Therapeutic Drug Monitoring of Protein Kinase Inhibitors in the Treatment of Non-small Cell Lung Cancer

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Abstract: Targeted therapy with protein kinase inhibitors (PKIs) represents one of the important treatment options for non-small cell lung cancer (NSCLC). It has contributed to improve patients' survival and quality of life significantly. These anticancer drugs are administrated orally in flat-fixed doses despite the well-known large interpatient pharmacokinetic variability and the possible need for dose individualization. To optimize and individualize dosing of PKIs, and thereby increasing the effectiveness and safety of the treatment, therapeutic drug monitoring (TDM) is the most frequently mentioned method. Unlike other areas of medicine, TDM has been rather exceptional in oncological practise since there is a little evidence or no data for concentration-effect relationships of PKIs. Therefore, the aim of this review is to summarize the pharmacokinetic characteristics of PKIs and provide the evidence supporting the use of TDM for personalised treatment of patients with NSCLC.

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Introduction

Twenty years ago, in addition to conventional chemotherapy, targeted molecules began to be used in lung cancer treatment, which significantly contributed to prolonged and improved lives of patients (Huang et al., 2020). Nevertheless, lung cancer remains the leading cause of cancer-related death in both sexes worldwide (Siegel et al., 2022).

Protein kinase inhibitors (PKIs) are one of the widely represented drugs for targeted anticancer treatment. In the pharmacotherapy of lung cancer, PKIs are used in patients with non-small cell lung cancer (NSCLC), that represents about 80% of all cases of lung cancer (Kastelijn et al., 2019). PKIs are enzyme inhibitors that disrupt the signalling pathway in the cell by blocking the action of one or more of the specific kinases, mostly tyrosine kinases. Such an inhibition affects the proliferation and survival of the tumour cells (Arora and Scholar, 2005). Targeted PKI treatment is indicated for patients in whom the presence of driving mutations, especially activating mutations of EGFR (epidermal growth factor receptor) and ALK (anaplastic lymphoma kinase), is identified (Kastelijn et al., 2019). More than 50 tyrosine kinase inhibitors are currently approved for the treatment of various malignancies, and the number is expected to increase (Cohen et al., 2021).

These small molecule inhibitors show high inter-individual variability in some pharmacokinetic parameters, which translates into significantly different drug concentrations in blood (de Wit et al., 2015; Petit-Jean et al., 2015; Fahmy et al., 2021). For instance, with gefitinib, the first tyrosine kinase inhibitor used in the treatment of NSCLC, up to 16-fold interindividual variability of exposure with repeated administration, is reported (Zhao et al., 2011). Regardless, the "one-dose-fits-all" approach to PKI dosing still dominate. Consequently, some patients are at risk of treatment failure in the case of underdosing or increased toxicity in the case of overdose leading to treatment-limiting side effects (Lankheet et al., 2014; Menz et al., 2021). Additionally, due to oral administration of PKIs, high demanding patients' adherence may also contribute to significant differences in the therapeutic response of these drugs in individuals (Greer et al., 2016).

In context of personalized cancer therapy, therapeutic drug monitoring (TDM) appears to be a valuable tool to tailor the treatment of the individual patients. TDM may help to adapt PKIs dosage regimen to a specific patient based on the measured concentrations of drugs in the blood at designed intervals (Kang and Lee, 2009). This method offers the possibility to reduce toxicity while maintaining efficacy (Kang and Lee, 2009; Groenland et al., 2019). Unlike the common practice of determining the levels of certain groups of drugs, such as antibiotics, antiepileptics, immunosuppressants, TDM is performed exceptionally for oncology drugs (Clarke et al., 2021). For now, one of the limitations is the lack of information about relationship among plasma concentration, efficacy and toxicity of most PKIs (Mueller-Schoell et al., 2021). However, positive results with individualized imatinib

Table 1 – Basic characteristic of EMA- and FDA-approved small protein kinase inhibitors in NSCLC therapy (by January 2023)

PKIs	Target kinases	Type of kinase inhibitor	Recommend dose regimen (mg)	Fasted or Fed state
Afatinib	EGFR, HER2	Tyrosine	40 od	Fasted 3 h before or 1 h after meal
Alectinib	ALK	Tyrosine	600 bid	Fed
Brigatinib	ALK	Tyrosine	90 od for the first 7 d 180 od from 8th d	NI
Capmatinib	MET	Tyrosine	400 bid	NI
Ceritinib	ALK, ROS1	Tyrosine	450 od	Fed
Crizotinib	ALK, ROS1, MET	Tyrosine	250 bid	NI
Dabrafenib*	BRAF V600E	Serine/ Threonine	150 bid	Fasted 1 h before or 2 h after meal
Dacomitinib	EGFR, HER2	Tyrosine	45 od	NI
Entrectinib	ROS1, TRK, ALK	Tyrosine	600 od	NI
Erlotinib	EGFR	Tyrosine	150 od	Fasted 1 h before or 2 h after meal
Gefitinib	EGFR	Tyrosine	250 od	NI
Larotrectinib	TRK	Tyrosine	100 bid	NI
Lorlatinib	ALK, ROS1	Tyrosine	100 od	NI
Mobocertinib	EGFR	Tyrosine	160 od	NI
Osimertinib	EGFR T790M	Tyrosine	80 od	NI
Pralsetinib	RET	Tyrosine	400 od	Fasted 2 h before or 1 h after meal
Selpercatinib	RET	Tyrosine	< 50 kg 120 bid > 50 kg 160 bid	NI
Tepotinib	MET	Tyrosine	450 od	Fed
Trametinib*	MEK1/2	Serine/ Threonine	2 od	Fasted 1 h before or 2 h after meal

PKIs are listed alphabetically; source: EPAR – www.ema.europa.eu; NDA – www.fda.gov
*used in combination with dabrafenib or trametinib in NSCLC therapy; ALK – anaplastic lymphoma kinase; bid – twice daily; BRAF – v-raf murine sarcoma viral oncogene homolog B1; d – day; EGFR – epidermal growth factor receptor; EMA – European Medicines Agency; FDA – US Food and Drug Administration; HER2 – human epidermal growth factor receptor 2; MEK – mitogen-activated protein kinase; MET – mesenchymal-epithelial-transition; NSCLC – non-small cell lung cancer; od – once daily; PKIs – protein kinase inhibitors; RET – rearranged during transfection; NI – not important; ROS1 – proto-oncogene 1; TRK – tropomyosin receptor kinase

dosage using TDM have been demonstrated and its guideline has also been published (Clarke et al., 2021).

Therefore, the aim of this review is to summarize an overview of the current knowledge and evidence of the possibilities to tailor the dosage of selected PKIs using TDM, including the necessary pharmacokinetic parameters for personalized pharmacotherapy of patients with NSCLC.

Literature search

PubMed searches were performed using Boolean logic operations till January 2023. Search terms "pharmacokinetics", "therapeutic drug monitoring", "TDM", "individualized dosing", "exposure-response" and "exposure response" were combined with the name of the individual PKI registered by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) in NSCLC treatment to identify relevant references. Results were limited to studies in adult humans and English full-text articles published until January 2023. A total of 864 reports were identified from the initial literature search, out of which 15 relevant publications were found.

In addition, the references listed in the relevant articles were also examined and registration information from the EMA and FDA was reviewed.

Pharmacokinetics of currently approved PKIs in NSCLC

List of EMA- and FDA-approved small protein kinase inhibitors in NSCLC therapy with its basic characteristic is summarized in Table 1. Compared to traditional intravenously applied cytotoxic drugs, PKIs are administrated orally on daily basis, particularly once a day, enabling outpatient treatment. An overview of pharmacokinetic (PK) properties of the selected PKIs is shown in Table 2.

Oral bioavailability ranges from 34% for larotrectinib up to 95% for dabrafenib. Some PKIs such as afatinib, dabrafenib, trametinib and erlotinib are recommended to be taken in the fasting state. The reason is that a high fat meal reduces C_{max} and AUC (area under concentration-time curve) and *vice versa* for erlotinib (approximately twofold higher exposure in fed condition) (Ling et al., 2008).

Most PKIs reach the maximum plasma concentration relatively fast (1–4 h), tepotinib is the only exception (8 h). The drugs are extensively distributed into tissues and are highly protein bound to alpha-1-acid glycoprotein and albumin resulting in a large volume of distribution and a long half-life.

Most of them undergo extensive metabolism, mainly via CYP3A4 with secondary contribution of other CYP enzymes. The exception is afatinib, which metabolism is negligible. The first mentioned PKIs are substrate of cytochrome P450 enzymes, the drug-drug interaction potential is considered high. Their exposure may be affected by concomitant use of other drugs that act on the same metabolic ways. Additionally, some of these drugs undergo auto-inhibition or auto-induction that make their metabolism at steady-state less predictable. Finally, cigarette smoking

has been known to induce CYP1A enzyme, thus significantly decreasing of erlotinib concentration, which is particularly important in the population of lung cancer patients (Petit-Jean et al., 2015).

All mentioned PKIs are predominantly excreted in the feces, with only a minor fraction being eliminated with the urine. These drugs are excreted as metabolites, except afatinib. Relatively large fraction of the dose of alectinib, ceritinib, crizotinib, pralsetinib and tepotinib may be excreted as parent compound.

Therapeutic drug monitoring of PKIs

Variability observed in clinical response between individuals ranges between 24–84% (Groenland et al., 2019). A broad range of factors, such as genetic heterogeneity of drug targets, pharmacogenetic background of the patient, patient's adherence to treatment, food intake, drug formulation, concomitant medication, and others, influence the absorption, distribution, metabolism, and excretion of drugs (Groenland et al., 2019; Janssen et al., 2020). Dose individualization through measurement of drug concentrations might reduce the interpatient variability in exposure and thereby favourably influence treatment outcome (de Wit et al., 2015).

In addition to individualized dosing, TDM can be used to diagnose unexpected toxicities or lack of therapeutic response, to detect and monitor drug interactions, to guide underdosing during dosage reduction or withdrawal of therapy, as well as to control adherence treatment (Kang and Lee, 2009). There are several general criteria for drugs to be suitable for TDM: availability of validated sensitive bioanalytical method, unpredictable and wide inter-individual pharmacokinetic variability in systemic exposure (which affects efficacy and tolerability), narrow therapeutic index, long-term therapy and correlation between plasma drug concentrations and clinical effects (Lankheet et al., 2014; Yu et al., 2014).

Proven relationship between exposure and response is fundamental for attempting to conduct TDM with added value (de Wit et al., 2015). Associations between drug concentration and therapeutic response have been summarized in several recent reviews (Verheijen et al., 2017; Janssen et al., 2020; Fahmy et al., 2021; Mueller-Schoell et al., 2021). Unfortunately, most PKIs don't have well defined thresholds for efficacy and toxicity, yet. In the absence of evidence-based TDM targets, Verheijen et al. (2017) suggest using the average population exposure of the approved effective dose, because the TDM targets of PKIs on average correspond to about 80% of the observed mean or median trough concentration (C_{min}). Proposed pharmacokinetic targets of PKIs are presented in Table 3.

To personalize PKIs dosing through TDM, the measurement of steady-state trough or just before the next dose concentration is often used in clinical practice (Verheijen et al., 2017). Trough levels are more practical than area under the plasma concentration-time curve due to daily dose and long half-life of PKIs and are less to be influenced by absorption and distribution problems (Kang and Lee, 2009). Ideally,

Table 2 – Summary of steady-state pharmacokinetics of PKIs after multiple daily oral doses in cancer patients

PKIs	Absorption			AUC (ng×h/ml)	Distribution	
	C_{max} (ng/ml)	T_{max} (h)	F (%)		Vd/F (l)	PPB (%)
Afatinib	38	3	92; ↓ with meal	631	2,870	95.0
Alectinib	676	4	37 ↑ with meal	5,400	4,016	99.0
Brigatinib	552 (90 mg) 1,452 (180 mg)	2	ND	8,165 (90 mg) 20,276 (180 mg)	153 (180 mg)	66.0
Capmatinib	4,780	1–2	70	20,200	164	96.0
Ceritinib	674 (750 mg)	4–6[a]	ND ↑ with meal	14,000 (750 mg)	4,230[a] (750 mg)	97.0
Crizotinib	327	4	43	3,084	1,177[b] (50 mg)	91.0
Dabrafenib	1,478	2	95 ↓ with meal	4,341	70.3	99.7
Dacomitinib	108	6	80	2,342	1,889[b] (20 mg)	98.0
Entrectinib	3,130 (nM)	4–6[a]	>50	48,000 (nM×h)	551 (M5-81)	99.0
Erlotinib	1,995	4	59 ↑ with meal	41,300	232	95.0
Gefitinib	104.5[c]	3–7	59	2,631[c]	1,400	91.0
Larotrectinib	788	1	34	4,351	374[a]	70.0
Lorlatinib	577	2	81	5,650	390[a]	66.0
Mobocertinib	70.4	4	37	862[ac]	3,510	99.0
Osimertinib	501 nmol/l	6	ND	11,258 nmol/l	986	99.0
Pralsetinib	2,830	2–4	ND	43,900	268	97.0
Selpercatinib	2,980 (180 mg)	2	73	51,600 (180 mg)	323[a]	97.0
Tepotinib	1,291	8	72 ↑ with meal	27,438	34.6[b]	98.0
Trametinib	22.2	1.5	72; ↓ with meal	370	214	97.4

PKIs are listed alphabetically. [a]single dose administration; [b]single intravenous dose; [c]healthy volunteers
AUC – area under concentration-time curve; CL/F – apparent clearance; C_{max} – maximum concentration; F – oral bioavailability; ND – not determined; OHD – hydroxy-dabrafenib; PKIs – protein kinase inhibitors; PPB – plasma protein binding; T_{max} – time to reach C_{max}; $T_{1/2}$ – half-life; UD – unchanged drug; Vd/F – apparent volume of distribution

Metabolism	$T_{1/2}$ (h)	CL/F (l/h)	Excretion		References
Enzymes (main metabolite)			Feces (%)	Urine (%)	
negligible	36.3	64.2	85% UD	4% UD	Afatinib; Wind et al. (2017)
CYP3A4 (M4)	32	502	98 (84% UD 9% as M4)	<1	Alectinib; Hirota et al. (2019)
in vitro CYP2C8; CYP3A4	25	12.7 (180 mg)	65 (41% UD)	25 (86% UD)	Brigatinib; Hirota et al. (2019)
CYP3A4	6.54	19.8	78 (42% UD)	22	Capmatinib
in vitro CYP3A	41[a] (750 mg)	33 (750 mg)	92 (68% UD)	1.3	Ceritinib; Hirota et al. (2019)
in vitro CYP3A	42[a]	81	63 (53% UD)	22 (<2% UD)	Crizotinib; Hirota et al. (2019)
CYP2C8; CYP3A4 (OHD)	8	34.4	71	23	Dabrafenib
CYP2D6	70.3	26.9	78.8 (20% UD)	3.2 (<1% UD)	Dacomitinib
CYP3A4 (M5)	20 (M5-40)	19.6 (M5-52.4)	83 (22% as M5)	3	Entrectinib
CYP3A4/5 (OSI-420); CYP1A2	36.2	4.47	90 (1% UD)	9 (0.3% UD)	Erlotinib
CYP3A4; CYP2D6 (M523595)	41[b]	30	80.8 (4% UD)	3.6 (0.5% UD)	Gefitinib
CYP3A4	2.9[a]	98[a]	58 (5% UD)	39 (20% UD)	Larotrectinib
CYP3A4; UGT1A4	23.6[a]	17.7	41 (9% UD)	48 (<1% UD)	Lorlatinib
CYP3A (AP32960)	17.6	108	76 (6% UD)	3.57 (1.3% UD)	Mobocertinib; Zhang et al. (2021)
in vitro CYP3A4/5	48	14.2	67.8 (1.2% UD)	14.2 (0.8% UD)	Osimertinib; Brown et al. (2017)
in vitro CYP3A4; CYP2D6; CYP2A1	22.2	9.1	73 (66% UD)	6 (4.8% UD)	Pralsetinib (2020, 2021)
CYP3A4	37[ac]	6	69 (14% UD)	24 (12% UD)	Selpercatinib
in vitro CYP3A4; CYP2C8	32	20.4	85 (50% UD)	15 (50% UD)	Tepotinib
non-CYP450	93.6–115.2	5.4	80	<0.1 UD	Trametinib

Table 3 – Summary of proposed pharmacokinetic targets of PKIs defined as trough plasma concentration

PKIs	Proposed target (ng/ml)	Mean/median exposure (ng/ml)	Exposure-response relationship	Associated para-meter(s)	References
Afatinib	NA	$C_{min,ss}$ ≥ 14.4	no		Verheijen et al. (2017), Wind et al. (2017)
Alectinib	≥ 435	$C_{min,ss}$ = 517	yes	PFS	Groenland et al. (2021)
Brigatinib	NA	$C_{min,ss}$ = 226 (90 mg) 520 (180 mg)	yes	PFS, OS	Brigatinib; Mueller-Schoell et al. (2021)
Capmatinib	NA	$C_{min,ss}$ = 562.42	not yet characterized		Capmatinib
Ceritinib	NA	$C_{min,ss}$ = 871 (750 mg)	inconclusive	ORR	Ceritinib; Verheijen et al. (2017)
Crizotinib	≥ 235	$C_{min,ss}$ = 244	yes	PFS	Groenland et al. (2021)
Dabrafenib	NA	$C_{min,ss}$ = 46.6	no		Dabrafenib; Ouellet et al. (2014)
Dacomitinib	NA	$C_{min,ss}$ = 73.1	inconclusive	PFS, tumour shrinkage	Dacomitinib
Entrectinib	NA	NA	no		Entrectinib
Erlotinib	> 500	$C_{min,ss}$ = 1,011	no		Hidalgo et al. (2001), Lankheet et al. (2014), Kenmotsu et al. (2022)

samples should be taken at steady-state, which is after 5 half-lives, e.g. 8 days for erlotinib.

Currently, validated analytical method combining liquid chromatography with tandem mass spectrometry is applied to facilitate therapeutic monitoring of the PKIs in routine practice (Zhou et al., 2021).

Afatinib

The relationship between plasma drug exposure and response for afatinib is sparse. No correlation between trough concentration and efficacy was found (Afatinib). Nevertheless, daily doses under 20 mg affected treatment effectiveness in terms of a significantly shorter progression free survival (PFS) (Lim et al., 2018). In contrast, the relationship between afatinib trough plasma concentrations and the occurrence of the adverse events were reported. The severity of diarrhea and rash positively

PKIs	Proposed target (ng/ml)	Mean/median exposure (ng/ml)	Exposure-response relationship	Associated parameter(s)	References
Gefitinib	≥ 200	$C_{min,ss}$ = 266	yes	OS	Zhao et al. (2011), Fahmy et al. (2021), Mueller-Schoell et al. (2021)
Larotrectinib	NA	$C_{min,ss}$ = 33	no		Larotrectinib
Lorlatinib	NA	$C_{min,ss}$ = 114.97	no		Chen et al. (2021)
Mobocertinib	NA		no		Gupta et al. (2022)
Osimertinib	NA	$C_{min,ss}$ = 166	no		Brown et al. (2017), Mueller-Schoell et al. (2021)
Pralsetinib	NA	$C_{min,ss}$ = 1,150	no		Pralsetinib (2020)
Selpercatinib	NA		not yet characterized		Selpercatinib
Tepotinib	NA		not yet characterized		Xiong et al. (2022)
Trametinib	≥ 10.6	C_{min} = 12.1	yes	PFS	Trametinib; Ouellet et al. (2016)

PKIs are listed alphabetically; NA – not available; ORR – objective response rate; OS – overall survival; PFS – progression free survival; PKIs – protein kinase inhibitors

correlated with higher exposure of afatinib (Wind et al., 2017). Due to undefined TDM target, Verheijen et al. (2017) proposed to use a steady-state C_{min} 14.4–27.4 ng/ml of the standard dose of afatinib 40 mg.

Alectinib

The previously proposed C_{min} threshold of 435 ng/ml for alectinib was proven to prolong PFS in observational study with NSCLC patients (Groenland et al., 2021). The authors of the study state that TDM of alectinib should be part of the clinical routine (Groenland et al., 2021).

Brigatinib

Threshold for brigatinib has not been established yet. Exposure-response analyses showed positive trends in association between exposure to brigatinib represented mean of trough concentrations at steady-state and PFS and overall survival (OS) (Brigatinib).

Capmatinib

The exposure-response relationship was inconclusive due to small number of patients (Capmatinib).

Ceritinib

The results of exposure-response analyses for efficacy did not show a clear relationship between systemic exposure and objective response rate (ORR) or PFS in ALK-positive NSCLC patients. Only a trend towards higher ORR with higher C_{min} was reported (Ceritinib; Verheijen et al., 2017). No threshold for ceritinib has been proposed so far. Meanwhile, ceritinib C_{min} could be interpreted in reference to the mean C_{min} of 871 ng/ml at dosage 750 mg od as target for TDM (Ceritinib; Verheijen et al., 2017).

Crizotinib

Significant exposure-therapeutic efficacy correlations have been described for crizotinib before. In an observational study in ALK-positive NSCLC patients, exposure-response (E-R) analyses were performed using a previously proposed C_{min} threshold of ≥ 235 ng/ml for crizotinib (Groenland et al., 2021). In this study, the ≥ 235 ng/ml threshold was associated with longer PFS. As well as for alectinib, the authors of the study state that TDM of crizotinib should be part of the clinical routine (Groenland et al., 2021).

Dabrafenib

No consistent data for dabrafenib exposure-response relationship exist thus far. Recent study could not prove significant correlation between dabrafenib (measured as only parent drug) exposure and response (Raynal et al., 2022) in patients treated for metastatic melanoma. Verheijen et al. (2017) in the review suggested to target C_{min} 99.6 ng/ml for guided dosing, which was based on the median sum of parent dabrafenib and its active hydroxyl metabolite in melanoma patients.

Dacomitinib

Only limited exposure-response data exists for dacomitinib in patients with locally advanced/metastatic NSCLC with EGFR-activating mutations. Drug exposure suggested slightly positive relationship E-R for PFS and statistically significant for tumour shrinkage (Dacomitinib).

Entrectinib

No apparent relationship between entrectinib parent (or M5 metabolite) steady-state exposure and efficacy was observed in E-R analyses in 76 patients with NTRK- (neurotrophic tyrosine receptor kinase), ROS1- (proto-oncogene 1), or ALK-positive, locally advanced or metastatic tumours. Results of the analyses suggested that doses higher than 600 mg are unlikely to produce greater efficacy (Mercier et al., 2022).

Erlotinib

Steady-state concentration ranged from 580 to 1,820 ng/ml in standard dosing regimen at 150 mg per day (Hidalgo et al., 2001). At this dosage in phase I study,

the values of the minimum concentration at steady-state exceeded 500 ng/ml in the majority of patients (Hidalgo et al., 2001). In preclinical studies, plasma concentration of 500 ng/ml showed EGFR inhibition associated with an antiproliferative activity (Hidalgo et al., 2001). This value was reported as a target threshold for erlotinib in several reviews (Yu et al., 2014; Verheijen et al., 2017; Mueller-Schoell et al., 2021) despite of lacking the relationship between efficacy and exposure of total and unbound erlotinib in patients with EGFR-mutated NSCLC (Kenmotsu et al., 2022).

Gefitinib

In study with NSCLC patients, overall survival was linked to gefitinib trough concentration. Patients with C_{min} ≥ 200 ng/ml had significantly higher overall survival (14.6 months compared to 4.7 months) (Zhao et al., 2011). Yet, a later retrospective analysis in NSCLC patients disputed it (Xin et al., 2015). The PFS for the group patients with lower trough concentration < 200 ng/ml were not inferior to patients with higher (C_{min} ≥ 200 ng/ml) trough concentration (Xin et al., 2015). For now, a threshold C_{min} of ≥ 200 ng/ml for TDM gefitinib is reported in the most recent reviews (Fahmy et al., 2021; Mueller-Schoell et al., 2021).

Larotrectinib

Larotrectinib exposure did not have a statistically significant effect on the probability of a response (Larotrectinib).

Lorlatinib

The E-R analysis for efficacy was not statistically significant for either efficacy end points (ORR, intracranial ORR) in patients with NSCLC (Chen et al., 2021).

Mobocertinib

In the exposure-efficacy analyses, systemic exposure based on the molar sum of exposures to mobocertinib and its active metabolites was not a statistically significant predictor of clinical response (ORR) (Gupta et al., 2022).

Osimertinib

No evidence of relationship between osimertinib exposure (AUC_{ss}) and efficacy was observed at the dose range (20–240 mg) studied in patients with NSCLC (Brown et al., 2017). Interestingly, in recent study, increased osimertinib plasma exposure was associated with higher risk of death (shorter PFS and OS in unselected NSCLC patients) (Rodier et al., 2022). In the absence of an exposure-response target, the geometric mean C_{min} of 166 ng/ml at approved dose of 80 mg od (once daily) could be used as a reference to guide TDM (Verheijen et al., 2017; Mueller-Schoell et al., 2021).

Pralsetinib
Results from registration-enabling study in patients with NSCLC revealed no relevant or consistent relationships between increasing pralsetinib exposure and efficacy or safety endpoints. However, pralsetinib mean C_{trough} of 1,150 ng/ml with the 400 mg od dose was associated with rapid declines in brain lesion size and prevention from developing new central nervous system metastases during the study. This value was close to the predicted brain IC90 of pralsetinib for rearranged during transfection (RET) inhibition in humans (1,514 ng/ml) (Pralsetinib, 2020).

Selpertinib
The exposure-response relationship is largely unknown (Selpercatinib).

Tepotinib
The relationships between exposure and response for tepotinib is inconclusive because of the limited data. No clear association of tepotinib exposure (AUC) with efficacy and safety was observed in study by Xiong and his colleagues (2022).

Trametinib
Population pharmacokinetic analysis demonstrated association between clinical efficacy and trametinib trough concentrations (Ouellet et al., 2016). Patients with observed C_{min} above the median 10.6 ng/ml in phase II had longer PFS than those below median. This was not confirmed in phase III, where median was higher (13.6 ng/ml) (Ouellet et al., 2016). On the other hand, trametinib C_{min} threshold of 10.6 ng/ml is consistent with its preclinical target concentration of 10.4 ng/ml that inhibits the MEK (mitogen-activated protein kinase) pathway (Ouellet et al., 2016). Noted in study by Ouellet et al. (2016), exposure-response relationship was evaluated only for trametinib alone, not for combination therapy with dabrafenib. However, recent study did not confirm the above-mentioned positive relationship when combined with dabrafenib (Goldwirt et al., 2021).

Discussion and Conclusion

Current fixed dosing strategy is associated with decreased efficacy or on the other hand causing unnecessary toxicities (Lankheet et al., 2014; Groenland et al., 2019). There is growing evidence for potential benefits of dosing adjustment based on pharmacokinetic targets in treatment not only of lung cancer with most PKIs. The consensus guideline for TDM of imatinib has been already developed (Clarke et al., 2021). Positive examples of treatment optimalization and individualization of PKIs from practice in patients with lung cancer are emerging (Catalán-Latorre et al., 2021).

We have summarized the available evidence on average C_{min} and proposed targets of PKIs for treatment of patients with NSCLC. Unfortunately, for a considerable number of PKIs, statistically significant exposure-response correlations are still lacking. Likewise, most of pharmacokinetic targets have not been established, yet, or they are

waiting to be validated in prospective studies. Currently, for none of the discussed agents, TDM is performed as the standard of care.

Despite the mentioned unknows, provided data could be beneficial in cases of suspected nonadherence to therapy, pharmacokinetic drug-drug interactions, or unexpected toxicity (Groenland et al., 2019). After selecting the most effective drug for a specific tumour type, dose individualization could further help in the personalized treatment of NSCLC patients.

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