Sorafenib and Lenvatinib in the Management of Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the most common malignancy of the liver and ranks high among cancer-related complications and death globally. In the United States alone, HCC represents the 9th leading cause of cancer-related deaths. It is particularly prevalent in Asia and Africa, and results in around 21,000 deaths annually (Ferlay et al., 2010). As with other cancers, the diagnosis of HCC is often made when the disease has progressed to a significant stage and this limits suitable treatment strategies. Therefore, therapeutic drugs are often compared based on their overall survival duration and time taken for the tumour to progress (Balogh et al., 2016). This review compares the therapeutic efficacies of one of the earlier drugs, sorafenib, and one of the more recent drugs, lenvatinib. It throws light on the results obtained in different phases of clinical trials in terms of survival duration, tumour response rate, recurrence rate, and time taken for the tumour to progress. It also compares the adverse drug reactions of the two drugs as demonstrated in different studies and their therapeutic efficacies in intermediate and advanced stages of HCC.

Intermediate HCC is more challenging as compared to early stage HCC in terms of prognosis and treatment options, as most of the treatment strategies that work for early stage HCC have proved to be unsatisfactory for intermediate stage HCC. For several decades, transarterial chemoembolization (TACE) has proved to be the most widely used treatment for intermediate HCC; however, its prognosis has been mostly poor and there is a higher rate of recurrence with this treatment option (Forner et al., 2018). Additionally, it lowers the functioning capacity of the liver and leads to an ineffective body response in fighting intermediate stage HCC (Hiraoka et al., 2017). As

a result, several other treatment strategies have been considered for treating intermediate HCC (Ikeda et al., 2014).

One of the earliest and widely used treatment strategies for intermediate HCC is the oral multi-tyrosine kinase inhibitor (TKI), sorafenib (Raoul et al., 2018). As it is a potent TKI, it functions by inhibiting receptor tyrosine kinases such as KIT, RET, PDGFR, and VEGFR1-3 and other signaling molecules such as B-Raf and Raf-1 that are involved in important pathways of apoptosis, angiogenesis, and tumour proliferation (Chang et al., 2007). It is not only beneficial for intermediate stage HCC, but also an effective treatment strategy for advanced HCC as shown by a phase III study (Llovet et al., 2008). It has also been shown that in patients who have had a recurrence of HCC following TACE, sorafenib has increased the time of progression of the disease and the overall survival duration of patients (Ogasawara et al., 2014).

Since its development, several clinical trials have been conducted to assess its efficacy, safety, and adverse reactions in patients suffering from different stages of HCC. Phase I trials have been conducted in patients with advanced stages of HCC using 400 mg of sorafenib twice a day. These trials identified toxicities related to skin and digestive system in patients with the use of this drug (Strumberg et al., 2006). A phase II trial that was conducted in patients who had not previously received any treatment for HCC using the same dosage as the Phase I trials revealed drug toxicities such as diarrhea, fatigue, and hand-foot skin reactions. Considering the efficacy of the treatment, the response rate of the tumour was quite low with only 2.2% of patients showing any decipherable tumour response. Expert assessments showed that the survival duration of sorafenib was 9.2 months and the time of progression of the tumour

was 5.5 months (Abou-Alfa et al., 2006). Despite the fact that the results of the Phase I and Phase II clinical trials were not very promising, due to lack of effective alternative strategies, Phase III clinical trials were conducted. These trials were conducted in patients with advanced HCC and used the same dosage of sorafenib as the first two clinical trials. These studies found that although the time of progression was not greatly affected, the survival benefit offered by sorafenib was definitively higher when compared to placebo, leading to its approval for HCC treatment (Cheng et al., 2009).

Following these clinical trials and the approval of sorafenib for management of HCC, several studies have been conducted to evaluate the efficacy of this drug in patients with varying stages and symptoms of HCC. One such hallmark study is the GIDEON study that tested the efficacy and safety of sorafenib in a total of 3202 patients residing in 39 countries around the world. This study found similar survival and tumour progression rates as the clinical trials, while reporting regional differences in the responses and management of HCC in patients (Marrero et al., 2016). Similarly, other studies have compared the differences in efficacy between sorafenib and TACE and found that treatment with sorafenib offered a survival advantage to patients, which was not seen in patients on TACE therapy (Arizumi et al., 2015).

According to global treatment guidelines and the BCLC staging system, sorafenib has been used for the past decade as the first line of treatment for advanced stages of HCC (Bruix and Sherman, 2011). According to European guidelines, sorafenib has been recommended for patients with intermediate HCC who have not responded to TACE or have experienced recurrence after TACE therapy (European Association for the Study of the Liver, 2012). In contrast, Japanese guidelines have considered

disease-related factors such as liver function, extrahepatic spread, vascular invasion, and tumour size for recommending sorafenib as a treatment strategy for HCC (Kudo et al., 2014).

Due to limitations of the efficacy and safety of sorafenib in HCC patients, several studies have compared the effects of combinations of sorafenib with other drugs over sorafenib therapy alone. The categories of molecular targeting drugs that have been combined with sorafenib include anti-angiogenic agents, mTOR pathway inhibitors, MEK/ERK pathway inhibitors, EGF/EGFR pathway inhibitors, histone deacetylase inhibitors, and interferons; however, none of the agents that have been used in combination with sorafenib have proven to be particularly effective over sorafenib alone in phase III clinical trials (Huang et al., 2020). A European phase III trial that investigated the effectiveness of sorafenib combined with TACE showed that this combination did not eliminate tumour progression in the treated patients, nor did it provide any additional survival benefit to the patients (Meyer et al., 2017). In contrast, studies conducted in the Chinese population have found that adding sorafenib to TACE increased the survival time of patients by at least 50% (Zhu et al., 2014). The Japanese TACTICS trial that tested the effectiveness of TACE and sorafenib combination therapy found that the tumour progression incidence in the treated patients was significantly lower as compared to patients who were treated with TACE alone (Wu et al., 2017).

Over about a decade after the approval of sorafenib for the treatment of HCC, lenvatinib emerged as the first line of treatment for different stages of HCC. The REFLECT trial was conducted by Kudo et al. (2018) that showed the effectiveness and safety of lenvatinib for advanced stage HCC. This result was confirmed by different

studies conducted around the world which showed that lenvatinib monotherapy had potent anti-tumour activity especially in patients who had portal vein invasion (Hiraoka et al., 2019; Takeda et al., 2019). In patients with intermediate stages of HCC who had previously been exposed to TACE therapy, treatment with lenvatinib demonstrated a survival duration of 37.9 months and a tumour progression duration of 16 months (Kudo et al., 2019). These numbers are comparatively much higher than those achieved by sorafenib and hence, lenvatinib has a stronger efficacy as compared to sorafenib for the treatment of intermediate HCC.

The pharmacokinetics of lenvatinib is quite different from that of sorafenib and so, its appropriate dosage for treatment varies with the patient's body weight. As a result, the body weight is used to calculate an appropriate therapeutic dose that can improve prognosis of the tumour, protect liver function, and eliminate the chances of tumour progression (Ueshima et al., 2019). An important side effect during the use of lenvatinib is thyroid toxicity and therefore, thyroid abnormalities need to be continually monitored in HCC patients who are being treated with lenvatinib. Specifically, continued use of lenvatinib can lead to hypothyroidism, destructive thyroiditis, and thyrotoxicosis; however, lenvatinib is still considered safer than sorafenib in terms of adverse drug reactions in patients (Kobayashi et al., 2019).

Similar to sorafenib, lenvatinib is a multi-tyrosine kinase inhibitor (TKI) and its molecular targets are VEGF receptors, fibroblast growth factor receptors, platelet-derived growth factor receptor, RET, and KIT (Boss et al., 2012). The REFLECT trial has sufficiently proved the effectiveness of lenvatinib over sorafenib in terms of both primary and secondary endpoints such as time to progression and survival duration,

and this result has been replicated by several other studies conducted by different groups around the world (Kudo et al., 2018). It also has better outcomes for HCC patients with major portal vein tumour thrombosis as compared to sorafenib (Kuzuya et al., 2020). Another study conducted by Kudo (2018) found that in patients who were previously unresponsive to TACE, treatment with lenvatinib showed statistically significant results in terms of a considerable decrease in tumour size in around 61% of the patients. Additionally, systemic treatment with lenvatinib and even sorafenib is much more valuable than TACE and therefore, the preferred treatment strategy for HCC (Kudo, 2018). Therefore, lenvatinib has been considered a suitable treatment option for patients who do not respond to TACE or who face recurrence after treatment with TACE (Arizumi et al., 2017). In case of advanced stages of HCC, lenvatinib has been shown to have a tumour response rate of about 40% with no significant damage to liver function (Kudo et al., 2018).

Phase I trials of lenvatinib conducted in various countries around the world have shown the beneficial effects of the drug not only for HCC, but also for thyroid cancer, colon cancer, melanoma, and endometrial cancer. These trials reported various drug toxicities such as fatigue, proteinuria, and hypertension, and the therapeutic dosage of lenvatinib that was determined from these trials was 12 mg per day (Boss et al., 2012; Hong et al., 2015). Following the success of phase I trials, phase II trials of lenvatinib were conducted using the dosage of 12 mg per day and these trials revealed a survival duration of 18.7 months, a tumour progression time of 7.4 months, and a recurrence rate of 37% for metastatic HCC (Ikeda et al., 2017). Phase III trials were conducted in advanced stage patients who had no previous exposure to systemic

chemotherapy and in whom the efficacies of sorafenib and lenvatinib were compared. This trial proved the potent efficacy of lenvatinib over sorafenib in increasing survival duration, reducing the incidence of progression, increasing the time taken for the tumour to progress, and reducing the recurrence rate of HCC in patients (Ann-Lii et al., 2017).

The toxicity profile of lenvatinib is quite similar to sorafenib; however, it is different in being toxic to the thyroid gland. Some of its toxic effects in cancer patients have been documented to be hand-foot syndrome, hypertension, diarrhea, and thrombocytopenia. Out of these, thrombocytopenia has been documented in about 25% of the patients, hypertension in about 17% of the patients, and peripheral edema in about 15% of the patients (Zhu et al., 2016). Additionally, some of the less common side effects of the drug are proteinuria, nephrotic syndrome, cardiac dysfunction, and delayed wound healing (Suyama and Iwase, 2018).

As per current international guidelines, lentavinib is recommended as the preferred drug of choice for treating intermediate and advanced stages of HCC in patients. Following clinical trials, several real-world studies have been conducted to check the efficacy, safety, and adverse reactions of the drug in HCC patients. A clinical study conducted with 92 Korean patients demonstrated a tumour response rate of 21%, time for tumour progression of about 4.6 months, and survival duration of 10.7 months. These results show a lower efficacy of lentavinib as compared to the results obtained from phase III trials; however, the differences in the results have been attributed to differences in tumour characteristics and liver function of patients (Cheon et al., 2020). Another study conducted by Fuchigami et al. (2020) on the efficacy of lenvatinib in HCC patients found that the tumour response rate was 48%, which was closer to the results

obtained in the phase III clinical trials. This study also reported that the efficacy of the drug varied greatly with the extent of the HCC in patients. For instance, the tumour response rate was around 63% in patients with stage B HCC and the rate was around 21% in patients with stage C HCC. Additionally, the tumour response rate was 75% in patients with stage A HCC and 66% in patients who were experiencing a recurrence following TACE therapy (Fuchigami et al., 2020).

However, despite the considerably higher beneficial effects of lenvatinib over sorafenib, some studies have noticed drug resistance in a small group of patients who were treated with lenvatinib. Fu et al. (2020) found c-Met is a predictive biomarker for drug resistance against lenvatinib, and activation of the MAPK/ERK and the PI3K/AKT pathways by the HGF/c-Met axis contributes to lenvatinib resistance in susceptible patients.

In conclusion, both sorafenib and lenvatinib have proven efficacies for intermediate and advanced stages of HCC. However, lenvatinib has demonstrated better survival durations, better tumour response rates, lower tumour progression rates, and lower recurrence rates. As per current guidelines, lenvatinib is a preferred drug of choice for treatment of HCC and it is one of the most widely used drugs for treatment of various types of cancers such as thyroid, endometrial, and HCC. The greatest disadvantage of lenvatinib is its thyrotoxic reactions in as many as 25% of patients. However, with continual monitoring and targeted strategies, lenvatinib continues to be the preferred drug for the treatment of HCC.

References

Abou-Alfa, G. K., Ricci, S., Amadori, D., Santoro, A., Figer, A., & De Greve, J. (2006). Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol, 24*, 4293-4300.

Ann-Lii, C., Richard, S. F., & Shukui, Q. (2017). Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC). *J Clin Oncol, 35*(Suppl 15), Abstr 4001.

Arizumi, T., Minami, T., Chishina, H., Kono, M., Takita, M., Yada, N., . . . Kudo, M. (2017). Impact of Tumor Factors on Survival in Patients with Hepatocellular Carcinoma Classified Based on Kinki Criteria Stage B2. *Digestive Diseases, 35*(6), 583-588. doi:10.1159/000480186

Arizumi, T., Ueshima, K., Minami, T., Kono, M., Chishina, H., Takita, M., . . . Kudo, M. (2015). Effectiveness of Sorafenib in Patients with Transcatheter Arterial Chemoembolization (TACE) Refractory and Intermediate-Stage Hepatocellular Carcinoma. *Liver Cancer, 4*(4), 253-262. doi:10.1159/000367743

Balogh, J., Victor, D., Asham, E. H., Burroughs, S. G., Boktour, M., Saharia, A., . . . Monsour, H. (2016). Hepatocellular carcinoma: A review. *Journal of Hepatocellular Carcinoma, Volume 3*, 41-53. doi:10.2147/jhc.s61146

Boss, D. S., Glen, H., Beijnen, J. H., Keesen, M., Morrison, R., Tait, B., . . . Evans, T. R. (2012). 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. doi:10.1038/bjc.2012.154

Bruix, J., & Sherman, M. (2011). American association for the study of liver diseases. Management of hepatocellular carcinoma: An update. *Hepatology, 53*, 1020-1022.

Chang, Y. S., Adnane, J., Trail, P. A., Levy, J., Henderson, A., Xue, D., . . . Wilhelm, S. (2006). Sorafenib (BAY 43-9006) inhibits tumor growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models. *Cancer Chemotherapy and Pharmacology, 59*(5), 561-574. doi:10.1007/s00280-006-0393-4

Cheng, A., Kang, Y., Chen, Z., C, T., Qin, S., & Kim, J. (2009). 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. *Lancet Oncol, 10*, 25-34.

Cheon, J., Chon, H., Bang, Y., Park, N., Shin, J., Kim, K., . . . Ryoo, B. (2020). Real-World Efficacy and Safety of Lenvatinib in Korean Patients with Advanced

Hepatocellular Carcinoma: A Multicenter Retrospective Analysis. *Liver Cancer, 9*(5), 613-624. doi:10.1159/000508901

Ferlay, J., Shin, H., Bray, F., Forman, D., Mathers, C., & Parkin, D. M. (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer, 127*(12), 2893-2917. doi:10.1002/ijc.25516

Forner, A., Reig, M., & Bruix, J. (2018). Hepatocellular carcinoma. *The Lancet, 391*(10127), 1301-1314. doi:10.1016/s0140-6736(18)30010-2

Fuchigami, A., Imai, Y., Uchida, Y., Uchiya, H., Fujii, Y., Nakazawa, M., . . . Mochida, S. (2020). Therapeutic efficacy of lenvatinib for patients with unresectable hepatocellular carcinoma based on the middle-term outcome. *Plos One, 15*(4). doi:10.1371/journal.pone.0231427

European Association for the Study of the Liver. (2012). EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatology, 56*(4), 908-943. doi:10.1016/j.jhep.2011.12.001

Fu, R., Jiang, S., Li, J., Chen, H., & Zhang, X. (2020). Activation of the HGF/c-MET axis promotes lenvatinib resistance in hepatocellular carcinoma cells with high c-MET expression. *Medical Oncology, 37*(24). doi:10.1007/s12032-020-01350-4

Hiraoka, A., Kumada, T., Kariyama, K., Takaguchi, K., Atsukawa, M., Itobayashi, E., . . . Michitaka, K. (2018). Clinical features of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions: Multicenter analysis. *Cancer Medicine, 8*(1), 137-146. doi:10.1002/cam4.1909

Hiraoka, A., Kumada, T., Kudo, M., Hirooka, M., Koizumi, Y., Hiasa, Y., . . . Michitaka, K. (2017). Hepatic Function during Repeated TACE Procedures and Prognosis after Introducing Sorafenib in Patients with Unresectable Hepatocellular Carcinoma: Multicenter Analysis. *Digestive Diseases, 35*(6), 602-610. doi:10.1159/000480256

Hong, D. S., Kurzrock, R., Wheler, J. J., Naing, A., Falchook, G. S., Fu, S., . . . Nemunaitis, J. (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. *Clinical Cancer Research, 21*(21), 4801-4810. doi:10.1158/1078-0432.ccr-14-3063

Huang, A., Yang, X., Chung, W., Dennison, A. R., & Zhou, J. (2020). Targeted therapy for hepatocellular carcinoma. *Signal Transduction and Targeted Therapy, 5*(1). doi:10.1038/s41392-020-00264-x

Ikeda, K., Kudo, M., Kawazoe, S., Osaki, Y., Ikeda, M., Okusaka, T., . . . Kumada, H. (2016). Phase 2 study of lenvatinib in patients with advanced hepatocellular

carcinoma. *Journal of Gastroenterology, 52*(4), 512-519. doi:10.1007/s00535-016-1263-4

Ikeda, M., Mitsunaga, S., Shimizu, S., Ohno, I., Takahashi, H., Okuyama, H., . . . Okusaka, T. (2013). Efficacy of sorafenib in patients with hepatocellular carcinoma refractory to transcatheter arterial chemoembolization. *Journal of Gastroenterology, 49*(5), 932-940. doi:10.1007/s00535-013-0853-7

Kobayashi, M., Kudo, M., Izumi, N., Kaneko, S., Azuma, M., Copher, R., . . . Ikeda, S. (2019). Cost-effectiveness analysis of lenvatinib treatment for patients with unresectable hepatocellular carcinoma (uHCC) compared with sorafenib in Japan. *Journal of Gastroenterology, 54*(6), 558-570. doi:10.1007/s00535-019-01554-0

Kudo, M. (2018). Extremely High Objective Response Rate of Lenvatinib: Its Clinical Relevance and Changing the Treatment Paradigm in Hepatocellular Carcinoma. *Liver Cancer, 7*(3), 215-224. doi:10.1159/000492533

Kudo, M., Finn, R. S., Qin, S., Han, K., Ikeda, K., Piscaglia, F., . . . Cheng, A. (2018). Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: A randomised phase 3 non-inferiority trial. *The Lancet, 391*(10126), 1163-1173. doi:10.1016/s0140-6736(18)30207-1

Kudo, M., Matsui, O., Izumi, N., Iijima, H., Kadoya, M., & Imai, Y. (2014). JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the Liver Cancer Study Group of Japan. *Liver Cancer, 3*, 458-468.

Kudo, M., Ueshima, K., Chan, S., Minami, T., Chishina, H., Aoki, T., . . . Nishida, N. (2019). Lenvatinib as an Initial Treatment in Patients with Intermediate-Stage Hepatocellular Carcinoma Beyond Up-To-Seven Criteria and Child–Pugh A Liver Function: A Proof-Of-Concept Study. *Cancers, 11*(8), 1084. doi:10.3390/cancers11081084

Kuzuya, T., Ishigami, M., Ito, T., Ishizu, Y., Honda, T., Ishikawa, T., & Fujishiro, M. (2020). Sorafenib vs. Lenvatinib as First-line Therapy for Advanced Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis. *Anticancer Research, 40*, 2283-2290. doi:10.21873/anticanres.14193

Llovet, J. M., Ricci, S., Mazzaferro, V., Hilgard, P., Gane, E., Blanc, J., . . . Bruix, J. (2008). Sorafenib in Advanced Hepatocellular Carcinoma. *New England Journal of Medicine, 359*(4), 378-390. doi:10.1056/nejmoa0708857

Marrero, J. A., Kudo, M., Venook, A. P., Ye, S., Bronowicki, J., Chen, X., . . . Lencioni, R. (2016). Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. *Journal of Hepatology, 65*(6), 1140-1147. doi:10.1016/j.jhep.2016.07.020

Meyer, T., Fox, R., Bird, D., Watkinson, A., Hacking, N., Stocken, D., . . . Palmer, D. H. (2012). TACE 2: A randomized placebo-controlled, double-blinded, phase III trial evaluating sorafenib in combination with transarterial chemoembolisation (TACE) in patients with unresectable hepatocellular carcinoma (HCC). *Journal of Clinical Oncology, 30*(15_suppl). doi:10.1200/jco.2012.30.15_suppl.tps4150

Ogasawara, S., Chiba, T., Ooka, Y., Kanogawa, N., Motoyama, T., Suzuki, E., . . . Yokosuka, O. (2014). Efficacy of Sorafenib in Intermediate-Stage Hepatocellular Carcinoma Patients Refractory to Transarterial Chemoembolization. *Oncology, 87*(6), 330-341. doi:10.1159/000365993

Raoul, J., Kudo, M., Finn, R. S., Edeline, J., Reig, M., & Galle, P. R. (2018). Systemic therapy for intermediate and advanced hepatocellular carcinoma: Sorafenib and beyond. *Cancer Treatment Reviews, 68*, 16-24. doi:10.1016/j.ctrv.2018.05.006

Strumberg, D., Awada, A., Hirte, H., Clark, J., Seeber, S., Piccart, P., . . . Schwartz, B. (2006). Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumours: Is rash associated with treatment outcome? *European Journal of Cancer, 42*(4), 548-556. doi:10.1016/j.ejca.2005.11.014

Suyama, K., & Iwase, H. (2018). Lenvatinib. *Cancer Control, 25*(1), 107327481878936. doi:10.1177/1073274818789361

Takeda, H., Nishijima, N., Nasu, A., Komekado, H., Kita, R., Kimura, T., . . . Osaki, Y. (2019). Long-term antitumor effect of lenvatinib on unresectable hepatocellular carcinoma with portal vein invasion. *Hepatology Research, 49*(5), 594-599. doi:10.1111/hepr.13294

Ueshima, K., Nishida, N., Hagiwara, S., Aoki, T., Minami, T., Chishina, H., . . . Kudo, M. (2019). Impact of Baseline ALBI Grade on the Outcomes of Hepatocellular Carcinoma Patients Treated with Lenvatinib: A Multicenter Study. *Cancers, 11*(7), 952. doi:10.3390/cancers11070952

Wu, F., Chen, J., Bai, T., Zhu, S., Yang, T., Qi, L., . . . Li, L. (2017). The safety and efficacy of transarterial chemoembolization combined with sorafenib and sorafenib mono-therapy in patients with BCLC stage B/C hepatocellular carcinoma. *BMC Cancer, 17*(1). doi:10.1186/s12885-017-3545-5

Zhu, K., Chen, J., Lai, L., Meng, X., Zhou, B., Huang, W., . . . Shan, H. (2014). Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: Treatment with Transarterial Chemoembolization Combined with Sorafenib—A Retrospective Controlled Study. *Radiology, 272*(1), 284-293. doi:10.1148/radiol.14131946

Zhu, C., Ma, X., Hu, Y., Guo, L., Chen, B., Shen, K., & Xiao, Y. (2016). Safety and efficacy profile of lenvatinib in cancer therapy: A systematic review and meta-analysis. *Oncotarget, 7*(28), 44545-44557. doi:10.18632/oncotarget.10019