

# Pharmacokinetic-Based Drug–Drug Interactions with Anaplastic Lymphoma Kinase Inhibitors: A Review

This article was published in the following Dove Press journal:  
*Drug Design, Development and Therapy*

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**Abstract:** Anaplastic lymphoma kinase (ALK) inhibitors are important treatment options for non-small-cell lung cancer (NSCLC), associated with ALK gene rearrangement. Patients with ALK gene rearrangement show sensitivity to and benefit clinically from treatment with ALK tyrosine kinase inhibitors (ALK-TKIs). To date, crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, and entrectinib have received approval from the US Food and Drug Administration and/or the European Medicines Agency for use during the treatment of ALK-gene-rearrangement forms of NSCLC. Although the oral route of administration is convenient and results in good compliance among patients, oral administration can be affected by many factors, such as food, intragastric pH, cytochrome P450 enzymes, transporters, and p-glycoprotein. These factors can result in increased risks for serious adverse events or can lead to reduced therapeutic effects of ALK-TKIs. This review characterizes and summarizes the pharmacokinetic parameters and drug–drug interactions associated with ALK-TKIs to provide specific recommendations for oncologists and clinical pharmacists when prescribing ALK-TKIs.

**Keywords:** ALK, TKIs, NSCLC, PK, drug–drug interactions

## Introduction

Lung cancer is one of the most common and lethal malignancies worldwide, and non-small cell lung cancer (NSCLC) is the most frequently occurring form of lung cancer.<sup>1</sup> NSCLC has been shown to be driven by various activated oncogenes.<sup>2</sup> NSCLC was first associated with activating mutations in the epidermal growth factor receptor (EGFR).<sup>3</sup> Because of the high clinical response rates to EGFR inhibitors among patients with NSCLC associated with EGFR mutations, the detection of activating mutations in EGFR and the utilization of EGFR inhibitors introduced a new therapeutic strategy to combat NSCLC.<sup>4</sup> In addition to mutations in EGFR, mutations in anaplastic lymphoma kinase (ALK) have been associated with NSCLC.<sup>5</sup> ALK gene rearrangements occur in approximately 5% of NSCLC patients, indicating that ALK may represent a new and promising molecular target for NSCLC treatment.<sup>6</sup> To date, several ALK tyrosine kinase inhibitors (ALK-TKIs) have been developed and are widely available in clinical practice, some of which have received approval by the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA),<sup>7</sup> such as crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, and entrectinib.

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All ALK-TKIs are administered orally, which makes administration flexible and convenient and improves quality of life. However, despite these advantages, the oral route of administration also increases the risk of potential drug–drug interactions (DDIs), leading to high interpatient variability and subsequent risks for increased toxicity and/or reduced treatment efficacy.

DDIs can be classified into pharmacodynamic DDIs and pharmacokinetic (PK) DDIs.<sup>8</sup> PK DDIs are defined as drug interactions that affect absorption, distribution, metabolism, and excretion, leading to the altered bioavailability of a drug and possible unfavorable outcomes.<sup>9</sup> Pharmacodynamic DDIs refer to interactions during which active compounds alter pharmacological effects, which can be additive, antagonistic, or synergistic.<sup>10,11</sup>

The primary objective of this review article is to present an overview of existing PK and DDI data for each of the FDA- and EMA-approved ALK-TKIs. In addition, we will provide specific recommendations designed to guide oncologists and clinical pharmacists through the process of managing DDIs during treatment with ALK-TKIs.

## PK Parameters of ALK-TKIs

Crizotinib is a first-generation ALK-TKI, ceritinib, alectinib, and brigatinib are second-generation ALK-TKIs, and lorlatinib is a third-generation ALK-TKI. For entrectinib, it is a potent oral inhibitor of the tyrosine kinases tropomyosin receptor kinases (TRK) A/B/C, c-ros oncogene 1 (ROS1), and ALK. After oral intake, the median maximum plasma concentration ( $C_{max}$ ) of crizotinib, ceritinib, alectinib, and entrectinib are reached from 4 to 6 hours, whereas the median times to achieve  $C_{max}$  for brigatinib and lorlatinib are 1 to 4

hours and 1.2 to 2 hours, respectively.<sup>12–24</sup> Among the six existing ALK-TKIs, lorlatinib has been shown to have the highest bioavailability (81%).<sup>21</sup> For lorlatinib,<sup>23</sup> 66% is bound to plasma proteins, whereas greater than 90% of the other five ALK-TKIs are bound to plasma proteins. All six ALK-TKIs have been demonstrated to be well-distributed in tissues. Crizotinib and ceritinib have been associated with poor central nervous system (CNS) penetration, whereas alectinib, brigatinib, lorlatinib, and entrectinib have been shown to cross the blood-brain barrier (BBB), allowing their distribution to CNS tissues. Crizotinib, ceritinib, alectinib, brigatinib, and entrectinib have been shown to be predominantly metabolized by the cytochrome P450 (CYP450) pathway,<sup>12–24</sup> whereas lorlatinib has been shown to be predominantly metabolized by both CYP3A4 and UDP-glucuronosyltransferase (UGT1A4).<sup>22</sup> For all six agents, the mean plasma elimination half-lives ( $t_{1/2}$ ) are longer than 20 hours. Apart from lorlatinib,<sup>22</sup> these agents are predominantly excreted through the feces.<sup>12–24</sup> The PK parameters of the six agents are listed in Table 1.

## Crizotinib

### Absorption

Following a single-dose administration of crizotinib, the median time to achieve  $C_{max}$  for crizotinib ranges from 4 to 6 hours, and a steady-state concentration can be achieved within 15 days of repeated administration, with a median accumulation ratio of 4.8.<sup>12–14</sup> The mean absolute bioavailability of crizotinib is 43%.<sup>12,13</sup>

### Distribution

The Steady state volume of distribution ( $V_{ss}$ ) for crizotinib is 1772 L, following a single, intravenous dose. The

**Table 1** PK Parameters for ALK-TKIs

PK	Absorption		Distribution		Metabolism	$T_{1/2}$ (h)	CL/F (L/h)	Excretion	
	$T_{max}$ (h)	F (%)	$V_d/V_{ss}$ (L)	PB (%)	Enzymes			Feces (%)	Urine (%)
Crizotinib <sup>11,12</sup>	4–6 <sup>a</sup>	43	1772*	91	CYP3A	42 <sup>a</sup>	100 <sup>a</sup> 60 <sup>b</sup>	63	22
Ceritinib <sup>14,15</sup>	4–6 <sup>a</sup>	NK	4230	97	CYP3A	41 <sup>a</sup>	88.5 <sup>a</sup> 33.2 <sup>b</sup>	92	1.3
Alectinib <sup>17,18</sup>	4 <sup>b</sup>	37	475*	>99	CYP3A4	33	81.9	98	<0.5
Brigatinib <sup>19,20</sup>	1–4 <sup>a</sup>	NK	153*	91	CYP3A4 CYP2C8	25 <sup>b</sup>	12.7 <sup>b</sup>	65	25
Lorlatinib <sup>21,22</sup>	1.2 <sup>a</sup> 2 <sup>b</sup>	81	305*	66	CYP3A4 UGT1A4	24 <sup>a</sup>	11 <sup>a</sup> 18 <sup>b</sup>	41	48
Entrectinib	4–6 <sup>a</sup>	>50	551	>99	CYP3A4	20	19.6	83	3

**Notes:**  $T_{max}$ , time to achieve  $C_{max}$ ;  $V_d$ , apparent volume of distribution; PB, Plasma protein binding;  $T_{1/2}$ , elimination half-life; CL/F, apparent clearance; F, absolute bioavailability; NK, not known. \*Steady state volume of distribution ( $V_{ss}$ ). <sup>a</sup>Single dose administrations, <sup>b</sup>Multiple dose administrations at steady state.

protein binding percentage of crizotinib is 91%, and the blood-to-plasma concentration ratio is approximately.<sup>12,13</sup>

### Elimination

After a single dose, the mean  $t_{1/2}$  of crizotinib is 42 hours, with a mean apparent clearance (CL/F) of 100 L/h. When administered at an oral dosage of 250 mg, twice daily, the  $t_{1/2}$  is approximately 43–51 hours, with a mean CL/F of 60 L/h.<sup>12,13</sup> Crizotinib has been shown to be primarily metabolized by CYP3A and was also shown to be a CYP3A inhibitor.<sup>12,13</sup> This auto-inhibition of CYP3A could explain why the mean CL/F of crizotinib is lower under steady-state conditions than after a single, oral dose.<sup>13,14</sup>

### Metabolism

Crizotinib is predominantly metabolized by CYP3A, which also significantly mediated the formation of the crizotinib lactam and O-desalkyl metabolites, to a significant extent.<sup>12,13</sup>

### Excretion

Following the administration of a single dose of radiolabeled crizotinib, 63% (53% of which was unchanged) of the administered dose was recovered in feces and 22% (2.3% of which was unchanged) was recovered in urine.<sup>12,13</sup>

## Ceritinib

### Absorption

After a single oral administration of ceritinib to patients, the  $C_{max}$  of ceritinib is achieved after approximately 4 to 6 hours.<sup>15,16</sup> A steady-state concentration can be achieved within 15 days of repeated administration, and the accumulation ratio is 6.2 after 3 weeks.<sup>15,16</sup> The absolute bioavailability of ceritinib has not been established but, based on the proportion of metabolites that have been excreted in mass balance studies, the lower limit of oral absorption has been estimated to be approximately 25%.<sup>15,16</sup>

### Distribution

Ceritinib is 97% bound to plasma proteins. The  $V_d$  is 4230 L, following a single dose in patients. The mean blood to-plasma ratio in humans is 1.35.<sup>15,16</sup>

### Elimination

Following a single dose, under fasted conditions, the  $t_{1/2}$  of ceritinib is 41 hours.<sup>15</sup> The geometric mean CL/F under steady-state conditions is 33.2 L/h, which is lower than after a single dose in patients (88.5 L/h).<sup>15</sup>

### Metabolism

CYP3A is the major enzyme involved in the metabolism of ceritinib.<sup>15</sup> Following a single dose of radiolabeled ceritinib, unchanged ceritinib was the major circulating component (82%) in plasma, whereas 11 metabolites were identified at low levels (each accounting for  $\leq 2.3\%$  of the initial amount).<sup>15,16</sup> Ceritinib has also been shown to be a CYP3A inhibitor, suggesting that the non-linearity pharmacokinetics of ceritinib may be attributable to the auto-inhibition of CYP3A.

### Excretion

After a single dose of radiolabeled ceritinib, 92% of the administered dose was recovered in the feces (68% of which was unchanged) and 1.3% was recovered in the urine.<sup>15,16</sup>

## Alectinib

### Absorption

Alectinib reaches  $C_{max}$  within 4 to 6 hours, after the administration of multiple doses of alectinib, under fed conditions in patients.<sup>17,18</sup> A steady-state concentration of alectinib can be achieved within 7 days, after which it remains stable, with a median accumulation ratio of 5.6.<sup>18,19</sup> The absolute bioavailability of alectinib is 37%.<sup>19</sup>

### Distribution

The  $V_{SS}$  for alectinib is 475 L.<sup>19</sup> Protein binding percentages for both alectinib and M4 are greater than 99%.<sup>18,19</sup> The mean blood-to-plasma ratios for alectinib and M4 are 2.64 and 2.50, respectively.<sup>18,19</sup> As a result of its lipophilic properties, alectinib exhibits good penetration through the BBB, which leads to high concentrations in the cerebrospinal fluid (CSF).<sup>19</sup>

### Elimination

In patients, the CL/F is 81.9 L/h for alectinib, and 217 L/h for M4, and the  $t_{1/2}$  is 33 hours for alectinib, and 31 hours for M4.<sup>19</sup>

### Metabolism

Alectinib is predominantly metabolized into M4 by CYP3A4.<sup>18</sup> Subsequently, M4 is metabolized into M6, also by CYP3A4.<sup>18</sup> Following the administration of a single radiolabeled dose, unchanged alectinib is the primary circulating moiety found in plasma, constituting 61% of total radioactivity, whereas M4 constituted 15% of the total radioactivity in plasma.<sup>18,19</sup>

## Excretion

Following a single radiolabeled dose of alectinib, 97.8% of the radioactivity is recovered in the feces and 0.46% is recovered in the urine.<sup>17–19</sup> In the feces, 84% of alectinib is unchanged, whereas 5.8% of M4 is unchanged.<sup>17–19</sup>

## Brigatinib

### Absorption

Following a single dose of brigatinib, the median time to  $C_{\max}$  ranged between 1 and 4 hours.<sup>20,21</sup> The absolute bioavailability of brigatinib has not been established. The mean accumulation ratio after repeated dosing is 1.9 to 2.4.<sup>20,21</sup>

### Distribution

Brigatinib is 91% bound to plasma proteins, and its blood-to-plasma concentration ratio is 0.69.<sup>20,21</sup> The  $V_{ss}$  for brigatinib is 153 L.<sup>21</sup>

### Elimination

The mean CL/F of brigatinib under steady-state conditions is 12.7 L/h, and its mean  $t_{1/2}$  is 25 hours after multiple daily doses of 180 mg brigatinib.<sup>20,21</sup>

### Metabolism

Brigatinib is metabolized primarily by CYP2C8 and CYP3A4.<sup>20</sup> Following a single radiolabeled dose, unchanged brigatinib represents the major circulating radioactive component, accounted for 92% of radioactivity, whereas its primary metabolite, AP26123, accounted for 3.5% of the radioactivity.<sup>20,21</sup>

### Excretion

Following a single dose of radiolabeled brigatinib, the percent recovery of the administered dose was 65% in feces and 25% in urine.<sup>20,21</sup> Unchanged brigatinib represented 41% and 86% of the total radioactivity in feces and urine, respectively.<sup>20,21</sup>

## Lorlatinib

### Absorption

The median time to achieve  $C_{\max}$  for lorlatinib is 1.2 hours, following a single oral dose, and 2 hours, following multiple daily doses.<sup>22</sup> The steady-state concentration of lorlatinib can be reached within 23 hours.<sup>23</sup> The mean absolute bioavailability is 81%.<sup>22,23</sup>

### Distribution

Lorlatinib is 66% bound to plasma proteins. The blood-to-plasma ratio is 0.99 and the CSF-to-plasma ratio is 0.75.<sup>22</sup> The  $V_{ss}$  is 305 L, after a single intravenous dose.<sup>22,23</sup>

## Elimination

The mean  $t_{1/2}$  of lorlatinib is 24 hours.<sup>22</sup> The mean oral CL/F is 11 L/h (35%), following a single oral dose, and 18 L/h (39%) under steady-state conditions, suggesting autoinduction.<sup>22,23</sup>

## Metabolism

Lorlatinib is metabolized primarily by CYP3A4 and UGT1A4, with minor contributions from CYP2C8, CYP2C19, CYP3A5, and UGT1A3.<sup>23</sup> Following a single radiolabeled dose, a benzoic acid metabolite (M8) of lorlatinib, which is pharmacologically inactive, accounted for 21% of the circulating radioactivity in plasma.<sup>22,23</sup>

## Excretion

Following a single dose of radiolabeled lorlatinib, 41% of the radioactivity was excreted in feces (less than 1% was unchanged) and 48% was excreted in urine (approximately 9% was unchanged).<sup>22,23</sup>

## Entrectinib

### Absorption

The time to achieve  $C_{\max}$  for entrectinib ranges from 4 to 6 hours after oral administration of a 600 mg dose.<sup>24</sup> The oral bioavailability of entrectinib is estimated to be at least 50% based on total radioactivity recovered in urine and in feces.<sup>24</sup>

### Distribution

Entrectinib and its active major metabolite M5 are both > 99% bound to plasma proteins.<sup>24</sup> The  $V_d/F$  is 551 L and 81.1 L for entrectinib and M5, respectively.<sup>24</sup> The blood-to-plasma ratio is 1.3 for entrectinib and 1.0 for M5.<sup>25</sup>

### Elimination

The CL/F is 19.6 L/h and 52.4 L/h for entrectinib and M5, respectively.<sup>24</sup> The  $t_{1/2}$  of entrectinib and M5 were estimated to be 20 and 40 hours, respectively.<sup>24</sup>

### Metabolism

Entrectinib is metabolized primarily by CYP3A4.<sup>24</sup> The active metabolite M5 is the only major active circulating metabolite and circulating M5 exposures at steady-state in patients were 40% of the corresponding entrectinib exposure.<sup>24</sup>

### Excretion

Following oral administration of a single oral dose of radiolabeled entrectinib, 83% of radioactivity was excreted in feces (36% was unchanged and 22% was M5) and 3% was excreted in excretion in urine.<sup>24</sup>

## PK DDIs

### PK DDIs: Absorption

Absorption-related drug interactions are commonly associated with drugs that undergo incomplete absorption (eg, have low bioavailability, first-pass effects, or are dependent on drug transporters).<sup>26</sup> Important factors that can affect drug absorption include acid-reducing agents (ARAs), food, drug transporter inhibitors or inducers, and intestinal CYP inhibitors or inducers.<sup>8</sup>

#### Intragastric pH

Oral bioavailability is determined by absorption and first-pass effect. Dissolution in stomach is the first step in drug absorption, and only when a drug dissolves into small molecules, it can pass through the intestinal mucosa to the portal circulation. The effect of pH on the absorption of an oral drug depends on its chemical nature. Weak-base drugs may show decreased absorption as a result of decreased solubility at higher pH values.<sup>27,28</sup>

Patients with cancer frequently use ARAs, such as proton pump inhibitors (PPIs), H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs), and antacids, to treat diseases caused by the hypersecretion of gastric acid. For drugs that exhibit pH-dependent solubility (eg, weak-base drugs), the elevation of gastric pH by ARAs may decrease solubility and absorption and, subsequently, reduce treatment efficacy.<sup>27</sup> Effects of ARAs on the absorption of ALK-TKIs are listed in Table 2.

#### Crizotinib

Crizotinib exhibits pH-dependent aqueous solubility, with solubility decreasing from more than 10 mg/mL at pH 1.6 to less than 0.1 mg/mL at pH 8.2.<sup>29</sup> In a pharmacokinetic study, the administration of crizotinib following 5 days of treatment with 40 mg esomeprazole, once daily, resulted in a 10% decrease in the area under the curve (AUC), which is not considered to be clinically meaningful.<sup>13</sup>

#### Ceritinib

Ceritinib is a weak-basic agent and displays pH-dependent solubility, with solubility decreasing from 11.9 to 0.01 mg/mL as pH values increase from 1 to 6.8.<sup>30</sup> In clinical practice, the coadministration of a single dose of ceritinib with 40 mg esomeprazole, once daily, for 6 days, in healthy subjects, resulted in decreases in the AUC and C<sub>max</sub> of ceritinib, by 76% and 79%, respectively.<sup>31</sup> However, the coadministration of ceritinib with PPIs for 6 days in ALK-positive cancer patients, the AUC and C<sub>max</sub> of ceritinib

decreased by 30% and 25%, respectively.<sup>31</sup> Consistent with the steady-state PK results, the effects of PPIs on the steady-state exposure of ceritinib is not considered to be clinically meaningful.<sup>16,31</sup>

#### Alectinib

Alectinib shows pH-dependent solubility, the solubility of alectinib ranging from 7.45 μg/mL at pH 1 to 0.013 at pH 6 in aqueous buffers.<sup>32</sup> A pharmacokinetic study showed that administration of alectinib following multiple doses of esomeprazole (40 mg once daily for 6 days), the AUC and C<sub>max</sub> increased by 22% and 16% for alectinib, and increased by 10% and 2% for M4, respectively.<sup>33</sup> Due to the low solubility of alectinib in the stomach at all pH values, the impact of gastric pH changing on its solubility and oral absorption seems with no clinically relevant.<sup>19</sup>

#### Brigatinib

Brigatinib is classified as a high-solubility agent, with solubility decreasing from 157.1 to 2.5 mg/mL as pH values increase from 1.6 to 7.5.<sup>34</sup> Thus far, no studies have been performed to assess the effects of ARAs on the absorption of brigatinib; however, considering its high solubility, the absorption of brigatinib is not expected to be significantly altered by the presence of ARAs. Therefore, dose adjustment is not required when brigatinib is co-administered with ARAs.<sup>20,21</sup>

#### Lorlatinib

Lorlatinib exhibits pH-dependent aqueous solubility that decreases over the pH range from 2.55 to 8.02, from 32.38 mg/mL to 0.17 mg/mL, respectively.<sup>35</sup> Drug-interaction studies have demonstrated that the co-administered of rabeprazole (20 mg, once daily), resulted in a 29% decrease in C<sub>max</sub>, and 1% decrease in AUC, which was not considered to be clinically meaningful.<sup>36</sup>

#### Entrectinib

Entrectinib has low and pH-dependent solubility, and its solubility decreases with increasing pH.<sup>25</sup> When entrectinib was co-administered with lansoprazole (30 mg qd) under fasting condition, the AUC and C<sub>max</sub> decreased by 25% and 23% for entrectinib, and decreased by 16% and 17% for M5, respectively.<sup>25</sup> Based on the results, coadministration of entrectinib with a PPI did not significantly alter the exposure of entrectinib.<sup>25</sup> Thus, no dose adjustment is required for coadministration of PPI with entrectinib.<sup>24,25</sup>

**Table 2** Effect of ARAs on the Absorption of ALK-TKIs

Drug	Condition	Mean Change		Clinically Significant	Recommendations
		AUCR	C <sub>max</sub> R		
Crizotinib <sup>13</sup>	Esomeprazole 40 mg once daily for 5 days	0.9	1.0	No	Dose adjustment is not required for coadministration of crizotinib with ARAs
Ceritinib <sup>16,31</sup>	Esomeprazole 40 mg once daily for 6 days	0.24 (healthy subjects) 0.70 (patients) 0.98 (at steady state)	0.21 (healthy subjects) 0.75 (patients) 0.93 (at steady state)	No	Dose adjustment is not required when ceritinib is co-administered with ARAs
Alectinib <sup>19,33</sup>	Esomeprazole 40 mg once daily for 6 days	1.22 (alectinib) 1.10 (M4) 1.17 (alectinib+M4)	1.16 (alectinib) 1.02 (M4) 1.13 (alectinib+M4)	No	Dose adjustment is not required for coadministration of alectinib with ARAs
Brigatinib <sup>20,21</sup>	No studies	No data	No data	No	Dose adjustment is not required for coadministration of brigatinib with ARAs
Lorlatinib <sup>36</sup>	Rabeprazole 20 mg once daily for 5 days	1.01	0.71	No	Dose adjustment is not required for coadministration of lorlatinib with ARAs
Entrectinib <sup>24,25</sup>	Lansoprazole 30 mg once daily	0.75 (entrectinib) 0.84 (M5)	0.77 (entrectinib) 0.83 (M5)	No	Dose adjustment is not required for coadministration of entrectinib with ARAs

**Notes:** C<sub>max</sub>R and AUCR are mean C<sub>max</sub> and AUC ratios when the substrate was given with/without a perpetrator.

## Food

Food–drug interactions can have one of the following four pharmacokinetic effects on the absorption of an orally administered drug: delay, increase, decrease, or no effect.<sup>37</sup> The mechanisms of food effects on oral drug absorption include increased gastrointestinal pH values, increased bile salt secretion, delayed gastric emptying, increased hepatic blood and gastrointestinal fluid flow, changes in the activity of drug transporters and intestinal enzymes, and binding to the drug.<sup>38</sup> During the daily lives of patients, the oral administration of drugs, either with or without food, can have several advantages and disadvantages. Therefore, understanding whether a specific orally administered drug should be taken with or without food is essential. Effects of food on the absorption of ALK-TKIs are listed in Table 3.

### Crizotinib

Crizotinib is classified as a class 4 compound (low solubility and low permeability) by the Biopharmaceutics Classification System (BCS).<sup>29</sup> According to pharmacokinetic studies, the coadministration of crizotinib with a high-fat meal resulted in slight reductions (approximately 14%) in both the AUC and C<sub>max</sub>.<sup>39</sup> Thus, crizotinib may be taken either with or without food.<sup>12,39</sup>

### Ceritinib

Ceritinib is classified as a BCS class 4 compound.<sup>30</sup> In a food-effect trial, conducted in healthy subjects, a 500-mg dose of ceritinib administered with a high-fat meal (1000 calories and 58 grams of fat) increased the ceritinib AUC by 73% and the C<sub>max</sub> by 41%, whereas a low-fat meal (330 calories and 9 grams of fat) increased the ceritinib AUC by 58% and the C<sub>max</sub> by 43%.<sup>15</sup> When the dose of ceritinib increased to 750 mg, the AUC and C<sub>max</sub> increased by 64% and 58%, with a high-fat meal, and by 39% and 42%, with a low-fat meal, respectively, compared with fasted conditions.<sup>40,41</sup> In a dose-optimization study performed in patients, receiving a 450-mg dose of ceritinib daily, with food (100 to 500 calories and 1.5 to 15 grams of fat), resulted in similar steady-state exposure to ceritinib and more favorable gastrointestinal tolerability than receiving 750 mg, daily, under fasted conditions.<sup>41</sup> Therefore, the recommended dosage of ceritinib is 450 mg, orally, once daily, with food.<sup>15</sup>

### Alectinib

Alectinib is classified as a BCS class 4 agent.<sup>32</sup> A study examining the effects of food on the pharmacokinetics of alectinib showed that a high-fat meal markedly increased the combined exposure to alectinib and M4, by 211% for AUC and 231% for C<sub>max</sub>, after the oral administration of

**Table 3** Effects of Food on the Absorption of ALK-TKIs

Drugs	BCS	Design	Condition	Mean Change		Clinically Significant	Recommendations
				AUCR	C <sub>max</sub> R		
Crizotinib <sup>12,39</sup>	4	250 mg single dose	High-fat meal	0.86	0.86	No	Taken with or without food
Ceritinib <sup>15,40,41</sup>	4	500 mg single dose	High-fat meal Low-fat meal	1.73 1.58	1.41 1.43	Yes	Taken with food
		750 mg single dose	High-fat meal Low-fat meal	1.64 1.39	1.58 1.42		
		450 mg multiple dose	Low-fat meal	Similar with 750 mg daily under fasted conditions			
Alectinib <sup>18,32,42</sup>	4	600 mg single dose	High-fat meal	2.92 (alectinib) 3.28 (M4) 3.11 (alectinib+M4)	2.70 (alectinib) 3.77 (M4) 3.31 (alectinib+M4)	Yes	Taken with food
Brigatinib <sup>20,43</sup>	1	180 mg single dose	High-fat meal	0.98	0.87	No	Taken with or without food
Lorlatinib <sup>22,36</sup>	4	100 mg single dose	High-fat meal	1.05	0.91	No	Taken with or without food
Entrectinib <sup>24,25</sup>	2	600 mg single dose	High-fat meal	1.15 (entrectinib) 1.0 (M5)	1.06 (entrectinib) 1.0 (M5)	No	Taken with or without food

a single dose of alectinib, with toxicities being well-tolerated.<sup>32,42</sup> As a result, alectinib is recommended to be administered with food.<sup>18</sup>

#### Brigatinib

Brigatinib is considered as a BCS class 1 substance (high solubility and high permeability).<sup>34</sup> During food-effect studies, the brigatinib AUC and C<sub>max</sub> were reduced by 2% and 13%, respectively, in healthy subjects when administered with a high-fat meal (920 calories, 58 grams carbohydrate, 59 grams fat and 40 grams protein).<sup>43</sup> Therefore, patients were instructed to take brigatinib without regard to meals.<sup>20</sup>

#### Lorlatinib

Lorlatinib meets the criteria for a BCS class 4 compound.<sup>35</sup> The administration of lorlatinib with a high-fat meal (1000 calories, with 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat) resulted in a 5% increase in the AUC and a 9% decrease in the C<sub>max</sub> compared with fasted conditions.<sup>36</sup> Food did not have a clinically meaningful effect on lorlatinib exposure. Thus, lorlatinib may be administered without regard to food.<sup>22</sup>

#### Entrectinib

Entrectinib is considered as a BCS class 2 compound.<sup>25</sup> When a single dose 600 mg entrectinib was administered with a high-fat, high-calorie meal, the entrectinib AUC and C<sub>max</sub> were increased by 15% and 6%, respectively.<sup>25</sup> Moreover, food has no effect on the exposure of M5, indicating that food did not have a significant effect on entrectinib exposure.<sup>25</sup> Therefore, entrectinib is recommended to be administered with or without food.<sup>24</sup>

#### Drug Transporters

Drug transporters are located throughout the body, especially in the intestinal gut, liver, kidney, and the BBB, where they play important roles in the membrane transport of many drugs.<sup>44,45</sup> Drug transporters may be divided into two large families, the ATP-binding cassette transporters (ABCs) and the solute carrier transporters (SLCs). The ABCs are efflux drug transporters, including P-gp, multidrug resistance-associated protein 2 (MRP2), and breast cancer resistance protein (BCRP). Conversely, the SLCs are influx drug transporters, including organic anion transporting peptides (OATPs), organic anion transporters (OATs), and organic cation transporters (OCTs). The inhibition and induction of drug transporters can have significant impacts on the pharmacokinetics of drugs by altering the absorption,

**Table 4** The Potential DDIs Between Drug Transporters and ALK-TKIs

Drugs	Substrates	Recommendations
Crizotinib <sup>12,13,48</sup>	P-gp, OATP1B1/3, OATP2B1, OCT2	NA
Ceritinib <sup>15,16</sup>	P-gp (major), BCRP (weak)	EMA: Caution is advised when concomitant use of P-gp inhibitors and inducers.
Alectinib <sup>18,19,57</sup>	NA	EMA: Clinically relevant DDIs with P-gp inhibitors and inducers are not likely to happen.
Brigatinib <sup>20,21</sup>	P-gp, BCRP	FDA/EMA: No dose adjustment is required for brigatinib during coadministration with P-gp and BCRP inhibitors.
Lorlatinib <sup>22,23</sup>	NA	EMA: Clinically relevant DDIs with P-gp and BCRP inhibitors or inducers are not likely to appear.
Entrectinib <sup>24</sup>	NA	NA

**Abbreviation:** NA, not applicable/not available.

distribution, metabolism, and elimination.<sup>46</sup> Likewise, elacridar, a P-gp and ABCG2 inhibitor, can increase the oral bioavailability of crizotinib.<sup>47</sup> Therefore, more attention should be paid to the DDIs mediated by drug transporters. The potential DDIs between drug transporters and ALK-TKIs are mentioned in Table 4. The potential DDIs between ALK-TKIs and other transporter substrates are mentioned in Table 5.

### Crizotinib

Based on in vitro data, crizotinib is transported by the P-gp, OATP1B1/2, OATP2B1, and OCT2.<sup>12,13</sup> A mouse model study, conducted by Tang,<sup>43</sup> demonstrated that the oral availability and brain accumulation of crizotinib were primarily restricted by P-gp, at a non-saturating dose, and coadministration with elacridar was able to substantially increase the oral availability of crizotinib. Shu et al<sup>48</sup> reported the effect of the co-administered of entecavir on the PK of crizotinib in NSCLC patients. The crizotinib AUC<sub>ss</sub> increased by 22% but C<sub>max, ss</sub> decreased by 7%. Moreover, the incidence of adverse reaction of crizotinib was significantly increased.

Crizotinib inhibits the P-gp, OCT1/2, OATP1B1/3, OATP2B1, OATP4C1, multidrug and toxin extrusion

**Table 5** The Potential DDIs Between ALK-TKIs and Other Transporter Substrates

Drugs	Inhibitor	Recommendations
Crizotinib <sup>12,13,49,50</sup>	P-gp, OCT1/2, OATP1B1/3, OATP2B1, OATP4C1, MATE1, MATE2-K	EMA: Close clinical surveillance is recommended when using these substrates.
Ceritinib <sup>15,16,56,57</sup>	P-gp, BCRP, OATP1B1/3, OAT1, OCT2	EMA: Caution should be exercised with concomitant use of these substrates.
Alectinib <sup>18,19,59</sup>	P-gp, BCRP, BSEP	EMA: Appropriate monitoring is recommended when co-administered with these substrates.
Brigatinib <sup>20,21</sup>	P-gp, BCRP, OCT1, MATE1, MATE2-K	EMA: Patients should be closely monitored when concomitant use of these substrates with a narrow therapeutic index.
Lorlatinib <sup>22,23</sup>	P-gp, OCT1, OAT3, MATE1, OATP1B1/3, BCRP	NA
Entrectinib <sup>24</sup>	P-gp, BCRP, OATP1B1, and MATE1	NDA: Dose adjustment for P-gp substrates when co-administered with entrectinib is not needed.

**Abbreviation:** NA, not applicable/not available.

protein (MATE1), and MATE2-K, but not OAT1/3, or bile salt export pump transporter (BSEP).<sup>11,12,49,50</sup> Razaet al<sup>51</sup> reported that crizotinib significantly increased the sensitivity of P-gp over-expressing cells in response to doxorubicin and paclitaxel. Therefore, crizotinib may have the potential to increase the plasma concentrations of co-administered P-gp substrates, and close clinical surveillance is recommended when crizotinib is administered with these agents.

A significant association between ABCB1 single nucleotide polymorphisms (SNPs) and the functionality of P-gp has been demonstrated by previous studies.<sup>52–54</sup> Because crizotinib is a substrate of P-gp, ABCB1 SNPs may lead to differences in the intracellular versus extracellular concentrations of crizotinib. Fujiwara et al<sup>55</sup> recently reported that one patient, with the 1236TT-2677TT-3435TT genotype, represented a distinct outlier,



with crizotinib AUC and  $C_{max}$  values on day 15 that were 2.8- and 2.6-fold greater than the mean, respectively, compared with other genotypes.

#### Ceritinib

Ceritinib is a good substrate for P-gp and a weak substrate for BCRP.<sup>15,16</sup> If ceritinib is administered with P-gp inhibitors, an increase in ceritinib concentrations is likely.<sup>16</sup> Caution is necessary with the concomitant use of P-gp inhibitors or inducers. Based on in vitro data, ceritinib is a weak inhibitor of OATP1B1/3, OAT1, OCT2, and is predicted to inhibit P-gp and BCRP, but not MRP2, OAT3, or OCT1.<sup>16,56</sup> Ceritinib may have the potential to increase the plasma concentrations of co-administered drugs that are transported by P-gp and BCRP.<sup>56,57</sup> Caution should be exercised with the concomitant use of P-gp and BCRP substrates.<sup>16</sup>

#### Alectinib

Alectinib is not a substrate for P-gp, BCRP, or OATP1B1/3, but M4 is a substrate for P-gp.<sup>18,19,58</sup> Because alectinib inhibits P-gp, that coadministration of P-gp inhibitors is not expected to have clinically relevant effects on M4 exposure.<sup>19</sup> In vitro, alectinib and M4 are inhibitors of P-gp, BSEP, and BCRP. Therefore, alectinib and M4 may have the potential to increase the plasma concentrations of co-administered P-gp, BSEP, and BCRP substrates.<sup>19,59</sup> Thus, appropriate monitoring is recommended when alectinib is co-administered with these substrates.<sup>19</sup>

#### Brigatinib

Brigatinib is a substrate for P-gp and BCRP.<sup>20,21</sup> Due to the high solubility and high permeability of brigatinib, in vitro, P-gp and BCRP inhibitors are unlikely to alter systemic exposure, and no dose adjustments are necessary for brigatinib when coadministered with P-gp and BCRP inhibitors.<sup>21</sup> Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K, in vitro.<sup>20,21</sup> Therefore, brigatinib may have the potential to increase the concentrations of co-administered substrates for these transporters.<sup>21</sup> Patients should be closely monitored when brigatinib is concomitantly used with those substrates with narrow therapeutic indexes (eg, digoxin, dabigatran, and methotrexate).<sup>21</sup>

#### Lorlatinib

Based on in vitro data, lorlatinib is not a substrate for P-gp or BCRP, and these efflux mechanisms are expected to

have minimal effects on its absorption.<sup>22,23</sup> Lorlatinib may have the potential to inhibit P-gp, OCT1, OAT3, MATE1, OATP1B1/3, and intestinal BCRP, and mediate DDIs by inhibiting these drug transporters, at clinically relevant concentrations.<sup>23</sup> The DDIs between drug transporter substrates and lorlatinib still require investigating in in vivo studies.<sup>23</sup>

#### Entrectinib

Entrectinib is not a substrate of P-gp, BCRP, or OATP1B1/3. However, M5 is a substrate of P-gp and BCRP.<sup>24</sup> Based on in vitro data, entrectinib and M5 have a potential inhibitory effect on P-gp, BCRP, OATP1B1, and MATE1.<sup>24</sup> A clinical DDI study showed that coadministration of entrectinib single dose 600 mg increased digoxin AUC and  $C_{max}$  by 18% and 28%, respectively.<sup>24</sup> Therefore, dose adjustment for P-gp substrates when co-administered with entrectinib is not needed.<sup>24</sup>

#### Intestinal CYP Enzymes

CYP enzymes metabolize a wide variety of drugs. CYPs are localized in both the liver and intestine. Thus, for many orally administered drugs, the first-pass drug clearance is contributed to by both liver and intestine.<sup>60</sup> CYP3A (CYP3A4 and 3A5) and CYP2C9 represent the major intestinal CYPs, accounting for 80% and 14%, respectively, of total CYP enzymes.<sup>61</sup> The activities of hepatic and intestinal CYP3A share commonalities, but also exhibit differences. For example, rifampicin is an inducer of hepatic and intestinal CYP3A, but the effects of grapefruit juice appeared to be selective for intestinal CYP3A and are not sensitive to hepatic CYP3A.<sup>60</sup>

Because intestinal CYP enzymes and P-gp share common locations and common inhibitors and inducers, they might act as a coordinated absorption barrier against oral drugs. Without efflux transporters, the high concentration of orally administered drugs in the gut might easily saturate CYP enzymes in enterocytes, resulting in fewer metabolites and more unchanged drug being released into the blood.<sup>60</sup> Therefore, the interplay between intestinal CYP enzymes and P-gp can enable highly efficient intestinal metabolism, which could have a substantial effect on the first-pass elimination of orally administered drugs.

For some orally administered drugs, intestinal CYP metabolism can eliminate a large proportion of the drugs before they can reach the systemic circulation. Drugs that are intestinal CYP substrates not only suffer from low bioavailability but they are also more likely to be

susceptible to DDIs with other CYP substrates, inhibitors, or inducers.<sup>61</sup> However, because many drugs undergo extensive first-pass and are dependent on hepatic and intestinal CYP metabolism and transporters, distinguishing their individual contributions to altered drug bioavailability can be difficult.

## PK DDIs: Distribution

Distribution is largely determined by blood flow and the binding properties of drugs with plasma proteins.<sup>62</sup> ALK-TKIs can bind to several plasma proteins, such as albumin,  $\alpha$ 1-acid glycoprotein, lipoproteins, and immunoglobulins. The unbound drugs can cross the membrane, distribute to tissues, and exert biological activity. In theory, if two highly protein-bound drugs are combined, one drug can displace the other from its protein binding site, increasing the concentration of the unbound drug and altering its apparent distribution volume.<sup>63</sup> Crizotinib, ceritinib, alectinib, brigatinib, and entrectinib are highly bound to plasma proteins ( $\geq 90\%$ ),<sup>12,15,18,20,24</sup> and could theoretically interact with other highly protein-bound drugs, such as phenytoin and warfarin; however, little evidence exists to support clinically relevant interactions due to displacement from protein binding sites, likely because, although changes in protein binding can influence the pharmacokinetic parameters of a drug, they rarely alter the overall exposure to a drug.<sup>64</sup>

Drug distribution into tissues is mediated by transporters, and inhibition or induction of transporters can also influence the distribution of drugs.<sup>46</sup> For instance, crizotinib is a substrate of P-gp, which is consistent with crizotinib being relatively ineffective for cancer associated with brain metastasis. However, when co-administered with elacridar, the brain accumulation of crizotinib was increased.<sup>47</sup> Similar with crizotinib, brain accumulation of the ceritinib is restricted by P-gp and BRCP, and coadministration of P-gp and BRCP inhibitor can increase its brain accumulation.<sup>65</sup> For alectinib, lorlatinib, and entrectinib, they are not a substrate of P-gp and BRCP, this may be an important reason why they exhibit good penetration through the BBB.

## PK DDIs: Metabolism

Most PK DDIs involve the metabolism of drugs in vivo, especially those drugs metabolized by CYP enzymes.<sup>64</sup> Although some drugs are also metabolized at the small intestine, the primary site for drug metabolism is the liver.<sup>66</sup> Potent CYP inhibitors and inducers can modify the exposure of CYP substrates. Moreover, the competitive

binding of two substrates at the same CYP enzyme-binding site can also mediate DDIs. The five ALK-TKIs are CYP enzyme substrates; thus, the DDIs may occur when ALK-TKIs are co-administered with CYP enzyme inhibitors, inducers, and substrates.<sup>66</sup> The effects of CYP inhibitors and inducers on the exposure of ALK-TKIs are mentioned in Table 6. The effect of ALK-TKIs on the exposure of other CYP3A substrates are mentioned in Table 7.

### Crizotinib

The coadministration of a single 150-mg orally administered dose of crizotinib with ketoconazole, increased the crizotinib AUC and  $C_{max}$  by 216% and 44%, respectively.<sup>67</sup> When crizotinib was co-administered with another strong CYP3A inhibitor, itraconazole, the AUC and  $C_{max}$  of crizotinib increased by 57% and by 33%, respectively.<sup>13</sup> Therefore, the concomitant use of strong CYP3A inhibitors and crizotinib should be avoided. If the concomitant use of CYP3A inhibitors with crizotinib is unavoidable, the crizotinib dose should be reduced to 250 mg, once daily.<sup>12,13</sup> The effects of moderate CYP3A inhibitors on crizotinib exposure might also be clinically relevant, and the physiologically based pharmacokinetic (PBPK) model predicted a 17% increase in crizotinib AUC after treatment with moderate CYP3A inhibitors (diltiazem or verapamil).<sup>13</sup> Caution is recommended when co-administering crizotinib with moderate CYP3A inhibitors.

During the concomitant use of crizotinib with rifampin, a strong CYP3A inducer, the AUC and  $C_{max}$  of crizotinib decreased by 84% and 79%, respectively.<sup>67</sup> Therefore, the concomitant use of strong CYP3A inducers with crizotinib should be avoided. A clinical study was conducted to assess the effect of dexamethasone on the exposure and efficacy of crizotinib.<sup>68</sup> The results showed that dexamethasone has no effect on crizotinib exposure or efficacy.<sup>68</sup>

Crizotinib is a reversible and time-dependent inhibitor of CYP3A.<sup>13,69</sup> Coadministration of crizotinib increases the AUC and  $C_{max}$  values for midazolam (a sensitive CYP3A substrate), by 116% and 32%, 265% and 102%, and 250% and 139%, on average, at crizotinib dose levels of 100 mg daily, 250 mg twice daily, and 300 mg twice daily, respectively, suggesting that crizotinib is a moderate CYP3A inhibitor.<sup>29,69</sup> The warfarin (R) enantiomer is metabolized by CYP3A4, kubomura et al<sup>70</sup> reported a case of increased prothrombin time-international normalized ratio when crizotinib and warfarin were co-administered. Therefore, the concomitant use of crizotinib with sensitive CYP3A substrates should be avoided, if the

**Table 6** Effects of CYP Inhibitors and Inducers on the Exposure of ALK-TKIs

Drugs	CYP Enzymes		Mean Change		Clinically Significant	Recommendations
	Inhibitors	Inducers	AUCR	C <sub>max</sub> R		
Crizotinib <sup>12,13,67,68</sup>	Ketoconazole Itraconazole		3.16 1.57	1.44 1.33	Yes Yes	Avoiding concomitant use of strong CYP3A inhibitors, if concomitant use of is unavoidable, reduce the dose of crizotinib to 250 mg once daily.
		Diltiazem/ Verapamil	Rifampin	1.17 0.16	NK 0.21	
Ceritinib <sup>15,16,30</sup>	Ketoconazole fluconazole		2.89 1.37	1.22 1.32	Yes No	Avoiding concomitant use of strong CYP3A inhibitors, if concomitant use is unavoidable, reduce the dose by approximately one third.
		Rifampin efavirenz	0.30 0.57	0.56 0.61	Yes No	
Alectinib <sup>19,32,71</sup>	Posaconazole		1.75 (alectinib) 0.75 (M4) 1.36 (alectinib+M4)	1.18 (alectinib) 0.29 (M4) 0.93 (alectinib+M4)	No	No dose adjustments are required when alectinib is co-administered with CYP3A inhibitors or inducers.
		Rifampin	0.27 (alectinib) 1.79 (M4) 0.82 (alectinib+M4)	0.49 (alectinib) 2.20 (M4) 0.96 (alectinib+M4)	No	
Brigatinib <sup>72,73</sup>	Itraconazole		2.01	1.21	Yes	Avoiding coadministration of strong CYP3A inhibitors, if coadministration is unavoidable, reduce the brigatinib once daily dose by approximately 50%.
		Diltiazem/ Verapamil	1.32 1.40	1.08 1.08	Yes	
	Gemfibrozil		0.88	0.59	No	No dose adjustments are required when brigatinib is co-administered with CYP2C8 inhibitors
	Rifampin Efavirenz	0.20 0.52	0.40 0.85	Yes Yes	Avoiding coadministration of strong or moderate CYP3A inducers, if coadministration is unavoidable, increase the brigatinib once daily dose in 30 mg increments after 7 days of treatment, up to a maximum of twice the brigatinib dose.	

(Continued)

Table 6 (Continued).

Drugs	CYP Enzymes		Mean Change		Clinically Significant	Recommendations
	Inhibitors	Inducers	AUCR	C <sub>max</sub> R		
Lorlatinib <sup>22,23</sup>	Itraconazole		1.42	1.24	Yes	Avoiding coadministration of strong CYP3A inhibitors, if concomitant use is unavoidable, reduce the starting dose of lorlatinib from 100 mg to 75 mg, and from 75 mg to 50 mg if adverse reactions occurred.
		Rifampin	0.15	0.24	Yes	Avoiding coadministration of strong CYP3A inducers.
Entrectinib <sup>24,25</sup>	Itraconazole		6.04 (entrectinib) 2.52 (M5)	1.73 (entrectinib) 0.62 (M5)	Yes	For adults and pediatric patients 12 years and older with BSA greater than 1.5 m <sup>2</sup> , coadministration of entrectinib with moderate or strong CYP3A inhibitors should be avoided, if coadministration cannot be avoided, entrectinib 100 mg qd is recommended for strong CYP3A4 inhibitors, and 200 mg qd for moderate CYP3A4 inhibitors. For pediatric patients 12 years and older with BSA less than or equal to 1.5 m <sup>2</sup> , Avoiding coadministration of moderate or strong CYP3A inhibitors
	Erythromycin		3.40 (entrectinib) 2.08 (M5)	2.89 (entrectinib) 1.21 (M5)	Yes	
		Rifampin	0.23 (entrectinib) 0.13 (M5)	0.44 (entrectinib) 0.25 (M5)	Yes	Avoiding coadministration of moderate or strong CYP3A inducers.
		Efavirenz	0.44 (entrectinib) 0.53 (M5)	0.57 (entrectinib) 0.72 (M5)	Yes	

Table 7 Effects of ALK-TKIs on the Exposure of Other Drugs

Drugs	CYP Substrates	Change of CYP Substrates		Clinically Significant	Recommendations
		AUCR	C <sub>max</sub> R		
Crizotinib <sup>13,69</sup>	Midazolam	3.65	2.02	Yes	Avoiding concomitant use of crizotinib with CYP3A substrates. If concomitant use is unavoidable, reduce the dose of CYP3A substrates.
Ceritinib <sup>15,30</sup>	Midazolam	5.40	1.80	Yes	Avoiding coadministration of ceritinib with sensitive CYP3A and CYP2C9 substrates. If concomitant use is unavoidable, consider dose reduction of the CYP3A and CYP2C9 substrates.
	Warfarin	1.54	1.0	Yes	
Alectinib <sup>18,19,32</sup>	Midazolam	0.97	0.92	No	No dose adjustments are required when alectinib is co-administered with CYP3A substrates.
Brigatinib <sup>20,21</sup>	NA	NA	NA	NK	Coadministration of brigatinib with CYP3A substrates with a narrow therapeutic index should be avoided.
Lorlatinib <sup>22,23</sup>	Midazolam	0.36	0.50	Yes	Avoiding concomitant use of lorlatinib with CYP3A substrates.
Entrectinib <sup>24,25</sup>	Midazolam	1.50	0.79	No	Dose adjustment is not needed for sensitive CYP3A substrates when coadministered with entrectinib.

Abbreviations: NK, not known; NA, not applicable/not available.

concomitant use of crizotinib is unavoidable, reducing the dose of CYP3A substrates is recommended.

### Ceritinib

The coadministration of ceritinib with ketoconazole, under fasted conditions, for 14 days, increased the ceritinib AUC by 189% and  $C_{max}$  by 22%.<sup>15,16</sup> Thus, we recommend avoiding the concomitant use of strong CYP3A inhibitors with ceritinib, if the concomitant use of CYP3A inhibitors is unavoidable, the dose of ceritinib should be reduced by approximately one third.<sup>15</sup> The coadministration of ceritinib with rifampin for 14 days decreased the AUC and  $C_{max}$  of ceritinib by 70% and 44%, respectively.<sup>15</sup> Therefore, the concomitant use of crizotinib with strong CYP3A inducers should be avoided.<sup>15</sup>

PBPK modeling predicted that fluconazole (a moderate CYP3A4 inhibitor) can increase ceritinib AUC by 37% and  $C_{max}$  by 32%, while efavirenz (a moderate CYP3A4 inducer) can decrease ceritinib AUC by 43% and  $C_{max}$  by 39%.<sup>16,30</sup> A clinical trial to evaluate the effect of a moderate CYP3A4 inhibitor or inducer on ceritinib PK is considered unnecessary given the magnitude of predicted changes in steady-state exposures after coadministration with a moderate CYP3A4 inhibitor and inducer.<sup>16</sup> Restricting the concomitant use of moderate CYP3A4 inhibitors and inducers when using ceritinib is not recommended.<sup>16</sup>

Ceritinib has been classified as a strong CYP3A4 inhibitor and a weak CYP2C9 inhibitor. The concomitant use of midazolam with ceritinib increased the midazolam AUC by 440% and the  $C_{max}$  by 80%.<sup>15</sup> When co-administered with warfarin (a CYP2C9 substrate), the AUC of S-warfarin increased by 54%, whereas no statistically significant effect was observed for  $C_{max}$ .<sup>15,16</sup> These findings suggested that the coadministration of ceritinib with CYP3A4 or CYP2C9 substrates should be avoided, if concomitant use of such substrates is unavoidable, a dose reduction for the sensitive CYP substrates should be considered.<sup>15</sup>

### Alectinib

A clinical study was conducted to assess the DDIs between alectinib and CYP inhibitors, inducers, and substrates.<sup>19</sup> The coadministration of alectinib with posaconazole (a strong CYP3A inhibitor) increased the alectinib AUC and  $C_{max}$  by 75% and 18%, respectively, and reduced the M4 AUC and  $C_{max}$  by 25% and 71%, respectively.<sup>32,71</sup> The effects on the combined exposure to alectinib and M4 were minor, reducing the total  $C_{max}$  by 7% and increasing the total AUC by 36%.<sup>32,71</sup> The concomitant use of rifampicin with alectinib reduced the

alectinib AUC and  $C_{max}$  by 73% and 51%, respectively, and increased the M4 AUC and  $C_{max}$  by 79% and 120%, respectively.<sup>32,71</sup> The effects on the combined exposure to alectinib and M4 were minor, reducing the total AUC and  $C_{max}$  by 18% and 4%, respectively.<sup>32,71</sup> Based on these results, no dose adjustments are required when alectinib is co-administered with CYP3A inhibitors or inducers.<sup>19</sup>

In vitro, alectinib and M4 show weak, time-dependent inhibition of CYP3A4, and alectinib exhibits the weak induction of CYP3A4 and CYP2B6.<sup>18,19</sup> A study has shown that multiple doses of alectinib had no influence on the exposure to midazolam.<sup>32</sup> Alectinib is a weak inhibitor of CYP2C8, and a PBPK model study showed that alectinib had no clinically significant effects of on repaglinide (a substrate of CYP2C8) metabolism in vivo.<sup>32</sup> Therefore, no dose adjustment is required for co-administered CYP3A substrates.<sup>19</sup>

### Brigatinib

The coadministration of brigatinib with itraconazole increased the brigatinib AUC and  $C_{max}$  by 101% and 21%, respectively.<sup>72,73</sup> Compared with strong CYP3A4 inhibitors, moderate CYP3A inhibitors (eg, diltiazem and verapamil) may increase the AUC of brigatinib by approximately 40%.<sup>73</sup> Therefore, the coadministration of strong or moderate CYP3A inhibitors should be avoided, if the coadministration of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the brigatinib once-daily dose by approximately 50% for strong inhibitors and by 40%, for moderate inhibitors.<sup>20</sup>

Brigatinib is also a substrate for CYP2C8.<sup>20,21</sup> In healthy subjects, the coadministration of brigatinib with gemfibrozil (a strong CYP2C8 inhibitor) reduced the brigatinib AUC and  $C_{max}$  by 12% and 41%, respectively; however, these effects are not clinically meaningful, as total systemic exposure of brigatinib was not meaningfully altered.<sup>72</sup> The effect of gemfibrozil on the PK of brigatinib was unexpected, and the underlying mechanism for decreased AUC and  $C_{max}$  in the presence of gemfibrozil is unknown, it may be related to the inhibition of transporters that may be important for brigatinib uptake.

When co-administered with rifampicin, the AUC and  $C_{max}$  of brigatinib were decreased by 80% and 60%, respectively.<sup>72,73</sup> Therefore, the concomitant use of strong CYP3A inducers with brigatinib should be avoided.<sup>20,21</sup> Compared with strong CYP3A4 inducers, moderate CYP3A inducers may decrease the AUC of brigatinib by approximately 50%, based on PBPK model.<sup>73</sup> The

concomitant use of moderate CYP3A inducers with brigatinib should also be avoided, if the coadministration of moderate or strong CYP3A4 inducers is unavoidable, increase the brigatinib once-daily dose by 30-mg increments for 7 days of treatment, up to a maximum of twice the starting brigatinib dose.<sup>21</sup>

Brigatinib is an inducer for CYP3A4.<sup>21</sup> Clinical DDI studies examining CYP3A sensitive substrates have not yet been conducted; however, brigatinib may decrease the exposure to CYP3A substrates.<sup>21</sup> Therefore, the coadministration of brigatinib with CYP3A substrates with narrow therapeutic indexes should be avoided, as their effectiveness may be reduced.<sup>21</sup>

### Lorlatinib

When given concomitantly with itraconazole, the AUC of lorlatinib increased by 42% and the  $C_{max}$  increased by 24%.<sup>22</sup> Therefore, the coadministration of strong or moderate CYP3A inhibitors should be avoided, if a strong CYP3A4/5 inhibitor must be concomitantly administered, a dose reduction for lorlatinib is recommended.<sup>22</sup>

In DDI studies, rifampin reduced the mean lorlatinib AUC by 85% and reduced the  $C_{max}$  by 76%.<sup>22</sup> Thus, the concomitant administration of lorlatinib with strong CYP3A4/5 inducers should be avoided.<sup>22</sup> The effect of moderate CYP3A4/5 inducers on lorlatinib pharmacokinetics has not yet been clearly established; therefore, they may reduce lorlatinib plasma concentrations.<sup>23</sup> Thus, the concomitant use with moderate CYP3A4/5 inducers should also be avoided.<sup>22,23</sup>

In *in vitro* studies, lorlatinib is a time-dependent inhibitor and an inducer of CYP3A4/5.<sup>22</sup> The coadministration of lorlatinib with midazolam decreased the midazolam AUC and  $C_{max}$  by 64% and 50%, respectively.<sup>22</sup> Thus, the concurrent administration of lorlatinib with CYP3A4/5 substrates that have narrow therapeutic indices should be avoided.<sup>22</sup> Lorlatinib may have the potential to inhibit CYP2C9 and CYP1A2, based on *in vitro* studies, and may have the weak potential to induce CYP2B6.<sup>23</sup> Caution is recommended when co-administering lorlatinib with these CYP substrates.<sup>23</sup>

### Entrectinib

Entrectinib is metabolized primarily by CYP3A4 to form the major active metabolite M5.<sup>24</sup> Similarly, M5 is also primarily metabolized by CYP3A4.<sup>24</sup> Coadministration of itraconazole with entrectinib increased entrectinib AUC

and  $C_{max}$  by 504% and 73%, respectively, and increased M5 AUC by 152% but decreased the M5  $C_{max}$  by 38%.<sup>25</sup> Coadministration of erythromycin with entrectinib is predicted to increase entrectinib AUC by 240% and  $C_{max}$  by 189%, and increase M5 AUC by 108% and  $C_{max}$  by 21%.<sup>25</sup> Thus, for adults and pediatric patients 12 years and older with BSA greater than 1.5 m<sup>2</sup>, coadministration of entrectinib with moderate or strong CYP3A inhibitors should be avoided, if coadministration cannot be avoided, entrectinib 100 mg once daily is recommended for coadministration of strong CYP3A4 inhibitors, and 200 mg once daily is recommended for coadministration of moderate CYP3A4 inhibitors.<sup>24</sup> For pediatric patients 12 years and older with BSA less than or equal to 1.5 m<sup>2</sup>, coadministration of entrectinib with moderate or strong CYP3A inhibitors should be avoided.<sup>24</sup>

When co-administered with rifampicin, the AUC and  $C_{max}$  were decreased by 77% and 56% for entrectinib, and decreased by 87% and 75% for M5, respectively.<sup>25</sup> Concomitant use of efavirenz is expected to decrease entrectinib AUC and  $C_{max}$  by 56% and 43%, and decrease M5 AUC and  $C_{max}$  by 47% and 28%, respectively.<sup>25</sup> Based on these data, coadministration of entrectinib with moderate or strong CYP3A inducers should be avoided.<sup>24</sup>

*In vitro*, entrectinib and M5 exhibited inhibitory potential toward CYP3A4/5, CYP2D6, and CYP2C8/9.<sup>24,25</sup> A clinical DDI study showed that coadministration of entrectinib once daily with midazolam increase the midazolam AUC by 50% but decreased  $C_{max}$  by 21%.<sup>25</sup> The results suggest that dose adjustment is not needed for sensitive CYP3A substrates when co-administered with entrectinib.<sup>25</sup>

### PK DDIs: Elimination

Drug transporters, located in the kidney and liver, associated with hepatic CYP enzymes are important for the elimination of drugs.<sup>45,74,75</sup> For the six ALK-TKIs, liver elimination represents the major clearance pathway, with minor contributions from renal elimination. Thus, the inhibition or induction of hepatic transporters and CYP enzymes may increase or decrease the excretion of affected drugs, resulting in clinically relevant DDIs. However, clinical data supporting these possibilities are very limited, and more research is necessary to assess the effects of clinically relevant changes in hepatic transporters on the pharmacokinetics of crizotinib, ceritinib, brigatinib, and entrectinib. Because alectinib and lorlatinib are not substrates for transporters, coadministration with transporter inhibitors or inducers are not expected to have relevant

effects on the elimination of these two drugs.<sup>19,23</sup> In addition, ALK-TKIs also can affect the PK of other drugs by altering the expression and activity of enzymes and transporters, the effects of ALK-TKIs on the elimination of other substrates also should be examined.

Liver and kidney are the two major organs for the elimination of drugs. Thus, DDI related to elimination can occur due to the renal impairment (RI) or hepatic impairment (HI).<sup>76</sup> For drugs are primarily eliminated by the liver, HI may significantly impact their PK and cause DDIs.<sup>77</sup> Similarly, for drugs are primarily eliminated by the kidney, RI may significantly impact their PK and cause DDIs.<sup>78</sup> Moreover, RI can also affect the non-renal disposition of drugs that are eliminated by

the liver.<sup>76,78</sup> Therefore, it is important to know the effect of RI and HI on the exposure of drugs. The effect of RI and HI on the exposure of ALK-TKIs are illustrated in Table 8.

## Conclusions

ALK-TKIs have rapidly become an established component of regular oncology practice in the past few years.<sup>6,82</sup> This review of the PK of crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, and entrectinib highlighted the differences in absorption, metabolism, distribution, and excretion among these ALK-TKIs, which can influence their potential for DDIs.

Multiple clinically significant DDIs have been reported due to the inhibition or induction of hepatic CYP enzymes.

**Table 8** The Effect of RI and HI on the Exposure of ALK-TKIs

Drugs	RI		Recommendations	HI		Recommendations
	AUCR	C <sub>max</sub> R		AUCR	C <sub>max</sub> R	
Crizotinib <sup>12,13,79,80</sup>	Mild and moderate RI: Similar with NRF.		Mild and moderate RI: Dose adjustment is not needed. Severe RI: 250 mg once daily.	0.91 (mild)	0.91 (mild)	Mild HI: Dose adjustment is not needed. Moderate HI: 200 mg twice daily. Severe HI: 250 mg once daily.
				1.50 (moderate)	1.44 (moderate)	
	0.21 (severe)	0.66 (severe)		0.65 (severe)	0.73 (severe)	
Ceritinib <sup>16,30</sup>	1.09 (mild)	NK	Mild and moderate RI: Dose adjustment is not needed. Severe RI: No information is available.	1.18 (mild)	NK	Mild and moderate HI: Dose adjustment is not needed. Severe HI: 300 mg once daily.
	1.19 (moderate)			1.02 (moderate)		
Alectinib <sup>18,81</sup>	Mild and moderate RI: Similar with NRF Severe RI: Not studied		Mild and moderate RI: Dose adjustment is not needed. Severe RI: Withhold alectinib.	Alectinib+M4 1.36 (moderate) 1.76 (severe)	Alectinib +M4 1.16 (moderate) 0.98 (severe)	Mild and moderate HI: Dose adjustment is not needed. Severe HI: 450 mg twice daily.
Brigatinib <sup>20,21</sup>	Mild and moderate RI: Similar with NRF. Severe RI: 1.94	NK	Mild and moderate RI: Dose adjustment is not needed. Severe RI: Reduce the alectinib once daily by 50%.	Mild and moderate HI: Similar with NHF. Severe HI: 1.37	NK	Mild and moderate HI: Dose adjustment is not needed. Severe HI: Reduce the alectinib once daily by 40%.
Lorlatinib <sup>22</sup>	Mild and moderate RI: Similar with NRF. Severe RI: Not studied.		Mild and moderate RI: Dose adjustment is not needed. Severe RI: No information is available.	Mild HI: Similar with NHF. Moderate and severe HI: Not studied.		Mild HI: Dose adjustment is not needed. Moderate and severe HI: No information is available.
Entrectinib <sup>24</sup>	Mild and moderate RI: Similar with NRF. Severe RI: Not studied.		Mild and moderate RI: Dose adjustment is not needed. Severe RI: No information is available.	Mild HI: Similar with NHF. Moderate and severe HI: Not studied.		Mild HI: Dose adjustment is not needed. Moderate and severe HI: No information is available.

**Abbreviations:** NRF, normal renal function; NHF, normal hepatic function; NK, not known.

Except for alectinib, CYP inhibitors and inducers can significantly alter the exposure of ALK-TKIs and can lead to clinically relevant DDIs.<sup>12,15,20,22,24</sup> Thus, for crizotinib, ceritinib, brigatinib, lorlatinib, and entrectinib, the concomitant use of strong CYP3A inhibitors or inducers should be avoided. If concomitant use is unavoidable, the doses of these five ALK-TKIs should be reduced. In addition, all six ALK-TKIs are CYP3A inhibitors, and crizotinib, ceritinib, brigatinib, and lorlatinib can significantly influence the exposure of midazolam, indicating that clinical intervention is necessary when these four ALK-TKIs are co-administered with other CYP3A substrates.<sup>13,16,21,23</sup> In addition to hepatic CYP enzymes, intestinal CYP enzymes are also involved in drug metabolism, and the inhibition or induction of intestinal CYP enzymes may change the absorption of a drug.<sup>60</sup> For instance, grapefruit is an intestinal CYP inhibitor, which may increase the bioavailability of ALK-TKIs.<sup>13,16,19,21,23,24,83</sup> Thus, grapefruit juice or grapefruit should be avoided during treatment with ALK-TKIs.

PK interactions between food and orally administered drugs primarily affect drug absorption, which may have clinically relevant effects. For ceritinib and alectinib, food can significantly increase absorption, and the toxicities are well-tolerated.<sup>33,40,41</sup> As a result, they are recommended to be taken with food. In contrast, for crizotinib, brigatinib, lorlatinib, and entrectinib, the effects of food on their absorption are considered to have no clinical implications;<sup>22,24,39,43</sup> therefore, they can be taken either with or without food. ARAs can also affect the absorption of many orally administered drugs, however, based on the results of clinical trials, the effects of ARAs on the absorption of ALK-TKIs are not clinically significant.<sup>25,29-33,36</sup> Therefore, the concomitant use of ARAs is not contraindicated.

Transporters play an important role in the membrane transport of many drugs and are involved in intestinal tissue distribution, hepatic uptake, and biliary and renal excretion. The inhibition or induction of transporters by co-administered drugs can alter the PK of victim drugs, leading to transporter-mediated DDIs. Crizotinib, ceritinib, and brigatinib are substrates for P-gp and other transporters.<sup>13,16,21</sup> Thus, caution should be used when the concomitant use of these ALK-TKIs with strong transporter inhibitors or inducers. Furthermore, all six ALK-TKIs are transporter inhibitors (eg, P-gp), and close clinical surveillance is recommended when the coadministration of ALK-TKIs with P-gp or other transporter substrates is necessary.

In summary, PK DDIs can occur in every step during which a drug interacts with the body, including during

absorption, distribution, metabolism, and excretion, and many agents (eg, food, ARAs, transporter inhibitors/inducers, and CYP inhibitors/inducers) can lead to DDIs.<sup>9,84</sup> In this review, we presented the PK and DDIs of crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, and entrectinib in clinical practice, to help clinicians maximize efficacy and minimize the incidence of adverse events when prescribing ALK-TKIs.

## Disclosure

The authors report no conflict of interest regarding the publication of this paper.

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