concentrations are approximately 40- to 150-fold higher than the reported [protein-unbound] IC_{50} values) [30, 39–42]. Therefore, only low daily doses are necessary for binding, and pharmacodynamic effects may hold on longer than systemic exposure indicates. Indeed, a semi-mechanistic model for osimertinib showed that a daily dose for 2 weeks led to a delayed onset of tumor growth when compared with a single dose of osimertinib [43]. This indicates that, despite the irreversible binding of these drugs, lowering the dose frequency is not desirable because of the EGFR turnover time. Exposure–efficacy relationships with regard to afatinib, dacomitinib, and osimertinib in their current dosing schedule have not been found [40–42], whereas clear associations were found between exposure (in terms of area under the plasma concentration–time curve [AUC], trough concentrations, or average plasma concentrations) and the development of rash and diarrhea [40, 42, 44, 45]. Similar to erlotinib and gefitinib, it can be hypothesized that lower doses of afatinib, dacomitinib, and osimertinib could be sufficient for efficacy and will decrease toxicity. Indeed, for osimertinib and afatinib, preliminary results suggested that low-dose treatments (50% of the approved dose) resulted in efficacy similar to that with the approved dose [46–49].

In summary, EGFR SMIs seem to be dosed higher than necessary for maximal efficacy in *EGFR*-mutated NSCLC. Dose adjustments are not recommended, and more clinical studies are warranted to assess whether fixed lower doses of these drugs are indeed as effective as and less toxic than the standardized doses, without triggering faster acquired resistance.

4.3 $KRAS^{G12C}$ Inhibitors

Currently, no effective SMIs to target the $KRAS^{G12C}$ mutation are approved by the EMA. However, the FDA recently granted accelerated approval to sotorasib [50], and this drug is expected to also receive approval in the EU. Data are currently insufficient to support dose individualization of this drug. The current dose approved by the FDA is 960 mg QD, and the license holder is currently investigating the efficacy of 240 mg QD as an FDA postmarketing requirement [51].

4.4 Anaplastic Lymphoma Kinase Inhibitors

Three generations of ALK SMIs have been approved by the EMA. Crizotinib, which also inhibits c-ros oncogene 1 (ROS1) and MET, was the first ALK SMI to be approved [52]. Alectinib, ceritinib, and brigatinib form the second-generation and lorlatinib the third-generation ALK SMIs [53–55]. Positive exposure–efficacy relationships have already been observed in the clinical development studies of most ALK SMIs [56–60]. For some of these drugs, positive exposure–toxicity relationships were also found [59, 60] as well as high IIV (ranging from 30 to 60%) in exposure [56–60]. Moreover, the current standardized dosing of these drugs is based on the MTD found in clinical studies. However, it has been reported that, for at least crizotinib and alectinib, only 50–60% of the population in clinical practice reaches target exposure for efficacy [61], indicating a narrow therapeutic window for this drug class and showing the potential for dose individualization by means of TDM. Several (translational) studies and reviews have already proposed the optimal target concentrations or doses for the ALK inhibitors [16, 56, 61–64]. Thus, for this class of drugs, implementation of TDM is necessary to improve treatment outcomes with ALK SMIs.

4.5 B-Raf Proto-Oncogene/Mitogen-Activated Extracellular Signal-Regulated Kinase Inhibitors

Combination therapy with dabrafenib plus trametinib has been approved for lung adenocarcinoma harboring $BRAF^{V600}$ mutation as oncogenic driver [65]. For NSCLC, the exposure–response relationships for the combination of dabrafenib and trametinib are unknown. For trametinib in patients with melanoma, a relationship between median trough concentrations and efficacy outcomes was found, and high IIV (24–36%) in exposure was observed [66, 67]. Although a formal exposure–safety analysis has not yet been performed, mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors are well known to have a small therapeutic window because of their limited sensitivity towards *BRAF*-mutant cells over *BRAF*-wildtype cells [68, 69]. Therefore, the use of TDM for trametinib would be a rational choice. For dabrafenib, no exposure–response relationship has been established in melanoma, so the use of TDM is not substantiated. Whether these findings can be translated to NSCLC is unknown, since the pharmacokinetics and dynamics are dependent on tumor type [70, 71], and IC– values have been reported as comparable to or higher for $BRAF^{v600E}$-mutated NSCLC cell lines than for melanoma cells with the same driver mutation [70, 72–75]. Until exposure–response analyses are evaluated for NSCLC cohorts, TDM-guided dosing should not be carried out as standard care for the dabrafenib–trametinib combination in NSCLC. If treatment response is insufficient or extensive adverse effects are experienced, TDM-based dose guiding could be useful, targeting the predefined threshold of trametinib in melanoma [67] and the previously described population geometric mean for dabrafenib [70].

4.6 Neurotrophic Tyrosine Receptor Kinase Inhibitors

Larotrectinib and entrectinib have been approved for treatment of NSCLC with fusions in the *NTRK* genes. Entrectinib also inhibits ROS1 and ALK [76]. A remarkable observation with larotrectinib noted that patients in the highest quartile of exposure performed worse in terms of overall response rate than did those in the other quartiles. Although this was observed in a low number of patients (n=66) with various tumor types, it could indicate that patients receive higher doses than necessary [77]. Although clues indicate positive exposure–efficacy relationships, the lack of exposure–response analyses prevents the implementation of TDM-guided dosing (based on the geometric observed mean trough concentration), but it could be potentially useful in case of a treatment-related toxicity or inadequate response.

4.7 Where Should We Go?

Generally speaking, it is critical for the relationship between exposure and response to therapy to be elucidated to optimize the dosing strategy for these drugs. One important factor is the nature of the exposure metric used in these analyses. In addition, not only the drug but also the target needs to be taken into account to inform the dose adaptations. For the EGFR inhibitors, it is important to set up prospective studies to evaluate whether (fixed) lower doses of these drugs have similar efficacy outcomes and less toxicity. All ALK inhibitors show positive exposure–efficacy relationships and high IIV in exposure. In addition, for many of these drugs, clear targets for exposure have been described and positive exposure–safety relationships mentioned, so TDM-based dosing could be implemented directly for all patients. For some ALK inhibitors, no trough levels on which TDM could be based have been reported. The geometric population mean concentrations found in registration studies are frequently reported to be in the same order of magnitude as or even lower than the actual target concentrations for efficacy [78]. Therefore, until the target trough concentrations are established, dosing could be based on the geometric mean reported in these clinical trials. For the BRAF/MEK and NTRK inhibitors, exposure–response analyses should be performed in NSCLC, since there are clues for the superiority of TDM-guided dosing for these drugs. Dose modifications based on TDM might be valuable in cases with lack of efficacy or with toxicity, or when pharmacokinetic-based drug–drug interactions cannot be prevented.

5 Cytotoxic Agents

5.1 Where Do We Stand?

Although SMIs and immunotherapy are currently shifting the treatment paradigm in oncology, cytotoxic chemotherapy remains a cornerstone in the treatment of metastatic NSCLC. In general, the chemotherapeutic regimens in first-line therapy consist of a platinum-based agent (cisplatin or carboplatin) in combination with another chemotherapeutic such as pemetrexed, a taxane (docetaxel or albumin-bound [nab]-paclitaxel), gemcitabine, or vinorelbine. All these drugs, with the exception of carboplatin, are currently dosed on BSA, although there are hints that dosing based on other parameters might be of added value. For example, dosing to neutropenia has been proposed to be a prognostic factor for treatment outcomes with almost all cytotoxic agents (cisplatin, taxanes, gemcitabine, and vinorelbine) used in the treatment of NSCLC [79, 80]. Since TDM should only be considered to be beneficial if no biomarkers for drug effect are present (see Sect. 3), and since IIV in pharmacodynamic parameters are expected to be minimalized with toxicity-guided dosing [81], dosing on neutrophils is assumed to be superior to TDM. The specifics of this toxicity-guided dosing have been described previously [82]. Interestingly, dose reductions are performed for severe toxicities, but no dose increments are carried out in the absence of toxicity, despite the well-described toxicity–efficacy relationship (as summarized in Table 1). As a consequence, these patients may be receiving a subtherapeutic dose.

5.2 Platinum-Based Agents

Both cisplatin and carboplatin are cleared by the kidneys. The hydrolyzed active platinum metabolites bind irreversibly to proteins, so elimination is also dependent on protein turnover, which forms a non-renal elimination pathway [83, 84]. Given the more stable chemical structure of carboplatin compared with cisplatin, less carboplatin is hydrolyzed and undergoes bioactivation, resulting in more renal elimination of carboplatin compared with cisplatin [83].

5.2.1 Dose Individualization of Cisplatin

The AUC of unbound cisplatin has been observed to be statistically significantly related to response status during therapy [85]. Moreover, total and free platinum peak concentrations have been related to a deterioration of renal function [86–88]. Controversially, the incidence of nephrotoxicity was observed not to be altered by the infusion rate of cisplatin [89]. Currently, dosing of cisplatin is, like many cytotoxic agents, based on BSA. However, it has been shown that 44% of the IIV in cisplatin clearance can be explained by BSA [90]. Until now, no better predictors for the clearance of cisplatin have been found, so BSA-based dosing remains the recommended dosing strategy.

5.2.2 Dose Individualization of Carboplatin

As for cisplatin, the approved dosing of carboplatin is based on BSA, and systemic exposure has been related to its efficacy and toxicity [91, 92].

However, in clinical practice, BSA-based dosing is not routinely applied, with the dose instead individualized based on renal function according to the Calvert formula [93]. Glomerular filtration rate (GFR) has been generally considered to be the optimal measure for renal function. However, methods to measure this parameter are often inconvenient and time consuming [94]. Alternatively, calculation of an estimated GFR (eGFR) or creatinine clearance (CrCl) using a single serum creatinine measurement has been standard practice. However, serum creatinine is subject to active secretion, so CrCl is often an overestimation of the GFR [95]. As carboplatin does not undergo active secretion, whether CrCl is a good predictor for carboplatin clearance remains questionable. Indeed, it has been found that the use of serum creatinine does not represent carboplatin clearance accurately in patients with adequate renal function (eGFR > 50 mL/min) [96]. In addition, 24-h collection of urine to calculate the CrCl has also proven to be an inaccurate base for carboplatin dosing [97]. A flat dose (based on the mean carboplatin population clearance) of 695 mg in patients with eGFR > 50 mL/min resulted in similar variability in carboplatin exposure as serum creatinine-based dosing [96]. Implementation of markers that more accurately estimate the GFR are thus warranted. The addition of cystatin C in the calculation of the eGFR was shown to reduce bias and imprecision in carboplatin clearance [98]. Proenkephalin, a recently developed biomarker for glomerular filtration, more accurately predicted the eGFR than serum creatinine and is even useful in unstable and critically ill patients [99]. Major steps toward reaching target carboplatin exposure, especially in patients with systemic inflammation, could be made by including inflammatory markers in the dose calculation [100]. However, this dosing regimen needs prospective evaluation in a large patient cohort before implementation in clinical practice. Since a priori and a posterior dose optimization strategies could be synergistic, one might also argue for the additional implementation of TDM-guided dosing for carboplatin. Indeed, TDM-guided dosing of carboplatin has been used successfully in children and could therefore be promising for at least this patient group [101–103]. Further evaluation of this dosing strategy should be studied in an NSCLC population.

In summary, inclusion of cystatin C in the AUC-based dosing of carboplatin is feasible in clinical practice and could

be employed on indication. If cystatin C is not available, a fixed carboplatin dose of 695 mg every 3 weeks (Q3W) in patients with CrCl >50 mL/min could be recommended.

5.3 Pemetrexed

Pemetrexed is an antifolate agent that inhibits enzymes (including thymidylate synthase [TS]) in the folate pathway and, consequently, the formation of DNA precursors. Upon administration, pemetrexed is effectively transported intracellularly and polyglutamated [104]. This process is believed to play a pivotal role in both antitumor and toxic effects (such as nephrotoxicity and hematological toxicities), as pemetrexed pentaglutamate has a 100 times higher potency for TS inhibition than pemetrexed itself [105]. Measurement of the intracellular polyglutamated forms of pemetrexed thus would be an ideal marker for its pharmacological effects. However, the development of an analytic method has proven to be challenging [106]. Although it is unclear how well the polyglutamylated forms of pemetrexed correlate to pemetrexed plasma concentrations, a plasma exposure–toxicity relationship has been well-established in a generally broad range of doses (126–1362 mg) [107–109]. In addition, doses of pemetrexed 900–1000 mg/m^2 did not improve efficacy of treatment compared with standard dosing of 500 mg/m^2 Q3W [110]. Based on differences in doses, dose frequencies, and efficacy in the early clinical trial [111–113], and based on the analogy of methotrexate [114], it is expected that the exposure–efficacy relationship is AUC driven and that the current dose might be in the flat part of the exposure–efficacy curve. Therefore, standardized lower doses might be effective; however, trials to study this lower dose might not be ethical. Pemetrexed is mainly excreted by the kidneys, and renal function contributes substantially to total pemetrexed clearance [115, 116]. These results suggest that inclusion of renal function in a dosing algorithm for pemetrexed could result in less IIV in pemetrexed exposure and toxicity. A pharmacokinetic study to assess the suitability of renal function-based dosing in patients with adequate renal function is ongoing (NCT03655821). In addition, another study is determining whether renal function-based dosing with additional prophylactic therapy to prevent toxicity is feasible in patients with CrCl < 45 mL/min (NCT03656549). Given all this, implementation of TDM could also serve as a dose optimization strategy. However, since serum creatinine is part of the standard laboratory assessment during pemetrexed treatment and may be used in the dosing algorithm from the first cycle onward, renal function-based dosing is assumed to be superior to TDM as a dosing strategy.

5.4 Taxanes

The taxanes are currently dosed based on BSA without exception. High IIV in exposure to taxanes has been observed [90, 117–119], which may partly play a role in the unpredictability of treatment response and the development of toxicities.

5.4.1 Dose Individualization of Docetaxel

Results from studies of docetaxel AUC and time to progression in solid tumors (including NSCLC) have been contradictory [117, 120, 121]. Regarding toxicity–response relationships, it has been observed that the exposure to docetaxel is a predictor of severe toxicity, especially neutropenia, during the first course of treatment [122–124]. In addition, neutrophil counts are also associated with the toxicity and efficacy of docetaxel [79, 125, 126]. This could indicate that there is a balance in the optimal neutrophil nadir during docetaxel treatment. One could aim for an individualized dose that will both avoid severe hematological toxicities and be maximally effective [126]. However, as yet, no easily implemented dose individualization methods have been revealed. Neutropenia has particular potential as a prognostic marker for efficacy but cannot be implemented without solid knowledge of the efficacy and safety of toxicity-guided dosing [82].

5.4.2 Dose Individualization of Paclitaxel

The time above a certain paclitaxel plasma concentration is related to clinical efficacy [127, 128] and the development of the primary adverse events, neutropenia [127, 129, 130] and polyneuropathy [131, 132]. Two large randomized studies in patients with NSCLC assessed the feasibility of TDM of the time above a paclitaxel toxicity threshold concentration when combined with cisplatin 80 mg/m^2 or carboplatin (AUC 6). They both showed that pharmacokinetic-guided paclitaxel dosing targeting 26–31 h above a concentration of 42.7 µg/L (0.05 µM) resulted in a statistically significantly lower paclitaxel dose, similar efficacy results, and reduced adverse events compared with BSA-based (175–200 mg/m^2) dosing [133, 134]. This pharmacokinetic-guided dosing of paclitaxel has been shown to be feasible and can be based on a single sample 24 h after administration [135]. Since TDM is only possible after administration of a drug, a BSA-based starting dose is recommended in the first cycle, followed by a TDM-guided dose.

5.4.3 Dose Individualization of Nab-Paclitaxel

During treatment with nab-paclitaxel, longer times above a total paclitaxel concentration of 720 µg/L in plasma were associated with a ≥ 50% decrease in neutrophils [118]. Furthermore, in patients with NSCLC, weekly 100 mg/m^2 was more effective and less toxic than 300 mg/m^2 Q3W [136]. Although clinical study results are scarce, the available data regarding TDM-guided or neutrophil-guided dosing provide a valuable starting point for dose optimization of

nab-paclitaxel. More studies are required to assess the feasibility of these strategies.

5.5 Gemcitabine

After administration, gemcitabine is rapidly transported intracellularly and subsequently phosphorylated, with the most important and rate-limiting enzyme being deoxycytidine kinase (dCK) [137]. Saturation of the dCK has been shown to decrease the intracellular disposition of the active metabolites. Current clinical practice is a 30-min infusion of gemcitabine regardless of the dose. Logically, this would result in plasma concentrations above saturable levels, where the excess of gemcitabine in plasma will be inactivated by cytidine deaminase and would not contribute to its pharmacological effect [137].

Decreasing the infusion rate and/or lowering the gemcitabine dose are two easily adjusted factors that would lead to less saturation and consequently a more predictable dose–effect relationship. A meta-analysis ($n = 867$) found similar efficacy for the fixed dosing rate (10 mg/m^2/min) and the fixed infusion duration (30 min). However, the fixed dosing rate was associated with more toxicity [138]. This suggests that the current dosing of gemcitabine results in intracellular concentrations well within the therapeutic range and that increased infusion rates will push the intracellular concentrations toward toxic levels. Logically, a decreased dose of gemcitabine administered over a prolonged period could result in similar efficacy and toxicity.

Indeed, administration of gemcitabine 250 mg/m^2 over 6 h showed efficacy similar to that with 1000 mg/m^2 over 30 min [139]. Studies to test this prolonged infusion duration of low-dose gemcitabine in combination with 75 mg/m^2 cisplatin found beneficial efficacy results and a different toxicity profile for gemcitabine compared with historical cohorts [140, 141]. Whether the reduction in drug-related costs are beneficial given the costs related to the prolonged hospital stay remains debatable. In addition, it has been reported that prolonged infusions with chemotherapy carry higher chances of extravasation, posing additional risks for this treatment schedule [142].

5.6 Vinorelbine

Vinorelbine is a vinca alkaloid that binds to β-tubulin, resulting in inhibition of mitosis and activation of the apoptosis pathway. Currently, vinorelbine is dosed on BSA and can be administered either orally or intravenously on a weekly basis [143]. Although no relationship between BSA and the pharmacokinetics of vinorelbine has been found, dosing based on this parameter might still lead to a more efficacious and tolerable treatment [144]. In contrast, in patients with metastatic breast cancer, fixed dosing of vinorelbine (and capecitabine) could be an alternative, safe, and effective dosing strategy [145]. However, an assessment of pharmacokinetic and pharmacodynamic endpoints in a large NSCLC study cohort receiving vinorelbine has not yet been reported. Until data become available, dosing on BSA remains recommended.

5.7 Where Should We Go?

For many of the cytotoxic drugs, neutropenia is postulated to be a prognostic factor for treatment outcome. This has been assessed retrospectively for at least treatment regimens containing cisplatin [79], docetaxel [79, 125], nab-paclitaxel [146], gemcitabine [79, 125, 146], and/or vinorelbine [79]. Prospective studies are necessary to evaluate whether dosing toward a certain neutrophil count is feasible and enhances treatment outcomes. For carboplatin and pemetrexed, AUC-based dosing using renal function appears to be more rational to predict exposure to these agents. In the absence of reliable markers for renal function, a flat dose of carboplatin is feasible in patients with a relatively normal renal function. Paclitaxel could be dosed based on BSA, with subsequent cycles of therapy based on a TDM-dosing approach in case of severe toxicities or lack of efficacy.

6 Monoclonal Antibodies

6.1 Where Do We Stand?

Two classes of monoclonal antibodies (mAbs) have been approved for the treatment of NSCLC: immune-checkpoint inhibitors and the vascular endothelial growth factor receptor (VEGFR) inhibitors, bevacizumab and ramucirumab. The immune-checkpoint inhibitors include antibodies targeting programmed cell death protein 1 (PD-1; pembrolizumab and nivolumab), programmed cell death-ligand 1 (PD-L1; atezolizumab and durvalumab), and cytotoxic T-lymphocyte antigen-4 (CTLA-4; ipilimumab). Currently, dosing regimens are effective, and flat exposure–toxicity relationships are observed in a broad dose range. However, a rational for body weight-based dosing (as implemented for some of these drugs) is missing and further increases the high healthcare costs associated with these drugs.

6.2 Programmed Cell Death-Ligand 1 Antibodies

6.2.1 Exposure–Response Analyses

As target saturation is maximal at the current dosing of PD-(L)1 mAbs [147–151], it is obvious that flat exposure–response relationships are found. However, these

relationships are further complicated by the dynamic relationships between baseline factors, exposure, and disease progression. For example, tumor shrinkage may influence cachexia and thus clearance of mAbs, altering exposure to the mAbs [152–154]. This suggests that clearance of mAbs is related to tumor size and thus to patient response status. Indeed, for at least the PD-1 antibodies, it has been shown that baseline clearance is a better predictive tool for treatment outcome than is exposure [154–158]. This suggests that change in clearance during treatment with these agents could be used as a biomarker for treatment response in PD-(L)1 therapy. Although data are scarce and the exact driving mechanism(s) behind this effect should be explored, some studies have advocated that clearance-based dose adjustments could be made to reduce therapy costs while maintaining efficacy [159]. However, if clearance is merely a parameter to distinguish between responders and nonresponders, these dose adaptations should not be performed.

6.2.2 Dose Individualization

Although roughly all PD-(L)1 antibodies were initially dosed based on body weight, fixed dosing could lead to fewer preparation errors and lower healthcare costs. However, implementation of fixed doses is not yet common in clinical practice [160], or—when implemented—the fixed doses are supratherapeutic. The latter also becomes evident because no exposure–response or dose–response relationships have been found for any of the PD-L(1) antibodies.

The use of supratherapeutic doses is best illustrated for pembrolizumab, which is currently given in a 200 mg dose. Although NSCLC is often accompanied with weight loss [161, 162], this fixed dosing corresponds to the initial body weight-based-dosing of a patient weighing 100 kg. In addition, the time-dependent decrease in clearance of the PD-L(1) antibodies would result in higher exposure during longer treatment. Adaptation toward a (lower) fixed dose will result in less drug being discarded during preparation and decreased healthcare costs [163]. In line with the flat exposure–response relationship, similar efficacy has been described in a retrospective study of low doses of nivolumab (20 or 100 mg Q3W) compared with the standard dose of 3 mg/kg Q3W in patients with NSCLC [164]. This indicates that lower doses of PD-L(1) antibodies could be administered, potentially saving millions per year in healthcare [165]. Furthermore, it is currently believed that complete inhibition of the PD-1/PD-L1 complex is necessary during treatment and that patients should be treated until progression occurs. Although data on the optimal treatment durations for PD-(L)1 antibodies are scarce, some studies have observed durable responses in patients with lung cancer treated for 1–2 years followed by an intention to treat (for at least the PD-1 antibodies) [166–169].

6.3 Ipilimumab

Exposure–efficacy and –toxicity analyses in NSCLC are yet to be performed for ipilimumab. However, as discussed in Table 1 for other indications, positive dose–response and dose–toxicity relationships have been determined [170, 171]: a 10 mg/kg Q3W dose showed increased overall survival and toxicity when compared with the approved 3 mg/kg Q3W dose [172, 173]. For NSCLC, the currently approved ipilimumab dose is 1 mg/kg Q6W in combination with nivolumab 3 mg/kg Q3W and results in fewer adverse events than alternative ipilimumab regimens [174]. In case of toxicity, dosing is often temporarily halted or even discontinued [175]. Currently, nothing would indicate that the exposure–toxicity relationship would be different for NSCLC. Thus, if a positive exposure–efficacy relationship is present in NSCLC, it would be rational to adjust dosing of ipilimumab based on tolerability. Doses could be escalated in patients who do not experience adverse events and reduced in those who do. However, this strategy needs confirmation in a large number of patients (with NSCLC). Refining of the current body weight-based dosing into three weight group-based doses has been proposed. This strategy, involving using the complete contents of vials and the possibility of administering the preparation to another patient in case of treatment discontinuation, will contribute to healthcare cost savings [160].

6.4 Vascular Endothelial Growth Factor Inhibitors

The VEGF inhibitors ramucirumab and bevacizumab are currently dosed on body weight, although body weight has been shown to have only limited influence on the pharmacokinetics of these drugs. Hendrikx et al. [160] advocated the use of fixed dosing of mAbs when the effect of body weight on the clearance and volume of distribution was minimal [160]. In a more recent population pharmacokinetic meta-analysis of ramucirumab, the effect of body weight on both clearance and volume of distribution was around the arbitrary threshold to implement body weight-based dosing [176]. Based on the limited data available, no further optimization of the dosing regimen can be performed at this time.

For bevacizumab, body weight has only a small effect on clearance and volume of distribution [177]. Positive exposure–efficacy and exposure–toxicity relationships in doses of 7.5–15 mg/kg Q3W have been observed [178]. Therefore, it is time to implement fixed dosing of bevacizumab in the treatment of NSCLC at a dose of 600–800 mg Q3W.

6.5 Where Should We Go?

Currently, the dosing regimens for mAbs are effective and show a flat exposure–toxicity relationship in a large

proportion of patients. This indicates that additional precision dosing strategies might not be necessary. For ipilimumab, the feasibility of tolerability-guided dosing should be studied before this strategy is implemented. Costs associated with all mAbs are high. Therefore, dosing strategies could be optimized to decrease the financial burden on the healthcare system. Research to evaluate the efficacy of even lower doses than postulated by the "fixed-dose studies" (see Table 1) could be helpful for this. It is important to ensure that these drugs are dosed on the plateau of the exposure–efficacy curve on an individual basis. Since pharmacokinetic variability is generally low to moderate for these drugs [159, 176, 177], TDM-guided dosing would not be preferable, and only sufficiently high doses might prevent underexposure. In addition, it is not exactly known for how long and at which intervals patients should receive these mAbs, and additional research is warranted to evaluate the number of courses of treatment patients should receive for optimal outcomes.

7 Final Remarks

This review shows that the current dosing regimens of many of the drugs approved for the treatment of NSCLC need to be adapted to improve treatment outcomes or to restrict the ever-rising healthcare costs. However, challenges to implementing precision dosing also exist. Individualization, especially based on laboratory tests such the monitoring of drug concentrations, is subject to time, logistics, and availability of personnel [179]. In addition, for many drugs approved more than a decade ago, individualization could be based on the extended knowledge gained after approval of the drug. The extra effort required, delays in adjusting labels, and reluctance to prescribe drugs in an off-label dosing regimen all led to discrepancies between knowledge and the implementation of this knowledge. However, suboptimal dosing remains highly undesirable, and the urge to implement precision dosing to improve treatment remains high (Table 1).

Currently, most drugs used in the treatment of NSCLC are still dosed as one size fits all, based on BSA or body weight, despite an accumulation of evidence showing that dosing based on other parameters may improve treatment outcomes. For some drugs, precision dosing is sometimes not necessary to improve treatment outcomes. However, adaptation of the current dosing regimen might be beneficial for other factors, such as prescriber/pharmacy convenience or healthcare costs, while maintaining efficacy. This review provides an overview of studies already performed to optimize dosing in NSCLC. In addition, we provide the most promising and easily implemented dose optimization strategies. Most of these strategies can readily be rolled out in clinical practice or require further research.

Declarations

Funding No external funding was used in the preparation of this manuscript.

Conflict of interest RJ Boosman, EF Smit, ADR Huitema, and R ter Heine have no conflicts of interest that might be relevant to the contents of this manuscript. JA Burgers is a member of advisory boards for Roche and BMS and has received support from MSD for an investigator-initiated study. All of these conflicts are outside of the submitted work, and any reimbursement was paid to their institution. N Steeghs has provided consultation or attended advisory boards for AIMM Therapeutics, Boehringer Ingelheim, and Ellipses Pharma; has received research grants for the institute from AB Science, Abbvie, Actuate Therapeutics, Amgen, Array, AstraZeneca/MedImmune, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Cantargia, CellCentric, Cytovation, Deciphera, Genentech/Roche, GlaxoSmithKline, Incyte, Lilly, Merck Sharp & Dohme, Merus, Molecular Partners, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Taiho, and Takeda. All of these conflicts are outside of the submitted work, and any reimbursement was paid to their institution. AJ van der Wekken has received grants from AstraZeneca, Boehringer Ingelheim, Pfizer, Roche, and Takeda; has received payment for lectures from Pfizer, Boehringer Ingelheim, and Takeda; and is a member of the advisory boards of Boehringer Ingelheim, Takeda, and Janssen. All of these are outside of the submitted work. JH Beijnen has received payment for expert testimony for Hoyng Tokh Monegier (paid to their institution), is a part-time employee and (in)direct stockholder of Modra Pharmaceuticals and (jointly) holds a patent on oral taxane formulations clinically developed by Modra Pharmaceuticals. Modra Pharmaceuticals is a small spin-off company of the Netherlands Cancer Institute. All of these conflicts are outside of the submitted work.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material: Not applicable.

Code availability Not applicable.

Authors' contributions RJ Boosman: conceptualization, methodology, investigation, writing original draft. JA Burgers, EF Smit, N Steeghs: conceptualization, methodology, writing review and editing. AJ van der Wekken: writing review and editing. JH Beijnen: writing review and editing. ADR Huitema: conceptualization, methodology, writing review and editing, supervision. R ter Heine: conceptualization, methodology, writing review and editing, and supervision.

References

1. Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. J Natl Compr Canc Netw. 2009;7(1):99–108. https://doi.org/10.6004/jnccn.2009.0009.
2. Maloney A. A new paradigm. "Learn-Learn More"; dose-exposure-response at the center of drug development and regulatory approval. Clin Pharmacol Ther. 2017;102(6):942–50. https://doi.org/10.1002/cpt.710.
3. Mathijssen RH, Sparreboom A, Verweij J. Determining the optimal dose in the development of anticancer agents. Nat Rev

Clin Oncol. 2014;11(5):272–81. https://doi.org/10.1038/nrclinonc.2014.40.
4. Rybak MJ, Le J, Lodise T, Levine D, Bradley J, Liu C, et al. Executive summary: therapeutic monitoring of vancomycin for serious methicillin-resistant staphylococcus aureus infections: a revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. J Pediatr Infect Dis Soc. 2020;9(3):281–4. https://doi.org/10.1093/jpids/piaa057.
5. Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. Pharmacopsychiatry. 2018;51(1–02): e1. https://doi.org/10.1055/s-0037-1600991.
6. Brunet M, van Gelder T, Åsberg A, Haufroid V, Hesselink DA, Langman L, et al. Therapeutic drug monitoring of tacrolimus-personalized therapy: second consensus report. Ther Drug Monit. 2019;41(3):261–307. https://doi.org/10.1097/ftd.0000000000000640.
7. van Dijkman SC, Wicha SG, Danhof M, Della Pasqua OE. Individualized dosing algorithms and therapeutic monitoring for antiepileptic drugs. Clin Pharmacol Ther. 2018;103(4):663–73. https://doi.org/10.1002/cpt.777.
8. Touw DJ, Neef C, Thomson AH, Vinks AA. Cost-effectiveness of therapeutic drug monitoring: a systematic review. Ther Drug Monit. 2005;27(1):10–7. https://doi.org/10.1097/00007691-200502000-00004.
9. The Global Cancer Observatory. Cancer fact sheet trachea, bronchus and lung; 2020. Accessed 14 Apr 2021.
10. Toschi L, Rossi S, Finocchiaro G, Santoro A. Non-small cell lung cancer treatment (r)evolution: ten years of advances and more to come. Ecancermedicalscience. 2017;11:787. https://doi.org/10.3332/ecancer.2017.787.
11. Groenland SL, Mathijssen RHJ, Beijnen JH, Huitema ADR, Steeghs N. Individualized dosing of oral targeted therapies in oncology is crucial in the era of precision medicine. Eur J Clin Pharmacol. 2019;75(9):1309–18. https://doi.org/10.1007/s00228-019-02704-2.
12. Maloney A. Personalized dosing = approved wide dose ranges + dose titration. Clin Pharmacol Ther. 2021;109(3):566–7. https://doi.org/10.1002/cpt.1997.
13. Lyauk YK, Jonker DM, Lund TM. Dose finding in the clinical development of 60 US Food and Drug Administration-approved drugs compared with learning vs. confirming recommendations. Clin Transl Sci. 2019;12(5):481–9. https://doi.org/10.1111/cts.12641.
14. Salgia R, Pharaon R, Mambetsariev I, Nam A, Sattler M. The improbable targeted therapy: KRAS as an emerging target in non-small cell lung cancer (NSCLC). Cell Rep Med. 2021;2(1):100186. https://doi.org/10.1016/j.xcrm.2020.100186.
15. de Wit D, Guchelaar HJ, den Hartigh J, Gelderblom H, van Erp NP. Individualized dosing of tyrosine kinase inhibitors: are we there yet? Drug Discov Today. 2015;20(1):18–36. https://doi.org/10.1016/j.drudis.2014.09.007.
16. Verheijen RB, Yu H, Schellens JHM, Beijnen JH, Steeghs N, Huitema ADR. Practical recommendations for therapeutic drug monitoring of kinase inhibitors in oncology. Clin Pharmacol Ther. 2017;102(5):765–76. https://doi.org/10.1002/cpt.787.
17. Urata Y, Katakami N, Morita S, Kaji R, Yoshioka H, Seto T, et al. Randomized phase III study comparing gefitinib with erlotinib in patients with previously treated advanced lung adenocarcinoma: WJOG 5108L. J Clin Oncol. 2016;34(27):3248–57. https://doi.org/10.1200/jco.2015.63.4154.
18. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008;27(34):4702–11. https://doi.org/10.1038/onc.2008.109.
19. Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. 2016;17(5):577–89. https://doi.org/10.1016/s1470-2045(16)30033-x.
20. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(11):1454–66. https://doi.org/10.1016/s1470-2045(17)30608-3.
21. Xin S, Zhao Y, Wang X, Huang Y, Zhang J, Guo Y, et al. The dissociation of gefitinib trough concentration and clinical outcome in NSCLC patients with EGFR sensitive mutations. Sci Rep. 2015;5:12675. https://doi.org/10.1038/srep12675.
22. Food and Drug Administration. Center for drug evaluation and research. Clinical pharmacology and biopharmaceutics review(s) NDA 206995 review-Gefitinib. 2014.
23. European Medicines Agency. Tarceva: EPAR-Scientific Discussion. 2005.
24. Miyamoto S, Azuma K, Ishii H, Bessho A, Hosokawa S, Fukamatsu N, et al. Low-dose erlotinib treatment in elderly or frail patients with EGFR mutation-positive non-small cell lung cancer: a multicenter phase 2 trial. JAMA Oncol. 2020;6(7):e201250. https://doi.org/10.1001/jamaoncol.2020.1250.
25. Lampson BL, Nishino M, Dahlberg SE, Paul D, Santos AA, Jänne PA, et al. Activity of erlotinib when dosed below the maximum tolerated dose for EGFR-mutant lung cancer: Implications for targeted therapy development. Cancer. 2016;122(22):3456–63. https://doi.org/10.1002/cncr.30270.
26. Lind JS, Postmus PE, Heideman DA, Thunnissen EB, Bekers O, Smit EF. Dramatic response to low-dose erlotinib of epidermal growth factor receptor mutation-positive recurrent non-small cell lung cancer after severe cutaneous toxicity. J Thorac Oncol. 2009;4(12):1585–6. https://doi.org/10.1097/JTO.0b013e3181bbb2b9.
27. Yeo WL, Riely GJ, Yeap BY, Lau MW, Warner JL, Bodio K, et al. Erlotinib at a dose of 25 mg daily for non-small cell lung cancers with EGFR mutations. J Thorac Oncol. 2010;5(7):1048–53. https://doi.org/10.1097/JTO.0b013e3181dd1386.
28. Satoh H, Inoue A, Kobayashi K, Maemondo M, Oizumi S, Isobe H, et al. Low-dose gefitinib treatment for patients with advanced non-small cell lung cancer harboring sensitive epidermal growth factor receptor mutations. J Thorac Oncol. 2011;6(8):1413–7. https://doi.org/10.1097/JTO.0b013e31821d43a8.
29. Kwok WC, Ho JCM, Tam TCC, Lui MMS, Ip MSM, Lam DCL. Efficacy of gefitinib at reduced dose in EGFR mutant non-small cell lung carcinoma. Anticancer Drugs. 2019;30(10):1048–51. https://doi.org/10.1097/cad.0000000000000849.
30. Hirano T, Yasuda H, Tani T, Hamamoto J, Oashi A, Ishioka K, et al. In vitro modeling to determine mutation specificity of EGFR tyrosine kinase inhibitors against clinically relevant EGFR mutants in non-small-cell lung cancer. Oncotarget. 2015;6(36):38789–803. https://doi.org/10.18632/oncotarget.5887.
31. European Medicines Agency. Tarceva: EPAR-product information. 2019.
32. Foo J, Chmielecki J, Pao W, Michor F. Effects of pharmacokinetic processes and varied dosing schedules on the dynamics of acquired resistance to erlotinib in EGFR-mutant lung cancer. J

Thorac Oncol. 2012;7(10):1583–93. https://doi.org/10.1097/JTO.0b013e31826146ee.
33. Hayakawa H, Ichihara E, Ohashi K, Ninomiya T, Yasugi M, Takata S, et al. Lower gefitinib dose led to earlier resistance acquisition before emergence of T790M mutation in epidermal growth factor receptor-mutated lung cancer model. Cancer Sci. 2013;104(11):1440–6. https://doi.org/10.1111/cas.12284.
34. Fiala O, Hosek P, Pesek M, Finek J, Racek J, Stehlik P, et al. Serum concentration of erlotinib and its correlation with outcome and toxicity in patients with advanced-stage NSCLC. Anticancer Res. 2017;37(11):6469–76. https://doi.org/10.21873/anticanres.12102.
35. Yamada K, Miyamoto S, Azuma K, Ishii H, Bessho A, Fukamatsu N, et al. A multicenter phase II study of low-dose erlotinib in frail patients with EGFR mutation-positive, non-small cell lung cancer: thoracic oncology research group (TORG) trial 1425. J Clin Oncol. 2018;36:9063.
36. Timmers L, Boons CC, Moes-Ten Hove J, Smit EF, van de Ven PM, Aerts JG, et al. Adherence, exposure and patients' experiences with the use of erlotinib in non-small cell lung cancer. J Cancer Res Clin Oncol. 2015;141(8):1481–91. https://doi.org/10.1007/s00432-015-1935-0.
37. Ding PN, Lord SJ, Gebski V, Links M, Bray V, Gralla RJ, et al. Risk of treatment-related toxicities from egfr tyrosine kinase inhibitors: a meta-analysis of clinical trials of gefitinib, erlotinib, and afatinib in advanced EGFR-mutated non-small cell lung cancer. J Thorac Oncol. 2017;12(4):633–43. https://doi.org/10.1016/j.jtho.2016.11.2236.
38. Greig MJ, Niessen S, Weinrich SL, Feng JL, Shi M, Johnson TO. Effects of activating mutations on EGFR cellular protein turnover and amino acid recycling determined using SILAC mass spectrometry. Int J Cell Biol. 2015;2015: 798936. https://doi.org/10.1155/2015/798936.
39. Engelman JA, Zejnullahu K, Gale CM, Lifshits E, Gonzales AJ, Shimamura T, et al. PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. Cancer Res. 2007;67(24):11924–32. https://doi.org/10.1158/0008-5472.Can-07-1885.
40. Food and Drug Administration. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s) NDA 201292 Review–Afatinib; 2012.
41. Brown K, Comisar C, Witjes H, Maringwa J, de Greef R, Vishwanathan K, et al. Population pharmacokinetics and exposure-response of osimertinib in patients with non-small cell lung cancer. Br J Clin Pharmacol. 2017;83(6):1216–26. https://doi.org/10.1111/bcp.13223.
42. Food and Drug Administration. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s) NDA 211288 Review–Dacomitinib. 2018.
43. Yates JW, Ashton S, Cross D, Mellor MJ, Powell SJ, Ballard P. Irreversible inhibition of EGFR: modeling the combined pharmacokinetic-pharmacodynamic relationship of osimertinib and its active metabolite AZ5104. Mol Cancer Ther. 2016;15(10):2378–87. https://doi.org/10.1158/1535-7163.Mct-16-0142.
44. Nakao K, Kobuchi S, Marutani S, Iwazaki A, Tamiya A, Isa S, et al. Population pharmacokinetics of afatinib and exposure-safety relationships in Japanese patients with EGFR mutation-positive non-small cell lung cancer. Sci Rep. 2019;9(1):18202. https://doi.org/10.1038/s41598-019-54804-9.
45. Food and Drug Administration. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s) NDA 208065 Review–Osimertinib. 2015.
46. Sonobe S, Taniguchi Y, Saijo N, Naoki Y, Tamiya A, Omachi N, et al. 1381—the efficacy of a reduced dose (40mg) of Osimertinib with T790M-positive advanced non-small-cell lung cancer (427P). Esmo Asia. 2017.
47. Fang W, Huang Y, Gan J, Shao YW, Zhang L. Durable Response of low-dose afatinib plus cetuximab in an adenocarcinoma patient with a novel EGFR exon 20 insertion mutation. J Thorac Oncol. 2019;14(10):e220–1. https://doi.org/10.1016/j.jtho.2019.05.023.
48. Nakamura A, Tanaka H, Saito R, Suzuki A, Harada T, Inoue S, et al. Phase II study of low-dose afatinib maintenance treatment among patients with EGFR-mutated non-small cell lung cancer: North Japan Lung Cancer Study Group Trial 1601 (NJLCG1601). Oncologist. 2020;25(10):e1451–6. https://doi.org/10.1634/theoncologist.2020-0545.
49. Yokoyama T, Yoshioka H, Fujimoto D, Demura Y, Hirano K, Kawai T, et al. A phase II study of low starting dose of afatinib as first-line treatment in patients with EGFR mutation-positive non-small-cell lung cancer (KTORG1402). Lung Cancer. 2019;135:175–80. https://doi.org/10.1016/j.lungcan.2019.03.030.
50. Food and Drug Administration. FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC. https://fda.gov. Accessed 12 July 2021.
51. Amgen. Press release, Amgen Provides Updated Information On LUMAKRAS™ (Sotorasib) Dose Comparison Study. https://amgen.com. Accessed 12 July 2021.
52. Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;368(25):2385–94. https://doi.org/10.1056/NEJMoa1214886.
53. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017;377(9):829–38. https://doi.org/10.1056/NEJMoa1704795.
54. Soria JC, Tan DSW, Chiari R, Wu YL, Paz-Ares L, Wolf J, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017;389(10072):917–29. https://doi.org/10.1016/S0140-6736(17)30123-X.
55. Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol. 2018;19(12):1654–67. https://doi.org/10.1016/s1470-2045(18)30649-1.
56. Food and Drug Administration. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s) NDA 202570 Review–Crizotinib. 2011.
57. Food and Drug Administration. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s) NDA 208434 Review–Alectinib. 2015.
58. Food and Drug Administration. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s) NDA 205755 Review–Ceritinib. 2014.
59. Food and Drug Administration. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s) NDA 208772 Review–Brigatinib. 2016.
60. Food and Drug Administration. Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review(s) NDA 210868 Review–Lorlatinib. 2018.
61. Groenland SL, Geel DR, Janssen JM, de Vries N, Rosing H, Beijnen JH, et al. Exposure-response analyses of anaplastic lymphoma kinase inhibitors crizotinib and alectinib in non-small cell lung cancer patients. Clin Pharmacol Ther. 2021;109(2):394–402. https://doi.org/10.1002/cpt.1989.
62. Mueller-Schoell A, Groenland SL, Scherf-Clavel O, van Dyk M, Huisinga W, Michelet R, et al. Therapeutic drug

monitoring of oral targeted antineoplastic drugs. Eur J Clin Pharmacol. 2021;77(4):441–64. https://doi.org/10.1007/s00228-020-03014-8.
63. Gupta N, Wang X, Offman E, Rich B, Kerstein D, Hanley M, et al. Brigatinib dose rationale in anaplastic lymphoma kinase-positive non-small cell lung cancer: exposure-response analyses of pivotal ALTA Study. CPT Pharmacometr Syst Pharmacol. 2020;9(12):718–30. https://doi.org/10.1002/psp4.12569.
64. Yamazaki S. Translational modeling and simulation for molecularly targeted small molecule anticancer agents: case studies of multiple tyrosine kinase inhibitors, crizotinib and lorlatinib. In: Giordanetto FG, editor. Early drug development. 2018. https://doi.org/10.1002/9783527801756.ch16.
65. Planchard D, Smit EF, Groen HJM, Mazieres J, Besse B, Helland Å, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. 2017;18(10):1307–16. https://doi.org/10.1016/S1470-2045(17)30679-4.
66. Ouellet D, Kassir N, Chiu J, Mouksassi MS, Leonowens C, Cox D, et al. Population pharmacokinetics and exposure-response of trametinib, a MEK inhibitor, in patients with BRAF V600 mutation-positive melanoma. Cancer Chemother Pharmacol. 2016;77(4):807–17. https://doi.org/10.1007/s00280-016-2993-y.
67. Groenland SL, Janssen JM, Nijenhuis C, de Vries N, Rosing H, Wilgenhof S, et al. 567P Exposure-response analyses of dabrafenib and trametinib in melanoma patients. Ann Oncol. 2020;31:S486–7.
68. Corcoran RB, Settleman J, Engelman JA. Potential therapeutic strategies to overcome acquired resistance to BRAF or MEK inhibitors in BRAF mutant cancers. Oncotarget. 2011;2(4):336–46. https://doi.org/10.18632/oncotarget.262.
69. Ranzani M, Alifrangis C, Perna D, Dutton-Regester K, Pritchard A, Wong K, et al. BRAF/NRAS wild-type melanoma, NF1 status and sensitivity to trametinib. Pigment Cell Melanoma Res. 2015;28(1):117–9. https://doi.org/10.1111/pcmr.12316.
70. European Medicines Agency. Assessment report 315207, Mekinist and Tafinlar. 2017.
71. Corcoran RB, Atreya CE, Falchook GS, Kwak EL, Ryan DP, Bendell JC, et al. Combined BRAF and MEK inhibition with dabrafenib and trametinib in BRAF V600-mutant colorectal cancer. J Clin Oncol. 2015;33(34):4023–31. https://doi.org/10.1200/jco.2015.63.2471.
72. Stones CJ, Kim JE, Joseph WR, Leung E, Marshall ES, Finlay GJ, et al. Comparison of responses of human melanoma cell lines to MEK and BRAF inhibitors. Front Genet. 2013;4:66. https://doi.org/10.3389/fgene.2013.00066.
73. Liu L, Mayes PA, Eastman S, Shi H, Yadavilli S, Zhang T, et al. The BRAF and MEK inhibitors dabrafenib and trametinib: effects on immune function and in combination with immunomodulatory antibodies targeting PD-1, PD-L1, and CTLA-4. Clin Cancer Res. 2015;21(7):1639–51. https://doi.org/10.1158/1078-0432.Ccr-14-2339.
74. Scatena C, Franceschi S, Franzini M, Sanguinetti C, Romiti N, Caponi L, et al. Dabrafenib and trametinib prolong coagulation through the inhibition of tissue factor in BRAF(v600e) mutated melanoma cells in vitro. Cancer Cell Int. 2019;19:223. https://doi.org/10.1186/s12935-019-0938-3.
75. Negrao MV, Raymond VM, Lanman RB, Robichaux JP, He J, Nilsson MB, et al. Molecular landscape of BRAF-mutant NSCLC reveals an association between clonality and driver mutations and identifies targetable non-V600 driver mutations. J Thorac Oncol. 2020;15(10):1611–23. https://doi.org/10.1016/j.jtho.2020.05.021.
76. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. Lancet Oncol. 2020;21(2):271–82. https://doi.org/10.1016/s1470-2045(19)30691-6.
77. Food and Drug Administration. Center for Drug Evaluation and Research. Multi-disciplinary Review and Evaluation NDA 210861 and NDA 211710–larotrectinib. 2018.
78. Yu H, Steeghs N, Nijenhuis CM, Schellens JH, Beijnen JH, Huitema AD. Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. Clin Pharmacokinet. 2014;53(4):305–25. https://doi.org/10.1007/s40262-014-0137-2.
79. Di Maio M, Gridelli C, Gallo C, Shepherd F, Piantedosi FV, Cigolari S, et al. Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: a pooled analysis of three randomised trials. Lancet Oncol. 2005;6(9):669–77. https://doi.org/10.1016/s1470-2045(05)70255-2.
80. Kishida Y, Kawahara M, Teramukai S, Kubota K, Komuta K, Minato K, et al. Chemotherapy-induced neutropenia as a prognostic factor in advanced non-small-cell lung cancer: results from Japan Multinational Trial Organization LC00-03. Br J Cancer. 2009;101(9):1537–42. https://doi.org/10.1038/sj.bjc.6605348.
81. Centanni M, Krishnan SM, Friberg LE. Model-based dose individualization of sunitinib in gastrointestinal stromal tumors. Clin Cancer Res. 2020;26(17):4590–8. https://doi.org/10.1158/1078-0432.Ccr-20-0887.
82. Wallin JE, Friberg LE, Karlsson MO. Model-based neutrophil-guided dose adaptation in chemotherapy: evaluation of predicted outcome with different types and amounts of information. Basic Clin Pharmacol Toxicol. 2010;106(3):234–42. https://doi.org/10.1111/j.1742-7843.2009.00520.x.
83. Elferink F, van der Vijgh WJ, Klein I, Vermorken JB, Gall HE, Pinedo HM. Pharmacokinetics of carboplatin after i.v. administration. Cancer Treat Rep. 1987;71(12):1231–7.
84. Ivanov AI, Christodoulou J, Parkinson JA, Barnham KJ, Tucker A, Woodrow J, et al. Cisplatin binding sites on human albumin. J Biol Chem. 1998;273(24):14721–30. https://doi.org/10.1074/jbc.273.24.14721.
85. Schellens JH, Ma J, Planting AS, van der Burg ME, van Meerten E, de Boer-Dennert M, et al. Relationship between the exposure to cisplatin, DNA-adduct formation in leucocytes and tumour response in patients with solid tumours. Br J Cancer. 1996;73(12):1569–75. https://doi.org/10.1038/bjc.1996.296.
86. Campbell AB, Kalman SM, Jacobs C. Plasma platinum levels: relationship to cisplatin dose and nephrotoxicity. Cancer Treat Rep. 1983;67(2):169–72.
87. Reece PA, Stafford I, Russell J, Khan M, Gill PG. Creatinine clearance as a predictor of ultrafilterable platinum disposition in cancer patients treated with cisplatin: relationship between peak ultrafilterable platinum plasma levels and nephrotoxicity. J Clin Oncol. 1987;5(2):304–9. https://doi.org/10.1200/jco.1987.5.2.304.
88. Ibrahim ME, Chang C, Hu Y, Hogan SL, Mercke N, Gomez M, et al. Pharmacokinetic determinants of cisplatin-induced subclinical kidney injury in oncology patients. Eur J Clin Pharmacol. 2019;75(1):51–7. https://doi.org/10.1007/s00228-018-2552-z.
89. Mense ES, Smit AAJ, Crul M, Franssen EJF. The effect of rapid infusion of cisplatin on nephrotoxicity in patients with lung carcinoma. J Clin Pharm Ther. 2019;44(2):249–57. https://doi.org/10.1111/jcpt.12781.
90. 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(7):1100–6. https://doi.org/10.1038/bjc.2012.357.
91. Schmitt A, Gladieff L, Laffont CM, Evrard A, Boyer JC, Lansiaux A, et al. Factors for hematopoietic toxicity of carboplatin:

refining the targeting of carboplatin systemic exposure. J Clin Oncol. 2010;28(30):4568–74. https://doi.org/10.1200/jco.2010.29.3597.
92. Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol. 1992;10(4):520–8. https://doi.org/10.1200/jco.1992.10.4.520.
93. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol. 1989;7(11):1748–56. https://doi.org/10.1200/jco.1989.7.11.1748.
94. Delanaye P, Ebert N, Melsom T, Gaspari F, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 1: How to measure glomerular filtration rate with iohexol? Clin Kidney J. 2016;9(5):682–99. https://doi.org/10.1093/ckj/sfw070.
95. Dowling TC, Wang ES, Ferrucci L, Sorkin JD. Glomerular filtration rate equations overestimate creatinine clearance in older individuals enrolled in the Baltimore Longitudinal Study on Aging: impact on renal drug dosing. Pharmacotherapy. 2013;33(9):912–21. https://doi.org/10.1002/phar.1282.
96. Ekhart C, de Jonge ME, Huitema AD, Schellens JH, Rodenhuis S, Beijnen JH. Flat dosing of carboplatin is justified in adult patients with normal renal function. Clin Cancer Res. 2006;12(21):6502–8. https://doi.org/10.1158/1078-0432.Ccr-05-1076.
97. Millward MJ, Webster LK, Toner GC, Bishop JF, Rischin D, Stokes KH, et al. Carboplatin dosing based on measurement of renal function–experience at the Peter MacCallum Cancer Institute. Aust N Z J Med. 1996;26(3):372–9. https://doi.org/10.1111/j.1445-5994.1996.tb01925.x.
98. Schmitt A, Gladieff L, Lansiaux A, Bobin-Dubigeon C, Etienne-Grimaldi MC, Boisdron-Celle M, et al. A universal formula based on cystatin C to perform individual dosing of carboplatin in normal weight, underweight, and obese patients. Clin Cancer Res. 2009;15(10):3633–9. https://doi.org/10.1158/1078-0432.Ccr-09-0017.
99. Beunders R, van Groenendael R, Leijte GP, Kox M, Pickkers P. Proenkephalin compared to conventional methods to assess kidney function in critically ill sepsis patients. Shock. 2020;54(3):308–14. https://doi.org/10.1097/shk.0000000000001510.
100. Harris BDW, Phan V, Perera V, Szyc A, Galettis P, Martin JH, et al. Inability of current dosing to achieve carboplatin therapeutic targets in people with advanced non-small cell lung cancer: impact of systemic inflammation on carboplatin exposure and clinical outcomes. Clin Pharmacokinet. 2020;59(8):1013–26. https://doi.org/10.1007/s40262-020-00870-6.
101. Veal GJ, Errington J, Tilby MJ, Pearson ADJ, Foot ABM, McDowell H, et al. Adaptive dosing and platinum-DNA adduct formation in children receiving high-dose carboplatin for the treatment of solid tumours. Br J Cancer. 2007;96(5):725–31. https://doi.org/10.1038/sj.bjc.6603607.
102. Veal GJ, Errington J, Hayden J, Hobin D, Murphy D, Dommett RM, et al. Carboplatin therapeutic monitoring in preterm and full-term neonates. Eur J Cancer. 2015;51(14):2022–30. https://doi.org/10.1016/j.ejca.2015.07.011.
103. Picton SV, Keeble J, Holden V, Errington J, Boddy AV, Veal GJ. Therapeutic monitoring of carboplatin dosing in a premature infant with retinoblastoma. Cancer Chemother Pharmacol. 2009;63(4):749–52. https://doi.org/10.1007/s00280-008-0787-6.
104. Mendelsohn LG, Shih C, Chen VJ, Habeck LL, Gates SB, Shackelford KA. Enzyme inhibition, polyglutamation, and the effect of LY231514 (MTA) on purine biosynthesis. Semin Oncol. 1999;26(2 Suppl 6):42–7.
105. Shih C, Chen VJ, Gossett LS, Gates SB, MacKellar WC, Habeck LL, et al. LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res. 1997;57(6):1116–23.
106. Stoop MP, Visser S, van Dijk E, Aerts J, Stricker BH, Luider TM. High and individually variable enzymatic activity precludes accurate determination of pemetrexed, methotrexate and their polyglutamate metabolite concentrations in plasma. J Pharm Biomed Anal. 2018;148:89–92. https://doi.org/10.1016/j.jpba.2017.09.014.
107. Visser S, Koolen SLW, de Bruijn P, Belderbos HNA, Cornelissen R, Mathijssen RHJ, et al. Pemetrexed exposure predicts toxicity in advanced non-small-cell lung cancer: a prospective cohort study. Eur J Cancer. 2019;121:64–73. https://doi.org/10.1016/j.ejca.2019.08.012.
108. Latz JE, Karlsson MO, Rusthoven JJ, Ghosh A, Johnson RD. A semimechanistic-physiologic population pharmacokinetic/pharmacodynamic model for neutropenia following pemetrexed therapy. Cancer Chemother Pharmacol. 2006;57(4):412–26. https://doi.org/10.1007/s00280-005-0077-5.
109. Boosman RJ, Dorlo TPC, de Rouw N, Burgers JA, Dingemans AC, van den Heuvel MM, et al. Toxicity of pemetrexed during renal impairment explained - implications for safe treatment. Int J Cancer. 2021. https://doi.org/10.1002/ijc.33721.
110. Dickgreber NJ, Fink TH, Latz JE, Hossain AM, Musib LC, Thomas M. Phase I and pharmacokinetic study of pemetrexed plus cisplatin in chemonaive patients with locally advanced or metastatic malignant pleural mesothelioma or non-small cell lung cancer. Clin Cancer Res. 2009;15(1):382–9. https://doi.org/10.1158/1078-0432.Ccr-08-0128.
111. McDonald AC, Vasey PA, Adams L, Walling J, Woodworth JR, Abrahams T, et al. A phase I and pharmacokinetic study of LY231514, the multitargeted antifolate. Clin Cancer Res. 1998;4(3):605–10.
112. Rinaldi DA, Burris HA, Dorr FA, Woodworth JR, Kuhn JG, Eckardt JR, et al. Initial phase I evaluation of the novel thymidylate synthase inhibitor, LY231514, using the modified continual reassessment method for dose escalation. J Clin Oncol. 1995;13(11):2842–50. https://doi.org/10.1200/jco.1995.13.11.2842.
113. Rinaldi DA, Kuhn JG, Burris HA, Dorr FA, Rodriguez G, Eckhardt SG, et al. A phase I evaluation of multitargeted antifolate (MTA, LY231514), administered every 21 days, utilizing the modified continual reassessment method for dose escalation. Cancer Chemother Pharmacol. 1999;44(5):372–80. https://doi.org/10.1007/s002800050992.
114. Joerger M, Huitema AD, Krähenbühl S, Schellens JH, Cerny T, Reni M, et al. Methotrexate area under the curve is an important outcome predictor in patients with primary CNS lymphoma: A pharmacokinetic-pharmacodynamic analysis from the IELSG no. 20 trial. Br J Cancer. 2010;102(4):673–7. https://doi.org/10.1038/sj.bjc.6605559.
115. Latz JE, Chaudhary A, Ghosh A, Johnson RD. Population pharmacokinetic analysis of ten phase II clinical trials of pemetrexed in cancer patients. Cancer Chemother Pharmacol. 2006;57(4):401–11. https://doi.org/10.1007/s00280-005-0036-1.
116. de Rouw N, Boosman RJ, Huitema ADR, Hilbrands LB, Svensson EM, Derijks HJ, et al. Rethinking the application of pemetrexed for patients with renal impairment: a pharmacokinetic analysis. Clin Pharmacokinet. 2021;60(5):649–54. https://doi.org/10.1007/s40262-020-00972-1.
117. Bruno R, Hille D, Riva A, Vivier N, ten Bokkel Huinnink WW, van Oosterom AT, et al. Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol. 1998;16(1):187–96. https://doi.org/10.1200/jco.1998.16.1.187.

118. Chen N, Li Y, Ye Y, Palmisano M, Chopra R, Zhou S. Pharmacokinetics and pharmacodynamics of nab-paclitaxel in patients with solid tumors: disposition kinetics and pharmacology distinct from solvent-based paclitaxel. J Clin Pharmacol. 2014;54(10):1097–107. https://doi.org/10.1002/jcph.304.
119. Smorenburg CH, Sparreboom A, Bontenbal M, Stoter G, Nooter K, Verweij J. Randomized cross-over evaluation of body-surface area-based dosing versus flat-fixed dosing of paclitaxel. J Clin Oncol. 2003;21(2):197–202. https://doi.org/10.1200/jco.2003.01.058.
120. Charles KA, Rivory LP, Stockler MR, Beale P, Beith J, Boyer M, et al. Predicting the toxicity of weekly docetaxel in advanced cancer. Clin Pharmacokinet. 2006;45(6):611–22. https://doi.org/10.2165/00003088-200645060-00004.
121. Engels FK, Loos WJ, van der Bol JM, de Bruijn P, Mathijssen RH, Verweij J, et al. Therapeutic drug monitoring for the individualization of docetaxel dosing: a randomized pharmacokinetic study. Clin Cancer Res. 2011;17(2):353–62. https://doi.org/10.1158/1078-0432.Ccr-10-1636.
122. Bruno R, Olivares R, Berille J, Chaikin P, Vivier N, Hammershaimb L, et al. Alpha-1-acid glycoprotein as an independent predictor for treatment effects and a prognostic factor of survival in patients with non-small cell lung cancer treated with docetaxel. Clin Cancer Res. 2003;9(3):1077–82.
123. Ozawa K, Minami H, Sato H. Logistic regression analysis for febrile neutropenia (FN) induced by docetaxel in Japanese cancer patients. Cancer Chemother Pharmacol. 2008;62(3):551–7. https://doi.org/10.1007/s00280-007-0648-8.
124. Baker SD, Li J, ten Tije AJ, Figg WD, Graveland W, Verweij J, et al. Relationship of systemic exposure to unbound docetaxel and neutropenia. Clin Pharmacol Ther. 2005;77(1):43–53. https://doi.org/10.1016/j.clpt.2004.09.005.
125. Pallis AG, Agelaki S, Kakolyris S, Kotsakis A, Kalykaki A, Vardakis N, et al. Chemotherapy-induced neutropenia as a prognostic factor in patients with advanced non-small cell lung cancer treated with front-line docetaxel-gemcitabine chemotherapy. Lung Cancer. 2008;62(3):356–63. https://doi.org/10.1016/j.lungcan.2008.03.030.
126. Lombard A, Mistry H, Aarons L, Ogungbenro K. Dose individualisation in oncology using chemotherapy-induced neutropenia: example of docetaxel in non-small cell lung cancer patients. Br J Clin Pharmacol. 2021;87(4):2053–63. https://doi.org/10.1111/bcp.14614.
127. Joerger M, Huitema AD, Richel DJ, Dittrich C, Pavlidis N, Briasoulis E, et al. Population pharmacokinetics and pharmacodynamics of paclitaxel and carboplatin in ovarian cancer patients: a study by the European organization for research and treatment of cancer-pharmacology and molecular mechanisms group and new drug development group. Clin Cancer Res. 2007;13(21):6410–8. https://doi.org/10.1158/1078-0432.Ccr-07-0064.
128. Huizing MT, Giaccone G, van Warmerdam LJ, Rosing H, Bakker PJ, Vermorken JB, et al. Pharmacokinetics of paclitaxel and carboplatin in a dose-escalating and dose-sequencing study in patients with non-small-cell lung cancer. The European Cancer Centre. J Clin Oncol. 1997;15(1):317–29. https://doi.org/10.1200/jco.1997.15.1.317.
129. Jiko M, Yano I, Sato E, Takahashi K, Motohashi H, Masuda S, et al. Pharmacokinetics and pharmacodynamics of paclitaxel with carboplatin or gemcitabine, and effects of CYP3A5 and MDR1 polymorphisms in patients with urogenital cancers. Int J Clin Oncol. 2007;12(4):284–90. https://doi.org/10.1007/s10147-007-0681-y.
130. Xin DS, Zhou L, Li CZ, Zhang SQ, Huang HQ, Qiu GD, et al. TC > 0.05 as a pharmacokinetic parameter of paclitaxel for therapeutic efficacy and toxicity in cancer patients. Recent Pat Anticancer Drug Discov. 2018;13(3):341–7. https://doi.org/10.2174/1574892813666180305170439.
131. Mielke S, Sparreboom A, Steinberg SM, Gelderblom H, Unger C, Behringer D, et al. Association of Paclitaxel pharmacokinetics with the development of peripheral neuropathy in patients with advanced cancer. Clin Cancer Res. 2005;11(13):4843–50. https://doi.org/10.1158/1078-0432.Ccr-05-0298.
132. Hertz DL, Kidwell KM, Vangipuram K, Li F, Pai MP, Burness M, et al. Paclitaxel plasma concentration after the first infusion predicts treatment-limiting peripheral neuropathy. Clin Cancer Res. 2018;24(15):3602–10. https://doi.org/10.1158/1078-0432.Ccr-18-0656.
133. Joerger M, von Pawel J, Kraff S, Fischer JR, Eberhardt W, Gauler TC, et al. Open-label, randomized study of individualized, pharmacokinetically (PK)-guided dosing of paclitaxel combined with carboplatin or cisplatin in patients with advanced non-small-cell lung cancer (NSCLC). Ann Oncol. 2016;27(10):1895–902. https://doi.org/10.1093/annonc/mdw290.
134. Zhang J, Zhou F, Qi H, Ni H, Hu Q, Zhou C, et al. Randomized study of individualized pharmacokinetically-guided dosing of paclitaxel compared with body-surface area dosing in Chinese patients with advanced non-small cell lung cancer. Br J Clin Pharmacol. 2019;85(10):2292–301. https://doi.org/10.1111/bcp.13982.
135. Joerger M, Kraff S, Jaehde U, Hilger RA, Courtney JB, Cline DJ, et al. Validation of a commercial assay and decision support tool for routine paclitaxel therapeutic drug monitoring (TDM). Ther Drug Monit. 2017;39(6):617–24. https://doi.org/10.1097/ftd.0000000000000446.
136. Socinski MA, Manikhas GM, Stroyakovsky DL, Makhson AN, Cheporov SV, Orlov SV, et al. A dose finding study of weekly and every-3-week nab-Paclitaxel followed by carboplatin as first-line therapy in patients with advanced non-small cell lung cancer. J Thorac Oncol. 2010;5(6):852–61. https://doi.org/10.1097/jto.0b013e3181d5e39e.
137. Mini E, Nobili S, Caciagli B, Landini I, Mazzei T. Cellular pharmacology of gemcitabine. Ann Oncol. 2006;17(Suppl 5):v7-12. https://doi.org/10.1093/annonc/mdj941.
138. Qiu MT, Ding XX, Hu JW, Tian HY, Yin R, Xu L. Fixed-dose rate infusion and standard rate infusion of gemcitabine in patients with advanced non-small-cell lung cancer: a meta-analysis of six trials. Cancer Chemother Pharmacol. 2012;70(6):861–73. https://doi.org/10.1007/s00280-012-1974-z.
139. Patil V, Noronha V, Joshi A, Chougule A, Kannan S, Bhattacharjee A, et al. Phase III non-inferiority study evaluating efficacy and safety of low dose gemcitabine compared to standard dose gemcitabine with platinum in advanced squamous lung cancer. EClinicalMedicine. 2019;9:19–25. https://doi.org/10.1016/j.eclinm.2019.03.011.
140. Zwitter M, Kovac V, Smrdel U, Kocijancic I, Segedin B, Vrankar M. Phase I-II trial of low-dose gemcitabine in prolonged infusion and cisplatin for advanced non-small cell lung cancer. Anticancer Drugs. 2005;16(10):1129–34. https://doi.org/10.1097/00001813-200511000-00013.
141. Xiong JP, Feng M, Qiu F, Xu J, Tao QS, Zhang L, et al. Phase II trial of low-dose gemcitabine in prolonged infusion and cisplatin for advanced non-small cell lung cancer. Lung Cancer. 2008;60(2):208–14. https://doi.org/10.1016/j.lungcan.2007.10.004.
142. Kreidieh FY, Moukadem HA, El Saghir NS. Overview, prevention and management of chemotherapy extravasation. World J Clin Oncol. 2016;7(1):87–97. https://doi.org/10.5306/wjco.v7.i1.87.
143. Piccirillo MC, Daniele G, Di Maio M, Bryce J, De Feo G, Del Giudice A, et al. Vinorelbine for non-small cell lung cancer.

Expert Opin Drug Saf. 2010;9(3):493–510. https://doi.org/10.1517/14740331003774078.
144. Wong M, Balleine RL, Blair EY, McLachlan AJ, Ackland SP, Garg MB, et al. Predictors of vinorelbine pharmacokinetics and pharmacodynamics in patients with cancer. J Clin Oncol. 2006;24(16):2448–55. https://doi.org/10.1200/jco.2005.02.1295.
145. Schott AF, Rae JM, Griffith KA, Hayes DF, Sterns V, Baker LH. Combination vinorelbine and capecitabine for metastatic breast cancer using a non-body surface area dosing scheme. Cancer Chemother Pharmacol. 2006;58(1):129–35. https://doi.org/10.1007/s00280-005-0132-2.
146. Kan M, Imaoka H, Watanabe K, Sasaki M, Takahashi H, Hashimoto Y, et al. Chemotherapy-induced neutropenia as a prognostic factor in patients with pancreatic cancer treated with gemcitabine plus nab-paclitaxel: a retrospective cohort study. Cancer Chemother Pharmacol. 2020;86(2):203–10. https://doi.org/10.1007/s00280-020-04110-3.
147. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28(19):3167–75. https://doi.org/10.1200/jco.2009.26.7609.
148. Elassaiss-Schaap K, Rossenu S, Lindauer A, Kang SP, de Greef R, Sachs JR, et al. Using model-based "Learn and Confirm" to reveal the pharmacokinetics-pharmacodynamics relationship of pembrolizumab in the KEYNOTE-001 trial. CPT Pharmacometr Syst Pharmacol. 2017;6(1):21–8.
149. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54. https://doi.org/10.1056/NEJMoa1200690.
150. Deng R, Bumbaca D, Pastuskovas CV, Boswell CA, West D, Cowan KJ, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs. 2016;8(3):593–603. https://doi.org/10.1080/19420862.2015.1136043.
151. Song X, Pak M, Chavez C, Liang M, Lu H, Schwickart M, et al. Pharmacokinetics and pharmacodynamics of MEDI4736, a fully human anti-programmed death ligand 1 (PD-L1) monoclonal antibody, in patients with advanced solid tumors. J Clin Oncol. 2015;33(15_suppl):e14009–e. https://doi.org/10.1200/jco.2015.33.15_suppl.e14009.
152. Baverel PG, Dubois VFS, Jin CY, Zheng Y, Song X, Jin X, et al. Population pharmacokinetics of durvalumab in cancer patients and association with longitudinal biomarkers of disease status. Clin Pharmacol Ther. 2018;103(4):631–42. https://doi.org/10.1002/cpt.982.
153. Dai HI, Vugmeyster Y, Mangal N. Characterizing exposure-response relationship for therapeutic monoclonal antibodies in immuno-oncology and beyond: challenges, perspectives, and prospects. Clin Pharmacol Ther. 2020;108(6):1156–70. https://doi.org/10.1002/cpt.1953.
154. Turner DC, Kondic AG, Anderson KM, Robinson AG, Garon EB, Riess JW, et al. Pembrolizumab exposure-response assessments challenged by association of cancer cachexia and catabolic clearance. Clin Cancer Res. 2018;24(23):5841–9. https://doi.org/10.1158/1078-0432.Ccr-18-0415.
155. Agrawal S, Feng Y, Roy A, Kollia G, Lestini B. Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy. J Immunother Cancer. 2016;4(72):eCollection 2016. https://doi.org/10.1186/s40425-016-0177-2.
156. Bajaj G, Wang X, Agrawal S, Gupta M, Roy A, Feng Y. Model-based population pharmacokinetic analysis of nivolumab in patients with solid tumors. CPT Pharmacometr Syst Pharmacol. 2017;6(1):58–66. https://doi.org/10.1002/psp4.12143.
157. Liu C, Yu J, Li H, Liu J, Xu Y, Song P, et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. Clin Pharmacol Ther. 2017;101(5):657–66. https://doi.org/10.1002/cpt.656.
158. Wang R, Zheng J, Shao X, Ishii Y, Roy A, Bello A, et al. Development of a prognostic composite cytokine signature based on the correlation with nivolumab clearance: translational PK/PD analysis in patients with renal cell carcinoma. J Immunother Cancer. 2019;7(1):348. https://doi.org/10.1186/s40425-019-0819-2.
159. Centanni M, Moes D, Trocóniz IF, Ciccolini J, van Hasselt JGC. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. Clin Pharmacokinet. 2019;58(7):835–57. https://doi.org/10.1007/s40262-019-00748-2.
160. Hendrikx J, Haanen J, Voest EE, Schellens JHM, Huitema ADR, Beijnen JH. Fixed dosing of monoclonal antibodies in oncology. Oncologist. 2017;22(10):1212–21. https://doi.org/10.1634/theoncologist.2017-0167.
161. Topkan E. Weight gain as a surrogate marker of longer survival in advanced non-small cell lung cancer patients. Ann Transl Med. 2016;4(19):381. https://doi.org/10.21037/atm.2016.09.33.
162. Del Ferraro C, Grant M, Koczywas M, Dorr-Uyemura LA. Management of anorexia-cachexia in late stage lung cancer patients. J Hosp Palliat Nurs. 2012;14(6). https://doi.org/10.1097/NJH.0b013e31825f3470.
163. Heinhuis KM, Barkman HJ, Beijnen JH, Hendrikx J. A cost analysis study of the implementation of fixed-dosing of monoclonal antibodies in the Netherlands Cancer Institute. Int J Clin Pharm. 2021;43(1):181–90. https://doi.org/10.1007/s11096-020-01131-z.
164. Yoo SH, Keam B, Kim M, Kim SH, Kim YJ, Kim TM. Low-dose nivolumab can be effective in non-small cell lung cancer: alternative option for financial toxicity. ESMO Open. 2018;3(5):e000332. https://doi.org/10.1136/esmoopen-2018-000332.
165. Renner A, Burotto M, Rojas C. Immune checkpoint inhibitor dosing: can we go lower without compromising clinical efficacy? J Glob Oncol. 2019;5:1–5. https://doi.org/10.1200/JGO.19.00142.
166. Gray JE, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC-update from PACIFIC. J Thorac Oncol. 2020;15(2):288–93. https://doi.org/10.1016/j.jtho.2019.10.002.
167. Herbst RS, Garon EB, Kim DW, Cho BC, Perez-Gracia JL, Han JY, et al. Long-term outcomes and retreatment among patients with previously treated, programmed death-ligand 1-positive, advanced non-small-cell lung cancer in the KEYNOTE-010 Study. J Clin Oncol. 2020;38(14):1580–90. https://doi.org/10.1200/jco.19.02446.
168. Spigel DR, McCleod M, Hussein MN, Waterhouse DM, Einhorn L, Horn L, et al. CheckMate 153: Randomized results of continuous vs 1-year fixed-duration nivolumab in patients with advanced non-small cell lung cancer. Ann Oncol. 2017;28:Abstract 1297O.
169. von Pawel J, Bordoni R, Satouchi M, Fehrenbacher L, Cobo M, Han JY, et al. Long-term survival in patients with advanced non-small-cell lung cancer treated with atezolizumab versus docetaxel: results from the randomised phase III OAK study. Eur J Cancer. 2019;107:124–32. https://doi.org/10.1016/j.ejca.2018.11.020.
170. Feng Y, Roy A, Masson E, Chen TT, Humphrey R, Weber JS. Exposure-response relationships of the efficacy and safety of ipilimumab in patients with advanced melanoma. Clin Cancer Res. 2013;19(14):3977–86. https://doi.org/10.1158/1078-0432.Ccr-12-3243.
171. Sharma P, Siefker-Radtke A, de Braud F, Basso U, Calvo E, Bono P, et al. Nivolumab alone and with ipilimumab in previously

treated metastatic urothelial carcinoma: CheckMate 032 nivolumab 1 mg/kg plus ipilimumab 3 mg/kg expansion cohort results. J Clin Oncol. 2019;37(19):1608–16. https://doi.org/10.1200/jco.19.00538.
172. Ascierto PA, Del Vecchio M, Robert C, Mackiewicz A, Chiarion-Sileni V, Arance A, et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2017;18(5):611–22. https://doi.org/10.1016/s1470-2045(17)30231-0.
173. Ascierto PA, Del Vecchio M, Mackiewicz A, Robert C, Chiarion-Sileni V, Arance A, et al. Overall survival at 5 years of follow-up in a phase III trial comparing ipilimumab 10 mg/kg with 3 mg/kg in patients with advanced melanoma. J Immunother Cancer. 2020;8(1). https://doi.org/10.1136/jitc-2019-000391.
174. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18(1):31–41. https://doi.org/10.1016/s1470-2045(16)30624-6.
175. European Medicines Agency. Yervoy: EPAR-Product information. 2021.
176. O'Brien L, Westwood P, Gao L, Heathman M. Population pharmacokinetic meta-analysis of ramucirumab in cancer patients. Br J Clin Pharmacol. 2017;83(12):2741–51. https://doi.org/10.1111/bcp.13403.
177. 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(5):779–86. https://doi.org/10.1007/s00280-007-0664-8.
178. Yang K, Wang YJ, Chen XR, Chen HN. Effectiveness and safety of bevacizumab for unresectable non-small-cell lung cancer: a meta-analysis. Clin Drug Investig. 2010;30(4):229–41. https://doi.org/10.2165/11532260-000000000-00000.
179. Menz BD, Stocker SL, Verougstraete N, Kocic D, Galettis P, Stove CP, et al. Barriers and opportunities for the clinical implementation of therapeutic drug monitoring in oncology. Br J Clin Pharmacol. 2021;87(2):227–36. https://doi.org/10.1111/bcp.14372.
180. European Medicines Agency. Xalkori: EPAR-Product information. 2020.
181. European Medicines Agency. Alecensa: EPAR-Product information. 2020.
182. European Medicines Agency. Zykadia: EPAR-Product information. 2020.
183. European Medicines Agency. Alunbrig: EPAR-Product information. 2020.
184. European Medicines Agency. Lorviqua: EPAR-Product information. 2020.
185. European Medicines Agency. Tafinlar: EPAR-Product information. 2020.
186. European Medicines Agency. Mekinist: EPAR-Product information. 2020.
187. European Medicines Agency. Vitrakvi: EPAR-Product information. 2020.
188. European Medicines Agency. Rozlytrek: EPAR-Product information. 2020.
189. Scheithauser W, Ramanathan RK, Moore M, Macarulla T, Goldstein D, Hammel P, et al. Dose modification and efficacy of nab-paclitaxel plus gemcitabine vs. gemcitabine for patients with metastatic pancreatic cancer: phase III MPACT trial. J Gastrointest Oncol. 2016;7(3):469–78.
190. Bellesoeur A, Ollier E, Allard M, Hirsch L, Boudou-Rouquette P, Arrondeau J, et al. Is there an exposure-response relationship for nivolumab in real-world NSCLC patients? Cancers (Basel). 2019;11(11):1784. https://doi.org/10.3390/cancers11111784.
191. Chatterjee MS, Elassaiss-Schaap J, Lindauer A, Turner DC, Sostelly A, Freshwater T, et al. Population pharmacokinetic/pharmacodynamic modeling of tumor size dynamics in pembrolizumab-treated advanced melanoma. CPT Pharmacometr Syst Pharmacol. 2017;6(1):29–39. https://doi.org/10.1002/psp4.12140.
192. Zielinski CC. A phase I study of MEDI4736, NNT-PD-L1 antibody in patients with advanced solid tumors. Transl Lung Cancer Res. 2014;3(6):406–7. https://doi.org/10.3978/j.issn.2218-6751.2014.08.07.
193. Segal NH, Hamid O, Hwu W, Massard C, Butler M, Antonia S, et al. 1058PD—a Phase I multi-arm dose-expansion study of the anti-programmed cell death-ligand-1 (Pd-L1) antibody Medi4736: preliminary data. Ann Oncol. 2014;25:iv365. https://doi.org/10.1093/annonc/mdu342.11.
194. Morrissey KM, Marchand M, Patel H, Zhang R, Wu B, Phyllis Chan H, et al. Alternative dosing regimens for atezolizumab: an example of model-informed drug development in the postmarketing setting. Cancer Chemother Pharmacol. 2019;84(6):1257–67. https://doi.org/10.1007/s00280-019-03954-8.
195. Smit EF, Garon EB, Reck M, Cappuzzo F, Bidoli P, Cohen RB, et al. Exposure-response relationship for ramucirumab from the randomized, double-blind, phase 3 REVEL trial (docetaxel versus docetaxel plus ramucirumab) in second-line treatment of metastatic non-small cell lung cancer. Cancer Chemother Pharmacol. 2018;82(1):77–86. https://doi.org/10.1007/s00280-018-3560-5.
196. European Medicines Agency. Cyramza: EPAR-Product information. 2020.
197. European Medicines Agency. Avastin: EPAR-Product information. 2020.