同　意　撤　回　文　書

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研究課題名：
「ヒト T リンパ球向性ウイルス(HTLV-1)陽性者および健常人における免疫動態の解析」

上記研究への同意を以下のとおり撤回します。

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２．提供した試料等が本研究終了後に保存されることについて

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平成　　年　　月　　日

本人署名：＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

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様式 3

ヒトＴリンパ球向性ウイルス（HTLV-1）陽性者および健常人における免疫動態解析（説明書）

1. はじめに

私たちは、ヒトＴリンパ球向性ウイルス（HTLV-1）陽性者における免疫の状態を解析する臨床研究を計画しております。以下をお読みいただき、もしご理解いただけるようでしたら、血液検査時に多少多めの血液をご提供いただくこと、また骨髄やリンパ節、皮膚生検の際の標本の一部を使わせていただくことにご同意いただければ、幸いです。

本研究に参加するかどうかはご自身の自由意思で決めていただきます。参加されなくても、これからの治療に差し支えることはなく、適切な治療を受けることができます。また一旦ご参加いただいた後いつでも、ご自由に参加を取りやめることができます。その場合も、今後の治療について一切の不利益を受けることはありません。

2. 研究目的

ヒトＴリンパ球向性ウイルス（HTLV-1）は九州に多く存在するウイルスで、日本全国に約 110 万人の感染者がいると考えられています。感染者の多くは一生本ウイルスに関係する病気を発症しませんが、一部（5%程度）は成人Ｔ細胞白血病（Adult T-cell Leukemia: ATL）という血液の腫瘍を発症します。また ATL の約 1/30 の頻度で、HTLV-1 関連脊髄症（HTLV-1-associated Myelopathy: HAM）という神経の病気を発症する人がいることも知られています。

しかし、どういう人がウイルスに感染し、また病気を発症し、どういう人が病気を発症しないのか、ということは十分には分かっていません。またこれらの病気を治療するのは容易ではなく、現在新しい治療法が多く試みられていますが、そのそれぞれがどういう患者さんに相応しいのか、もよく分かっていません。さらに、HTLV-1 は主にヒトＴリンパ球という白血球に感染しますが、ヒトにはこれら感染細胞をやっつける働き（「免疫」と呼ばれます）が備わっており、そのバランスが崩れることが病気の発症に関わっているのではないか、ということが最近言われるようになりました。ただその詳細は、まだよく分かっていません。

これらの疑問に答えるため、私たちは HTLV-1 感染者の血液、もしくは骨髄・リンパ節・皮膚などを解析することで、HTLV-1 をめぐるバランスを明らかにしたいと思っています。そして HTLV-1 をめぐる病気やその治療法の開発に寄与し、今後の患者さんのお役に立ちたいと考えています。

3. 研究に参加いただける方

・ATL 患者、HAM 患者、HTLV-1 キャリア、その他 HTLV-1 陽性の方、また HTLV-1 陰性の方若干名

・満年齢 20 歳以上の方

・文書による同意が得られた方

上記の全てに当てはまる方の参加をお願いしています。

4. 検体ならびに検査の方法について

本研究の趣旨にご賛同いただけた方からは、通常の採血時に血液を多少余分に採取させていただきます。採血場所は担当医師が所属する医療機関とし、採血量は現在の健康状態に問題を生じない量です。また、診療上の必要に応じて骨髄やリンパ節、皮膚から生検という形で組織を採取することがありますが、その標本を一部供与いただき、解析を行いたいと考えています。具体的には HTLV-1 ウィルスの量やその他、免疫に関する項目について検査を行う予定としています。研究に参加したことによる、健康上の不利益が生じた際には、あなたの健康保険の範囲内で適切な処置を行います。

また、一部の検査に関しては患者さんからいただいた血液検体などを他の研究施設へ送付し、解析を行うこともありますが、送付にあたっては個人を特定できる情報を取り除く処理を行いますので、あなたの分析結果は、分析を行う研究者を含む誰にも、あなたのものであると分からなくなります。

5. 本研究の参加に伴って予想される利益、不利益について

この研究への参加によるあなたの費用負担は発生せず、謝礼もありません。この研究がすぐにあなたの診療に有用な情報を提供する可能性がありますが、必ずしもそうなるとは限りません。

検査の際の採血量が若干増えますが、健康上の問題を生じることはありません。また治療法への介入はないため、診療上の不利益を被ることはありません。しかし新しい発見につながれば、今後の HTLV-1 感染者における診断・治療の進歩に役立つ可能性があります。

6. 本臨床研究への参加とその撤回について

あなたがこの研究に参加されるかどうかは、あなたご自身の自由な意思でお決め下さい。たとえ参加に同意されない場合でも、あなたは一切不利益を受けませんし、これからの外来でのフォローアップに影響することもありません。また、あなたが研究の参加に同意した場合であっても、いつでも研究への参加をとりやめることが

できます。参加を取り消した場合は、それまでのデータや試料は原則、破棄しますが、患者さんの同意が得られれば、そのまま使用させていただきます。ただし、学会等で公表後は、破棄できない場合があります。

7. 研究期間と参加いただく患者さんの人数

本研究は佐賀大学医学部附属病院臨床研究倫理審査委員会承認日から平成29年3月31日までの研究期間で研究全体として約130名の患者さんの参加を予定しております。当院では、計70名の患者さんおよび15名の健常な方の参加を予定しております。

8. プライバシー保護について

本研究に関係する全ての研究者は、「ヘルシンキ宣言」（日本医師会訳）[1)]および「臨床研究に関する倫理指針」（平成20年厚生労働省告示第415号）[2)]に従って本試験を実施します。

1) http://www.med.or.jp/wma/helsinki08_j.html

2) http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/index.html

あなたの名前や病名、家族歴などの医療情報を登録する場合には、プライバシーを保護するために資料から氏名などの個人識別情報を取り去り、符号をつけて取り扱います。あなたと符号を結びつける対応表は、担当医師において厳重に保管します。この研究に関して得られるデータは、集積されて学会や論文として公表されることがありますが、そのような場合でも匿名化されているため提供者の個人情報は守られます。

9. 研究終了後の試料の取り扱い

ご提供いただいた試料は、原則として本研究のために使用し、研究終了後は破棄されます。ただ、この分野の研究進歩はめざましく、近い将来特定の白血球の遺伝子型が特定の病気と相関することが判明する可能性もあり得ます。このため、もしご同意が得られるなら、今回の検討が終了した後、新たな検討に備えて一部の検体を保存したいと考えています。もちろんその場合でも、『8.参加した患者さんのプライバシー保護について』で説明したように個人情報は保護されます。なお将来、試料を再び用いる場合は、改めてその研究計画を倫理審査委員会に申請し、承認された後に用います。

10. 研究に関する資料の閲覧について

本研究に関連する臨床研究計画書などの資料は、あなたが希望された場合、他の研究参加者の個人情報保護やこの研究の独創性の確保に支障がない範囲で、入手または閲覧

することができます。ただし、閲覧を希望されてから上記の個人情報保護および研究の独創性の確保のために、種々の手続きあるいは研究実施者および研究実施組織における協議を行ないます。その結果、資料の提示まで時間がかかることや希望された資料の一部のみの提示となる場合がある事をご了承下さい。

11. 費用について

ご参加いただくにあたって、あなたに費用を負担していただくことはありません。また、ご参加いただくにあたっての謝金などのお支払いもありません。

12. 健康被害が発生した場合の対応と補償について

本研究は、科学的に計画され慎重に行われますが、この研究への参加による採血行為によりいつもと違う症状または身体の不調がありましたら、すぐに担当医師にお知らせ下さい。ただちに適切な処置および治療を行います。この場合の治療も、通常の診療と同様にあなたの健康保険を用いて行われます。

また、本研究で発生した健康被害に対して、医療費・医療手当または保証金などの特別な補償はありません。この点を十分にご理解いただき、研究への参加をご判断下さい。

13. 研究の資金源と利益相反について

本研究の実施に必要な事務的な費用は、佐賀大学医学部血液・呼吸器・腫瘍内科の委任経理金から賄われます。

臨床研究における利益相反（ＣＯＩ（シーオーアイ）：Conflict of Interest）とは「主に経済的な利害関係によって公正かつ適正な判断がゆがめられてしまうこと、またはゆがめられているのではないかと疑われかねない事態」のことを指します。具体的には、製薬企業や医療機器メーカーから研究者へ提供される謝金や研究費、株式、サービス、知的所有権などがこれにあたります。このような経済活動が、臨床研究の結果を特定の企業や個人にとって有利な方向に歪曲させる可能性を判断する必要があり、そのために利害関係を管理することが定められています。

当院の倫理委員会では、関連する企業や団体などと研究の信頼性を損ねるような利害関係を有していないこと（利益相反関係にないこと）を確認しております。

14. 研究に参加された場合に守っていただきたい事項

本研究中は、研究担当者の指示に従って下さいますようお願いいたします。また、分からないことや何か異常が起きましたら、すぐに私たち担当者に知らせてください。

15.本研究から生じる知的財産権の帰属について

この研究から生じる特許権などの知的財産権は、佐賀大学または共同研究者に帰属します。

16.研究に関するお問い合わせ先

この研究について何か分からないことや心配なことがありましたら、どんなことでも担当医もしくは下記の実施責任者にご相談下さい。

実施責任者：佐賀大学医学部血液・呼吸器・腫瘍内科　助教　進藤岳郎

研究責任者：佐賀大学医学部血液・呼吸器・腫瘍内科　教授　木村晋也

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以上、この研究の内容について十分ご理解いただいたうえで、本研究に参加することをお決めになりましたら、同意書に署名及び捺印をし、日付の記入をお願いいたします。その後に、説明文書とともに患者さん用の同意書をお渡しいたします。
なお、この研究内容は、佐賀大学医学部附属病院臨床研究倫理審査委員会で審議を受け、医学的、倫理的に適切であることが承認されたものであります。

また、本委員会における審査の内容や委員会に関する情報は佐賀大学医学部附属病院治験センターホームページの「情報公開」のコーナーにおいてご覧いただくことができます。

(URL: http://www.hospital.med.saga-u.ac.jp/chiken/)

様式第１９

学　会　等　発　表　実　績

委託業務題目「アンメットメディカルニーズにおける抗がん薬のPK/PDに基づく最適化医療の実施に関する研究」
機関名：国立がん研究センター

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Clinical pharmacology of EGFR/Met inhibitors in non-small cell lung cance	Yagishita S, Hamada A	Current Drug Target	2014	国外

（注１）発表者氏名は、連名による発表の場合には、筆頭者を先頭にして全員を記載すること。
（注２）本様式はexcel形式にて作成し、甲が求める場合は別途電子データを納入すること。

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Current Drug Targets, 2014, *15*, 000-000

Clinical Pharmacology of EGFR/Met Inhibitors in Non-Small Cell Lung Cancer

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Abstract: Development of molecular targeting agents, starting with imatinib for chronic myeloid leukemia or gefitinib for non-small cell lung cancer (NSCLC), has recently progressed at a rapid rate. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have already been developed to the 2nd and 3rd generation, and novel drug development targeted towards Met activation, which is an EGFR-TKI resistance mechanism, is ongoing. Although the era of new anticancer agents is moving towards an era of molecular targeting agents, the methods used for drug development are not different than before. In addition to the importance of pharmacokinetics (PK) and pharmacodynamics (PD) for drug development, emerging evidence is also demonstrating the significance of pharmacogenomics, since certain types of gene alteration may greatly affect drug metabolism, excretion, and notably, clinical efficacy. It is desirable to determine optimal doses of anticancer drugs by taking into account these factors that could potentially influence PK/PD. The following article reviews the clinical development of EGFR/Met inhibitors for NSCLC and the clinical pharmacology of these drugs.

Keywords: Epidermal growth factor receptor, Met, non-small cell lung cancer, pharmacology.

1. INTRODUCTION

The findings of molecular studies of non-small cell lung cancer (NSCLC) brought a paradigm-shift in therapeutic strategy from that of conventional cytotoxic drugs to individual molecular targeted agents (MTAs). Since the development of the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) gefitinib, there has been rapid progress in search of new molecular targets and in the development of MTAs, including agents for targets such as anaplastic lymphoma kinase (ALK) translocation or rearranged during transfection (RET) fusion [1, 2]. Moreover, there has also been great progress in the investigation of drug resistance. Prime examples of such resistance are the secondary mutation of the EGFR exon 20, leading to the EGFR T790M mutant, or Met activation, which leads to EGFR-TKI resistance. Overcoming therapeutic resistance is an issue of great significance in molecular targeting therapy and the development of innovative MTAs are a demand of the times [3-5].

In past development of conventional cytotoxic drugs, the "3 + 3 design" was frequently used, in which side effects were treated as surrogates of clinical effects because of the close correlation of drug exposure, side effects, and clinical effects. Hence, the maximal tolerated dose (MTD) and the recommended dose (RD) were determined in compliance with the prevalence of intolerable toxicities (dose-limiting toxicities (DLT)), with the aim of adjusting the blood concentration of an agent for a therapeutic window with as low a side effect and as high a therapeutic effect as possible. Although the influence of several gene polymorphisms on drug absorption or metabolism was already recognized at that time, it was not considered in terms of drug development (Table 1).

Recent drug development of MTAs has been undertaken in almost the same manner as for previous drugs. However, various problems are emerging with such an approach. One problem is the drug administration method. As typified by EGFR-TKIs, most of the newly developed MTAs are orally administered drugs, and it is difficult to predict their pharmacokinetics (PK) and pharmacodynamics (PD) due to various factors that potentially influence their absorption or the first-pass effect. Secondly, there are differences in side effects between conventional cytotoxic drugs and MTAs, such as the skin rash or diarrhea of EGFR-TKIs. Thirdly, since most MTAs are exposed chronically, their side effects, when considered as surrogates of clinical effects, may differ from those of cytotoxic drugs, in which PK parameters such as maximum concentration (Cmax) and area under the blood concentration-time curve (AUC) correlate with side effects and MTD. As a consequence, the DLT might have to be changed to be suitable for MTAs. A further problem has arisen that was discovered based on accumulating evidence of pharmacogenomic (PGx) studies. Recent studies in genetic research have elucidated various genetic factors that impact clinical response, like EGFR mutation for EGFR-TKI therapy, or on PK profiles such as gene polymorphisms of metabolic enzyme, cytochrome P450 (CYP), or ATP-binding cassette (ABC) transporter. These data undermine the

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1389-4501/14 $58.00+.00

Table 1. EGFR-TKIs for NSCLC.

Generation	1st Generation		2nd Generation	
Compound	Gefitinib	Erlotinib	Afatinib	Dacomitinib
Target	EGFR		EGFR, HER2, HER4	
Phase	Approved	Approved	Approved	Phase III
MTD	700 mg QD	200 mg QD	50 mg BID	45 mg QD
Clinical dose	250 mg QD	150 mg QD	40 mg BID	45 mg QD
Bioavailability	60%	59%	Unknown	Unknown
Plasma protein binding	90%	95%	95%	97-8%
Transporter	ABCB1, ABCG2	ABCB1, ABCG2	ABCB1, ABCG2	Unknown
Cytochrome P450	CYP3A4	CYP3A4/5, CYP1A1/2	Michael Addition	CYP2D6, CYP3A4
Cmax (ng/mL) ss	384 [1)]	2384 [2)]	83.3 [3)]	112 [4)]
$t_{1/2}$ (hr) ss	41.3 [1)]	25.9 [2)]	40.4 [3)]	59-85 [4)]
AUC (ng · hr/mL) ss	16660 [1)]	42679 [2)]	1240 [3)]	2250 [4)]

1) 225 mg QD administration for 14 days. 2) 150 mg QD administration for 23 days. 3) 40 mg BID administration for 28days. 4) 45 mg QD administration for 14 days. MTD; maximum tolerated dose, SS; steady state

assumption of a triangular relationship between blood concentration, side effects, and clinical effect for MTAs. There is therefore an urgent need for drug development that takes into account such various factors that could potentially influence the MTA effect. Furthermore, these accumulating data also indicate the increasing importance of PK, PD, and PGx in the development and proper use of MTAs in clinical practice. In this review, we summarize the current development of EGFR/Met inhibitors and the clinical pharmacology of these drugs.

2. EGFR-TKIS FOR NSCLC

The EGFR pathway is part of a complex signal-transduction network that is central to critical processes in cell proliferation. In 2002, gefitinib was the first approved EGFR-TKI for the treatment of locally-advanced or metastatic NSCLC in Japan. Gefitinib is a low-molecular weight quinazoline derivative that inhibits EGFR tyrosine kinase activity by hydrogen-bonding with M793 in the kinase adenosine triphosphate (ATP)-binding site, thereby reversibly inhibiting the binding of ATP, and is therefore called a "reversible EGFR-TKI". In 2004, the correlation between EGFR mutation and the clinical response to this EGFR-TKI was demonstrated [6]. The prevalence of EGFR mutation was shown to vary across different ethnicities; approximately 10% of NSCLC in Caucasians and 35% in Asians [7]. Since then, several EGFR-TKIs have been developed, some of which have already been approved for clinical use (Fig. **1**, Table **1**).

2.1. First Generation EGFR-TKIs

2.1.1. Gefitinib

Gefitinib and erlotinib belong to the 1st generation EGFR-TKIs, which reversibly inhibit the binding of ATP. In a phase I trial of gefitinib, patients were treated with daily doses of up to 700 mg gefitinib. The MTD was determined as 700 mg with a DLT of grade 3 reversible diarrhea [8, 9]. The RD was determined as 250 mg QD based on similar clinical activity to, and a lower incidence of grade 3 or worse toxicity compared with 500 mg QD [10, 11]. After oral administration of gefitinib, peak plasma concentrations are achieved within 3 to 7 h, with a mean oral bioavailability of 60%. Elimination of gefitinib is primarily by hepatic CYP3A4 metabolism and the inactive metabolites are excreted in feces [12].

2.1.2. Erlotinib

Erlotinib, the second EGFR-TKI to be approved, was evaluated using daily doses of up to 200 mg in a phase I trial [13]. The MTD was determined as 200 mg with grade 3 or 4 diarrhea and the RD for NSCLC was determined as 150 mg QD. Peak plasma concentrations occur 4 h after oral administration with a mean oral bioavailability of 59%. Erlotinib is metabolized primarily by CYP3A4/5 and to a lesser extent by CYP1A1/2 and CYP2C8. Elimination is primarily by excretion in feces.

Major side effects of 1st generation EGFR-TKI therapies were diarrhea and skin rash in 50% or more of treated patients. Other side effects included hepatic toxicity, dry skin, nausea, vomiting, pruritis, anorexia, and fatigue. Interstitial lung disease (ILD) occurred in approximately 5% of patients in an Asian population. Up to one third of these cases were fatal.

2.2. Second Generation EGFR-TKIs

The ultimate issues in EGFR-TKI therapy are the inevitable therapeutic resistance and recurrence. The tumors of 20 to 40% of patients with an EGFR mutation are intrinsically

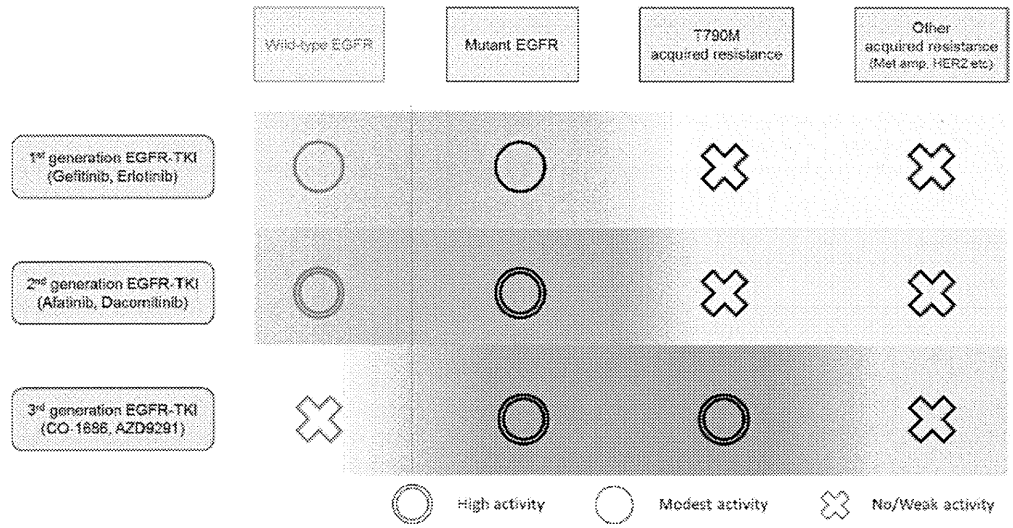

Fig. (1). Varios current EGFR-TKIs and their clinical activity.

resistant to EGFR-TKIs, called intrinsic resistance. The mechanisms of intrinsic resistance are reported to be the presence of a threonine-to-methionine substitution at amino acid position 790 (T790M) in the EGFR gatekeeper residue, Met activation, ALK translocation, improvement of drug metabolism due to enzyme induction or gene polymorphisms, and BCL2-like 11 (BIM) polymorphisms [3, 14-16]. The mechanisms of acquired resistance include T790M mutation (50%), Met amplification (5-10%), PIK3CA mutation (~5%), small-cell lung cancer transformation (1%), and epithelial-mesenchymal transition (1%) [3-5]. Second generation EGFR-TKIs have been developed to overcome acquired resistance, especially that involving the T790M mutation. These EGFR-TKIs form an irreversible covalent bond to a unique cysteine residue at a 797 in the EGFR catalytic domain, which results in the inhibition of ATP binding and also inhibition of the other members of the HER family, HER2 and HER4.

2.2.1. Afatinib

Afatinib was recently approved as an EGFR-TKI and was evaluated using daily doses of up to 50 mg in a phase I trial [17]. The MTD and RD were determined as 50 mg QD, with the most common side effects being diarrhea and skin rash. The recommended starting dose was modified to 40 mg QD in a phase II trial because the 40 mg QD therapy showed a similar objective response and fewer grade 3 adverse events compared with 50 mg QD therapy [18]. Peak plasma concentrations are generally reached within 3 to 5 h after oral dosing. The absolute bioavailability of afatinib in humans is unknown. Afatinib is metabolized primarily by Michael addition rather than by cytochrome P450. Elimination is primarily by excretion in feces [19]. In the phase III trial LUX-Lung 3 whose primary endpoint was progression-free survival (PFS), afatinib significantly prolonged median PFS compared with cisplatin plus pemetrexed as first-line chemotherapy in patients with EGFR mutation positive stage IIIB/IV lung adenocarcinoma (median PFS 11.1 vs. 6.9 months, p=0.001) [20]. In contrast, in the LUX-Lung 4 trial, which evaluated the efficacy (primary endpoint: objective response rate) of afatinib for patients who experienced progression during prior gefitinib or erlotinib therapy, afatinib showed unsatisfactory results as 2nd or 3rd line chemotherapy for this EGFR-TKI resistant population (response rate (RR) 8.2%, median PFS 4.4 months) [21].

2.2.2. Dacomitinib

Another second generation EGFR-TKI, dacomitinib, was investigated in a phase I trial using daily doses of up to 60 mg. The MTD and RD were determined as 45 mg QD, with common side effects being stomatitis, skin rash, and diarrhea [22]. Peak concentrations of dacomitinib in plasma occurred 12 h after oral dosing. Elimination of dacomitinib is primarily by CYP2D6 and CYP3A4 metabolism [23]. In a randomized phase II trial, dacomitinib showed a promising effect in 2nd or 3rd line therapy for unselected NSCLC patients compared with erlotinib (median PFS; 2.86 vs. 1.91 months) [24]. However, a recent interim result of the phase III ARCHER 1009 trial, whose primary endpoint being PFS, revealed little efficacy of dacomitinib for unselected NSCLC (dacomitinib vs. erlotinib, RR; 11.4% vs 8.2%, median PFS; 2.6 vs. 2.6 months, median overall survival (OS); 7.9 vs. 8.4 months) [24, 25]. Another phase III trial, ARCHER 1050, which is evaluating the efficacy (primary endpoint: PFS) of dacomitinib in treatment-naïve NSCLC patients with EGFR mutation, is still ongoing (ClinicalTrials.gov: NCT01774721).

As a whole, 2nd generation EGFR-TKIs seem to have equivalent efficacy compared with 1st generation EGFR-TKIs, with obviously enhanced side effects such as diarrhea or skin rash (Table **2**). Moreover, although these drugs were initially intended to overcome resistance that was acquired mainly by EGFR T790M mutation, to date neither afatinib nor dacomitinib have demonstrated significant efficacy towards EGFR mutated tumors with acquired resistance.

2.3. Third Generation EGFR-TKI

The clinical efficacy of 2nd generation EGFR-TKIs was limited partly because of enhanced adverse events, which were assumed to be a result of concomitant inhibition of wild-type EGFR. This assumption led to the development of

Table 2. Frequently observed side effects related to EGFR-TKI treatment.

	1st Generation		2nd Generation		3rd Generation	
All Grade / Grade3-4 (%)	**Gefitinib[1)]**	**Erlotinib[1)]**	**Afatinib[1)]**	**Dacomitinib[2)]**	**CO-1686[3)]**	**AZD9291[4)]**
Rash	43 / 0	85 / 14	96 / 15	58 / 10	4 / 0	27 / 0
Diarrhea	48 / 1	62 / 5	90 / 16	78 / 12	23 / 0	20 / 1
Dry skin	13 / 0	21 / 1	31 / 0	30 / <1	-	11 / 0

1) Data from package inserts 2) Data from [68] 3) Data from [27] 4) Data from [28]

3rd generation EGFR-TKIs, which were designed to selectively inhibit the T790M mutated EGFR with less activity against wild-type EGFR.

2.3.1. CO-1686

CO-1686 is a newly developed 3rd generation EGFR-TKI, which irreversibly and selectively inhibits mutant EGFRs, in particular the T790M mutated EGFR. In a preclinical study, CO-1686 demonstrated a significant growth inhibitory effect towards T790M mutant-expressing tumors with minimal effect on wild-type EGFR *in vitro* and *in vivo*. Recently, CO-1686 demonstrated a good tolerability and promising efficacy in the phase I part of a phase I/II trial that included patients with EGFR mutated, recurrent, advanced NSCLC previously treated with an EGFR-TKI [27]. In this trial, CO-1686 was evaluated using daily doses of up to 1000 mg, and the expansion cohorts including three dosing cohorts (500/625/750 mg BID) for two different patient cohorts (a 2nd line patient cohort and a >2nd line patient cohort) are still ongoing. The reported results showed that grade 3/4 toxicities were hyperglycemia (22%), QTc prolongation (7%), vomiting (3%), decreased appetite (1%), and nausea (1%). The proportion of toxicities that were related to wild-type EGFR inhibition was low, and was comparable to that of the placebo arm in previous trials (diarrhea 21%, rash 5%). In an analysis of 40 patients with the EGFR-T790M mutation, CO-1686 showed promising activity (RR 58%) and an encouraging PFS (not reached, current estimates exceed 12 months). A randomized phase II/III trial of CO-1686 or erlotinib for the treatment of naïve EGFR mutated patients (TIGER1 trial), a phase II single-arm trial for T790M positive 2nd line patients after EGFR-TKI failure (TIGER2 trial / NCT02147990), and a randomized phase III trial evaluating CO-1686 or chemotherapy for 2nd line T790M positive patients after EGFR-TKI failure (TIGER3 trial) are in progress.

2.3.2. AZD9291

AZD9291 is also a mutant selective, irreversible 3rd generation EGFR-TKI that has shown antitumor activity against both an EGFR activating mutation and the EGFR T790M mutation while maintaining a margin of selectivity against the wild-type EGFR. In a currently ongoing open-label phase I trial, up to 240 mg AZD9291 was administered once a day [28]. In a dose escalation cohort of this trial, no DLTs have been seen at any dose evaluated and the MTD has not been defined. The recommended phase II dose was determined as 80 mg QD based on both its activity in T790M positive patients and on the low incidence of toxicity. The frequently observed side effects of 80 mg QD in the cohort (n=74) were (any grade (%) / Grade ≥3 (%)): rash (27/0), diarrhea (20/1), nausea (14/0) and dry skin (11/0). Characteristic side effects of AZD9291 were: hyperglycemia (n=3), QT prolongation (n=4), and an ILD-like event (n=6). The RR according to T790M status was 65% in T790M positive patients and 22% in T790M negative patients, indicating the T790M specific activity of AZD9291 as expected. Two phase II trials that are evaluating the efficacy and tolerability of 80 mg QD for T790M positive patients (AURA trial / NCT01802632 and AURA2 trial / NCT02094261) are ongoing, and a phase III trial to compare AZD9291 and platinum-based chemotherapy in second-line, EGFR-TKI pre-treated patients (AURA3 trial / NCT0215981) is under consideration.

In summary, the development of 3rd generation EGFR-TKIs appears to be running smoothly and these inhibitors are promising for the treatment of EGFR-TKI resistant tumors with the EGFR-T790M mutation, which accounts for more than 50% of resistant cases. As expected, these mutant selective EGFR-TKIs clearly showed a lower incidence of rash, diarrhea, or dry skin that were assumed to occur as a result of wild-type EGFR inhibition. This lower incidence of side effects enabled dose escalation, higher PK and considerable efficacy (Table **2**).

3. MET INHIBITOR FOR NSCLC

Met is a heterodimeric receptor tyrosine kinase with a natural ligand, hepatocyte growth factor (HGF), that is produced by stromal and mesenchymal cells in an endocrine or paracrine manner [29]. Met can be altered and activated through receptor overexpression, gene amplification, mutation or alternative splicing. Met activation induces subsequent activation of multiple signaling pathways involved in proliferation, survival, angiogenesis, morphogenesis, cell scattering, motility, migration and invasion [30, 31].

Met is often concomitantly expressed with the EGFR in NSCLC, and the importance of cross-talk between Met and the HER family has been well described. Activation of Met depends on EGFR overexpression, and, conversely, HGF stimulation promotes EGFR activation [32, 33]. Moreover, Met plays a key role in EGFR-TKI resistance by driving HER3-dependent activation of PI3K [34]. Therefore, a Met inhibitor for NSCLC has been considered in order to overcome EGFR-TKI resistance (Table **3**).

3.1. Onartuzumab

Onartuzumab is a humanized monovalent monoclonal antibody that blocks HGF binding and prevents downstream cellular signaling of Met. In a phase I trial, onartuzumab was

Table 3. Met inhibitors for NSCLC.

Compound	Tivantinib	Crizotinib	Onartuzumab
Target	Met	Met, ALK, ROS1	Met
Type	TKI		MoAb
Phase	Phase III	Approved as ALK inhibitor Phase I as Met inhibitor	Phase III
MTD	360 mg BID	250 mg BID	Not identified up to 30 mg/kg
Recommended dose / clinical dose	360 mg BID for EM[1)] 240 mg BID for PM[1)]	250 mg BID	15 mg/kg
Transporter	Unknown	ABCB1	-
Cytochrome P450	CYP2C19	CYP3A4/5, CYP2B6	-
Cmax (ng/mL)	2719 [2)]	493 [3)]	348 (μg/ml) [4)]
$t_{1/2}$ (hr)	6.5 [2)]	39.5 [3)]	11.5 (days) [4)]
AUC (ng · hr/mL)	26655 [2)]	4608 [3)]	1740 (μg · day/mL) [4)]

1) EM: extensive metabolizer of CYP2C19, PM: poor metabolizer of CYP2C19. 2) 360 mg BID administration for 22 days. 3) 250 mg BID administration for 15 days. 4) 15 mg/kg single-agent administration. Abbreviations; TKI: tyrosine kinase inhibitor, MoAb: monoclonal antibody

evaluated using doses of up to 30 mg/kg without exhibiting an MTD, and the RD was determined as 15 mg/kg based on preclinical PK/PD modeling [35, 36]. In a randomized phase II trial in unselected recurrent NSCLC with coprimary endpoints being PFS in the intent-to-treat group and Met-positive group, patients were assigned erlotinib plus onartuzumab (EO) or erlotinib plus a placebo (EP). There was no significant improvement in PFS or OS in the overall population (n=137, PFS hazard ratio (HR), 1.09; p=0.69; OS HR, 0.80; p=0.34). However, the EO population that was immunohistochemically (IHC) positive for Met did show improved PFS and OS (n=62; PFS HR 1.71, p=0.06; OS HR 2.61, p=0.004) [37]. Recently, the results of a randomized phase III trial (METLung trial, OAM4971g), which evaluated the survival benefit (primary endpoint: OS) of EO compared with EP for patients with previously treated Met IHC positive stage IIIb/IV NSCLC, were presented [38]. In that trial, Met expression status was determined using an IHC assay with the CONFIRM anti-total MET SP44 monoclonal antibody (Ventana). This trial was stopped due to the futility of EO at the time of enrolling 499 patients (EO vs. EP; median OS 6.8 vs. 9.1 months, HR 1.27, p=0.068; median PFS 2.7 vs. 2.6 months, HR 0.99, p=0.92). Despite the futility of this phase III trial, there is still room for consideration of the use of a biomarker (another antibody for IHC, the *MET/CEP7* ratio of FISH, or a Met point mutation) or enrichment of the study population (limit for patients with EGFR mutation or EGFR-TKI resistance) for Met-targeted therapy. Exploratory analyses of a phase III trial and the result of ongoing phase III trial which evaluate OS benefit with EO vs. EP in patients with Met positive and EGFR mutation positive NSCLC (NCT01887886) are awaited.

3.2. Tivantinib

Tivantinib is an oral tyrosine kinase inhibitor of Met that inhibits Met in a non-ATP competitive manner. Tivantinib stabilizes the inactive configuration of Met and disrupts Met phosphorylation and downstream signaling. Doses of tivantinib of up to 400 mg BID were evaluated in a phase I trial [39]. The frequently observed grade 3/4 DLTs were: fatigue, mucositis, palmar-plantar erythrodysesthesia, hypokalemia, and febrile neutropenia. The MTD and recommended phase II dose were determined as 360 mg BID. Peak plasma concentrations of tivantinib occurred 2 to 4 h after oral dosing. Elimination of tivantinib is primarily by CYP2C19 metabolism. In this trial, a patient with a CYP2C19*2 polymorphism developed grade 4 febrile neutropenia and grade 3 mucositis with higher AUC and Cmax of tivantinib. As a consequence, the RD was modified according to individual CYP2C19 polymorphism [40]. In a reported randomized phase II trial whose primary endpoint was PFS, erlotinib plus tivantinib (ET) improved PFS and OS over erlotinib plus placebo (EP) in a subset of patients with non-squamous NSCLC, which was a population enriched for Met overexpression (ET vs. EP; median PFS 132 vs. 68 days, HR 0.71, p=0.12; median OS 302 vs. 208 days, HR 0.72, p= 0.18) [41]. Based on these results, two phase III trials that compared the efficacy of ET and EP were conducted. The MARQUEE trial enrolled 1048 patients with 2nd or 3rd line non-squamous NSCLC for the aim of evaluating OS benefit, but was terminated early with futility [42]. The interim results showed a trend toward clinical benefit of ET in terms of RR (ET vs. EP, 10.3% vs. 6.5%, p<0.05), PFS (median PFS 3.6 vs. 1.9 months, HR 0.74, p<0.0001) and OS (median OS 9.3 vs, 5.9 months, HR 0.70, p=0.03). Another phase III ATTENTION trial, which evaluated OS benefit in Asian patients with 2nd or 3rd line non-squamous wild-type EGFR NSCLC, was also stopped when 307 patients had been randomized based on a higher incidence of ILD in the ET treated group [43]. Recently reported results of this trial showed some sign for benefit of PFS (ET vs. EP; median PFS 2.9 vs. 2.0 months, HR 0.719, p=0.019) and OS (median

OS 12.9 vs. 11.2 months, HR 0.891, p=0.427), although the data lacked statistical power. Another exploratory single-arm phase II trial evaluating ET treatment in patients with EGFR-TKI resistance was reported [44]. The subgroup analysis for Met IHC expression in this trial indicated the possibility of efficacy in ET treatment (Met IHC High vs. Low, median PFS 125 vs. 43 days, RR 9.1% vs. 0.0%).

3.3. Crizotinib

Crizotinib is a multi-target TKI for Met, ALK and ROS1, and is already approved for treatment of ALK translocation positive NSCLC. After oral administration of crizotinib, peak plasma concentrations are achieved within 5 h, with a mean oral bioavailability of 43%. Elimination of crizotinib is primarily by CYP3A4 and lesser extent by CYP2B6. The ongoing phase I expansion cohort of crizotinib for Met-amplified NSCLC was recently presented and showed promising results [45]. In this trial, patients were stratified based on Met amplification status that was defined as the ratio of Met gene copy number gain relative to centromere 7 (*MET/CEP7*), which was determined by FISH. Of the 14 patients that received 250 mg crizotinib BID treatment, the RR was 0% in the Low Met group (n=2), 17% in the Intermediate Met group (n=6) and 67% in the High Met group (n=6) with durable response (Intermediate vs. High Met, median duration of response 16 vs. 73.6 weeks). Based on these encouraging results, exploration of the optimal *MET/CEP7* ratio associated with clinical benefit is ongoing.

Although the concept of targeting Met is a reasonable approach, some of the Met inhibitors still could be effective for certain types of patients. Therefore, further exploration of valid biomarkers or enrichment for an appropriate patient population is urgently needed.

4. FACTORS INFLUENCING PHARMACOKINETICS AND PHARMACODYNAMICS

There is no room for argument regarding the importance of PK/PD in cancer chemotherapy and its development. However, a range of factors potentially impact PK/PD values. Non-genetic factors include food effects, physiological factors, lifestyle, comorbidities, and co-administration of other drugs. There is also accumulating evidence for modulation by genetic factors including by gene polymorphisms that influence drug absorption or metabolism. Here we discuss some of the factors that influence the PK/PD of EGFR or Met inhibitors (Table **4**).

4.1. Food Effect

Some important factors can have a tremendous impact on the absorption of drugs given orally such as food effect, poor bioavailability due to co-administration of drugs that affect gastric emptying time, or gastric pH.

Food intake can influence the extent of drug absorption after oral administration by increasing or decreasing absorption, or it can leave absorption unchanged. Erlotinib absorption is a prime example of food effect: when taken with food, a single-dose of erlotinib showed an approximate doubling in the concentration of the AUC and multiple doses showed 37-66% increases in the AUC [46]. On the other hand, when gefitinib was given with a high-fat breakfast, small increases in the AUC were seen but these increases were not clinically significant. There was a 39% decrease in the AUC when afatinib was administered with, compared to without food, which resulted in a recommendation of taking without food [8, 17]. Inappropriate usage of drugs can lead to loss of efficacy or serious side effects, even to a fatal adverse event. Food effect studies are therefore imperative during current drug development.

4.2. Co-Administration of Other Drugs

Co-administration of other drugs can influence the PK profile of cancer chemotherapy through drug-drug interaction. Proton pump inhibitors or histamine H_2-receptor antagonists induce lower gastric pH, resulting in lower bioavailability/AUC. Certain types of anticonvulsant or rifampicin may induce the activity of metabolic enzymes, especially CYP3A4, and increase drug clearance. Conversely, macrolide antibiotics or grapefruit juice may inhibit drug metabolism and result in an increased drug exposure and side effects. As most MTAs are eliminated by CYP3A4, these influences of drug-drug interaction cannot be negligible in clinical practice. Of the EGFR-TKIs, only afatinib is not metabolized by cytochrome P450.

4.3. ABC Transporter

Pharmacokinetic processes are highly dependent on the interplay of drugs with drug transporters in organs such as the intestine, kidney and liver. Gene polymorphism of ABC transporters is now increasingly recognized to have a significant role as a determinant of individual variability in response to various commonly prescribed drugs. There are 48 known ABC transporters, including three major transporters referred to as ABCB1 (P-glycoprotein), multidrug resistance-associated protein-2 (MRP2, ABCC2), and breast cancer-resistant protein (BCRP, ABCG2) that are known to influence the oral absorption and disposition of a wide variety of drugs [47]. As a consequence, the expression levels of these transporters have considerable influence on individual susceptibility to drug induced side effects, interactions and treatment efficacy.

Several studies evaluated the influence of ABC transporter polymorphism on the plasma concentration, effect, or side effects of EGFR-TKIs. A major functional polymorphism of ABCG2, 421C>A, was reported to be associated with gefitinib induced diarrhea in a cohort including 124 patients, and with increased plasma and cerebrospinal fluid concentration in 88 patients treated with erlotinib [48, 49]. In a study investigating the correlation between gefitinib induced side effects and the ABCG2 gene polymorphism 421C>A or 376C>T, no evident association was found in a relatively small cohort including 75 Japanese NSCLC patients [50]. The ABCG2 polymorphism -15622C>T, which is located in the promoter region, has also been reported to be associated with gefitinib induced diarrhea, increased plasma erlotinib concentration, and lower ABCG2 expression [51, 52]. The only novel report of the impact of ABCB1 polymorphism on EGFR-TKI therapy was a report of the association between the 1236TT-2677TT-3435TT genotype and a higher concentration of erlotinib, and the risk of developing toxicity [53].

Table 4. Factors that influence drug pharmacokinetics and pharmacodynamics.

Food Effect				
Drug	**Food**	**Effect on Drug Exposure**	**Recommendation**	**Reference**
Gefitinib	High-fat breakfast High-fat meal	↓AUC 14%, ↓Cmax 34% ↑AUC 32%, ↑Cmax 37%	No specific advise	[69]
Erlotinib	High-fat and High-calorie breakfast	↑AUC 200% (single dose) ↑AUC 37-66% (multiple dose)	Intake without food	[46]
Afatinib	High-fat breakfast	↓AUC 39%, ↓Cmax 50%, ↑tmax	Intake without food	[17]

Co-Administration of Other Drugs		
Drug	**Influence**	**Mechanism**
Proton pump inhibitor (omeprazole etc)	↓AUC of gefitinib, erlotinib	Sustained elevation of gastric pH
Histamine H2-receptor antagonist (famotidine, ranitidine etc)	↓AUC of gefitinib, erlotinib	Sustained elevation of gastric pH
CYP3A4 inducer (phenytoin, rifampicine etc)	↓AUC of gefitinib, erlotinib	Enhanced CYP3A4 metabolism
CYP3A4 inhibitor (macrolide, grapefruit juice etc)	↑AUC of gefitinib, erlotinib	Decreased CYP3A4 metabolism

ABC Transporter				
Drug	**Transporter**	**Polymorphism**	**Influence**	**Reference**
Gefitinib	ABCG2	15622C/T	15622C/T polymorphism and TT haplotype are associated with gefitinib induced grade 2/3 diarrhea	[52]
		421C>A (Q141K)	421C>A polymorphism is associated with gefitinib induced diarrhea	[48]
		421C>A, 376C>T	421C>A and 376C>T were not evidently associated with gefitinib induced side effects	[50]
		34G>A	34G>A is associated with gefitinib incuced skin rash	[70]
Erlotinib	ABCB1	1236TT, 2677TT, 3435TT	1236TT-2677TT-335TT genotype are associated with higher plasma erlotinib concentration and the risk of developing toxicity	[53]
	ABCG2	15622C>T, 1143C/T	-15622C/T and 1143C/T are associated with lower ABCG2 expression and higher erlotinib plasma concentration	[51]
		421C>A	421C>A is associated with higher plasma and cerebrospinal fluid erlotinib concentration.	[49]

Cytochrome P450			
Drug	**Polymorphism**	**Influence**	**Reference**
Erlotinib	CYP1A2	The AUC of erlotinib in smokers were 2.8-fold lower than non-smokers	[54]
Tivantinib	CYP2C19	PMs had 1.9-fold higher AUC of tivantinib compared with EMs	[40]

AUC; area under the curve, PM; poor metabolizer, EM; extensive metabolizer

4.4. Cytochrome P450

The cytochrome P450 superfamily (CYP) is a group of enzymes that plays a major role in the metabolism of lipophilic drugs. There are more than 30 types of CYP enzymes, and the majority of TKIs are metabolized by a CYP, especially by CYP3A4/5. Drug metabolism by CYP can be affected by several factors such as co-administration of other drugs, lifestyle or gene polymorphisms. Conversely, variability of CYP activity can impact on clinical outcome.

The difference in erlotinib PK according to smoking status is a famous example of CYP effects. A single dose of 150 mg or 300 mg erlotinib was administered to healthy males; the AUC of erlotinib in smokers was 2.8-fold lower than that of non-smokers due to the induction of CYP1A2 by

smoking [54]. The influence of CYP2C19 gene polymorphism on the metabolism of the Met inhibitor, tivantinib, was studied in a Japanese phase I trial [40]. CYP2C19 exists as wild-type CYP2C19*1, and two functionally deficient variants, CYP2C19*2 and CYP2C19*3. Approximately 20% of Asians, whose alleles consist of either CYP2C19*2 or CYP2C19*3, are poor metabolizers (PMs), whilst others, who possess at least one allele of wild-type CYP2C19*1, are extensive metabolizers (EMs). In the phase I trial that included 33 EMs and 14 PMs and that evaluated the safety and PK of tivantinib, the MTD was 360 mg BID for EMs and 240 mg for PMs with frequently observed side effects such as neutropenia, leukopenia, anemia, fatigue and anorexia. The PMs displayed a 1.9-fold higher AUC compared with EMs at a dose of 240 mg tivantinib BID. Thus, the RD for tivantinib in the phase II trial was determined as 360 mg BID for EMs and 240 mg BID for PMs. Several studies have described the impact of CYP gene polymorphisms on the efficacy or side effects of TKIs. However, the clinical utility of such knowledge should be proven in a large cohort study [55].

4.5. Physiological Factors

Physiological factors such as age, sex, body size, comorbidity or organ function can have some influence on the PK/PD profile [56, 57]. Aging is associated with lower activity of various cytochrome P450 enzymes such as CYP2D6 (1.4-fold), CYP2C19 (1.8-fold), or CYP3A4 (1.8-fold), and lower renal excretion (2-fold) compared with that of healthy adults [58-60]. The influence of body size on cytotoxic drug plasma concentration change is also well known. The American Society of Clinical Oncology provided tentative recommendations for appropriate cytotoxic drug dosing for obese patients as full weight-based dosing in 2012; however, there are limited data regarding the impact of obesity or low body weight on MTA plasma concentrations or clinical effects [61, 62]. Although ideally, optimal dose determination should be done in accordance with each of the above factors, specific dose subgroup analysis is not usually conducted in clinical trials or clinical practice, as there are too many of these factors and the factors are too complex.

CONCLUSION

Individualized drug selection and optimal dose determination is the ultimate goal of cancer chemotherapy development and clinical pharmacology. Most phase I trials are targeted at general solid tumors, start with roughly drawn doses, and advance development of the drug by taking into consideration the tumor types on which the drug has obvious efficacy, or, to some extent, the demands of the market. Nonetheless, since it is currently known that cancer types differ based on tumor origin, histological subtypes, gene alteration, or intratumoral heterogeneity, this makes it difficult to develop MTAs in the same manner as previous drugs. The EGFR-TKIs or Met inhibitors are prime examples of the need to take the above factors into account when developing drugs, as these drugs failed to show clinical benefit in an inappropriate study population based on ambiguous rationale. Clearly a more precise setting of the study population, evaluation of treatment efficacy in the study population, and further optimal dose determination or modification are needed.

Attention has recently been focused on the concept of therapeutic drug monitoring (TDM) for targeted therapy or a phase 0 trial, which would be a possible way for idealized dose optimization. The concept of TDM has been well established in the use of antibiotics, immunosuppressives, and antiepileptics. However, its use for cancer chemotherapy has been limited, partly because of the difficulty of multiple blood sampling for PK analysis [63]. As most MTAs are exposed chronically and their PK profiles are different from those of cytotoxic chemotherapy, several studies have demonstrated the possibility of estimating the steady-state drug concentration and further clinical efficacy by using a single trough-level measurement [64, 65]. Additionally, a phase 0 trial is a novel way of assessing not only PD but also PK or PGx. A phase 0 trial is a new form of clinical trial that involves microdoses of the drug in a very small number of patients and that aims to assess drug activity, especially PD [66, 67]. This concept can also be applied to assessments of drug-drug interaction, pharmacogenetic factors or many other physiological factors, and the following PK change.

Although there are still many hurdles to overcome before reaching our ultimate goal, the evaluation of PK/PD/PGx must become of greater and greater importance in future drug development. It should also be noted that these efforts aimed at dose optimization should be made not only in the development phase but also even after drug approval.

LIST OF ABERRATIONS

ABC transporter	=	ATP-binding cassette transporter
ABCB1	=	P-glycoprotein
ALK	=	Anaplastic lymphoma kinase
ATP	=	Adenosine triphosphate
AUC	=	Area under the curve
BCRP	=	Breast cancer-resistant protein, ABCG2
BIM	=	BCL2-like 11
CEP7	=	Centromere 7
Cmax	=	Maximum concentration
CYP	=	Cytochrome P450
DLT	=	Dose-limiting toxicities
EGFR-TKIs	=	Epidermal growth factor tyrosine kinase inhibitors
EM	=	Extensive metabolizer
EO	=	Erlotinib plus onartuzumab
EP	=	Erlotinib plus placebo
EP	=	Erlotinib plus placebo
ET	=	Erlotinib plus tivantinib
HGF	=	Hepatocyte growth factor
IHC	=	Immunohistochemistry
ILD	=	Interstitial lung disease
MRP2	=	Multidrug resistance-associated protein-2, ABCC2

MTAs	=	Molecular targeted agents
MTD	=	Maximal tolerated dose
NSCLC	=	Non-small cell lung cancer
OS	=	Overall survival
PD	=	Pharmacodynamics
PFS	=	Progression-free survival
PGx	=	Pharmacogenomix
PK	=	Pharmacokinetics
PM	=	Poor metabolizer
RD	=	Recommended dose
RET	=	Rearranged during transfection
RR	=	Response rate
T790M	=	Threonine-to-methionine substitution at amino acid position 790
TDM	=	Therapeutic drug monitoring

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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Received: July 09, 2014 **Revised: August 18, 2014** **Accepted: October 21, 2014**