



Baxter, M.A., Glen, H. and Evans, T.R.J. (2018) Lenvatinib and its use in the treatment of unresectable hepatocellular carcinoma. *Future Oncology*, 14(20), pp. 2021-2029. (doi:[10.2217/fon-2017-0689](https://doi.org/10.2217/fon-2017-0689)).

This is the author's final accepted version.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

<http://eprints.gla.ac.uk/159272/>

Deposited on: 09 April 2018

Enlighten – Research publications by members of the University of Glasgow
<http://eprints.gla.ac.uk>

TITLE Lenvatinib and its use in the treatment of unresectable hepatocellular carcinoma

AUTHORS Baxter MA¹, Glen H¹, Evans TRJ^{1,2}

AFFILIATIONS 1 Beatson West of Scotland Cancer Centre, Glasgow, UK

2 Institute of Cancer Sciences, University of Glasgow, Glasgow, UK

ADDRESS FOR CORRESPONDENCE

Beatson West of Scotland Cancer Centre

1053 Great Western Road

Glasgow, G12 OYN

United Kingdom

Tel: 01417013000

Fax:

Email: markbaxter3@nhs.net

FUNDING TRJ Evans has received funding from Eisai for support of clinical trials, and honoraria for consultancies and advisory boards including for HCC.

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver accounting for approximately 90% of cases. Patients often present at an advanced stage when treatment options are limited. Sorafenib, a multi-targeted tyrosine kinase inhibitor, has been the first-line treatment in this setting for almost a decade. Several subsequent targeted therapies have failed to demonstrate significant improvement in survival. The results of the REFLECT study suggest that lenvatinib, a multi-kinase inhibitor, may have promise as a first-line treatment in patients with advanced HCC. This article will review the development of lenvatinib and the evidence behind its potential use in patients with advanced HCC.

Key Words:

Hepatocellular carcinoma, Drug development, Lenvatinib, Sorafenib, Pharmacokinetics, Multi-Kinase Inhibitor, REFLECT

Introduction

Primary liver cancer is the second most common cause of death from cancer worldwide, estimated to be responsible for nearly 745,000 deaths worldwide in 2012 (9.1% of the total) [1]. Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver accounting for approximately 90% of cases [2] with an incidence of 5-20/100,000 per year depending on geographical location [3]. Chronic liver disease secondary to Hepatitis B and C is the most common cause worldwide but other risk factors include non-alcoholic steatohepatitis, tobacco smoking, and alcohol [2].

The management of HCC is dependent on the tumour stage according to the Barcelona Clinic Liver Cancer staging system. Outcomes have been improving in recent decades but median 5 year survival remains very low for stage C and D disease; 20months and 6-11months respectively [4].

Early disease is potentially curable with resection, ablation or liver transplantation, while intermediate stage disease may be controlled for a sustained period with trans-arterial chemoembolisation [5].

Progression of the disease has been associated with growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). VEGF acts on the tyrosine kinase receptors VEGFR-1, VEGFR-2 and VEGFR-3 and increased levels of VEGF have been shown to correlate with angiogenic activity, tumour progression and poor prognosis [6].

Based on this knowledge, several targeted therapies have emerged as potential treatments, including tyrosine kinase inhibitors (TKIs). Newer-generation TKIs are often referred to as multi-kinase inhibitors (MKIs) because they act on multiple intracellular targets. One of these, sorafenib, provided hope that targeted therapies may provide an effective therapeutic option and paved the way for testing of novel agents.

Two Phase III trials with sorafenib published in 2008 and 2009 demonstrated a significant survival benefit. The first, the SHARP study, was conducted in Europe, Australia and America and was a double-blind, placebo controlled trial of 602 patients. It demonstrated that sorafenib conferred a median overall survival of 10.7 months compared to 7.9 months with placebo (HR: 0.69; 95% CI: 0.55-0.87; $p < 0.001$) [7]. The second was conducted in the Asia-Pacific region with 271 patients randomised in the same way. It also demonstrated a survival benefit; 6.5 months with sorafenib compared to 4.2 months with placebo (HR: 0.68; 95% CI: 0.50-0.93; $p = 0.014$) [8].

Unfortunately, following these results many newer agents or combination regimes failed to improve survival in the first-line setting including sunitinib, brivanib, linifanib and erlotinib [9-12]. It is felt that the reasons for past failures in effective drug development are heterogenous. Several authors have discussed lack of understanding of critical drivers, flaws in trial design and marginal pre-clinical antitumour potency. Importantly, lack of understanding of TKI pharmacokinetics has often resulted in significant patient toxicity and subsequent trial failure [13-15].

Recently the PD-1 inhibitor nivolumab and the multi-kinase inhibitor (MKI) regorafenib have shown promise. The non-randomised single-arm Checkmate-040 trial of nivolumab in sorafenib-naïve and -experienced patients has indicated an increased response rate and a 9 month survival rate of 74% (CI 67-79) [16, 17] while the Phase III RESOURCE trial of regorafenib versus placebo, following progression on sorafenib, has indicated a survival advantage [18]. In this study of 573 patients,

median survival was 10.6 months (95% CI 9.1-12.1) for regorafenib versus 7.8 months (95% CI 6.3-8.8) for placebo, hazard ratio of 0.63 (95% CI 0.50–0.79; one-sided $p < 0.0001$).

Lenvatinib, another MKI, has shown activity against a range of solid tumours [19] and has been approved for use in radioiodine-refractory differentiated thyroid cancer following the SELECT study, which showed improved progression free survival and response rate in radioiodine-refractory differentiated thyroid cancer. In this study, patients treated with lenvatinib had a significant increase in progression-free survival (18.3 months vs. 3.6 months; HR = 0.21; CI = 0.14–0.31, $P < 0.001$) and response rate (64.8% vs. 1.5% with placebo) [20].

Subsequent investigation of lenvatinib in advanced HCC has demonstrated anti-tumour efficacy. This review will discuss the pharmacokinetic (PK) and pharmacodynamic parameters, clinical efficacy and tolerability of lenvatinib in patients with advanced HCC.

Pharmacology

Lenvatinib (E7080; 4-[3-chloro-4-(N'-cyclopropylureido) phenoxy] 7-methoxyquinoline-6-carboxamide mesylate) is an oral inhibitor of several tyrosine kinases developed by Eisai Co. **Figure 1** displays the chemical structure of Lenvatinib. It has a molecular formula of $C_{21}H_{19}ClN_4O_4 \cdot CH_3SO_3H$ and has a molecular weight of 522.96.

Lenvatinib has a broad spectrum of action. The kinase inhibitory profile was determined by Eisai, using homogeneous time resolved fluorescence (HTRF) assays, a universal tool for tyrosine kinase screening. Lenvatinib inhibits angiogenesis via inhibition of the VEGF receptors 1-3, fibroblast growth factor receptor 1-4 and platelet-derived growth factor (PDGF) receptors alpha and beta (**Table 1**). Simultaneously, it is also able to inhibit tumour cell proliferation via inhibition of the proto-oncogenes KIT and RET [21-24]. The most important difference between this drug and other TKIs is the ability of lenvatinib to potentially inhibit FGFR-1.

Pre-Clinical Studies

Preclinically, Lenvatinib was observed to have effects on angiogenesis, lymphangiogenesis and tumour proliferation.

In vitro Matsui et al., demonstrated that lenvatinib inhibits VEGF-stimulated proliferation of human umbilical vein endothelial cells (HUVECs – universally used in the investigation of angiogenesis) [25] and VEGF- and SCF-stimulated HUVEC capillary tube formation [22]. It was also shown to inhibit VEGF- and bFGF-stimulated human microvascular endothelial cell (HMVEC) proliferation *in vitro* in a dose dependent manner [21].

The effect of lenvatinib on angiogenesis has also been examined *in vivo*. The human breast cancer cell lines MDA-MB-231 and MDA-MB-435 were implanted sub-cutaneously in the flanks of nude mice and grown as xenografts. Mice were treated with lenvatinib for one week, then the tumours were excised and stained by immunohistochemistry with anti-CD31 antibody to assess microvessel density (MVD) as a measure of angiogenesis. MVD was significantly reduced after treatment with lenvatinib in xenografts of both cell lines by 72% and 52% respectively ($p < 0.05$), which corresponded to regression of the MDA-MB-231 xenografts and growth arrest of the MDA-MB-435

xenografts [25]. Similarly, when the small cell lung cancer cell line H146 was grown as xenografts in nude mice, decreased tumour MVD was observed after treatment with lenvatinib (59% reduction, $p < 0.01$) which corresponded to regression of the xenografts [22].

Lenvatinib also appears to affect lymphangiogenesis. When nude mice bearing MDA-MB-231 xenografts were treated, there was a significant reduction in lymphatic vessel density (91%, $p < 0.05$), whereas no effect was observed after treatment with bevacizumab. This corresponded to a complete inhibition of both lymph node metastasis and lung metastasis in E7080-treated mice [25].

When effects of proliferation were assessed, it was noted that lenvatinib had only weak anti-proliferative activity *in vitro* against human lung cancer (H460) and human colorectal cancer (Colo205) cells with IC_{50} values of 14 $\mu\text{mol/L}$ and 26 $\mu\text{mol/L}$ respectively. In contrast, when administered orally to nude mice bearing H460 and Colo205 xenografts (at doses of 1, 3, 10, 30 and 100 mg/kg, once a day for 14 days), significant tumour growth inhibition was observed at all doses tested (Eisai, unpublished data). Eisai therefore concluded that the effect of lenvatinib observed in tumour xenografts was most likely due to inhibition of angiogenesis.

Further to this, it has also been suggested that lenvatinib may also have direct anti-metastatic effects. *In vitro* studies using 2 human tumour cell lines demonstrated that lenvatinib inhibits tumour cell invasion and migration, possibly via effects on signalling of FGFR1 and PDGFR α [26].

Lenvatinib in Solid Tumours

Lenvatinib has demonstrated efficacy in several advanced solid tumours including medullary and differentiated thyroid cancer, non-small cell lung cancer, metastatic renal cell carcinoma, colorectal cancer, sarcoma, and melanoma with the most common toxicities being hypertension, proteinuria, diarrhoea, nausea and stomatitis [19, 27-29].

Phase 1 studies in a non-HCC setting suggested the use of lenvatinib at a dose of up to 25mg once daily [19], with subsequent use of 24mg as the dose in the Phase III SELECT study in thyroid cancer [30]. The main toxicities observed and occurring in greater than 50% of patients were hypertension, diarrhoea, fatigue and reduced appetite. 67.8% of patients required dose reductions with 14.2% discontinuing due to toxicity.

Lenvatinib was observed to be rapidly absorbed after oral intake. Excretion occurred via urine and faeces [31]. Peak plasma concentrations were reached at 1.6 hours following a single dose of 24mg with a terminal half-life of 34.5 hours [31]. Lenvatinib is metabolised in several ways including via cytochrome P450 3A, aldehyde oxidase and conjugation with glutathione [32, 33]. 2.5% is excreted unchanged and the probability of drug-drug interaction is low [34].

Patients with HCC have impaired liver function and therefore dose-finding studies were required in this population, to determine the effect of the disease process on metabolism and potential dose-limiting toxicities [35].

Phase 1 and Pharmacokinetics/Pharmacodynamics

The first evidence of anti-tumour activity of lenvatinib in patients with HCC came from work by Ikeda et al. in Japan during their dose-escalation study [36]. They recruited 20 patients with treatment

refractory HCC stratified according to hepatic function measured using Child-Pugh (CP) scores; CP-A (score 5-6) and CP-B (score 7-8).

Patients were treated with oral lenvatinib once daily with dose escalation every 28 day treatment cycle to establish a maximum tolerated dose (MTD). Concomitant use of strong CYP3A4 inhibitors were prohibited. Patients in the CP-A group had a starting dose of 12mg once daily, which was approximately 50% of the MTD recommended for solid tumours [19, 24]. Once this dose was confirmed as tolerable, CP-B patients were added.

Overall, dose-limiting toxicities (DLTs) occurred in 5 patients; 3 in CP-A and 2 in CP-B. When the dose was escalated to 16mg there were 2 DLTs reported among 3 patients and therefore 12mg was determined to be the MTD in the CP-A group. 12mg was then evaluated in the CP-B group. In this group, 1 patient experienced grade 3 hepatic encephalopathy, 1 patient experienced grade 3 liver derangement and 5 patients experienced grade 2 renal impairment. The dose was therefore reduced to 8mg with no DLTs and 8mg was determined to be the MTD for CP-B hepatic impairment.

Following oral administration, rapid absorption was seen with a maximum concentration reached within 2 hours and exposure increased with increasing lenvatinib dose. Plasma lenvatinib concentrations increased after repeated dosing but the pharmacokinetic (PK) profile did not appear to be influenced by Childs-Pugh score.

At 12mg, most PK parameters were comparable between solid tumours and CP-A apart from C_{24h} which was higher for the CP-A group. Pharmacodynamic parameters were influenced by lenvatinib; circulating endothelial progenitor cells (CEP) decreased significantly along with c-Kit⁺ circulating endothelial cells (CECs), while blood/plasma IL-6, IL-10, G-CSF and VEGF increased significantly.

In the 20 patients, there was no complete response seen but partial response was observed in 3 patients – 1 in CP-A 12mg, 1 in CP-A 16mg and 1 in CP-B 8mg. 10 patients (50%) had a stable response with 6 patients progressing. Any tumour shrinkage was observed in 14 patients with a median TTP of 5.4 months in the CP-A group and 3.6 months in the CP-B group. Alpha-fetoprotein (aFP) reduced for the majority of patients.

Phase 2 and Safety

In the subsequent Phase II trial [37], 46 patients with CP-A liver dysfunction, were recruited in Japan and Korea. It was a single-arm, open-label study of lenvatinib monotherapy at a dose of 12mg once daily in 28 day cycles. The primary endpoint was time to progression (TTP) per modified RECIST, with secondary endpoints including objective response rate (ORR), disease control rate (DCR) and overall survival (OS).

The median TTP was 7.4 months (95% CI: 5.5-9.4m) as assessed by Immune Related Response Criteria (IRRC) as per mRECIST but 12.8 months (95% CI: 7.2-14.7m) by investigator assessment. This was promising in comparison to Phase II trials with sorafenib where TTP was 4.2months [38].

17 patients (37%) achieved a partial response and 19 patients (41%) had stable disease \geq 8 weeks. Subgroup analysis indicated that lenvatinib activity was maintained regardless of tumour status, type of hepatitis, previous chemotherapy or alpha-fetoprotein (aFP) levels – with a suggestion that those with Hepatitis B had the greatest benefit [35]. Median OS was 18.7 months (12.7-25.1m).

The main adverse events seen were hypertension, palmar-plantar syndrome, reduced appetite, proteinuria and fatigue (**Table 2**). No dose reductions were required for hypertension despite grade

3 incidence being 54%. Although hepatic encephalopathy was the most common SAE (five patients) in the study, all five patients had the predisposing risk factors of constipation and dehydration. These were managed with conservative management and dose modification.

Of note, 74% of patients required a dose reduction. It has previously been suggested in Phase I and II trials with lenvatinib that anti-angiogenic toxicity is related to weight i.e. it is increased in those with lower weight. This is supported in this study by the finding that those patients requiring a dose modification had a significantly lower median weight than those patients who did not (54.1kg v 67.6kg). Additionally, increased lenvatinib levels are seen in those with liver impairment [35, 37]. In this study, dose reduction was significantly associated with cycle 1, day 15 trough levels (62.4ng/ml v 33.9ng/ml).

These findings led to a larger Phase III trial in a similar population with planned doses of 8 mg in patients with weight <60 kg and 12 mg in those with a weight >60kg.

Phase 3

The REFLECT trial was a multicentre, randomised, open-label, non-inferiority study to compare the efficacy and safety of lenvatinib versus sorafenib as a first line systemic treatment in patients with unresectable HCC [39].

Eligible patients had a confirmed histological / cytological diagnosis of unresectable HCC with CP-A liver dysfunction and at least one measurable target lesion according to mRECIST. Patients were excluded if prior systemic anti-cancer therapy (including anti-VEGF therapy) had been given or if they had invasion of the main portal vein. This differed from the SHARP study, which permitted macroscopic vascular invasion [7].

Patients were randomised in a 1:1 ratio to receive either oral lenvatinib 12mg (if >60kg) or 8mg (if <60kg) once daily or 400mg sorafenib twice daily orally. Treatment was continued until disease progression or unacceptable toxicity.

The primary endpoint of the study was overall survival (OS), with the goal of demonstrating non-inferiority, with a pre-defined margin of 1.08. Secondary endpoints were progression free survival (PFS), time to progression (TTP), objective response rate (ORR) and quality of life (QoL).

Following screening, 954 patients were enrolled with 478 being allocated to the lenvatinib group and 476 to the sorafenib group. Patients were stratified according to: region, ECOG-PS score, vascular invasion and/or extrahepatic spread and body weight. Levels of aFP were not included.

The primary endpoint was reached with median OS being non-inferior; 13.6 months for the lenvatinib group and 12.3 months for sorafenib (HR = 0.92, 95% CI: 0.79-1.06). Additionally, lenvatinib showed significant improvements in the 3 secondary efficacy endpoints (**Table 3**): PFS was 7.4 months vs 3.7 months (HR 0.66, 95% CI = 0.57-0.77, p<0.00001), TTP was 8.9 months vs 3.7 months (HR 0.63, 95% CI = 0.53-0.73, p<0.00001) and ORR was 24% v 9% (p<0.00001).

Overall, this trial has shown that lenvatinib is statistically non-inferior to sorafenib in terms of overall survival but confers a significantly better progression-free survival, time to progression and response rate. In light of these results, lenvatinib is a new first-line therapeutic option for the treatment of advanced HCC.

Discussion

Since the publication of the SHARP study in 2008 and subsequent approval of sorafenib as a first-line agent in advanced HCC, progress to identify further therapeutic options has been slow. Multiple Phase III studies in this setting have been negative.

One challenge has been to identify key pathways implicated in hepatocellular carcinogenesis and disease progression. This is compounded by the relative lack of tumour tissue from patients with advanced disease for biological studies as most patients are diagnosed on radiological criteria, and the limited available tumour tissue is invariably taken from patients with early, resectable disease.

However, there is now a growing understanding of the multiple signalling pathways involved (eg, Ras/Raf/MAPK, WNT- β -catenin, EGFR, insulin-like growth factor receptor, AKT-mTOR, Notch, and Hedgehog) and their components represent future potential downstream molecular targets for therapy in HCC [40]. The use of mutation specific therapeutics may prove challenging as somatic genomic profiling has suggested that less than 10% of patients with HCC have actionable mutations [41].

The REFLECT study of the multi-kinase inhibitor lenvatinib, is the first Phase III study to demonstrate efficacy of a novel agent as an alternative to sorafenib in patients with advanced disease. The study also demonstrated lenvatinib was comparable to sorafenib in safety profile (**Table 4**).

The study itself had a number of strengths. Firstly, it was based on strong pre-clinical data, with lenvatinib also showing significant benefit in other solid tumours. Secondly, the trial design included appropriate weight-based dosing and was a non-inferiority trial design. The open-label design is a potential limitation, but the results were confirmed by independent imaging review and major protocol deviations were few and balanced between the drugs [39].

Despite the above, lenvatinib did not achieve superiority in overall survival. As aFP was not included as a stratification factor, there was an imbalance favouring the sorafenib arm, with more patients with an aFP >200 being allocated to the lenvatinib arm. In post-hoc analysis after adjustment of the AFP imbalance, lenvatinib proved nominally superior to sorafenib in OS ($p=0.0342$) [42].

An imbalance was also seen in the number of Hepatitis C related HCC patients, again favouring the sorafenib arm. Additionally, by excluding patients with a high tumour burden or portal vein thrombosis, both arms had a better prognostic population than would be expected likely resulting in a longer post-progression survival and therefore dilution of the OS benefit.

Overall, the findings of the REFLECT trial show that lenvatinib was statistically non-inferior to sorafenib in OS with clinically significant improvement in PFS, TTP, and ORR. These results suggest that lenvatinib is an alternative first-line systemic anti-cancer therapy for patients with unresectable HCC, and may well replace sorafenib as standard of care in this disease due to its superior secondary endpoints of PFS, TTP, and ORR.

Recently, the anti-PD1 antibody, nivolumab, has been licensed by the FDA as a second-line therapy based on the results from non-randomised single arm phase II Checkmate-040 study discussed above [17]. Given the differing modes of actions of sorafenib, lenvatinib and nivolumab (**Table 5**), future studies are likely to explore the optimal combination therapy regimens of targeted therapy with immuno-oncology agents. An example is the open-label Phase 1b study of lenvatinib with pembrolizumab which is currently recruiting [43].

Conclusion

Lenvatinib is the first agent since the approval of sorafenib for the treatment of HCC approximately 10 years ago to show statistically significant non-inferiority to sorafenib in the first line setting. These results suggest Lenvatinib may be a new first-line option for unresectable advanced HCC. This coupled with the emergence of immune checkpoint inhibitors, may pave the way for an exciting future in the treatment of advanced HCC.

Executive Statements

Levatinib activity

- Lenvatinib is an oral multikinase inhibitor that potently blocks multiple protein kinases involved in tumour proliferation including VEGF receptors 1-3, fibroblast growth factor receptors 1-4 and platelet-derived growth factor (PDGF) receptor alpha and beta

Phase II evidence

- In a Phase II study of Lenvatinib in patients with advanced hepatocellular carcinoma who had progressed on sorafenib, the median TTP was 7.4 months (95% CI: 5.5-9.4m) as assessed by IRRC per mRECIST but 12.8 months (95% CI: 7.2-14.7m) by investigator assessment
- Median OS was 18.7 months (12.7-25.1m)

Phase III evidence

- In a double-blind, randomized, Phase III trial, patients who received lenvatinib had an overall survival of 13.6 months vs 12.3 months with sorafenib (HR = 0.92, 95% CI: 0.79-1.06) – reaching non-inferiority
- Lenvatinib showed clinically meaningful and significant improvements in the 3 secondary efficacy endpoints; PFS, TTP and ORR

Toxicities

- Although 74% of patients in the Phase II trial required a dose reduction, many of the toxicities are class effects associated with all TKIs and with appropriate and prompt management they are usually manageable
- The main adverse events seen were hypertension, palmar-plantar syndrome, reduced appetite, proteinuria and fatigue

Conclusion

- Lenvatinib is the first agent to demonstrate non-inferiority to sorafenib in the first-line setting in advanced hepatocellular carcinoma
- It has shown significant improvements in PFS, TTP and ORR, which are clinically meaningful, when compared to sorafenib
- It has a tolerable toxicity profile

Figure 1



Figure 1 - Chemical structure of E7080 [34].

Table 1

Kinase	IC ₅₀ (nM)
VEGFR1	22
VEGFR2	4.0
VEGFR3	5.2
FGFR1	46
PDGFR α	51
PDGFR β	39
EGFR	6500
c-kit	100

Table 1 - Kinase inhibitory profile of lenvatinib [22]. c-kit = receptor for stem cell factor; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor cell surface receptor; IC₅₀ = half maximal inhibitory concentration; PDGFR = platelet-derived growth factor receptor; VEGFR = vascular endothelial growth factor receptor.

Table 2

This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

Adverse Event	Any Grade, n=46	Grade 3, n=46	Grade 4, n=46
Hypertension	35 (76.1%)	25 (54.3%)	0
Palmar-Plantar Syndrome	30 (65.2%)	4 (8.7%)	0
Decreased appetite	28 (60.9%)	1 (2.2%)	0
Proteinuria	28 (60.9%)	9 (19.6%)	0
Fatigue	25 (54.3%)	0	0
Diarrhoea	20 (43.5%)	6 (13.0%)	0
Constipation	19 (41.3%)	0	0
Nausea	17 (37.0%)	1 (2.2%)	0
Dysphonia	17 (37.0%)	0	0
Thrombocytopenia	16 (34.8%)	9 (19.6%)	1 (2.2%)
Peripheral oedema	16 (34.8%)	0	0
Decreased weight	14 (30.4%)	2 (4.6%)	0

Table 2 – Adverse events with Lenvatinib in Phase 2 study occurring in >30% patients. Adapted from [37].

Table 3

Efficacy Outcome Median (95% CI)	Total Population		Patients with HBV	
	Lenvatinib (n=478)	Sorafenib (n=476)	Lenvatinib (n=259)	Sorafenib (n=244)
OS (months)	13.6 (12.1-14.9)	12.3 (10.4-13.9)	13.4 (11.6-14.6)	10.2 (8.6-12.4)
HR (95% CI)	0.92 (0.79-1.06)		0.83 (0.68-1.02)	
PFS (months)	7.4 (6.9-8.8)	3.7 (3.6-4.6)	7.3 (5.6-9.1)	3.6 (2.6-3.6)
HR (95% CI)	0.66 (0.57-0.77)		0.62 (0.50-0.75)	
TTP (months)	8.9 (7.4-9.2)	3.7 (3.6-5.4)	7.6 (6.6-9.2)	3.6 (3.4-3.7)
HR (95% CI)	0.63 (0.53-0.73)		0.58 (0.47-0.72)	
ORR (%)	24.1 (20.2-27.9)	9.2 (6.6-11.8)	20.8 (15.9-25.8)	8.2 (4.8-11.6)
Odds Ratio (95% CI)	3.13 (2.15-4.56)		3.15 (1.80-5.53)	

Table 3 – REFLECT study results of investigator review according to mRECIST. Table created from results published in [39]. CI: confidence interval, HR: Hazard Ratio, OR: Odds Ratio.

Table 4

	Lenvatinib (n=476)	Sorafenib (n=475)
Overall	98.7%	99.4%
Hypertension	42.2%	30.3%
Diarrhoea	38.7%	46.3%
Reduced appetite	34.0%	26.3%
Weight loss	30.9%	22.3%
Palmar-plantar erythrodysesthaesia	26.9%	52.4%

Table 4: Most common treatment related adverse events (all grades) in the REFLECT study. Table created from figures in paper [39].

Table 5

	Sorafenib	Nivolumab	Lenvatinib
Class of drug	Multi Tyrosine Kinase Inhibitor	Immune checkpoint inhibitor (Immunoglobulin G4 monoclonal antibody)	Multi Tyrosine Kinase Inhibitor
Site of action	VEGFR 1-3 PDGFR- β Raf-1 B-RAF	Blocks PDL-1 binding to PD-1	VEGFR 1-3 FGFR 1-4 PDFGR- α/β EGFR Kit RET
Route of administration	Oral	Intravenous	Oral
Licensed for use	Hepatocellular Renal Thyroid	Melanoma Urothelial Squamous cell lung Renal Hepatocellular	Thyroid Renal

Table 5: Comparison of characteristics of Sorafenib, Nivolumab and Lenvatinib [7, 16, 39].

References:

1. Ferlay J, Soerjomataram I, Dikshit R *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer* 136(5), E359-386 (2015).
2. Chuang SC, Lee YC, Hashibe M, Dai M, Zheng T, Boffetta P. Interaction between cigarette smoking and hepatitis B and C virus infection on the risk of liver cancer: a meta-analysis. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 19(5), 1261-1268 (2010).
3. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. *Journal of clinical gastroenterology* 47 Suppl S2-6 (2013).
4. Verslype C, Rosmorduc O, Rougier P. Hepatocellular carcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology* 23(suppl_7), vii41-vii48 (2012).
5. Llovet JM, Real MI, Montana X *et al.* Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet (London, England)* 359(9319), 1734-1739 (2002).
6. Bertino G, Demma S, Ardiri A *et al.* Hepatocellular carcinoma: novel molecular targets in carcinogenesis for future therapies. *BioMed research international* 2014 203693 (2014).
7. Llovet JM, Ricci S, Mazzaferro V *et al.* Sorafenib in advanced hepatocellular carcinoma. *The New England journal of medicine* 359(4), 378-390 (2008).
8. Cheng AL, Kang YK, Chen Z *et al.* Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *The Lancet. Oncology* 10(1), 25-34 (2009).
9. Cheng AL, Kang YK, Lin DY *et al.* Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 31(32), 4067-4075 (2013).
10. Johnson PJ, Qin S, Park JW *et al.* Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 31(28), 3517-3524 (2013).
11. Cainap C, Qin S, Huang W-T *et al.* Linifanib Versus Sorafenib in Patients With Advanced Hepatocellular Carcinoma: Results of a Randomized Phase III Trial. *Journal of Clinical Oncology* 33(2), 172-179 (2015).
12. Zhu AX, Rosmorduc O, Evans TR *et al.* SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 33(6), 559-566 (2015).
13. Llovet JM, Hernandez-Gea V. Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design. *Clinical cancer research : an official journal of the American Association for Cancer Research* 20(8), 2072-2079 (2014).
14. Tamai T, Hayato S, Hojo S *et al.* Dose Finding of Lenvatinib in Subjects With Advanced Hepatocellular Carcinoma Based on Population Pharmacokinetic and Exposure-Response Analyses. *Journal of clinical pharmacology* 57(9), 1138-1147 (2017).
15. Bouattour M, Rousseau B, Wassermann J, Payance A, Huillard O. Negative Trials for Foreseeable Safety Reasons in Advanced Hepatocellular Carcinoma: How Long Are We Going to Take Lightly Pharmacokinetics of Tyrosine Kinase Inhibitors? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 33(22), 2484-2485 (2015).

16. Melero I, Sangro B, Yau TC *et al.* Nivolumab dose escalation and expansion in patients with advanced hepatocellular carcinoma (HCC): The CheckMate 040 study. *Journal of Clinical Oncology* 35(4_suppl), 226-226 (2017).
17. Todd S, Crocenzi ABE-K, Thomas Cheung Yau, Ignacio Melero, Bruno Sangro, Masatoshi Kudo, Chiun Hsu, Jorg Trojan, Tae-You Kim, Su-Pin Choo, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Adyb Baakili, Christine Marie Dela Cruz, Lixin Lang, Jaclyn Neely, Theodore Welling. Nivolumab (Nivo) in Sorafenib (Sor)-Naive and -Experienced Pts with Advanced Hepatocellular Carcinoma (Hcc): Checkmate 040 Study. Nivolumab (nivo) in sorafenib (sor)-naive and -experienced pts with advanced hepatocellular carcinoma (HCC): CheckMate 040 study. . *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* (35), (suppl; abstr 4013) (2017).
18. Bruix J, Qin S, Merle P *et al.* Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet (London, England)* 389(10064), 56-66 (2017).
19. Yamada K, Yamamoto N, Yamada Y *et al.* Phase I dose-escalation study and biomarker analysis of E7080 in patients with advanced solid tumors. *Clinical cancer research : an official journal of the American Association for Cancer Research* 17(8), 2528-2537 (2011).
20. Kiyota N, Robinson B, Shah M *et al.* Defining Radioiodine-Refractory Differentiated Thyroid Cancer: Efficacy and Safety of Lenvatinib by Radioiodine-Refractory Criteria in the SELECT Trial. *Thyroid : official journal of the American Thyroid Association* 27(9), 1135-1141 (2017).
21. Ikuta K, Yano S, Trung VT *et al.* E7080, a multi-tyrosine kinase inhibitor, suppresses the progression of malignant pleural mesothelioma with different proangiogenic cytokine production profiles. *Clinical cancer research : an official journal of the American Association for Cancer Research* 15(23), 7229-7237 (2009).
22. Matsui J, Yamamoto Y, Funahashi Y *et al.* 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. *International journal of cancer* 122(3), 664-671 (2008).
23. Tohyama O, Matsui J, Kodama K *et al.* Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. *Journal of thyroid research* 2014 638747 (2014).
24. Yamamoto N NH, Yamada Y, Honda K, Wakui H, Sasaki T, Et Al. . A phase I and dose-finding study of lenvatinib (E7080) in Japanese patients with advanced solid tumors. . (2013).
25. Matsui J, Funahashi Y, Uenaka T, Watanabe T, Tsuruoka A, Asada M. 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. *Clinical cancer research : an official journal of the American Association for Cancer Research* 14(17), 5459-5465 (2008).
26. Glen H, Mason S, Patel H, Macleod K, Brunton VG. E7080, a multi-targeted tyrosine kinase inhibitor suppresses tumor cell migration and invasion. *BMC cancer* 11 309 (2011).
27. Boss DS, Glen H, Beijnen JH *et al.* A phase I study of E7080, a multitargeted tyrosine kinase inhibitor, in patients with advanced solid tumours. *British journal of cancer* 106(10), 1598-1604 (2012).
28. Nishio M, Horai T, Horiike A *et al.* Phase 1 study of lenvatinib combined with carboplatin and paclitaxel in patients with non-small-cell lung cancer. *British journal of cancer* 109(3), 538-544 (2013).
29. Molina AM, Hutson TE, Larkin J *et al.* 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 Chemotherapy and Pharmacology* 73(1), 181-189 (2014).

30. Schlumberger M, Tahara M, Wirth LJ *et al.* Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *The New England journal of medicine* 372(7), 621-630 (2015).
31. Dubbelman AC, Rosing H, Nijenhuis C *et al.* Pharmacokinetics and excretion of (14)C-lenvatinib in patients with advanced solid tumors or lymphomas. *Investigational new drugs* 33(1), 233-240 (2015).
32. Gupta A, Jarzab B, Capdevila J, Shumaker R, Hussein Z. Population pharmacokinetic analysis of lenvatinib in healthy subjects and patients with cancer. *British journal of clinical pharmacology* 81(6), 1124-1133 (2016).
33. Inoue K, Asai N, Mizuo H, Fukuda K, Kusano K, Yoshimura T. Unique metabolic pathway of [(14)C]lenvatinib after oral administration to male cynomolgus monkey. *Drug metabolism and disposition: the biological fate of chemicals* 40(4), 662-670 (2012).
34. Inoue K, Mizuo H, Kawaguchi S, Fukuda K, Kusano K, Yoshimura T. Oxidative metabolic pathway of lenvatinib mediated by aldehyde oxidase. *Drug metabolism and disposition: the biological fate of chemicals* 42(8), 1326-1333 (2014).
35. Shumaker R, Aluri J, Fan J, Martinez G, Pentikis H, Ren M. Influence of hepatic impairment on lenvatinib pharmacokinetics following single-dose oral administration. *Journal of clinical pharmacology* 55(3), 317-327 (2015).
36. Ikeda M, Okusaka T, Mitsunaga S *et al.* Safety and Pharmacokinetics of Lenvatinib in Patients with Advanced Hepatocellular Carcinoma. *Clinical cancer research : an official journal of the American Association for Cancer Research* 22(6), 1385-1394 (2016).
37. Ikeda K, Kudo M, Kawazoe S *et al.* Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. *Journal of gastroenterology* 52(4), 512-519 (2017).
38. Abou-Alfa GK, Schwartz L, Ricci S *et al.* Phase II Study of Sorafenib in Patients With Advanced Hepatocellular Carcinoma. *Journal of Clinical Oncology* 24(26), 4293-4300 (2006).
39. Kudo M, Finn RS, Qin S *et al.* Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet (London, England)* doi:10.1016/s0140-6736(18)30207-1 (2018).
40. Galuppo R, Ramaiah D, Ponte OM, Gedaly R. Molecular therapies in hepatocellular carcinoma: what can we target? *Digestive diseases and sciences* 59(8), 1688-1697 (2014).
41. Sun W, Sohal D, Haller DG *et al.* Phase 2 trial of bevacizumab, capecitabine, and oxaliplatin in treatment of advanced hepatocellular carcinoma. *Cancer* 117(14), 3187-3192 (2011).
42. Kudo M. Lenvatinib in Advanced Hepatocellular Carcinoma. *Liver Cancer* 6 253-263 (2017).
43. Nct03006926 CGI. A Trial of Lenvatinib Plus Pembrolizumab in Subjects With Hepatocellular Carcinoma. (2018).