Critical Reviews in Oncology / Hematology 163 (2021) 103366

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Clinical pharmacology and drug-drug interactions of lenvatinib in thyroid cancer

Stefano Fogli [a,*], Giulia Gianfilippo [a], Federico Cucchiara [a], Marzia Del Re [a], Laura Valerio [b], Rossella Elisei [b], Romano Danesi [a]

[a] Unit of Clinical Pharmacology and Pharmacogenetics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[b] Endocrine Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

ARTICLE INFO

Keywords:
Lenvatinib
Pharmacokinetics
Pharmacodynamics
Adverse drug reactions
Drug-drug interactions

ABSTRACT

Lenvatinib is a non-selective tyrosine kinase inhibitor (TKI) with high in vitro potency against vascular endothelial growth factor receptors. Although this drug is used to treat several cancer types, it is the most effective TKI used in patients with thyroid cancer. Lenvatinib is well tolerated and the most common adverse drug reactions can be adequately managed by dose adjustment. Particularly, blood pressure and cardiac function monitoring, as well as antihypertensive treatment optimization, may be required in patients treated with lenvatinib. Dose reduction should be taken into account in patients with body weight <60 kg or severe hepatic failure. No significant change in lenvatinib pharmacokinetics has been observed with other patient-related factors and very few data are available on lenvatinib pharmacogenetics. Lenvatinib can be administered orally regardless of food and no clinically relevant drug-drug interactions have been reported.

1. Introduction

Receptor tyrosine kinases are important druggable targets that play a role in the development of several pathophysiological processes including angiogenesis, cell proliferation, and immune system regulation (Suyama and Iwase, 2018; Chae et al., 2017; Koch and Claesson-Welsh, 2012; Roussos et al., 2011). Lenvatinib (Fig. 1) is an orally active multi-tyrosine kinase inhibitor (TKI) used to treat several cancer types including thyroid cancer, hepatocellular carcinoma, and renal cell carcinoma (in combination with everolimus) (Hamieh et al., 2020; Spallanzani et al., 2018). However, lenvatinib and sorafenib are the only two TKIs approved in patients with advanced and progressing radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC). Noteworthy, in countries where the two drugs are available, lenvatinib is the most commonly used as first-line treatment because of improved clinical response, as compared to sorafenib. Although no head-to-head comparison was carried out between the two drugs, substantial clinical differences emerged from two phase-III clinical trials, named DECISION for sorafenib (Brose et al., 2014) and SELECT for lenvatinib (Schlumberger et al., 2015), where progression-free survival (PFS) was 10.8 and 18.3 months, respectively. This difference was probably underestimated since, in the placebo group, patients in the SELECT trial had a worse PFS than those enrolled in the DECISION study (3.6 vs 5.8 months respectively) (Brose et al., 2014; Schlumberger et al., 2015). Beyond randomized clinical trials, lenvatinib also demonstrated to promote clinically relevant objective response rates and PFS in the real-life setting (Rendl et al., 2020).

In the current review article, we discuss the clinical pharmacology of lenvatinib to provide detailed information on its pharmacodynamics, pharmacokinetics, and drug-drug interaction potential that may be useful for its use in clinical practice.

2. Pharmacodynamics

Lenvatinib belong to the quinoline-based compound class (Fig. 1) that recognizes several derivatives with potent anticancer activity (Li and Zhu, 2021). This drug is a nonselective inhibitor since it can interact with different molecular targets, including vascular endothelial growth factor receptors (VEGFR1–3), fibroblast growth factor receptors (FGFR1–4), platelet-derived growth factor receptor-alpha (PDGFRα), mast/stem cell growth factor receptor (KIT) and rearranged during transfection receptor (RET) proto-oncogenes (Fogli et al., 2020). From the functional point of view, lenvatinib was found to inhibit neo-vessel assembly and maturation, and vascular permeability of tumor

* Corresponding author at: Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 55, 56126 Pisa, Italy.
E-mail address: stefano.fogli@unipi.it (S. Fogli).

https://doi.org/10.1016/j.critrevonc.2021.103366
Received 14 August 2020; Received in revised form 21 April 2021; Accepted 3 May 2021
Available online 26 May 2021

microenvironment (Matsui et al., 2008a, b; Tohyama et al., 2014; Yamamoto et al., 2014; Okamoto et al., 2013; Koyama et al., 2014; Cabanillas and Habra, 2016). At the molecular level, lenvatinib can target the ATP binding site of VEGFR2 through the cyclopropane ring, thus inhibiting tyrosine kinase activity and related signaling pathways (Okamoto et al., 2015). The concentrations at which lenvatinib exhibits its half-maximal inhibitory effect (IC50) on VEGFR phosphorylation are in the low nanomolar range (Matsui et al., 2008b). Lenvatinib also inhibits FGFR1 and PDGFR tyrosine kinases, but with IC50 mean values of 50−100-fold higher than those found for VEGFRs (Matsui et al., 2008a).

Several studies investigated in vivo pharmacodynamic biomarkers able to predict lenvatinib response in cancer patients (Tohyama et al., 2014; Yamada et al., 2011; Hong et al., 2015). In a phase 1-dose escalation study, a pharmacodynamic analysis was carried out in patients with advanced solid tumors using circulating endothelial cells and progenitor cells, as biomarkers of active blood vessels turnover and angiogenesis (Yamada et al., 2011). Noteworthy, c-KIT positive circulating endothelial and progenitor cells were significantly reduced by lenvatinib treatment, whereas no effect was observed on c-KIT negative cells. Changes in c-KIT positive circulating endothelial and progenitor cells correlated with lenvatinib response in patients with advanced solid tumors (Yamada et al., 2011). Furthermore, it has been demonstrated that higher pre-dose levels of stromal cell-derived factor-1-alpha (SDF1α) could predict lenvatinib resistance in NSCLC patients, while drug-induced increase in granulocyte-colony stimulating factor (G-CSF) levels was related to shorter PFS (Nishio et al., 2013). Changes in plasma angiogenic proteins (i.e., increased VEGF and SDF1α and reduced soluble VEGFR2) were also found to correlate with lenvatinib-induced tumor shrinkage and adverse drug reactions (Koyama et al., 2014). Finally, a decrease in the angiopoietin-1 ratio was found to be associated with longer PFS in melanoma patients treated with lenvatinib at 10 mg twice daily (Hong et al., 2015) (Table 1).

3. Pharmacokinetics

Lenvatinib is administered once daily by oral route at doses from 8 to 24 mg, depending on cancer types and treatment schedules (e.g., 24 mg in RAI-refractory DTC or 18 mg in combination with 5 mg everolimus in advanced renal cell carcinoma). After oral administration and absorption, lenvatinib binds extensively to plasma proteins (98–99 %), mainly albumin. A bi-exponential decay in lenvatinib plasma concentrations was observed after Cmax, with an elimination t1/2 of 28 h (Dubbelman et al., 2012). Lenvatinib is mainly metabolized in the liver by cytochrome P450 (CYP), mostly through CYP3A4 (> 80 %), and was found to be a substrate of ATP-binding cassettes (ABC) transporters, i.e., P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) (Gupta et al., 2016; Ozeki et al., 2019). These enzymes are associated with drug disposition by regulating the absorption and elimination of the substrate drug (Lin, 2007). Lenvatinib metabolites are formed by decyclopropylation, demethylation, N-oxidation, and O-dearylation (De Mattia et al., 2019). Lenvatinib is excreted via the biliary route and no accumulation after multiple daily doses was observed (Yamada et al., 2011; Boss et al., 2012). Findings from phase 1 studies with lenvatinib given at 3.2–32 mg demonstrated linear pharmacokinetics with a dose-dependent increase in AUC and Cmax (Yamada et al., 2011; Hong et al., 2015; Boss et al., 2012; Nakamichi et al., 2015) (Fig. 2).

4. Clinical use of lenvatinib and potential implication in target population

Nowadays, lenvatinib represents the first therapeutic option in the treatment of locally advanced or metastatic RAI-refractory DTC. The most relevant implication for the target population is to prolong progression-free survival (PFS) as much as possible, to offer patients new therapeutic options that include molecules selective for specific oncogene alterations (Wirth et al., 2020; Subbiah et al., 2018; Groussin et al., 2020; Liu et al., 2017).

In the target population, lenvatinib has been tested in a phase III, multicenter, randomized, placebo-controlled trial (SELECT study), in which patients with progressive locally advanced or metastatic RAI-refractory DTC were treated with lenvatinib or placebo. The study showed that patients treated with lenvatinib had a significantly longer progression-free survival (PFS) than those who received placebo (18.3 vs 3.6 months, respectively) (Schlumberger et al., 2015). At the time of data cut-off, no difference in overall survival was observed between the two groups; nonetheless, it should be noted that patients progressing in the placebo cohort were eligible to cross over to active treatment, thus partially compromising the overall survival analysis (Schlumberger et al., 2015). Based on the positive results, in terms of safety and efficacy, the FDA and EMA approved lenvatinib for the treatment of patients with RAI-refractory DTC. Other studies provide evidence on the efficacy and safety of lenvatinib in the real-life setting, although with a lower PFS value than that obtained in clinical trials (Locati et al., 2019; Aydemirli et al., 2020; Masaki et al., 2020). Lenvatinib is generally well tolerated; however, serious adverse events due to drug-induced VEGFR inhibition may occur (Matrone et al., 2017) (Fig. 2). Although few data on the quality of life for this patient population are available, according to an Italian study, there is a trend towards improving global health and reducing disease-related symptoms. Finally, the impact of some adverse drug reactions, such as anorexia, weight loss, and fatigue continue to

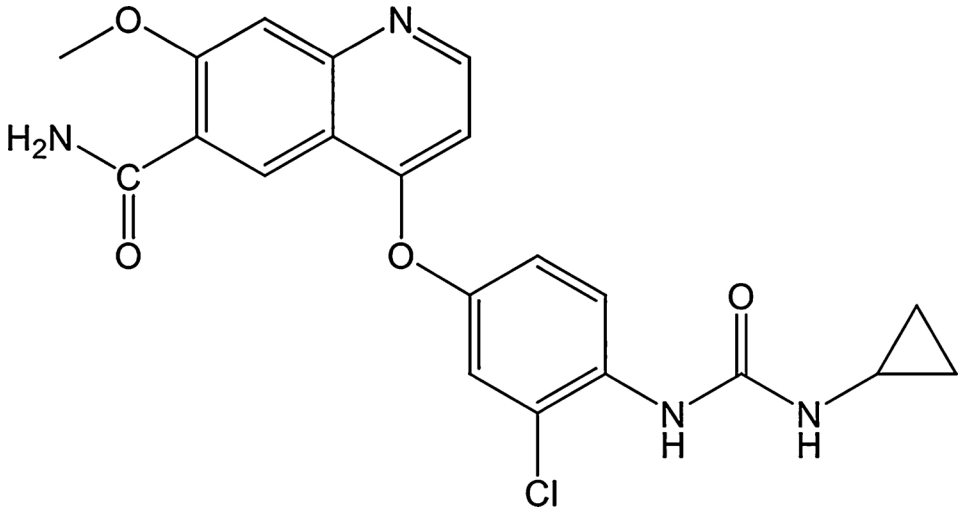

Fig. 1. Chemical structure of lenvatinib (4-[3-chloro-4-(cyclopropylcarbamoylamino)phenoxy]-7-methoxyquinoline-6-carboxamide).

Table 1
In vivo pharmacodynamic biomarkers of lenvatinib response.

Cancer type	Study type	Schedules	Biomarker	Predicted response	References
Solid tumors	Phase 1	[a]bid (2 week-on/1 week-off)	Plasma VEGF, sVEGFR2, and HGF	Hypertension, proteinuria, and fatigue	(Koyama et al., 2014)
Solid tumors	Phase 1	13 mg bid (2 week-on/1-week off)	c-KIT positive CEP and CEC	Treatment duration	(Yamada et al., 2011)
	Phase 1	0.5−20 mg bid (2 week-on/1 week-off)	Plasma VEGF, sVEGFR2, and SDF1α	Tumor shrinkage and adverse drug reactions	(Nishio et al., 2013)
Melanoma		10 mg bid (1 week-on/1 week-off)	angiopoietin-1	PFS	(Hong et al., 2015)

CEC: circulating endothelial cells.
CEP: circulating progenitor endothelial cells.
[a] Dosage is not reported.

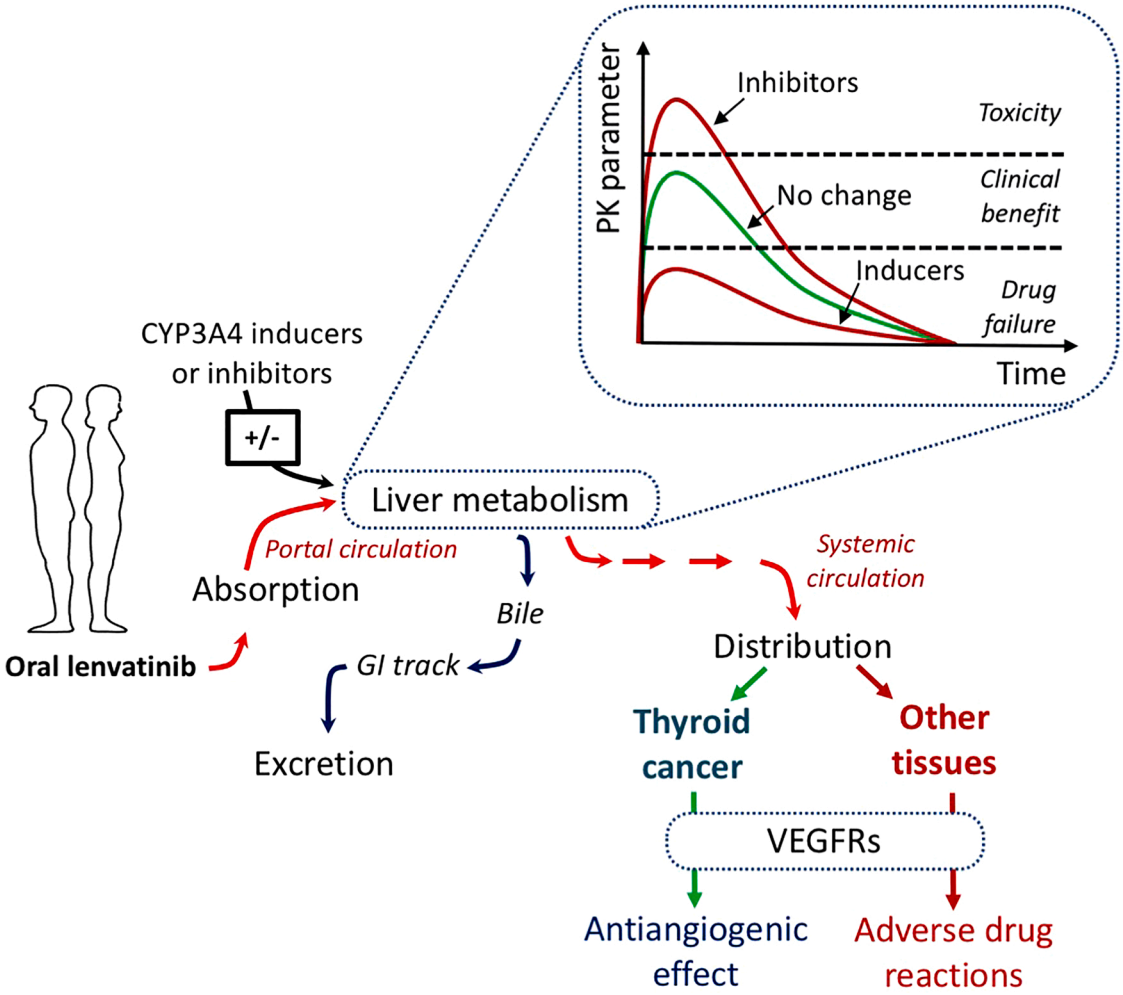

Fig. 2. Overview of lenvatinib pharmacodynamics and pharmacokinetics and the possible clinical consequences of drug-drug interactions.

represent the major clinical problem in the management of this drug (Giani et al., 2021).

5. Adverse drug reactions (ADRs)

The most common adverse events observed in patients treated with lenvatinib are hypertension, proteinuria, diarrhea, fatigue, hand-foot syndrome, and thrombocytopenia. The most frequently reported grade ≥3 ADRs are thrombocytopenia (25.4 %), hypertension (17.7 %) and peripheral edema (15.5 %) (Zhu et al., 2016). Probably drug-related life-threatening adverse events include pulmonary embolism and hemorrhagic stroke. Lenvatinib was found to cause proteinuria up to irreversible renal failure (Paschke et al., 2018; Furuto et al., 2018; Cavalieri et al., 2018). According to VEGF blockade, proteinuria and arterial hypertension were commonly observed in patients treated with lenvatinib (Fig. 2). Keizer and colleagues, using a pharmacokinetic/pharmacodynamic model, demonstrated that the development of proteinuria was associated to lenvatinib plasma concentrations and the increase in diastolic pressure (Keizer et al., 2010). Dose suspension or reduction should be considered in the presence of systolic or diastolic pressure ≥160 mmHg and ≥100 mmHg, respectively, despite optimal management, or proteinuria grade ≥2 (Schlumberger et al., 2015).

Lenvatinib treatment has also been associated with hepatotoxicity (Anon, 2015). No ALT elevations or hepatotoxicity has been reported in phase I and II studies on advanced cancer patients (Boss et al., 2012; Molina et al., 2014; Cabanillas et al., 2015). In a phase 3 clinical trial

carried out on thyroid cancer patients treated with lenvatinib 24 mg daily, hepatic failure was found in 0.4 % of cases (Schlumberger et al., 2015). Most recently, it has been postulated that liver cancer cell killing by lenvatinib may be caused by an increase in toxic autophagosome formation and a decrease in the synthesis of protective mitochondrial proteins (Roberts et al., 2020).

Cardiac function should be monitored after VEGF/VEGFR-targeted therapies, since QT prolongation is a drug class effect. Corrected QT prolongation (any grade, 8%; grade ≥3, 1.5 %) was found in patients with thyroid cancer treated with lenvatinib (Schlumberger et al., 2015). However, in a study carried out on 52 healthy subjects orally administered with lenvatinib at 32 mg as a single dose, no clinically relevant effect on the QTc interval was observed (Shumaker et al., 2014a).

6. Variability factors in drug response

6.1. Physiological factors

In a phase 2 study carried out on patients with hepatocellular carcinoma, an increase in lenvatinib AUC was observed with decreasing body weight. In particular, the cut-off value for body weight of 57.8 kg was able to predict the group at high risk for early drug withdrawal or dose reduction. As a consequence of this, the Authors recommended a starting dose of 12 and 8 mg for patients weighing ≥60 kg and <60 kg, respectively (Tamai et al., 2017) (Table 2). Nonetheless, in a pooled dataset from 779 subjects taking 3.2−32 mg of oral lenvatinib, the influence of body weigh on lenvatinib pharmacokinetics was found to be marginal (2.8 % of CL/F variation) with no dose adjustment required (Gupta et al., 2016). In the same study, the Authors demonstrated that pharmacokinetics was also unaffected by other patient-related factors including age, sex, and race (Gupta et al., 2016).

6.2. Hepatic/renal impairment

Several lines of evidence suggest that a dose reduction of lenvatinib could be required in patients with severe hepatic and/or renal impairment (Shumaker et al., 2015a; Dubbelman et al., 2015). However, no relationship was found between alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin levels and lenvatinib pharmacokinetics. Furthermore, although alkaline phosphatase and albumin showed a significant effect (-11.7 % and -6.3 % in lenvatinib clearance, respectively), these changes were not considered as clinically relevant (Gupta et al., 2016). In a recent review article, it has been underlined that patients with severe hepatic impairment showed an increase in lenvatinib AUC by 170 %, as compared to those with mild to moderate hepatic impairment or healthy volunteers. Therefore, the starting lenvatinib dose should be 14 mg rather than 24 mg in this specific patient population (Hussein et al., 2017) (Table 2).

Population PK analysis showed that renal function did not affect lenvatinib pharmacokinetics (Gupta et al., 2016); however, it has been noted that the patient population studied had a median creatinine clearance of 98.0 mL/min (range 17.0–268.0), most probably because patients with severe renal impairment are usually excluded from clinical trials (Hussein et al., 2017). Although no data have been published so far on lenvatinib, hemodialysis did not substantially change the efficacy and safety of targeted drugs belonging to the same class (e.g., axitinib, pazopanib, cabozantinib, and sorafenib) (Klajer et al., 2020). Consistent with these findings, hepatic or renal impairment has a negligible effect on albumin binding to lenvatinib (Hussein et al., 2017; Mano and Mizuo, 2019) (Table 2).

Table 2
Overview of variability factors in lenvatinib pharmacokinetics and pharmacodynamics.

Factor type	Examples	Recommendation
Physiological	Body weight, age, sex, race	Dose reduction may be required for patient <60 kg.
Pathological	Hepatic/renal impairment	No dose adjustment needed for mild-to-moderate failure. Dose reduction may be required for severe failure.
	Arrhythmogenic conditions (e.g., electrolyte abnormalities)	Periodically ECG monitoring. Dose adjustment required with QT interval prolongation >500 ms.
Pharmacogenetics	CYP3A4/5 and ABC transporter polymorphisms	No dose adjustment required.
Pharmacokinetic-based DDIs	Food, pH elevating drugs	Administered regardless of food. No dose adjustment required.
	CYP3A4/ ABC transporters inducers or inhibitors	No dose adjustment required.
Pharmacodynamic-based DDIs	QT prolongation agents (e.g., 5-HT3 antagonists, macrolides, antidepressants)	NK-1 inhibitors should be used instead of 5-HT3 antagonists. Caution is required with dihydropyridine calcium channel blockers and loop/ thiazide diuretics.

RAS: Renin-Angiotensin System.

6.3. Pharmacogenetics

Scientific literature is still lacking on the effect of genetic variants in genes that code for proteins involved in lenvatinib metabolism and disposition. Ozeki and co-workers (Ozeki et al., 2019) investigated the effect of CYP3A4/5 and ABC transporter polymorphisms on lenvatinib pharmacokinetics in Japanese patients. Although a correlation between CYP3A4 or ABCC2 polymorphisms and lenvatinib steady-state concentrations was found, the incidence of hypertension, proteinuria, and hand-foot syndrome following lenvatinib treatment appeared to be unrelated to the patient genetic make-up (Ozeki et al., 2019) (Table 2).

6.4. Drug–drug interactions (DDIs)

Drug-drug interactions (DDIs) may occur when multiple drugs are simultaneously or sequentially taken by the same patient and can assume clinical relevance due to clinical toxicity or treatment failure (Fig. 2). The assessment of DDIs, therefore represents an essential part of drug clinical management in the evaluation of the benefit-risk ratio of specific treatments (Sachdev and Gupta, 2019). Clinical DDIs derives from pharmacokinetic changes induced by perpetrator drugs that cause interactions on victim drugs and include those involving biological processes that play a role in absorption (e.g., gastric acid suppression, P-glycoprotein modulation), metabolism (e.g., induction/inhibition of CYP enzymes), and disposition (e.g., competition for binding with plasma proteins). Pharmacodynamic DDIs generally occurs when two or more drugs compete for the same target (e.g., QT interval prolongation). DDIs can be predicted by using commercially available electronic databases (Roblek et al., 2015) or experimentally assessed in small trials without delaying approval of new medications. Examples of pharmacokinetic endpoints generally investigated are area under the concentration-time curve, maximum concentration, and/or trough concentrations (i.e., the lowest concentration of a drug before the next dose).

6.4.1. Pharmacokinetic-based DDIs of lenvatinib

Co-administration of enzyme inducers and inhibitors may affect the activity of CYP3A4/5 and ABC transporters, which may cause clinically relevant drug-drug interactions (DDIs) with lenvatinib. Rifampicin is a well-known CYP3A4 inducer (Chen and Raymond, 2006), and remains the mainstay of treatment for tuberculosis and atypical mycobacterial infections, chemoprophylaxis of meningococcal disease, and meningitis due to *Haemophilus* Influenzae (Li and Wald, 1986). P-gp inhibition by

single-dose rifampicin was found to increase lenvatinib AUC and Cmax (approximately 30 %); however, multiple doses of rifampicin only reduced lenvatinib AUC by 18 %, with no change in Cmax values. Such an effect may be negligible since repeated rifampicin administration can simultaneously cause the CYP3A4 and P-gp induction, thus mitigating the first dose-effect by rifampicin. Overall, these changes were considered to be non-clinically relevant (Shumaker et al., 2014b) (Table 2).

Ketoconazole is an antifungal agent that potently inhibits both CYP3A4 and P-gp (Achira et al., 1999). A phase 1 study on healthy adult subjects was carried out to investigate the effect of ketoconazole (given orally at 400 mg once daily for 18 consecutive days) on lenvatinib pharmacokinetics (Shumaker et al., 2015b). This study demonstrated that systemic exposure of lenvatinib (taken orally at 5 mg) increased slightly (15–19 %) when combined with ketoconazole. In the group receiving both lenvatinib and ketoconazole, the 90 % CI of AUC was within the 80–125 % bioequivalence interval. The mean lenvatinib Cl/F values were similar in subjects receiving the combination, as compared to those treated with lenvatinib alone (7.70 vs. 8.78 L/h, respectively) (Shumaker et al., 2015b). These findings suggest that the co-administration of ketoconazole produces only marginal and most probably not clinically relevant changes on lenvatinib pharmacokinetics (Shumaker et al., 2015b) (Table 2).

Concerning potential food-drug interaction, the high-fat meal did not significantly affect the bioavailability and pharmacokinetics of lenvatinib. Although absorption of lenvatinib was found to be delayed in fed condition, the drug can be administered regardless of food (Shumaker et al., 2014c). A meta-analysis using PK pooled data from 15 clinical studies suggest that pH elevating drugs, including proton pump inhibitors, H2 blockers, and antacids, did not affect lenvatinib pharmacokinetics (Gupta et al., 2016) (Table 2).

6.4.2. *Pharmacodynamic-based DDIs of lenvatinib*

Hypertension is an adverse reaction observed with drugs targeting the VEGF signaling pathways and about 40 % of patients with metastatic renal cell carcinoma developed hypertension when lenvatinib is combined with everolimus (Bendtsen et al., 2017; Bitting et al., 2014; Katsi et al., 2014). This may occur since inhibition of VEGF signaling cascade can reduce angiogenesis and the release of both prostacyclins and endothelial nitric oxide (Bhargava, 2009). Hypertension usually appears in the early stages of the treatment cycle (Kudo et al., 2018) and blood pressure monitoring before and after lenvatinib therapy should be carried out. Indeed, severe complications, including dissection of the aorta, may occur in poorly controlled hypertension (Zhu et al., 2016; Groden et al., 2017) and a >20 % reduction in the ejection fraction was found in a small percentage of patients treated with lenvatinib (Shah and Morganroth, 2015).

To minimize the need of discontinuing administration or dose reduction of lenvatinib in hypertensive patients, treatment with antihypertensive drugs should be optimized until reaching a stable dose for at least one week (Zhu et al., 2016; Cabanillas and Takahashi, 2019). Furthermore, the choice of the antihypertensive agent should be personalized according to the clinical profile of patients and drug-related properties. For example, caution is required in patients with hypokalemia, hypomagnesemia, congenital long QT syndrome, or who receive concomitant drugs leading to QT prolongation (Schlumberger et al., 2015; Shah and Morganroth, 2015). Furthermore, loop and thiazide diuretics induce hypokalemia and hypomagnesemia that may result in prolongation of QT interval, whereas the potassium-sparing diuretics, spironolactone and amiloride, was found to reduce the duration of the QTc interval (Klimas et al., 2015).

Dihydropyridine calcium channel blockers can trigger QT prolongation in hypertensive subjects, most probably due to counter-regulatory mechanisms, such as baroreflex activation and indirect sympathetic system stimulation. On the contrary, beta-blockers and renin-angiotensin-aldosterone inhibitors reduced sympathetic cardiac stimulation and the duration of the QT interval. These considerations appear to be clinically relevant since lenvatinib, as other TKIs of the same class (Kloth et al., 2015; Qi et al., 2014), was found to prolong QTc interval (Del Rosario et al., 2010). Findings from the SELECT trial demonstrated that 8.8 % of patients treated with lenvatinib experienced QTc interval prolongation, despite only 2% of them had values >500 ms (Schlumberger et al., 2015). These findings are in agreement with those derived from a phase III trial aimed at studying efficacy and safety of lenvatinib in patients with unresectable hepatocellular carcinoma (Kudo et al., 2018). The mechanism underlying QT interval prolongation was related to the interaction with cardiac hERG channels and the consequent reduction of the repolarizing current (Lee et al., 2010; Dong et al., 2013). According to these notions, lenvatinib should be discontinued in the presence of a QT interval prolongation >500 ms and possibly resumed at a reduced dose, once the QT interval prolongation has decreased to <480 ms or returned to baseline. Furthermore, a periodically ECG monitoring and reassessment of cardiac function is recommended in patients treated with lenvatinib or other drugs of the same class (Marina et al., 2019) (Table 2).

7. Conclusions

Lenvatinib is a potent TKI characterized by adverse drug reactions predictable on the basis of its mechanism of action and inhibitory activity on cellular kinases. Among them, hypertension and proteinuria are well-characterized complications of treatment and are mainly related to the suppression of VEGFR-2. Hypertension and most other adverse events of lenvatinib are observed within the first 6 months of treatment and are managed by close monitoring of patients, drug dose adaptation and, when needed, specific therapy (i.e., antihypertensives). Although CYP3A4 is involved in metabolic clearance of lenvatinib, no clinically relevant drug-drug interactions have been reported. However, a clinical monitoring of DDIs as a result of polypharmacy, may improves the safety of treatment and compliance of patients. Finally, QT prolongation is an adverse event common, and potentially underestimated, to many drug classes used in current clinical practice. Avoiding drug combinations that can clearly lengthen QT is a rational approach that does not mean excessive alarmism or depriving patients of necessary therapies. Also in this circumstance, the case-by-case evaluation of the comorbidities and the treatments administered represents the most reasonable approach to personalizing the safety of pharmacological treatments and is an integral component of “precision medicine”.

Declaration of Competing Interest

Stefano Fogli: Novartis, Teva, Roche, BMS, Lilly (scientific advisory board, consulting relationship, travel expenses); Giulia Gianfilippo: none; Federico Cucchiara: none; Marzia Del Re: Ipsen, Novartis, Pfizer, Sanofi Genzyme, AstraZeneca, Pierre-Fabre, Janssen (scientific advisory board, consulting relationship), Ipsen, AstraZeneca, Sanofi Genzyme (travel, accommodation, expenses); Laura Valerio: none; Rossella Elisei: Genzyme, Bayer, Sobi/Exelixis, and AstraZeneca (personal fees outside the submitted work); Romano Danesi: Ipsen, Novartis, Pfizer, Sanofi Genzyme, AstraZeneca, Janssen, Gilead, Lilly, Gilead, EUSA Pharma (scientific advisory board, consulting relationship), Ipsen, Sanofi Genzyme (travel, accommodation, expenses).

References

Achira, M., Suzuki, H., Ito, K., Sugiyama, Y., 1999. Comparative studies to determine the selective inhibitors for P-glycoprotein and cytochrome P4503A4. AAPS PharmSci 1, E18.

Anon, 2015. Lenvatinib (Lenvima) for thyroid cancer. Med. Lett. Drugs Ther. 57, e120–e121.

Aydemirli, M.D., Kapiteijn, E., Ferrier, K.R.M., Ottevanger, P.B., Links, T.P., van der Horst-Schrivers, A.N.A., et al., 2020. Effectiveness and toxicity of lenvatinib in refractory thyroid cancer: dutch real-life data. Eur. J. Endocrinol. 182, 131–138.

Bendtsen, M.A.F., Grimm, D., Bauer, J., Wehland, M., Wise, P., Magnusson, N.E., et al., 2017. Hypertension caused by lenvatinib and everolimus in the treatment of metastatic renal cell carcinoma. Int. J. Mol. Sci. 18.
Bhargava, P., 2009. VEGF kinase inhibitors: how do they cause hypertension? Am. J. Physiol. Regul. Integr. Comp. Physiol. 297, R1–5.
Bitting, R.L., Healy, P., Creel, P.A., Turnbull, J., Morris, K., Wood, S.Y., et al., 2014. A phase Ib study of combined VEGFR and mTOR inhibition with vatalanib and everolimus in patients with advanced renal cell carcinoma. Clin. Genitourin. Cancer 12, 241–250.
Boss, D.S., Glen, H., Beijnen, J.H., Keesen, M., Morrison, R., Tait, B., et al., 2012. A phase I study of E7080, a multitargeted tyrosine kinase inhibitor, in patients with advanced solid tumours. Br. J. Cancer 106, 1598–1604.
Brose, M.S., Nutting, C.M., Jarzab, B., Elisei, R., Siena, S., Bastholt, L., et al., 2014. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 384, 319–328.
Cabanillas, M.E., Habra, M.A., 2016. Lenvatinib: role in thyroid cancer and other solid tumors. Cancer Treat. Rev. 42, 47–55.
Cabanillas, M.E., Takahashi, S., 2019. Managing the adverse events associated with lenvatinib therapy in radioiodine-refractory differentiated thyroid cancer. Semin. Oncol. 46, 57–64.
Cabanillas, M.E., Schlumberger, M., Jarzab, B., Martins, R.G., Pacini, F., Robinson, B., et al., 2015. A phase 2 trial of lenvatinib (E7080) in advanced, progressive, radioiodine-refractory, differentiated thyroid cancer: a clinical outcomes and biomarker assessment. Cancer 121, 2749–2756.
Cavalieri, S., Cosmai, L., Genderini, A., Nebuloni, M., Tosoni, A., Favales, F., et al., 2018. Lenvatinib-induced renal failure: two first-time case reports and review of literature. Expert Opin. Drug Metab. Toxicol. 14, 379–385.
Chae, Y.K., Ranganath, K., Hammerman, P.S., Vaklavas, C., Mohindra, N., Kalyan, A., et al., 2017. Inhibition of the fibroblast growth factor receptor (FGFR) pathway: the current landscape and barriers to clinical application. Oncotarget 8, 16052–16074.
Chen, J., Raymond, K., 2006. Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. Ann. Clin. Microbiol. Antimicrob. 5, 3.
De Mattia, E., Cecchin, E., Guardascione, M., Foltran, L., Di Raimo, T., Angelini, F., et al., 2019. Pharmacogenetics of the systemic treatment in advanced hepatocellular carcinoma. World J. Gastroenterol. 25, 3870–3896.
Del Rosario, M.E., Weachter, R., Flaker, G.C., 2010. Drug-induced QT prolongation and sudden death. Med. 107, 53–58.
Dong, Q., Fu, X.X., Du LL, Zhao N., Xia, C.K., Yu, K.W., et al., 2013. Blocking of the human ether-a-go-go-related gene channel by imatinib mesylate. Biol. Pharm. Bull. 36, 268–275.
Dubbelman, A.C., Rosing, H., Thijssen, B., Gebretensae, A., Lucas, L., Chen, H., et al., 2012. Development and validation of LC-MS/MS assays for the quantification of E7080 and metabolites in various human biological matrices. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 887-888, 25–34.
Dubbelman, A.C., Rosing, H., Nijenhuis, C., Huitema, A.D., Mergui-Roelvink, M., Gupta, A., et al., 2015. Pharmacokinetics and excretion of (14)C-lenvatinib in patients with advanced solid tumors or lymphomas. Invest. New Drugs 33, 233–240.
Fogli, S., Porta, C., Del Re, M., Crucitta, S., Gianfilippo, G., Danesi, R., et al., 2020. Optimizing treatment of renal cell carcinoma with VEGFR-TKIs: a comparison of clinical pharmacology and drug-drug interactions of anti-angiogenic drugs. Cancer Treat. Rev. 84, 101966.
Furuto, Y., Hashimoto, H., Namikawa, A., Outi, H., Takahashi, H., Horiuti, H., et al., 2018. Focal segmental glomerulosclerosis lesion associated with inhibition of tyrosine kinases by lenvatinib: a case report. BMC Nephrol. 19, 273.
Giani, C., Valerio, L., Bongiovanni, A., Durante, C., Grani, G., Ibrahim, T., et al., 2021. Safety and quality-of-Life data from an italian expanded access program of lenvatinib for treatment of thyroid cancer. Thyroid 31, 224–232.
Groden, Pj, Lee, Tc, Bhattacharyya, S., Connors, J., Lorch, J., 2017. Lenvatinib-associated cervical artery dissections in a patient with radioiodine-refractory metastatic papillary thyroid carcinoma. Front. Med. (Lausanne) 4, 220.
Groussin, L., Clerc, J., Huillard, O., 2020. Larotrectinib-enhanced radioactive iodine uptake in advanced thyroid cancer. N. Engl. J. Med. 383, 1686–1687.
Gupta, A., Jarzab, B., Capdevila, J., Shumaker, R., Hussein, Z., 2016. Population pharmacokinetic analysis of lenvatinib in healthy subjects and patients with cancer. Br. J. Clin. Pharmacol. 81, 1124–1133.
Hamieh, L., Beck, R.L., Le, V.H., Hsieh, J.J., 2020. The efficacy of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma exhibiting primary resistance to front-line targeted therapy or immunotherapy. Clin. Genitourin. Cancer.
Hong, D.S., Kurzrock, R., Wheler, J.J., Naing, A., Falchook, G.S., Fu, S., et al., 2015. Phase I dose-escalation study of the multikinase inhibitor lenvatinib in patients with advanced solid tumors and in an expanded cohort of patients with melanoma. Clin. Cancer Res. 21, 4801–4810.
Hussein, Z., Mizuo, H., Hayato, S., Namiki, M., Shumaker, R., 2017. Clinical pharmacokinetic and pharmacodynamic profile of lenvatinib, an orally active, small-molecule, multitargeted tyrosine kinase inhibitor. Eur. J. Drug Metab. Pharmacokinet. 42, 903–914.
Katsi, V., Zerdes, I., Manolakou, S., Makris, T., Nihoyannopoulos, P., Tousoulis, D., et al., 2014. Anti-VEGF anticancer drugs: mind the hypertension. Recent Adv. Cardiovasc. Drug Discov. 9, 63–72.
Keizer, R.J., Gupta, A., Mac Gillavry, M.R., Jansen, M., Wanders, J., Beijnen, J.H., et al., 2010. A model of hypertension and proteinuria in cancer patients treated with the anti-angiogenic drug E7080. J. Pharmacokinet. Pharmacodyn. 37, 347–363.
Klajer, E., Garnier, L., Goujon, M., Schlurmann-Constans, F., Mery, B., Nguyen Tan Hon, T., et al., 2020. Targeted and immune therapies among patients with metastatic renal carcinoma undergoing hemodialysis: a systemic review. Semin. Oncol. 47, 103–116.
Klimas, J., Kruzliak, P., Rabkin, S.W., 2015. Modulation of the QT interval duration in hypertension with antihypertensive treatment. Hypertens. Res. 38, 447–454.
Kloth, J.S., Pagani, A., Verboom, M.C., Malovini, A., Napolitano, C., Kruit, W.H., et al., 2015. Incidence and relevance of QTc-interval prolongation caused by tyrosine kinase inhibitors. Br. J. Cancer 112, 1011–1016.
Koch, S., Claesson-Welsh, L., 2012. Signal transduction by vascular endothelial growth factor receptors. Cold Spring Harb. Perspect. Med. 2, a006502.
Koyama, N., Saito, K., Nishioka, Y., Yusa, W., Yamamoto, N., Yamada, Y., et al., 2014. Pharmacodynamic change in plasma angiogenic proteins: a dose-escalation phase 1 study of the multi-kinase inhibitor lenvatinib. BMC Cancer 14, 530.
Kudo, M., Finn, R.S., Qin, S., Han, K.H., Ikeda, K., Piscaglia, F., et al., 2018. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 391, 1163–1173.
Lee, H.A., Kim, E.J., Hyun, S.A., Park, S.G., Kim, K.S., 2010. Electrophysiological effects of the anti-cancer drug lapatinib on cardiac repolarization. Basic Clin. Pharmacol. Toxicol. 107, 614–618.
Li, K.I., Wald, E.R., 1986. Use of rifampin in Haemophilus influenzae type b infections. Am. J. Dis. Child. 140, 381–385.
Li, H.T., Zhu, X., 2021. Quinoline-based compounds with potential activity against drugresistant cancers. Curr. Top. Med. Chem. 21, 426–437.
Lin, J.H., 2007. Transporter-mediated drug interactions: clinical implications and in vitro assessment. Expert Opin. Drug Metab. Toxicol. 3, 81–92.
Liu, S.V., Macke, L.A., Colton, B.S., Imran, S.S., Christiansen, J., Chow-Maneval, E., et al., 2017. Response to entrectinib in differentiated thyroid cancer with a ROS1 fusion. JCO Precis Oncol 1.
Locati, L.D., Piovesan, A., Durante, C., Bregni, M., Castagna, M.G., Zovato, S., et al., 2019. Real-world efficacy and safety of lenvatinib: data from a compassionate use in the treatment of radioactive iodine-refractory differentiated thyroid cancer patients in Italy. Eur. J. Cancer 118, 35–40.
Mano, Y., Mizuo, H., 2019. Minimal impact of hepatic and renal impairment on plasma protein binding of lenvatinib, and identification of its major plasma binding protein. Biopharm. Drug Dispos. 40, 307–311.
Marina, M., Serra, M.F., Rio, P.D., Ceresini, G., 2019. Evaluation of the QTc interval during lenvatinib treatment in radioiodine-refractory differentiated thyroid cancer: reports from the real-life clinical practice. Future Oncol. 15, 7–12.
Masaki, C., Sugino, K., Saito, N., Akaishi, J., Hames, K.Y., Tomoda, C., et al., 2020. Efficacy and limitations of lenvatinib therapy for radioiodine-refractory differentiated thyroid cancer: real-world experiences. Thyroid 30, 214–221.
Matrone, A., Valerio, L., Pieruzzi, L., Giani, C., Cappagli, V., Lorusso, L., et al., 2017. Protein kinase inhibitors for the treatment of advanced and progressive radiorefractory thyroid tumors: from the clinical trials to the real life. Best Pract. Res. Clin. Endocrinol. Metab. 31, 319–334.
Matsui, J., Yamamoto, Y., Funahashi, Y., Tsuruoka, A., Watanabe, T., Wakabayashi, T., et al., 2008a. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. Int. J. Cancer 122, 664–671.
Matsui, J., Funahashi, Y., Uenaka, T., Watanabe, T., Tsuruoka, A., Asada, M., 2008b. Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. Clin. Cancer Res. 14, 5459–5465.
Molina, A.M., Hutson, T.E., Larkin, J., Gold, A.M., Wood, K., Carter, D., et al., 2014. A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of metastatic renal cell carcinoma (RCC). Cancer Chemother. Pharmacol. 73, 181–189.
Nakamichi, S., Nokihara, H., Yamamoto, N., Yamada, Y., Honda, K., Tamura, Y., et al., 2015. A phase 1 study of lenvatinib, multiple receptor tyrosine kinase inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother. Pharmacol. 76, 1153–1161.
Nishio, M., Horai, T., Horiike, A., Nokihara, H., Yamamoto, N., Takahashi, T., et al., 2013. Phase 1 study of lenvatinib combined with carboplatin and paclitaxel in patients with non-small-cell lung cancer. Br. J. Cancer 109, 538–544.
Okamoto, K., Kodama, K., Takase, K., Sugi, N.H., Yamamoto, Y., Iwata, M., et al., 2013. Antitumor activities of the targeted multi-tyrosine kinase inhibitor lenvatinib (E7080) against RET gene fusion-driven tumor models. Cancer Lett. 340, 97–103.
Okamoto, K., Ikemori-Kawada, M., Jestel, A., von Konig, K., Funahashi, Y., Matsushima, T., et al., 2015. Distinct binding mode of multikinase inhibitor lenvatinib revealed by biochemical characterization. ACS Med. Chem. Lett. 6, 89–94.
Ozeki, T., Nagahama, M., Fujita, K., Suzuki, A., Sugino, K., Ito, K., et al., 2019. Influence of CYP3A4/5 and ABC transporter polymorphisms on lenvatinib plasma trough concentrations in Japanese patients with thyroid cancer. Sci. Rep. 9, 5404.
Paschke, L., Lincke, T., Muhlberg, K.S., Jabs, W.J., Lindner, T.H., Paschke, R., 2018. Anti VEGF-TKI treatment and new renal adverse events not reported in phase III trials. Eur. Thyroid J. 7, 308–312.
Qi, W.X., Shen, Z., Tang, L.N., Yao, Y., 2014. Congestive heart failure risk in cancer patients treated with vascular endothelial growth factor tyrosine kinase inhibitors: a systematic review and meta-analysis of 36 clinical trials. Br. J. Clin. Pharmacol. 78, 748–762.
Rendl, G., Sipos, B., Becherer, A., Sorko, S., Trummer, C., Raderer, M., et al., 2020. Real-world data for lenvatinib in radioiodine-refractory differentiated thyroid cancer (RELEVANT): a retrospective multicentric analysis of clinical practice in Austria. Int. J. Endocrinol. 2020, 8834148.

Roberts, J.L., Poklepovic, A., Booth, L., Dent, P., 2020. The multi-kinase inhibitor lenvatinib interacts with the HDAC inhibitor entinostat to kill liver cancer cells. Cell. Signal. 70, 109573.
Roblek, T., Vaupotic, T., Mrhar, A., Lainscak, M., 2015. Drug-drug interaction software in clinical practice: a systematic review. Eur. J. Clin. Pharmacol. 71, 131–142.
Roussos, E.T., Condeelis, J.S., Patsialou, A., 2011. Chemotaxis in cancer. Nat. Rev. Cancer 11, 573–587.
Sachdev, K., Gupta, M.K., 2019. A comprehensive review of feature based methods for drug target interaction prediction. J. Biomed. Inform. 93, 103159.
Schlumberger, M., Tahara, M., Wirth, L.J., Robinson, B., Brose, M.S., Elisei, R., et al., 2015. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N. Engl. J. Med. 372, 621–630.
Shah, R.R., Morganroth, J., 2015. Update on cardiovascular safety of tyrosine kinase inhibitors: with a special focus on QT interval, left ventricular dysfunction and overall risk/benefit. Drug Saf. 38, 693–710.
Shumaker, R.C., Zhou, M., Ren, M., Fan, J., Martinez, G., Aluri, J., et al., 2014a. Effect of lenvatinib (E7080) on the QTc interval: results from a thorough QT study in healthy volunteers. Cancer Chemother. Pharmacol. 73, 1109–1117.
Shumaker, R.C., Aluri, J., Fan, J., Martinez, G., Thompson, G.A., Ren, M., 2014b. Effect of rifampicin on the pharmacokinetics of lenvatinib in healthy adults. Clin. Drug Investig. 34, 651–659.
Shumaker, R., Aluri, J., Fan, J., Martinez, G., Ren, M., Chen, K., 2014c. Evaluation of the effects of formulation and food on the pharmacokinetics of lenvatinib (E7080) in healthy volunteers. Int. J. Clin. Pharmacol. Ther. 52, 284–291.
Shumaker, R., Aluri, J., Fan, J., Martinez, G., Pentikis, H., Ren, M., 2015a. Influence of hepatic impairment on lenvatinib pharmacokinetics following single-dose oral administration. J. Clin. Pharmacol. 55, 317–327.
Shumaker, R., Aluri, J., Fan, J., Martinez, G., Thompson, G.A., Ren, M., 2015b. Effects of ketoconazole on the pharmacokinetics of lenvatinib (E7080) in healthy participants. Clin. Pharmacol. Drug Dev. 4, 155–160.
Spallanzani, A., Orsi, G., Andrikou, K., Gelsomino, F., Rimini, M., Riggi, L., et al., 2018. Lenvatinib as a therapy for unresectable hepatocellular carcinoma. Expert Rev. Anticancer Ther. 18, 1069–1076.
Subbiah, V., Gainor, J.F., Rahal, R., Brubaker, J.D., Kim, J.L., Maynard, M., et al., 2018. Precision targeted therapy with BLU-667 for RET-driven cancers. Cancer Discov. 8, 836–849.
Suyama, K., Iwase, H., 2018. Lenvatinib: a promising molecular targeted agent for multiple cancers. Cancer Control 25, 1073274818789361.
Tamai, T., Hayato, S., Hojo, S., Suzuki, T., Okusaka, T., Ikeda, K., et al., 2017. Dose finding of lenvatinib in subjects with advanced hepatocellular carcinoma based on population pharmacokinetic and exposure-response analyses. J. Clin. Pharmacol. 57, 1138–1147.
Tohyama, O., Matsui, J., Kodama, K., Hata-Sugi, N., Kimura, T., Okamoto, K., et al., 2014. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J. Thyroid Res. 2014, 638747.
Wirth, L.J., Sherman, E., Robinson, B., Solomon, B., Kang, H., Lorch, J., et al., 2020. Efficacy of selpercatinib in RET-altered thyroid cancers. N. Engl. J. Med. 383, 825–835.
Yamada, K., Yamamoto, N., Yamada, Y., Nokihara, H., Fujiwara, Y., Hirata, T., et al., 2011. Phase I dose-escalation study and biomarker analysis of E7080 in patients with advanced solid tumors. Clin. Cancer Res. 17, 2528–2537.
Yamamoto, Y., Matsui, J., Matsushima, T., Obaishi, H., Miyazaki, K., Nakamura, K., et al., 2014. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell 6, 18.
Zhu, C., Ma, X., Hu, Y., Guo, L., Chen, B., Shen, K., et al., 2016. Safety and efficacy profile of lenvatinib in cancer therapy: a systematic review and meta-analysis. Oncotarget 7, 44545–44557.

Stefano Fogli, PharmD, MD, PhD, Assistant Professor of Pharmacology at the University of Pisa. He has extensive experience and expertise in clinical pharmacokinetics and drug discovery. His current research field is on drug-drug interactions and therapeutic monitoring of monoclonal antibodies.

Giulia Gianfilippo, Postgraduate student at the Specialization School of Clinical Pharmacology and Toxicology at the University of Pisa. Her current work is focused on in vitro drug discovery.

Federico Cucchiara, MD, Resident in Clinical Pharmacology and Pharmacogenetics at the University Hospital of Pisa, Italy. His research work is mainly focused on the discovery and union of multiple disease hallmarks to guide physicians in data-driven clinical decisions.

Marzia Del Re, PharmD, Lab Manager at the Pharmacogenetic lab, Unit of Clinical pharmacology and Pharmacogenetics, University Hospital of Pisa. She is strongly involved in pharmacogenetic test for toxicity and treatment response/resistance to cancer treatments.

Laura Valerio, MD, PhD in Clinical Pathophysiology. Specialist in Endocrinology and Metabolism at the University of Pisa. Post-doc researcher in Endocrine Oncology at University of Pisa. Her research interest is mainly focused on advanced thyroid cancers treated with tyrosine kinase inhibitors.

Rossella Elisei, MD, Associate Professor of Endocrinology. Responsible of the Thyroid Oncology service of the Endocrinology Unit at the University Hospital of Pisa, Italy, mainly involved in the management of thyroid cancer patients, any type, any degree of aggressiveness.

Romano Danesi, MD, PhD Professor of Pharmacology at the University of Pisa. Head of Clinical Pharmacology and Pharmacogenetics Unit in the Department of Laboratory Medicine. His research work has been mainly focused on clinical pharmacology of anticancer agents and biomarker development for personalized treatments.