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EDITORIAL

Off-label, but on target: the evidence needed to implement alternative dosing regimens of anticancer drugs

INTRODUCTION

Over the past decades, dose selection of anticancer drugs has been dictated by the maximum tolerated dose (MTD), based on tolerability rather than efficacy.[1] Tolerability-driven dose selection is an efficient strategy to select a relatively safe dose over a short timeframe in a limited number of patients for development of the drug in subsequent further clinical trials focusing on efficacy.[2] This method of dose selection disregards exposure—response relationships, interpatient variability in pharmacokinetic drug exposure, long-term safety, and patient convenience.[2] Furthermore, novel anticancer drugs are expensive which puts serious strain on national health services.[3] Therefore, alternative dosing regimens aiming at improving tolerability, efficacy, patient convenience, and decreasing financial burden have been developed.[4] Although many studies show the benefit of a variety of alternative dosing strategies compared with the standard approved dose, these strategies rarely find their way to routine clinical practice.[5-9]

In some situations, optimized dosing regimens are studied by market authorization holders as part of post-marketing requirements. The outcomes of these studies are evaluated by the regulatory authorities and can result in drug label modifications and, thus, instant implementation in clinical practice.[1,2] However, most alternative dosing regimens are studied through investigator-initiated studies not supported by market authorization holders, are not evaluated by regulatory authorities, and the outcomes of these studies are not translated into the drug label and clinical practice. Guideline committees have the opportunity to evaluate the outcomes of the investigator-initiated studies, but this is not common practice thus far.

There are several possible reasons why these dosing regimens rarely find their way to daily practice. The 'off-label' status, the absence of financial reimbursement, or a lack of evidence on clinical endpoints are likely the predominant reasons. However, it may be questioned whether large-scale clinical trials on clinical endpoints are always required, especially if the exposure—response relationships are well-defined. Training of oncologists in clinical pharmacology tends to be minimal despite the fact that many drugs used have a narrow therapeutic window. Efficacy and adherence to regimen protocol tend to get preference over dose and schedule individualization.

Currently, there is a lack of consensus regarding the level of evidence required to implement alternative dosing regimens in clinical practice. In the future, this will most likely change as the Food and Drug Administration's (FDA) Project Optimus is implemented and a deeper understanding of the exposure—response relationship is explored during drug development.[10] However, for anticancer drugs currently approved, there is an unmet need to optimize the dose.[11] In this perspective, we provide practical recommendations on the level of evidence needed to facilitate and accelerate the adoption of alternative dosing regimens in practice. The focus of this perspective is on alternative dosing regimens and not on individualized dosing (e.g. therapeutic drug monitoring). Individualized dosing can be used to optimize the dose because it is well-known that the used fixed dosages leads to variable exposure levels and therefore not all patients are optimally treated.[12,13] Individualized dosing recommendations have recently been formulated by Groenland et al.[12]

CLASSIFICATION OF DOSING REGIMENS

Many anticancer drugs show an association between pharmacokinetic exposure (i.e. AUC as area under the curve of plasma concentrations versus time) and both treatment efficacy and toxicity.[12] Using this exposure to evaluate alternative dosing strategies is, thus, a rational approach. Based on pharmacokinetic exposure, alternative dosing regimens can be classified into the following three categories:

1. alternative dosing regimens leading to equivalent exposure;
2. alternative dosing regimens leading to lower or shorter exposure; and
3. alternative dosing regimens leading to higher exposure.

We postulate that the level of evidence to implement alternative dosing regimens in clinical practice should comply with specific requirements for each category, as outlined hereafter and summarized in Table 1 and Figure 1.

ALTERNATIVE DOSING REGIMENS LEADING TO EQUIVALENT EXPOSURE

Equivalent pharmacokinetic exposure means pharmacokinetic exposure levels that remain within the boundaries that demarcate clinically significant changes in treatment outcome. The main goals of alternative dosing regimens leading to equivalent exposure are to improve patient

Table 1. Recommended level of evidence needed for implementation of alternative dosing regimens

Type of dosing regimen	Evidence needed for implementation
Equivalent exposure	Exposure within no-effect boundaries[a]
Lower or shorter exposure	Non-inferiority on efficacy outcomes[b]
Higher exposure	Non-inferiority on efficacy outcomes compared with standard of care Superiority on efficacy compared with placebo

[a]Based on exposure—response analysis or conservative no-effect boundary of 80%-125% on the area under the curve.
[b]Default non-inferiority margin of 20% on clinical outcome.

convenience and tolerability, and to reduce pharmacokinetic variability or financial burden.

Subtypes of dosing regimens leading to equivalent exposure

Three subcategories of alternative dosing regimens ensuring equivalent exposure can be distinguished. Examples are provided in Table 2.

The first category is the administration of a higher dose with a longer dosing interval leading to equivalent cumulative exposure over time. Prolonging the dosing interval improves patient convenience, and decreases the burden on the hospital or outpatient facility capacity and is acceptable provided toxicity is not increased. Such dosing regimens are associated with higher peak drug concentrations and lower trough concentrations. This approach has been applied for several monoclonal antibodies for which it has been shown that these changes do not impact their efficacy and tolerance and can be applied for other drugs with no apparent association between peak concentration and toxicity.[9,15,21,26] For example, nivolumab was approved at a dose of 3 mg/kg every 2 weeks (Q2W).[20] Later, a flat dose of 240 mg Q2W and 480 mg every 4 weeks (Q4W) was approved based on similar average steady-state concentrations in modeling and simulation studies.[20,21]

The second category is a lower dose with food to improve drug oral bioavailability. Several lipophilic oral anticancer drugs show low oral bioavailability due to limited solubility within the hydrophilic digestive tract. Consequently, they dissolve better in the presence of fat and/or bile salts, leading to greater absorption (i.e. increased oral bioavailability) when taken with food.[14,16,29-33] A reduced dose with food will then lead to equivalent exposure compared with fasted intake. For some drugs, the amount of fat in the food has a significant impact on the solubility and bioavailability. For these drugs the amount of fat should be specified to decrease variability in absorption due to dietary differences in different parts of the world.[30,31] However, for many drugs the food effect is mainly driven by bile salts, which are secreted after every meal. The diet, and the amount of fat in the meal, is for those drugs less relevant.[32,33] In addition, a lower dose with food could cause fewer gastrointestinal side-effects and is often more palatable and convenient for patients.[5,16] Finally, a lower dose can reduce the pill and financial burden. Recently, the beneficial effect of food on ceritinib bioavailability was shown.[16] While in the pivotal randomized phase III study ceritinib was taken fasted in a dose of 750 mg once daily (QD), it was approved at 450 mg QD with food based on a pharmacokinetic study that demonstrated equivalent exposure and a beneficial toxicity profile when taken with food.[16] Similarly, equivalent exposure of pazopanib 600 mg QD with food and 800 mg QD fasted has been established.[5] This study was, however, conducted by academia and, in contrast to the aforementioned ceritinib example, did not result in label adjustments, leading to hesitated implementation.

The third category is pharmacokinetic boosting. In pharmacokinetic boosting, a nontherapeutic inhibitor of a metabolic enzyme is combined with a lower dose of a therapeutic drug that is metabolized by the same enzyme. Thereby, the oral bioavailability increases, and the systemic clearance of the therapeutic drug is reduced leading to similar exposure of the lower boosted dose compared with the standard dose, but with a possible reduction in interpatient variability in drug exposure and therefore more predictable treatment outcomes.[19] This concept has been used for decades in the field of antiretroviral therapy and is currently used in millions of people living with the human immunodeficiency virus.[34] In oncology, boosting is gaining momentum.[18,19,35-37] Recently similar pharmacokinetic exposure was shown for a reduced dose of erlotinib with the cytochrome P450 (CYP)3A inhibitor ritonavir compared with the standard erlotinib dose.[18] Several studies are currently ongoing in which the lower equivalent dose of olaparib in combination with the CYP3A inhibitor cobicistat is explored (NCT05078671) and in which ritonavir is used to facilitate the oral administration of docetaxel by increasing bioavailability to reach exposure levels comparable to the intravenous formulation (NCT04028388). A challenge that needs to be acknowledged when pharmacokinetic boosting is the potential interaction with other drugs in the heavily cotreated oncology patient population.[38] Nonetheless, this is manageable as drug labels and drug—drug interaction websites (such as www.cancer-druginteractions.org) provide information on drug interactions and many oncologists are already familiar with the management of pharmacokinetic interactions, for instance, from strong CYP3A inhibitors prescribed for antifungal therapy.

Level of evidence required for implementing dosing regimens leading to equivalent exposure

The requirements for implementing these alternative dosing regimens can be derived from the regulatory guidelines on the evaluation of drug—drug interactions and organ impairment on the pharmacokinetics of drugs.[39-44] These guidelines dictate the use of no-effect boundaries of exposure to determine clinically relevant changes in pharmacokinetics.[39,40] Based on the exposure—response relationship for efficacy and safety, an exposure range can be defined, within which no clinically relevant difference in efficacy and safety is expected. This exposure range is

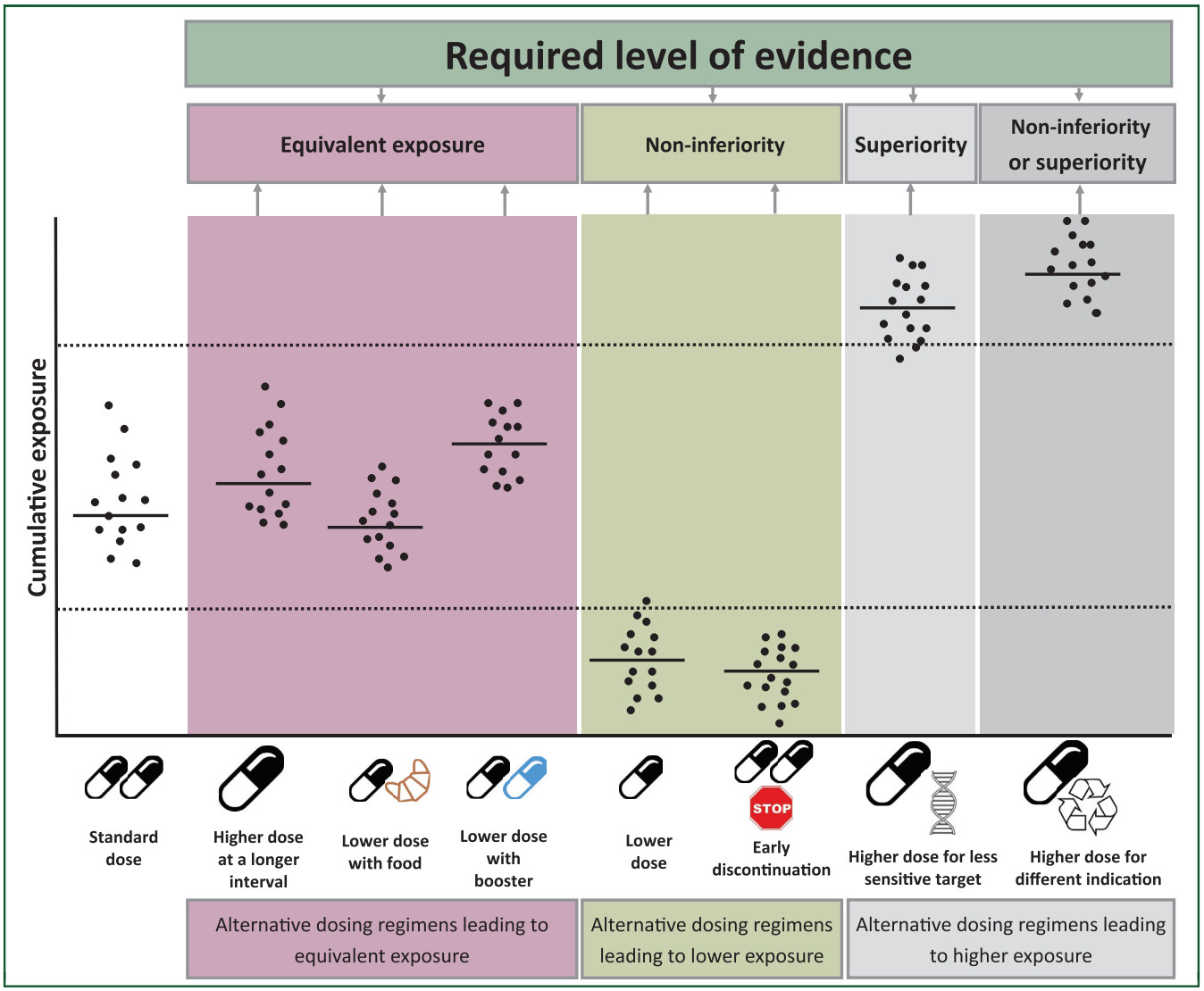

Figure 1. Required level of evidence needed for implementation of different types of alternative dosing regimens. The *y*-axis represents cumulative pharmacokinetic exposure. Dotted horizontal lines represent the clinical no-effect boundaries for exposure. On the *x*-axis different alternative dosing regimens are represented. These are categorized into three subtypes: leading to equivalent exposure (pink), lower or shorter exposure (green), or higher exposure (gray). Top bars indicate the proposed evidence required for implementation. The dots represent the relevant pharmacokinetic exposure parameter of alternative dosing regimens, chosen at random to illustrate the examples.

confined by the no-effect boundaries. For example, gefitinib has a significantly higher exposure when taken with food (AUC 132%) compared with fasted intake. This difference in exposure was considered not clinically relevant based on previous exposure—response analysis and therefore it can be taken with or without food.[45] Thus, no-effect boundaries demarcate equivalent exposure to either the fasted or fed intake of gefitinib, which are clinically equivalent. If knowledge on the exposure—response relationship is lacking, a conservative no-effect boundary of 80%-125% of the AUC is advised.[39,40]

To evaluate whether the pharmacokinetic exposure is within the defined no-effect boundaries, randomized cross-over studies are preferred. Pharmacokinetic interpatient variability is normally much larger than intrapatient variability. By using a cross-over design a much smaller group of patients, typically around 20, is required to show exposure within the no-effect boundaries. This is further explained by the guidance from the registration authorities.[46-48]

If the pharmacokinetic exposure and confidence interval of an alternative dosing regimen are within predefined no-effect boundaries, no further evaluation of treatment efficacy is required. If the exposure is outside these no-effect boundaries, further evidence on efficacy and/or safety is needed for implementation. Finally, once equivalence is demonstrated therapeutic drug monitoring can be considered to further optimize the exposure for the individual patient.

ALTERNATIVE DOSING REGIMENS LEADING TO LOWER OR SHORTER EXPOSURE

For targeted anticancer drugs currently overdosed due to tolerability-driven dose selection, lower dosages could be equally effective while being less toxic.[2] When this lower

Table 2. Alternative dosing regimens of anticancer drugs and recommendations for their implementation

Drug	Approved dosing regimen	Alternative dosing regimen	Available evidence	Translated into drug label	Author's recommendation	Reference
Alternative dosing leading to equivalent exposure						
Abiraterone	1000 mg fasted	250 mg fed	Exposure below bioequivalence margins + equivalent PSA change	No	Establish no-effect boundaries in exposure—response analysis + equivalent exposure	[14]
Atezolizumab	1200 mg Q3W	1680 mg Q4W 840 mg Q2W	Equivalent exposure and safety based on modeling	Yes	Implement in label agreement	[15]
Ceritinib	750 mg fasted	450 mg fed	Equivalent exposure and improved safety[16] Consistent efficacy[17]	Yes	Implement in label agreement	[16,17]
Cetuximab	250 mg/m^2 Q1W	500 mg/m^2 Q2W	Non-inferior efficacy	No	Implement in clinical practice	[9]
Erlotinib	150 mg QD	75 mg + ritonavir 200 mg QD	Comparable exposure in a single-dose PK study	No	Equivalent exposure needs to be demonstrated before implementation	[18]
Ibrutinib	140 mg QD	15 mg + itraconazole 200 mg QD	Comparable exposure in a single-dose PK study	No	Equivalent exposure needs to be demonstrated before implementation	[19]
Nivolumab	3 mg/kg Q2W	240 mg Q2W	Equivalent exposure based on modeling	Yes	Implement in label agreement	[20]
Nivolumab	240 mg Q2W	480 mg Q4W	Equivalent exposure based on modeling	Yes	Implement in label agreement	[21]
Pazopanib	800 mg fasted	600 mg fed	Equivalent exposure	No	Implement in clinical practice	[5]
Pembrolizumab	2 mg/kg Q3W	200 mg Q3W	Equivalent exposure based on modeling	Yes	Implement in label agreement	[22]
Pembrolizumab	200 mg Q3W	400 mg Q6W	Equivalent exposure based on modeling	Yes	Implement in label agreement	[23]
Sunitinib	50 mg 4 weeks on, 2 weeks off	50 mg 2 weeks on, 1 week off	Equivalent efficacy and improved safety	No	Implement in clinical practice	[24]
Alternative dosing regimens leading to lower or shorter exposure						
Cabazitaxel	25 mg/m^2	20 mg/m^2	Non-inferior efficacy + improved safety	Yes	Implement in label agreement	[25]
Dasatinib	70 mg BID	100 mg QD	Non-inferior efficacy	Yes	Implement in label agreement	[26]
Dasatinib	100 mg QD	50 mg QD	Similar efficacy + improved safety	No	Non-inferiority on clinical endpoints needs to be demonstrated before implementation	[27]
Imatinib	Until progression	Until undetectable BCR-ABL transcript levels	Meta-analysis of 12 cohort studies	No	Implement in clinical practice	[7]
Trastuzumab	12 months	6 months	Non-inferior efficacy	No	Implement in clinical practice	[8]
Alternative dosing regimens leading to higher exposure						
Imatinib	400 mg QD	400 mg BID for patients with GIST with KIT exon 9 mutation	Superior efficacy	No	Implement in clinical practice	[28]
Sunitinib	50 mg 4 weeks on, 2 weeks off	700 mg Q2W	Clinical trial ongoing	No	Superiority to standard-of-care needs to be demonstrated before implementation	NCT03909724

BID, twice daily; GIST, gastrointestinal stromal tumor; PK, pharmacokinetic; PSA, prostate specific antigen; QD, once daily; Q1W, every week; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks.

dosage leads to pharmacokinetic exposure within the no-effect boundaries, the level of evidence proposed in the previous section should be sufficient for implementation. Frequently knowledge on the exposure—response relationship is lacking, leading to selection of conservative no-effect boundaries. Consequently, lower dosages lead to a pharmacokinetic exposure below the no-effect boundaries, while equivalent efficacy can be expected as the drug is overdosed. These alternative dosing regimens will be discussed in the following section.

A significant proportion of the patients treated with new anticancer drugs experience treatment-related adverse events.[1] Because of adverse events, ~50% of the patients need a dose interruption, 26% need a dose reduction, and 10% permanently discontinue therapy.[1] A reduced dose or early discontinuation can result in fewer side-effects, while preserving efficacy. Furthermore, it can decrease the financial burden.

Subtypes of dosing regimens leading to lower or shorter exposure

As a result of the tolerability-driven dose selection, many of the currently approved anticancer drugs are dosed near the MTD, which has been established in relatively small studies over a short timeframe. This results in overdosed drugs that are poorly tolerated over a longer treatment period, while lower dosages might be as effective.[2] Dasatinib, a tyrosine kinase inhibitor, is used in the treatment of the chronic phase of chronic myeloid leukemia. It was originally approved at 70 mg twice daily (BID). Later, this dose was adjusted to 100 mg QD, which resulted in less hematological toxicity and fluid retention, while retaining efficacy.[26] Currently, an even lower dose of 50 mg QD is considered effective and safe for chronic myeloid leukemia.[27,49] In immunotherapy, several studies are investigating a lower

dose.[50] For example, pembrolizumab 300 mg instead of 400 mg every 6 weeks is tested in the DEDICATION-1/NVALT30 (EudraCT 2020-000493-15) trial. Equal efficacy of a lower dose is expected as phase I studies showed full target engagement at doses of 1 mg/kg Q3W, though two times this dose was registered.[51]

The treatment duration in patients with cancer has increased substantially over the past years. Chronic treatment with anticancer drugs leading to sustained side-effects impacts patient's quality of life. Early discontinuation is particularly interesting in the adjuvant setting and is, for example, proven feasible in patients with HER2-positive early breast cancer, in whom 6 months trastuzumab was shown equally effective as 12 months with less cardiotoxicity and fewer severe adverse events.[8,52] For anti-PD-1 immunotherapies initially given until disease progression, later trials supported the use for a predefined period of 2 years in specific cancers.[53] Table 2 lists various alternative dosing regimens leading to shorter or lower exposure.

Level of evidence required for implementing dosing regimens with lower or shorter exposure

A lower or shorter exposure does not guarantee comparable efficacy. Similar efficacy of these alternative dosing regimens should be demonstrated in a non-inferiority (NI) study, confirming that the alternative dosing regimen does not lead to worse treatment outcomes (median and confidence intervals outside the predefined NI margin) compared with the approved dosing regimen.[54,55] This NI margin should be substantiated with the effect size and variation encountered in earlier clinical studies. Smaller NI margins give more certainty on the outcome, but require a larger sample size. Larger NI margins and smaller sample sizes can be accepted when the alternative dosage results in better tolerability or patient convenience, in line with near-equivalence studies.[54-57] However, when data to substantiate smaller or larger NI margins are lacking, a default NI margin of 20% could be used, in line with the average NI margin for survival studies in the oncology setting.[57] If non-inferior outcomes are demonstrated, the alternative dosing regimen with a lower or shorter exposure can be implemented in clinical practice.

ALTERNATIVE DOSING REGIMENS LEADING TO HIGHER EXPOSURE

Although many anticancer drugs are dosed near or at the MTD, higher exposure might be tolerable and even beneficial in a subset or different patient population. For these patients, alternative dosing regimens leading to higher exposure are developed.

Subtypes of dosing regimens leading to higher exposure

Anticancer drugs are developed and tested in relatively unselected patient populations. However, in the era of personalized medicine and genetic testing, patients with less sensitive tumors can be identified. These tumors may require higher drug exposure levels, which can be reached by an alternative dosing regimen. For example, imatinib is dosed at 400 mg QD in patients with gastrointestinal stromal tumors. However, in patients with KIT exon 9-mutated gastrointestinal stromal tumor the higher dose of 400 mg BID leads to better treatment exposure and outcomes.[28]

Furthermore, a higher pharmacokinetic exposure might be necessary for different tumor types or locations. Intermittent high-dose sunitinib leading to higher peak concentrations has shown promising results in patients with advanced colorectal cancer.[58]

Level of evidence required for implementing dosing regimens leading to higher exposure

As alternative dosing regimens leading to higher pharmacokinetic exposure might increase toxicity, acceptable tolerability must be shown. Furthermore, the alternative dose regimen leading to higher exposure levels in patients with less sensitive oncogenic mutations must prove superior efficacy compared with the standard dose. If the alternative dosing regimen is tested for a different indication, the treatment needs to prove superiority compared with placebo or NI compared with standard of care. Table 2 lists various alternative dosing regimens leading to higher exposure.

FUTURE DIRECTIONS

Up until now, dose selection of most anticancer drugs is based on relatively small dose finding studies over a short timeframe with the aim to establish a safe dose for further research. As a result, after market authorization, multiple possibilities are within reach to improve the dosing regimen. We here provide practical recommendations for the level of evidence required for implementing alternative dosing regimens of anticancer drugs from a clinical pharmacological perspective, summarized in Figure 1.

The FDA recently implemented the Project Optimus, which will make clinical pharmacology the solid base for dosing regimen selection during anticancer drug development.[10] Instead of dose selection based on tolerability, drug developers are encouraged to use exposure—response analyses for dose finding and dose optimization. This will likely lead to better characterization of the optimal dose of new drugs before market authorization. However, this project does not include the large number of approved anticancer drugs currently on the market and potentially dosed suboptimally.

For already approved drugs, it remains important that alternative dosing regimens from investigator-driven studies are also evaluated to facilitate broader implementation of these data. Ideally, the dosing strategies from these studies should be incorporated in the drug label. However, only authorization holders can request label changes and authorization holders may not be eager to optimize the

dosage after approval. In this light, the FDA has started Project Renewal, which aims to update outdated labeling information of registered oncology drugs based on relevant scientific evidence from published literature.[59] This could potentially lead to label updates with new indications and dosing regimens. Project Renewal is currently a pilot focusing on generic drugs approved several decades ago with significant off-label use.[59] This project could also be promising for academia-driven dose optimization studies for more novel anticancer drugs.

We propose the use of our recommendations to implement alternative dosing regimens in practice. A legal framework adopting this guideline may facilitate this. Moreover, the efforts to optimize dosing regimens should not overshadow the equally important efforts still needed to further optimize the dose for the individual patient by reducing the interindividual variability in pharmacokinetic exposure.

CONCLUSION

Alternative dosing regimens can optimize cancer therapy by improving the risk-to-benefit ratio of currently approved anticancer drugs. In this perspective recommendations are formulated for evaluation of alternative dosing regimens based on existing guidelines from regulatory authorities. These recommendations could pave the way for implementation of optimized dosing regimens and thereby contribute to improved and sustainable anticancer therapy.

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