 Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

MANAGEMENT OF HYPERTENSION DURING LENVATINIB FOR ADVANCED THYROID CANCER: A SUGGESTED DIAGNOSTIC AND THERAPEUTIC ALGORITHM

Carla Colombo[1,3], Daniele Ceruti[3], Simone De Leo[1], Grzegorz Bilo[2, 4], Matteo Trevisan[3], Noemi Giancola[3], Claudia Moneta[3], Gianfranco Parati[2, 4], Luca Persani[1,5], Laura Fugazzola[1,3]

[1]Department of Endocrine and Metabolic Diseases, Istituto Auxologico Italiano IRCCS, Milan; [2]Department of Cardiology, San Luca Hospital, Istituto Auxologico Italiano, IRCCS, Milan, Italy; [3]Department of Pathophysiology and Transplantation, University of Milan, Milan; [4]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy; [5]Department of Biotechnology and Translational Medicine, University of Milan, 20100, Milan, Italy.

Short title: lenvatinib and hypertension

Keywords: Thyroid cancer, lenvatinib, hypertension, adverse event, treatment

Word count: 2865.

Corresponding Author:

Laura Fugazzola

Department of Pathophysiology and Transplantation, University of Milan

Division of Endocrine and Metabolic Diseases

Ospedale San Luca, IRCCS Istituto Auxologico Italiano

Piazzale Brescia, 20 - 20149 Milan, Italy

E-mail: laura.fugazzola@unimi.it

ABSTRACT

Background: Hypertension (HTN) is the most frequent adverse event during treatment with Lenvatinib (LEN), but data on its best management are limited.

Aim: To assess incidence, features and best management of LEN-related HTN in a consecutive single tertiary-care Centre cohort.

Methods: 29 patients followed for a mean time of 29.8 months (6-77 months).

Results: After a mean follow-up of 6.8 months, HTN was recorded in 76% of cases, as a *de novo* occurrence in half of them. HTN significantly correlated with LEN dose, and was of grade 1, grade 2 and grade 3 in 5%, 50% and 45% of patients, respectively. The majority (77%) of patients with HTN developed proteinuria. There was no correlation between HTN and either proteinuria or clinical features or best morphological response or any other AE, with the exception of diarrhoea. Patients with or without pre-existing HTN or any other cardiovascular disease had a similar incidence of HTN during LEN, thus excluding the impact of this potential predisposing factor. After evaluation by a dedicated cardiologist, medical treatment was introduced in 21/22 patients (polytherapy in 20 of them). The most frequently used drugs were calcium channel blockers (CCB) due to their effect on vasodilation. In case of poor control, CCB were associated with one or more anti-hypertensive drug.

Conclusion: HTN is a frequent and early adverse event in patients on LEN treatment. We suggest a diagnostic-therapeutic algorithm to be applied in clinical practice to allow efficient HTN control and improve patient compliance, reducing LEN discontinuation.

 Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

INTRODUCTION

Multikinase inhibitors (MKIs) with strong antiangiogenetic action are frequently used for the treatment of advanced radioiodine refractory differentiated thyroid cancer (RAI-R DTC) or medullary thyroid cancers (MTC) (1-3). In particular, in Europe, sorafenib and lenvatinib (LEN) can be used as first line and cabozantinib as second line treatment for RAI-R DTCs, while vandetanib and cabozantinib are first line compounds for MTCs. In phase III trials, these drugs demonstrated to significantly prolong progression free survival (PFS) (4-8).

The occurrence of several adverse events (AEs) has been reported, particularly during treatment with antiangiogenic drugs: hypertension (HTN), diarrhoea, decreased appetite, decreased weight, fatigue, proteinuria and others. These AEs virtually affect all patients and usually occur during the first months of treatment, often requiring dose reduction and/or drug discontinuation.

HTN represents one of the most frequent toxicities recorded during both clinical trials and real-life (RL) studies, and has a high incidence during LEN treatment (reviewed in **Table 1)**. Indeed, in the LEN registration trial SELECT, it was recorded in 67.8% of cases, and 41.8% of patients experienced grade ≥ 3 HTN according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (2). A similar incidence (72%) has been confirmed in RL studies, with 20.8% of patients experiencing a grade ≥ 3 HTN (9-22). Interestingly, LEN dose was found to correlate, though not significantly, with HTN incidence (23). Consistently, patients with unresectable hepatocarcinoma treated with lower LEN doses (8-12 mg/die) experienced HTN in only 25% of cases (10.4% grade ≥3) (24-26). As for the other toxicities developing during these chronic treatments, careful management should be adopted with the final aim not to either reduce the drug dose or discontinue it (27-29). HTN is usually initially managed using compounds commonly suggested for HTN, by the endocrinologist or oncologist, and a cardiologist's advice is required in more complicated or resistant cases. No specific clinical trial has ever been conducted to assess the best management of LEN-induced HTN. Capdevila *et al.* gave specific recommendations to reduce the incidence and severity of LEN-induced AEs (including HTN) suggesting to use, as a first line treatment, ACE-inhibitors (ACE-i) followed by

Calcium-Channel Blockers (CCB) and Beta-Blockers (BB) (27). In addition, some information on antihypertensive drugs and LEN reduction/interruption comes from a study on 25 patients on MKIs treatment developing persistent grade 2 HTN (11).

In order to get more insights into HTN during LEN, we performed careful specialist evaluations at baseline and during treatment in our cohort of patients with RAI-R DTC, and here suggest a protocol indicating the best management strategies according to the different clinical conditions.

PATIENTS AND METHODS

This is a retrospective, cohort study. We evaluated 29 consecutive patients with progressive, locally advanced or metastatic differentiated and poorly differentiated thyroid cancer who received LEN treatment during the period July 2016-November 2022, for an average time of 29.8 months (6-77 months) and were followed-up at our tertiary centre. All patients were MKIs-naïve and the clinico-pathological features and treatment details are reported in **Table 2**. All patients were followed up according to Italian and International guidelines and the functional status of patients was assessed by the Eastern Cooperative Oncology Group (ECOG) performance status scale (30-32). Tumour response rate (defined as the objective response rate, complete or partial, ORR) was evaluated according to the revised RECIST (Response Evaluation Criteria in Solid Tumours) criteria guidelines version 1.1 (33). All patients were submitted to surgery followed by levothyroxine TSH suppressive therapy, except two (#21 and #26) who are receiving LEN in a neo-adjuvant setting.

AEs were recorded on Electronic Hospital Records and were classified according to CTCAE version 5.0 (HTN, diarrhoea, fatigue, proteinuria, weight loss, anorexia and nausea, palmar-plantar erythrodysesthesia syndrome, stomatitis and other uncommon AEs).

At baseline, before starting LEN therapy, a dedicated cardiologist evaluated all patients, and HTN was scored by the CTCAE version v 5.0. During treatment, blood pressure (BP) values were checked daily at home and reported to the team by a dedicated Telegram account with titration of the anti-hypertensive treatment when needed (29). Moreover, BP was measured monthly during follow-up

 Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

visits and, in some cases, with 24-hour continuous pressure monitoring test. To note, the titration of the anti-hypertensive drugs and the variation of the therapeutic scheme, including the addition of other compound/s, was managed by the dedicated cardiologist with the aim to control BP without reducing LEN dose. All patients underwent a follow-up electrocardiogram at baseline and every 1-3 months. If needed, additional tests were performed (echocardiogram, electrocardiogram, renal arteries ultrasound). In all patients, proteinuria levels, creatinine clearance, electrolytes and thyroid function were assessed every 1-2 months.

Importantly, other potential causes of secondary HTN (pheochromocytoma, hyperaldosteronism, Cushing's syndrome, renovascular diseases) were always excluded.

Statistical analysis

We described quantitative data as mean ± standard deviation, and median with range, depending on normality of distribution (according to Shapiro Wilk test). Categorical variables were expressed by the absolute number and percentage.

Statistical group comparisons were performed using the Mann–Whitney U test and the Student's t test for respective nonparametric and parametric continuous variables. Categorical variables were compared using the $\chi 2$ Test or the Fisher's Exact Test. We defined the p-value for statistical significance as < 0.05.

Progression Free Survival and Overall Survival (OS) were defined as the time between the date of LEN initiation and either progression disease, or death, or the date of the last follow-up visit. PFS and OS were evaluated using Kaplan–Meier curves with 95% confidence interval (CI). All statistical analyses were performed using MedCalc Statistical Software version 19.2.0 (MedCalc Software bvba, Ostend, Belgium).

The study was performed in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration. All patients were enrolled in a protocol approved by the Ethical Committee of the Istituto Auxologico Italiano and provided informed consent to the use of their anonymized clinical data for research purposes (study code approval: 2022_03_08_03).

RESULTS

Prevalence, timing and grade of HTN in patients treated with LEN

After a mean follow-up of 6.8 months (1-32 months), 22/29 patients developed HTN (76%): *de novo* occurrence in 14 and worsening of pre-existing HTN in 8 of them. According to CTCAE v.5.0, 1/22 (5%) had HTN of grade 1, 11/22 (50%) grade 2 and 10/22 (45%) grade 3 **(Figure 1, Table 2)**.

HTN was more frequent in patients treated with LEN doses >14 mg (89% *vs* 54%, P=0.035); linear regression analysis showed that the grade of HTN positively correlated with LEN dose (P=0.011) **(Fig. 2A).** To note, none of the patients developed ECG variations with respect to baseline during LEN treatment, with the exception of 2 patients who developed a grade 1 QTc elongation.

Correlation between HTN and other AEs

Among the 22 patients with LEN-induced HTN, 17 (77%) also had proteinuria (7/17 grade 1, 6/17 grade 2 and 4/17 grade 3). Nevertheless, no correlation was found between HTN grade and proteinuria grade (P=0.187) **(Table 2, Figure 2B)**. In particular, among the 10 patients who developed a grade 3 HTN, 4 had grade 2, 4 had grade 1 proteinuria and 2 patients had no proteinuria Among the 11 patients who developed a grade 2 HTN, 3 had grade 1, 2 had grade 2, 3 had grade 3 proteinuria, and 3 had no proteinuria. Finally, the only patient who developed grade 1 HTN, had a grade 3 proteinuria. On the other hand, 3/7 patients without HTN developed proteinuria (2 grade 2 and 1 grade 1). Interestingly, 13/17 patients with proteinuria showed an improvement in the proteinuria grade during follow-up probably due to the effect of the antihypertensive medical drug used, such as angiotensin converting ACE-i or Angiotensin Receptor Blocker (ARB) (data not shown).

Among other LEN-related AEs, only diarrhoea correlated with the development of HTN (P=0.025) **(Figure 2B).**

Correlation between HTN, clinico-pathological features and tumour response to LEN

No significant differences were found between patients who developed or not HTN as far as some clinical features such as gender, age at LEN start, ECOG status and AJCC stage concerns (**Figure 3**). Interestingly, patients who developed HTN during LEN treatment did not have a significant higher

 Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

incidence of cardiovascular disease (pre-existing HTN and/or myocardial infarction and/or valvulopathies) prior to the start of the drug compared with patients who did not develop HTN (8 out of 22, 36% *vs* 5 out of 7, 71%; P= 0.104) **(Figure 3)**. The best ORR to LEN treatment was not different between patients who developed or not HTN. In particular, complete response (CR), partial response (PR) and stable disease (SD) were observed in 0%, 64% and 18% of patients with HTN, and in 0%, 86% and 14% of patients without HTN, respectively (P=0.84) **(Figure 3)**. To note, progressive disease was observed (18 % of cases) only in the group of patients developing HTN. In addition, PFS was similar in patients developing or not HTN (HR, 0.43; 95% CI, 0.11-1.64; log-rank P= 0.2175). Similarly, OS was not different among the two groups (log-rank P=0.150).

Treatment management of HTN during LEN

After evaluation by a dedicated cardiologist, medical therapy was introduced in the 13/14 patients who developed a *de novo* HTN. One patient has a grade 1 HTN (#14, **Table 2**) and no treatment has been started to date. In 7 cases the first drug was a CCB, alone (4 cases) or in combination with an ACE-i (2 cases) or with a BB (1 case). HTN was well controlled with CCB alone (1 case), CCB+ BB (1 case), or after the introduction of other drugs such as ARB + diuretic (D) (2 cases), ACE-i (2 cases), or >3 compounds (1 case). In 4 cases the first drug introduced was an ACE-i associated or not with BB, in 1 case a BB and in the remaining case the initial treatment was ARB+D. In these latter 6 cases, HTN was not controlled and CCB was always introduced, alone or in combination with other compounds.

The 8 patients who had HTN before the start of LEN treatment were on antihypertensive treatment with different drugs in mono or poly-therapy. One patient remained well controlled without changing treatment (#4, **Table 2**), while in 7 cases CCB was introduced or increased alone or in association with other compounds such as BB, ARB, alpha-blockers (AB), D, obtaining HTN control in all but 1 case (#21, **Table 2**).

Considering the whole cohort of 22 cases who developed HTN or experienced a worsening of a pre-existing HTN, we can summarise as follows: a) 21/22 (95%) patients were on antihypertensive

treatment: 1/21 in monotherapy and 20/21 in polytherapy; b) the only patient in monotherapy was on CCB; c) 4/5 patients treated with 2 drugs were well controlled with CCB+ACE-i/BB (3 cases) or with ACE-i/BB (1 case); d) 9/10 patients controlled with 3 drugs were on CCB+ARB/ACE-i+ and other drug; e) only 3/5 patients treated with ≥4 drugs were controlled (**Figure 4, panel A**). We recorded an adequate BP response in 18/21 patients (86%) and an improvement of proteinuria in 12/17 (71%). No patient had to reduce or discontinue LEN treatment due to HTN.

CCBs were the most common drugs, used in 17/21 patients, either in monotherapy (5% of cases) or, in case of poor BP control, in association with other anti-hypertensive drugs as ACE-i or BB (14%), with ARB/ACE-i + other anti-hypertensive drug (43%) or with a total of 4 anti-hypertensive drugs in 24% of patients. **(Figure 4, panel B)**. We preferred to use dihydropyridine CCB (eg, amlodipine), rather than non-dihydropyridine CCB (eg. verapamil), considering the high risk of drug interaction of the latter.

Based on the data above reported we have drawn a flow chart for the strategic management of HTN during LEN (**Figure 5**). In particular, CCB is suggested as first treatment. In case of proteinuria, ACE-i or ARB can be the first choice or the drugs to be added to CCB.

DISCUSSION

In the present RL series of patients with advanced thyroid cancer on LEN treatment, a 76% incidence of HTN was recorded with a mean onset of 6.8 months (range 1-32 months) after the start of treatment. This data is in accordance with the average HTN incidence of 72.4% reported in the RL studies available to date (10-23). HTN is the most common AE observed during treatment with MKIs and is frequently of grade ≥ 3 (45% of patients in the present series and 41.8% in the SELECT trial), warranting a prompt treatment in order not to worsen possible underlying cardiovascular disease and not to reduce or discontinue the anti-tumoral treatment (1-3). Interestingly, in our series of patients treated with doses ranging 4-24 mg/day, HTN incidence and grade were positively correlated to LEN dosage. A similar result, though not reaching statistical significance, was found in the randomised

 Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

study aimed to compare the efficacy and safety of LEN 24 mg vs 18 mg/die (23). On the other hand, no correlation was found neither with ORR, nor PFS nor OS, differently from previous data reporting a better ORR and PFS in patients developing HTN, included in the SELECT trial (34). The reasons for these discrepancies may lie in the different characteristics of the 2 cohorts. In particular, the present study has a lower number of patients, but is RL and monocentric, with patients starting with different LEN dosages and followed by a dedicated cardiologist.

Although the majority of our patients also developed proteinuria during LEN treatment, no correlation was found between its grade and that of HTN, confirming that the mechanisms by which MKI induce HTN and proteinuria are different, as hypothesised in a recent review which evaluated literature data regarding MKIs treatment and nephrotoxicity (35). Moreover, it is interesting to note that patients with or without pre-existing HTN or any other cardiovascular disease (including myocardial infarction, valvulopathies) had a similar incidence of HTN during LEN, confirming that the underlying mechanisms are probably related exclusively to the anti-angiogenic drug. The causes of MKI-induced HTN are still unknown, but some hypotheses pointed to the fact that MKIs, through the inhibition of VEGF-R, reduce the synthesis of NO (nitric oxide) leading to vasoconstriction and, hence, HTN (36). Interestingly, the inhibition of microcirculation in the gastrointestinal tract seems to contribute to the development of diarrhoea (37), which is the only AE correlated with HTN in the present series, suggesting a possible common pathogenesis. Based on the above-mentioned hypothesis, CCB, whose effect on vascular smooth muscle leads to vasodilation, was the most frequently used drug, alone (5% of cases) or in combination with one or two additional drugs (15 and 49%, respectively). The most frequent association was with ACE-i or ARB, due to the effect of these drugs on proteinuria, which was frequent in our cohort. The lack of correlation with HTN seems to indicate that proteinuria is directly induced by LEN treatment, through a still unknown mechanism.

The accurate cardiological evaluation, both at baseline and during LEN treatment, was crucial in assessing HTN and in choosing the best personalised medical therapy, as reported in our flow chart for the strategic management of HTN during LEN. Although 4 different drugs were needed in 20%

of cases, up to 75% of patients reached the BP control with the administration of 2 or 3 compounds. As a whole, we had adequate control of HTN in 19/22 patients (86%), improving compliance to LEN treatment, avoiding dosage reductions or drug discontinuation and reducing patients' cardiovascular risk.

CONCLUSIONS

HTN is the most frequent AE in patients treated with LEN, and in the present series its incidence and grade correlated with LEN dosage. An accurate cardiological evaluation and optimised medical therapy is crucial for the best management of this AE. CCBs should be always included in the therapeutic scheme, due to the vasodilation effect, and the association with ACE-i/ARBs has been shown to be frequently effective.

Declaration of interest

L.F. is a consultant for Eisai, Ipsen and Lilly. The remaining authors have nothing to disclose.

Funding

This study was partially funded by the Italian Ministry of Health.

Author Contribution Statement

CC, DC: Conceptualization, data collection, formal analysis, writing and editing; SDL, MT, NG, CM: Data collection, formal analysis, editing; GB: Data collection and editing; GP, LP: supervision; LF: Conceptualization, supervision, writing. All the authors were responsible for the final approval of the article.

 Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

References

1. Fugazzola L, Elisei R, Fuhrer D, Jarzab B, Leboulleux S, Newbold K, Smit J. European Thyroid Association guidelines for the treatment and follow-up of advanced radioiodine-refractory thyroid cancer. *European Thyroid Journal* 2019 **8** 227-245.
2. Dadu R, Cabanillas ME. Optimizing therapy for radioactive iodine-refractory differentiated thyroid cancer: current state of the art and future directions. *Minerva Endocrinology* 2012 **37** 335-356.
3. Stjepanovic N, Capdevila J. Multikinase inhibitors in the treatment of thyroid cancer: specific role of lenvatinib. *Biologics* 2014 **8** 29-39.
4. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Peña C, Molnár I, Schlumberger MJ; DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. *Lancet* 2014 26 **384** 319-328.
5. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *The New England Journal of Medicine* 2015 **372** 621-630.
6. Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR, Read J, Langmuir P, Ryan AJ, Schlumberger MJ. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *Journal of Clinical Oncology* 2012 **30** 134-141.
7. Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC, Niederle B, Cohen EE, Wirth LJ, Ali H, Hessel C, Yaron Y,

Ball D, Nelkin B, Sherman SI. Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 2013 **29** 3639-3646.

8. Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, Worden F, Brose M, Patel J, Leboulleux S, Godbert Y, Barlesi F, Morris JC, Owonikoko TK, Tan DSW, Gautschi O, Weiss J, de la Fouchardière C, Burkard ME, Laskin J, Taylor MH, Kroiss M, Medioni J, Goldman JW, Bauer TM, Levy B, Zhu VW, Lakhani N, Moreno V, Ebata K, Nguyen M, Heirich D, Zhu EY, Huang X, Yang L, Kherani J, Rothenberg SM, Drilon A, Subbiah V, Shah MH, Cabanillas ME. Efficacy of selpercatinib in *RET*-altered thyroid cancers. *The New England Journal of Medicine* 2020 **383** 825-835.
9. Ohkuwa K, Sugino K, Nagahama M, Kitagawa W, Matsuzu K, Suzuki A, Tomoda C, Hames K, Akaishi J, Masaki C, Ito K. Risk stratification in differentiated thyroid cancer with RAI-avid lung metastases. *Endocrine Connections* 2021 **10** 825-833.
10. Masaki C, Sugino K, Saito N, Akaishi J, Hames KY, Tomoda C, Suzuki A, Matsuzu K, Uruno T, Ohkuwa K, Kitagawa W, Nagahama M, Ito K. Efficacy and limitations of lenvatinib therapy for radioiodine-refractory differentiated thyroid cancer: real-world experiences. *Thyroid* 2020 **30** 214-221.
11. Jasim S, Iniguez-Ariza NM, Hilger CR, Chintakuntlawar AV, Ryder MM, Morris JC 3rd, Bible KC. Optimizing Lenvatinib therapy in patients with metastatic radioactive iodine-resistant differentiated thyroid cancers. *Endocrine Practice* 2017 **23** 1254-1261
12. Jerkovich F, Califano I, Bueno F, Carrera JM, Giglio R, Abelleira E, Pitoia Real-life use of lenvatinib in patients with differentiated thyroid cancer: experience from Argentina. *Endocrine* 2020 **69** 142-148.
13. Song E, Kim M, Kim EY, Kim BH, Shin DY, Kang HC, Ahn BC, Kim WB, Shong YK, Jeon MJ, Lim DJ. Lenvatinib for radioactive iodine-refractory differentiated thyroid carcinoma and candidate biomarkers associated with survival: A multicenter study in Korea. *Thyroid* 2020 30 732-738.

Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

14. Balmelli C, Railic N, Siano M, Feuerlein K, Cathomas R, Cristina V, Güthner C, Zimmermann S, Weidner S, Pless M, Stenner F, Rothschild SI. Lenvatinib in advanced radioiodine-refractory thyroid cancer - a retrospective analysis of the swiss lenvatinib Named patient program. *Journal of Cancer* 2018 **9** 250-255.
15. Berdelou A, Borget I, Godbert Y, Nguyen T, Garcia ME, Chougnet CN, Ferru A, Buffet C, Chabre O, Huillard O, Leboulleux S, Schlumberger M. Lenvatinib for the treatment of radioiodine-refractory thyroid cancer in real-life practice. *Thyroid* 2018 **28** 72-78.
16. Nervo A, Gallo M, Samà MT, Felicetti F, Alfano M, Migliore E, Marchisio F, Berardelli R, Arvat E, Piovesan A. Lenvatinib in advanced radioiodine-refractory thyroid cancer: a snapshot of real-life clinical practice. *Anticancer Research* 2018 **38** 1643-1649.
17. Kim SY, Kim SM, Chang H, Kim BW, Lee YS, Chang HS, Park CS. Safety of tyrosine kinase inhibitors in patients with differentiated thyroid cancer: real-world use of lenvatinib and sorafenib in Korea. *Frontiers in Endocrinology (Lausanne)* 2019 **10** 384.
18. Locati LD, Piovesan A, Durante C, Bregni M, Castagna MG, Zovato S, Giusti M, Ibrahim T, Puxeddu E, Fedele G, Pellegriti G, Rinaldi G, Giuffrida D, Verderame F, Bertolini F, Bergamini C, Nervo A, Grani G, Rizzati S, Morelli S, Puliafito I, Elisei R. 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. *European Journal of Cancer* 2019 **118** 35-40.
19. Aydemirli MD, Kapiteijn E, Ferrier KRM, Ottevanger PB, Links TP, van der Horst-Schrivers ANA, Broekman KE, Groenwold RHH, Zwaveling J. Effectiveness and toxicity of lenvatinib in refractory thyroid cancer: Dutch real-life data. *European Journal of Endocrinology* 2020 **182** 131-138.
20. Denaro N, Latina A, Cesario F, Bramardi F, Corrado L, Borretta G, Merlano MC. Lenvatinib long-term responses in refractory thyroid cancer: our mono-institutional real-life experience with the multidisciplinary approach and review of literature. *Oncology* 2019 **97** 206-210.

21. Sugino K, Nagahama M, Kitagawa W, Ohkuwa K, Uruno T, Matsuzu K, Suzuki A, Masaki C, Akaishi J, Hames KY, Tomoda C, Ogimi Y, Ito K. Clinical factors related to the efficacy of tyrosine kinase inhibitor therapy in radioactive iodine refractory recurrent differentiated thyroid cancer patients. *Endocrine Journal* 2018 **65** 299-306.
22. De Leo S, Di Stefano M, Persani L, Fugazzola L, Colombo C. Lenvatinib as first-line treatment for advanced thyroid cancer: long progression-free survival. *Endocrine* 2021 **72** 462-469.
23. Brose MS, Panaseykin Y, Konda B, de la Fouchardiere C, Hughes BGM, Gianoukakis AG, Joo Park Y, Romanov I, Krzyzanowska MK, Leboulleux S, Binder TA, Dutcus C, Xie R, Taylor MH. A Randomized Study of Lenvatinib 18 mg vs 24 mg in patients with radioiodine-refractory differentiated thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* 2022 **107** 776-787.
24. Burgio V, Iavarone M, Di Costanzo GG, Marra F, Lonardi S, Tamburini E, Piscaglia F, Masi G, Celsa C, Foschi FG, Silletta M, Amoruso DC, Rimini M, Bruccoleri M, Tortora R, Campani C, Soldà C, Viola MG, Forgione A, Conti F, Salani F, Catanese S, Giacchetto CM, Fulgenzi C, Coppola C, Lampertico P, Pellino A, Rancatore G, Cabibbo G, Ratti F, Pedica F, Della Corte A, Colombo M, De Cobelli F, Aldrighetti L, Cascinu S, Casadei-Gardini A. Real-life clinical data of lenvatinib versus sorafenib for unresectable hepatocellular carcinoma in Italy. *Cancer Management and Research* 2021 **13** 9379-9389.
25. Kuo YH, Lu SN, Chen YY, Kee KM, Yen YH, Hung CH, Hu TH, Chen CH, Wang JH. Real-world lenvatinib *versus* sorafenib in patients with advanced hepatocellular carcinoma: a propensity score matching analysis. *Frontiers in Oncology* 2021 **11** 737767.
26. Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, Takaguchi K, Kariyama K, Itobayashi E, Tajiri K, Shimada N, Shibata H, Ochi H, Tada T, Toyoda H, Nouso K, Tsutsui A, Nagano T, Itokawa N, Hayama K, Imai M, Joko K, Koizumi Y, Hiasa Y, Michitaka K, Kudo M. Real-life practice experts for HCC (RELPEC) study group, HCC

Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

48 group (hepatocellular carcinoma experts from 48 clinics in Japan). Prognostic factor of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions-multicenter analysis. *Cancer Medicine* 2019 **8** 3719-3728.

27. Capdevila J, Newbold K, Licitra L, Popovtzer A, Moreso F, Zamorano J, Kreissl M, Aller J, Grande E. Optimisation of treatment with lenvatinib in radioactive iodine-refractory differentiated thyroid cancer. *Cancer Treatment Review* 2018 **69** 164-176.
28. Cabanillas ME, Takahashi S. Managing the adverse events associated with lenvatinib therapy in radioiodine-refractory differentiated thyroid cancer. *Seminars in Oncology* 2019 **46** 57-64.
29. Colombo C, De Leo S, Trevisan M, Giancola N, Scaltrito A, Fugazzola L. Daily management of patients on multikinase inhibitors' treatment. *Frontiers in Oncology* 2022 **12** 903532.
30. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016 **26** 1-133.
31. Pacini F, Basolo F, Bellantone R, Boni G, Cannizzaro MA, De Palma M, Durante C, Elisei R, Fadda G, Frasoldati A, Fugazzola L, Guglielmi R, Lombardi CP, Miccoli P, Papini E, Pellegriti G, Pezzullo L, Pontecorvi A, Salvatori M, Seregni E, Vitti P. Italian consensus on diagnosis and treatment of differentiated thyroid cancer: joint statements of six Italian societies. *Journal of Endocrinological Investigations* 2018 **41** 849-876.
32. Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, Lee N, Machens A, Moley JF, Pacini F, Raue F, Frank-Raue K, Robinson B, Rosenthal MS, Santoro M, Schlumberger M, Shah M, Waguespack SG. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid* 2015 **25** 567–610.

33. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *European Journal of Cancer* 2009 **45** 228–247.
34. Wirth LJ, Tahara M, Robinson B, Francis S, Brose MS, Habra MA, Newbold K, Kiyota N, Dutcus CE, Mathias E, Guo M, Sherman SI, Schlumberger M. Treatment-emergent hypertension and efficacy in the phase 3 Study of (E7080) lenvatinib in differentiated cancer of the thyroid (SELECT). *Cancer* 2018 **124** 2365-2372.
35. Nervo A, Retta F, Ragni A, Piovesan A, Mella A, Biancone L, Manganaro M, Gallo M, Arvat E. Nephrotoxicity in advanced thyroid cancer treated with tyrosine kinase inhibitors: An update. *Critical Reviews in Oncology/Haematology* 2021 **168** 103533.
36. Ancker OV, Wehland M, Bauer J, Infanger M, Grimm D. The adverse effect of hypertension in the treatment of thyroid cancer with multi-kinase inhibitors. International Journal of Molecular Sciencies 2017 **18** 625.
37. Li J, Gu J. Risk of gastrointestinal events with newly approved (after 2011) vascular endothelial growth factor receptor tyrosine kinase inhibitors in cancer patients: a meta-analysis of randomized controlled trials. *European Journal of Clinical Pharmacology* 2017 **73** 1209-1217.

 Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

Legends to Figures

Figure 1: Prevalence and grade of hypertension (HTN) in patients treated with Lenvatinib (LEN). 22/29 patients developed HTN during treatment. Considering severity according to Common Terminology Criteria for Adverse Events (CTCAE) v.5.0, 1/22 (5%) had HTN of grade 1, 11/22 (50%) grade 2 and 10/22 (45%) grade 3 HTN, Hypertension; Gr, Grade according to CTCAE version 5.0; LEN, Lenvatinib

Figure 2: A) Correlation between hypertension (HTN) and Lenvatinib (LEN) dosage. Linear regression analysis showed that the grade of HTN positively correlated with LEN dose (P=0.011).

B) Correlation between HTN, proteinuria and diarrhoea during treatment with LEN. There was no significant correlation between HTN and proteinuria (P=0.187), while LEN-induced HTN had a significant positive correlation with diarrhoea (P=0.025).

Figure 3: Patients who developed hypertension (HTN) during Lenvatinib (LEN) treatment did not have a significant higher prevalence of cardiovascular disease (pre-existing HTN and/or myocardial infarction and/or valvulopathies) prior to the start of the drug compared with patients who did not develop HTN (8 out of 22, 36% *vs* 5 out of 7, 71%; P= 0.104). A response to LEN treatment (measured according to RECIST criteria) was not different between patients who developed or not HTN (82% and 100%, respectively). In particular, complete response (CR), partial response (PR) and stable disease (SD) were observed in 0%, 64% and 18% of patients with HTN, and in 0%, 86% and 14% of patients without HTN, respectively (P=NS). In addition, there was no significant correlation between HTN and other clinicopathological features analysed. To note, ORR: objective response rate. LEN, Lenvatinib; HTN, hypertension; AJCC, American Joint Committee on Cancer 8th edition staging system.

Figure 4:

Panel A: 21/22 (95%) patients were on antihypertensive treatment: 1/21 in monotherapy and 20/21 in polytherapy; b) the only patient in monotherapy was on Calcium-channel blocker (CCB); c) 4/5 patients treated with 2 drugs were well controlled with CCB+ Ace-inhibitor (ACE-i)/ Beta blocker

(BB) (3 cases) or with ACE-i/BB (1 case); d) 9/10 patients controlled with 3 drugs were on CCB+ Angiotensin receptor blocker (ARB)/ACE-i and other drug; e) only 3/5 patients treated with ≥ 4 drugs were controlled.

Panel B: CCB were the most common drugs, used in 17/21 patients, either in monotherapy (5% of cases) or, in case of poor pressure control, in association with other anti-hypertensive drugs as ACE-i or BB (14%), with ARB/ACE-i + other anti-hypertensive drug (43%) or with a total of 4 anti-hypertensive drugs in 24% of patients.

Figure 5: Graphical illustrations of the potential mechanisms underlying Multityrosine-kinase inhibitor (MKI)-induced hypertension (HTN) and proteinuria and the deriving suggested treatments in patients developing these Adverse Events (AEs). In addition, a diagnostic-therapeutic algorithm is suggested to be applied in clinical practice in the management of patients with MKI-induced HTN. MKI, Multityrosine Kinase Inhibitor; HTN, hypertension; NO, nitric oxide; Ca, Calcium; VEGF; Vascular endothelial growth factor; CCB, Calcium channel blockers; ACE-i, Angiotensin-converting enzyme inhibitors; VGCC, Voltage-gated calcium channels; BP, Blood Pressure; ARB, Angiotensin receptor blockers; D; Diuretics; AB, Alpha-blockers.

 Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

Table 1: Hypertension prevalence and CTCAE grade developed during MKI treatment in clinical trials and real-life studies

	Hypertension prevalence developed during MKI treatment (%)	**Hypertension Grade ≥ 3 CTCAE v 5.0 (%)**	**Patients (n)**	**Evaluation of hypertension medical treatment**
DECISION ***Brose MS et al., 2014***	40.6	9.7	207	No
SELECT ***Schlumberger M et al., 2015***	67.8	41.8	261	No
ZETA ***Wells SA et al., 2011***	32	9	231	No
EXAM ***Elisei E et al., 2013***	32.7	8.9	214	No
COSMIC-311 ***Brose MS et al., 2021***	28	8.8	125	No
LIBRETTO-001 ***Wirth LJ et al., 2022***	30	12	162	No
LEN real life studies (#9-22) mean (range)	72.4 (15-100)	20.8 (0-74)	1045	Only #11
Present study: LEN	76	45	29	Yes

Legend: MKI, multikinase inhibitor; CTCAE v 5.0, Common Terminology Criteria for Adverse Events version 5.0; ECOG, Eastern Cooperative Oncology Group; LEN, Lenvatinib.

Table 2: Clinical features of the series of 29 patients treated with Lenvatinib

Patient ID/ Gender	Age at D/ Age at LEN start (yrs)	Tumor histotype	pTNM/ AJCC Stage	Metastases (site)	LEN starting dose (mg)	ECOG status	BMR	Follow-up from LEN start (months)	Time to HTN worsening or onset (months)	HTN Grade (CTCAE)	HTN medical treatment, number (drug)
#1/F	36/39	FTC	T3bNXMX/I	LN, lung	20	0	PR	32	1	3	4 (ARB, CCB, BB, AB)
#2/F	79/79	PTC	T3bNXMX/II	LN	10	1	PR	17	6	2	2 (CCB, ACE-i)
#3/F	33/75	PTC	T2N1aMX/I	LN	10	1	PR	68	1	2	2 (ACE-i, CCB)
#4/F	42/58	FTC	T2NXM0 /I	lung, vertebrae	20	0	PR	77	12	2	3 (CCB, D, ACE-i)
#5/F	57/73	PTC	T3bNXMX/II	LN, lung	14	1	SD	23	3	2	2 (ACE-i, CCB)
#6/F	71/72	PTC	T4aNXMX/II	LN, vertebrae	10	0	PR	29	15	2	5 (AB, D, D, D, BB)
#7/M	65/65	FTC	M1*/IVb	LN, trachea, lung, sternum	24	0	SD	26	12	3	2 (ARB, BB)
#8/F	63/74	PDTC	T3NXM0/II	LN, lung	20	0	PR	38	15	2	3 (CCB, ARB, D)
#9/M	50/66	PTC	T2NXMX/I	LN, lung	20	1	SD	47	4	2	3 (BB, CCB, ACE-i)
#10/M	67/68	FTC	T4bNXM1/IVb	LN, lung, bone	20	0	PR	64	24	3	3 (ARB, D, CCB)
#11/M	58/60	HCC	T3aNXMX/II	LN, neck, skin	20	0	PD	38	1	3	3 (ARB, CCB, AB)
#12/M	60/73	PTC	T3bN1aMX/II	LN, lung, pleura	12	0	PR	14	1.5	2	1 (CCB)
#13/F	79/84	FTC	T3aNXMX/II	LN, lung, clavicle	4	1	PR	50	1	3	3 (ARB, BB, D)

Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

#14/M	19/21	FTC	T3N1bM0/I	LN, skin	18	0	PR	45	32	1	0
#15/F	71/71	PTC	T3bNXMX/II	LN, neck, mediastinum, vertebrae	20	1	PD	2	1	2	2 (ACE-i, BB)
#16/F	74/76	PDTC	T3bN1aMX/II	LN, neck	10	0	PR	32	12	2	3 (ARB, D, CCB)
#17/M	71/73	PTC	T3bN1bMX/II	LN, lung	20	0	PR	13	1	3	4 (AB, BB, ARB, CCB)
#18/M	56/71	PTC	T3NXM0/II	LN, trachea, lung	20	1	PR	7	4	3	5 (CCB, AB, BB, ARB, D)
#19/M	76/79	HCC	T4aNXMX/III	LN, multiple bones	20	1	PD	2	1	3	2 (BB, ACE-i)
#20/F	77/77	PDTC	T4bNXM1/IVb	LN, neck, lung	24	1	PD	5	2	2	3 (ARB, CCB, BB)
#21/F	49/55	FTC	M1*/II	LN, multiple bones	24	1	SD	29	1	3	5 (CCB, BB, AB, ARB, D)
#22/M	51/59	PDTC	T1aNXMX/I	LN	24	0	PR	3	3	3	3 (ACE-i, CCB, BB)
#23/F	45/65	PTC	T3bN1aMX/I	LN, lung	4	1	PR	5	/	/	/
#24/M	64/67	PTC	T3bN1bMX/II	LN, lung	14	0	PR	14	/	/	/
#25/F	78/90	PTC	T4aN1bMX/III	LN, vertebrae	4	0	PR	5	/	/	/
#26/M	85/85	PTC	M1*/IVb	LN, sternum, lung	4	1	PR	5	/	/	/
#27/M	54/66	PTC	T4aN1MX/I	LN, lung, neck	20	0	PR	59	/	/	/
#28/F	73/80	FTC	T4aN1aMX/III	LN, lung, bone	6	1	SD	16	/	/	/
#29/M	51/58	PDTC	T4aN1aM0/I	LN, skull, vertebra	24	1	PR	68	/	/	/

Legend: LEN, Lenvatinib; BMR, Best Morphological Response; HTN, Hypertension; PDTC: poorly differentiated thyroid cancer; FTC: follicular thyroid cancer; PTC: papillary thyroid cancer; HCC Hürtle Cell Carcinoma; LN, Lymph Node; AJCC 8th edition staging system; PR: partial response; SD: stable disease; PD: progressive disease; CR: complete response; LN: Lymph Nodes; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; CCB: Calcium channel blocker; ACE-i: Angiotensin converting enzyme -inhibitor; ARB: Angiotensin receptor blocker; BB: Beta blocker; D: Diuretic; AB: Alpha blocker.

*Patients with unresectable tumor

Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

Figure 1

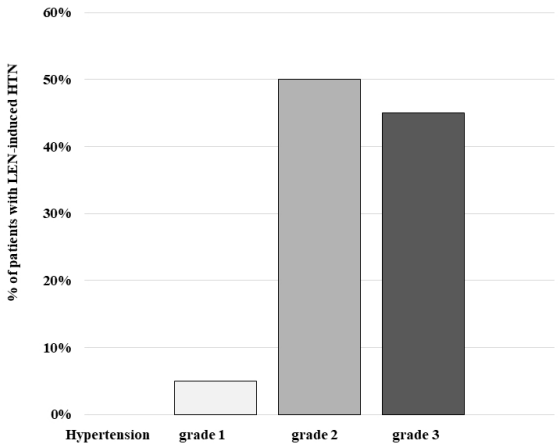

Figure 1: Prevalence and grade of hypertension (HTN) in patients treated with Lenvatinib. 22/29 patients developed HTN during treatment. Considering severity according to Common Terminology Criteria for Adverse Events (CTCAE) v.5.0, 1/22 (5%) had HTN of grade 1, 11/22 (50%) grade 2 and 10/22 (45%) grade 3 HTN, Hypertension; Gr, Grade according to CTCAE version 5.0; LEN, Lenvatinib.

338x190mm (96 x 96 DPI)

Figure 2

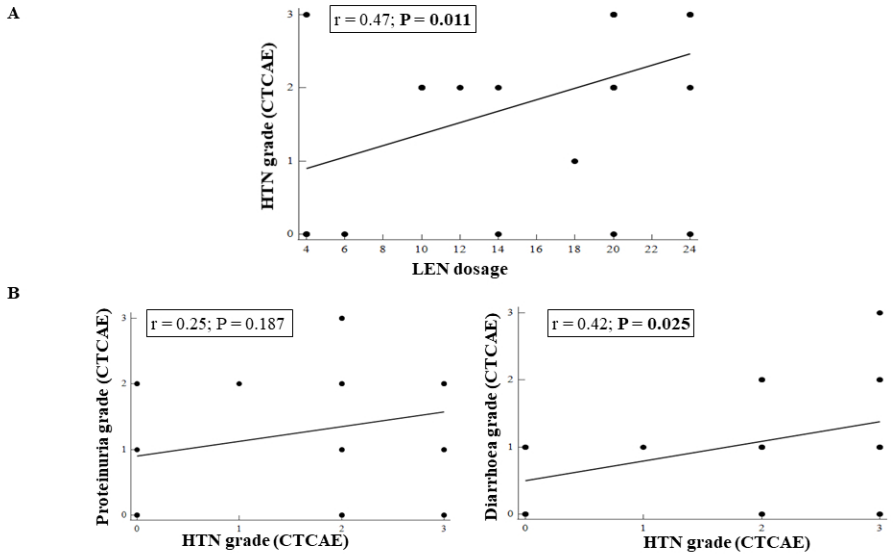

Figure 2: A) Correlation between hypertension (HTN) and Lenvatinib (LEN) dosage. Linear regression analysis showed that the grade of HTN positively correlated with LEN dose (P=0.011). B) Correlation between hypertension, proteinuria and diarrhoea during treatment with LEN. There was no significant correlation between HTN and proteinuria (P=0.187), while LEN-induced HTN had a significant positive correlation with diarrhoea (P=0.025).

275x190mm (96 x 96 DPI)

Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

Figure 3

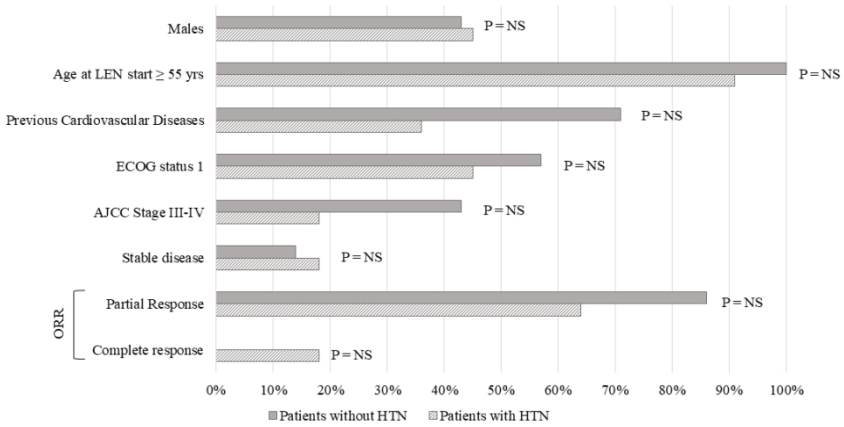

Figure 3: Patients who developed HTN during LEN treatment did not have a significant higher prevalence of cardiovascular disease (pre-existing HTN and/or myocardial infarction and/or valvulopathies) prior to the start of the drug compared with patients who did not develop HTN (8 out of 22, 36% vs 5 out of 7, 71%; P= 0.104). The response to LEN treatment (measured according to RECIST criteria) was not different between patients who developed or not HTN. In particular, complete response (CR), partial response (PR) and stable disease (SD) were observed in 0%, 64% and 18% of patients with HTN, and in 0%, 86% and 14% of patients without HTN, respectively (P=NS). In addition, there was no significant correlation between HTN and other clinicopathological features analysed. ORR: objective response rate. LEN, lenvatinib; HTN, hypertension; AJCC, American Joint Committee on Cancer 8th edition staging system.

338x190mm (96 x 96 DPI)

Figure 4

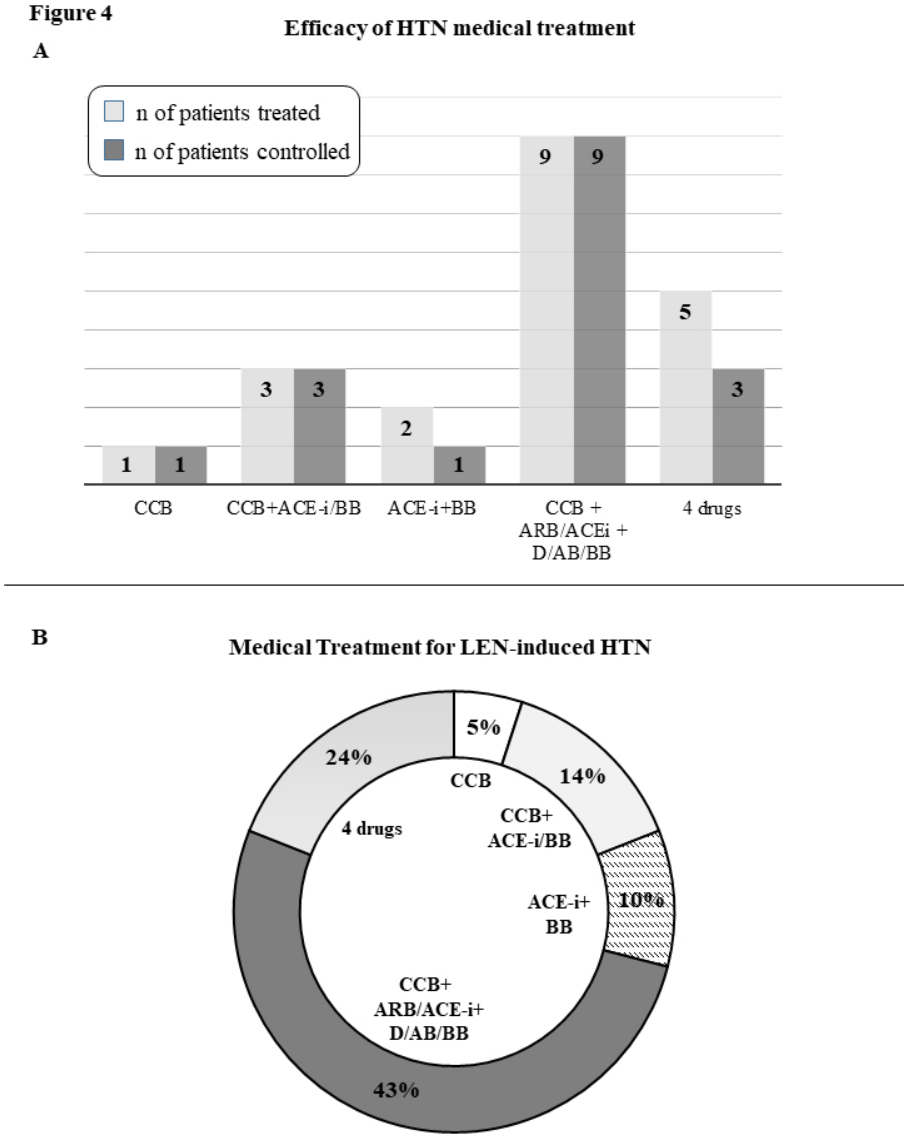

Figure 4: Panel A: 21/22 (95%) patients were on antihypertensive treatment: 1/21 in monotherapy and 20/21 in polytherapy; b) the only patient in monotherapy was on CCB; c) 4/5 patients treated with 2 drugs were well controlled with CCB+ACE-i/BB (3 cases) or with ACE-i/BB (1 case); d) 9/10 patients controlled with 3 drugs were on CCB+ARB/ACE-i+ and other drug; e) only 3/5 patients treated with 20/21 ⩾4 drugs were controlled. Panel B: Calcium channel blockers (CCB) were the most common drugs, used in 17/21 patients, either in monotherapy (5% of cases) or, in case of poor pressure control, in association with other anti-hypertensive drugs as ACE-i or BB (14%), with ARB/ACE-i + other anti-hypertensive drug (43%) or with a total of 4 anti-hypertensive drugs in 24% of patients.

190x254mm (96 x 96 DPI)

Accepted Manuscript published as ETJ-23-0047.R1. Accepted for publication: 25-Apr-2023

Figure 5

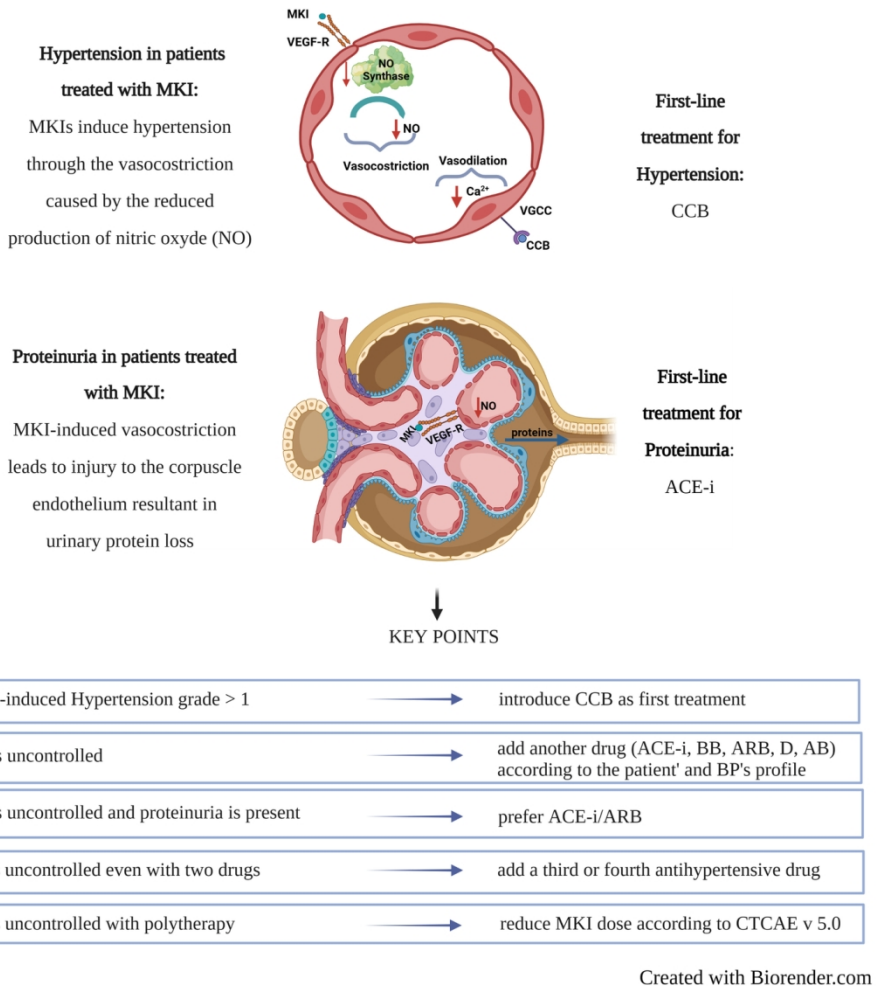

Figure 5: Graphical illustrations of the potential mechanisms underlying Multityrosine-kinase inhibitor (MKI)-induced hypertension (HTN) and proteinuria and the deriving suggested treatments in patients developing these Adverse Events (AEs). In addition, a diagnostic-therapeutic algorithm is suggested to be applied in clinical practice in the management of patients with MKI-induced HTN. MKI, Multityrosine Kinase Inhibitor; HTN, hypertension; NO, nitric oxide; Ca, Calcium; VEGF; Vascular endothelial growth factor; CCB, Calcium channel blockers; ACE-i, Angiotensin-converting enzyme inhibitors; VGCC, Voltage-gated calcium channels; BP, Blood Pressure; ARB, Angiotensin receptor blockers; D; Diuretics; AB, Alpha-blockers.

66x70mm (600 x 600 DPI)