Clinical trials at Eisai: Advances in combination targeted therapy for renal cell carcinoma

AUTHOR
Alton B. Kremer MD, PhD

Chief Clinical Officer
Chief Medical Officer
Eisai Inc.
100 Tice Blvd
Woodcliff Lake, NJ, USA

As a global leader in oncology, Eisai Inc. is developing a number of agents for the treatment of a wide range of cancer types, including kidney cancer. According to the American Cancer Society, kidney cancer represented an estimated 3.7% of all new cancer cases in 2015[1]. The most common type of kidney cancer (about 85% of all cases) is renal cell carcinoma (RCC)[2]. Lenvatinib, a multiple tyrosine kinase inhibitor (TKI) developed at Eisai, is currently approved in combination with everolimus and under investigation in combination with pembrolizumab for the treatment of RCC. This paper will describe the current challenges in the treatment of RCC and the ongoing research at Eisai aiming to fulfill these unmet medical needs.

Targeted treatments for improved cancer care

Thanks to recent drug development efforts, new therapies are emerging to provide cancer treatments that are tailored to the needs of individual patients. Unlike standard chemotherapy, these drugs specifically target the molecular components that drive tumour cell growth and metastasis. As a result, these targeted treatments can often avoid some of the serious side effects caused by chemotherapeutic agents. Although targeted therapies have revolutionized cancer care, their adoption has come with new challenges.

One consideration that must be made when identifying and evaluating a targeted treatment is that not all tumours are alike. A patient with breast cancer can respond to a particular treatment differently than a patient with kidney cancer, for example. In fact, even two people who have kidney cancer may have differing responses to a given treatment. To treat this wide array of patients with different forms of cancer, new drugs must be developed to target the molecular pathways responsible for tumour growth in each specific tumour type. These targeted treatments must therefore be developed with the biology of specific tumours in mind and evaluated in precise clinical settings.

A number of targeted systemic treatments are currently approved and available for the treatment of RCC. A major component of the antitumour activity of these agents is their inhibition of the molecular pathways involved in angiogenesis, the process by which new blood vessels are formed[3]. Whereas angiogenesis is a necessary, but regulated, physiological process in healthy tissues, it is also involved in tumour growth and metastasis in the context of cancer. This is because new vasculature is needed to provide nutrients and oxygen to the growing tumour. By selectively aiming at these pathways, these treatments inhibit the formation of new blood vessels in the tumour, thereby limiting tumour growth and metastasis. Systemic treatments for RCC that target the molecular pathways involved in angiogenesis include the TKIs sunitinib, pazopanib, axitinib, cabozantinib and sorafenib, inhibitors of the mammalian target of rapamycin (mTOR) everolimus and temsirolimus, and the monoclonal antibody bevacizumab (all except cabozantinib, which is only approved in the United States, are approved for the treatment of RCC in the United States, the European Union and Japan)[3].

Lenvatinib, a TKI developed at Eisai, has been approved in the United States for the treatment of patients with locally recurrent or metastatic, progressive, radioactive-iodine-refractory differentiated thyroid cancer based on the results of a phase 3 clinical trial[4]. Lenvatinib functions in part by inhibiting the angiogenesis-promoting activity of vascular endothelial growth factor (VEGF) receptors 1–3 and fibroblast growth factor (FGF) receptors 1–4 (Figure 1) and in part by inhibiting the tumour growth activity mediated

by platelet-derived growth factor receptor alpha, ret proto-oncogene, and stem cell factor receptor[5-7].

Because of its demonstrated antitumour activity, lenvatinib is also under investigation for the treatment of a range of other cancer types, and in May 2016 was approved by the United States Food and Drug Administration for the treatment of patients with advanced or metastatic RCC in combination with the mTOR inhibitor everolimus, following one prior antiangiogenic (VEGF-targeted) therapy[8]. A positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use was received for the combination in July 2016 and approval in the European Union is pending. Preclinical studies have been completed in an attempt to understand how this combination of lenvatinib and everolimus acts on a molecular level[9,10]. These studies have suggested that the activity of this combination may result from enhanced inhibitory activity against VEGF-induced angiogenesis and synergistic enhancement of inhibition of FGF-induced angiogenesis by the two agents, possibly due to dual targeting of the mTOR-S6K-S6 pathway[10]. In addition, the combination treatment provides both the antiangiogenic activity of lenvatinib and the antitumour activity of everolimus (Figure 2)[9]. The details of the phase 2 trial that led to the approval of this combination are provided below.

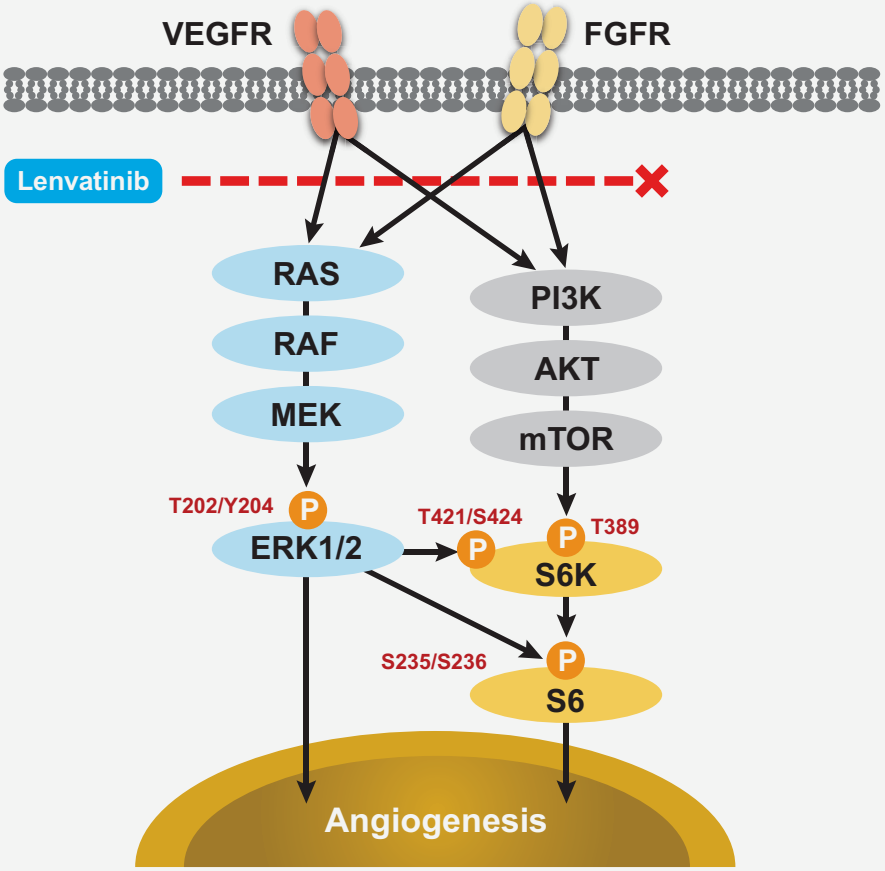


Figure 1 | Lenvatinib inhibits angiogenesis through its inhibition of the vascular endothelial growth factor receptors (VEGFR) and fibroblast growth factor receptors (FGFR).

A phase 2 study of lenvatinib in combination with everolimus for clear cell RCC

Whereas the discovery of agents targeting the VEGF pathway was an important breakthrough in the treatment of RCC, many patients do not show a long-lasting response to treatment as a result of the development of drug resistance by tumour cells[11]. It is therefore important to establish alternative treatment options for patients who experience disease progression after first-line therapy. The FGF pathway is thought to play a role in the development of tumour resistance to TKI therapy, therefore suggesting that lenvatinib-mediated inhibition of FGF receptors may be involved in reducing drug resistance[12].

To investigate a possible benefit of lenvatinib and everolimus combination therapy, a randomized phase 2 study recruited patients with advanced, metastatic, clear cell RCC who had received one prior VEGF-targeted treatment[13]. Patients were randomized to receive lenvatinib 18 mg/day plus everolimus 5 mg/day, lenvatinib 24 mg/day as a single agent, or everolimus 10 mg/day as a single agent. Tumour response assessments were made by investigator review every eight weeks until disease progression or the start of another anticancer treatment.

The primary objectives of the study were to determine progression-free survival for the combination compared with everolimus as well as for lenvatinib compared with everolimus. The combination significantly increased progression-free survival compared with everolimus alone (median 14.6 months compared with 5.5 months; hazard ratio [HR]: 0.40; 95% CI: 0.24–0.68; $p = 0.0005$). Single-agent lenvatinib also significantly improved progression-free survival compared with single-agent everolimus (median 7.4 months compared with 5.5 months; HR: 0.61; 95% CI: 0.38–0.98; $p = 0.048$; Figure 3).

Secondary endpoints of the study included progression-free survival for the combination compared with lenvatinib, objective response rate, evaluation of safety and tolerability, pharmacokinetics and overall survival. The PFS improvement of the combination of lenvatinib and everolimus compared with single-agent lenvatinib did not reach statistical significance (HR: 0.66; 95% CI: 0.39–1.10; $p = 0.12$; Figure 3). The objective response rate per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 was 43% for the 51 patients receiving lenvatinib in combination with everolimus compared with 6% for the 50 patients receiving single-agent everolimus (rate ratio: 7.2; 95% CI 2.3–22.5; $p < 0.0001$) and 27% of the 52 patients receiving single-agent lenvatinib (rate ratio: 1.6; 95% CI 0.9–2.8; $p = 0.10$; single-agent lenvatinib versus single-agent everolimus, rate ratio: 4.5; 95% CI 1.4–14.7; $p = 0.0067$). When assessing confirmed responses only, the objective response rate was 37% (95% CI 24–52) for the combination and 6% (95% CI 1–17) for everolimus[8].

At the primary data cutoff of the study (13 June 2014), there was no significant difference in overall survival between the combination and single-agent lenvatinib treatment arms, but a trend towards a longer median overall survival was observed in the combination arm (25.5 months versus 17.5 months; HR: 0.55; 95% CI 0.30–1.01)[13]. In a post-hoc updated

analysis (data cutoff 10 December 2014) there was a significant increase in median overall survival in patients receiving lenvatinib in combination with everolimus compared with those receiving single-agent everolimus (25.5 months versus 15. 4 months; HR: 0.51; 95% CI 0.30–0.88; p=0.024)[13]. An additional updated analysis (data cutoff 31 July 2015) did not show a significant difference in overall survival between treatment arms, but there was again a trend towards a longer median overall survival in the combination arm (25.5 months; 95% CI 16.4–32.1) compared with single-agent everolimus (15.4 months; 95% CI 11.8–20.6; p=0.065)[14]. In addition, an analysis with data cutoff 13 June 2014 demonstrated that lenvatinib combined with everolimus significantly prolonged progression-free survival regardless of baseline risk according to Memorial Sloan-Kettering Cancer Center criteria, baseline tumour size, or the site of metastasis[14].

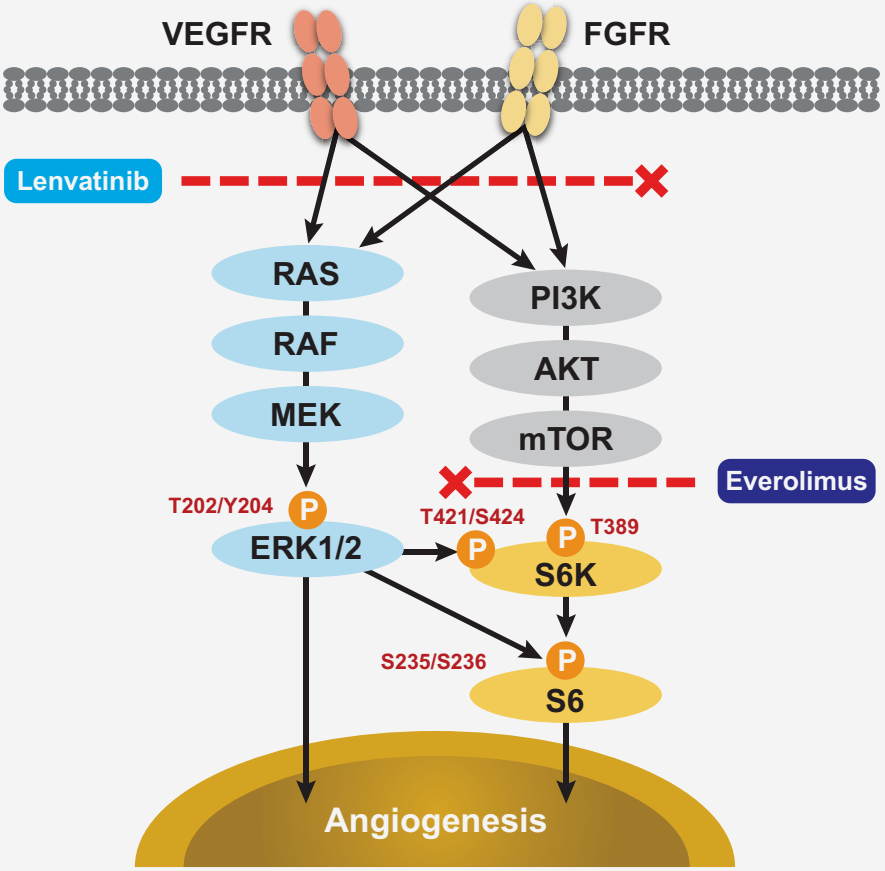
Almost all patients in this study experienced at least one treatment-related treatment-emergent adverse event. The most common adverse events associated with lenvatinib in combination with everolimus were diarrhoea and fatigue or asthenia with the most common grade 3 adverse events being diarrhoea, fatigue or asthenia, and hypertension. Serious adverse events occurred with similar frequency in each of the treatment arms (45% for lenvatinib plus everolimus, 44% for single-agent lenvatinib, and 38% for single-agent everolimus). Although adverse events were common, they were generally well managed by dose interruptions, dose reductions and discontinuations. Based on the results of this study, lenvatinib in combination with everolimus was approved by the United States Food and Drug Administration for treatment of patients with advanced or metastatic RCC who received one prior VEGF-targeted therapy[8].

A phase 3 study comparing lenvatinib (in combination with everolimus or in combination with pembrolizumab) and sunitinib

As demonstrated by the previous example, combination therapies are becoming increasingly important to maximize antitumour activity and control the potential for the development of drug resistance[15]. In addition, the combination of VEGF-targeting drugs with other anticancer agents has been an effective strategy for the treatment of a range of tumour types[16]. However, evaluating new combination therapies is a complex undertaking considering not only the number of possible drug combinations that exist, but also considering when a combination may be administered within the potential sequence of existing therapies. These considerations are especially important for clinicians who treat patients with advanced RCC given the growing number of treatments available for this patient population. The phase 2 study of lenvatinib plus everolimus for RCC demonstrated that this combination could provide a subsequent treatment option for patients who progressed after one previous VEGF-targeted treatment, so this therapy or other combination therapies could possibly also provide benefit to patients in other clinical settings.

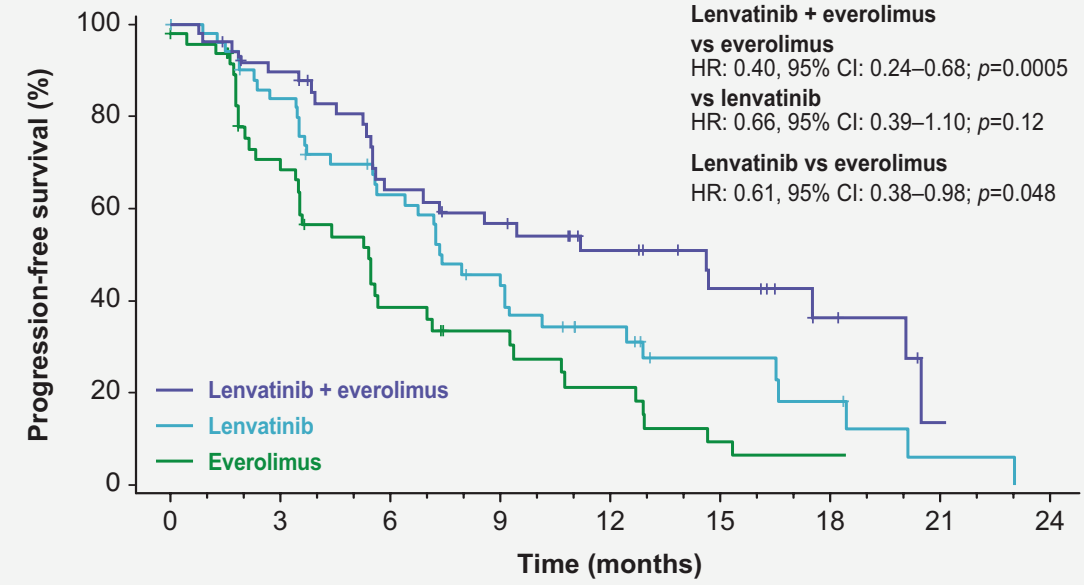
According to the United States' National Comprehensive Cancer Network guidelines for kidney cancer, there are four TKIs currently available in the first-line setting for relapsed or Stage IV unresectable clear cell RCC: axitinib, pazopanib, sorafenib and sunitinib[17]. To examine the possible utility of combination therapy for advanced clear cell RCC in the first-line setting, a phase 3 trial (NCT02811861) will compare single-agent sunitinib to lenvatinib either in combination with everolimus or in combination with pembrolizumab. Pembrolizumab is an antibody that targets the programmed cell death 1 (PD-1) receptor, which is expressed on the surface of tumour cells as a mechanism to evade destruction by the immune system. By targeting the PD-1 receptor, pembrolizumab treatment allows the body to mount an immune response against tumour cells[18]. It is possible that a combination of this immunotherapy with lenvatinib-mediated VEGF inhibition could provide an effective new first-line treatment option for patients with advanced clear cell RCC. In addition to this planned study, lenvatinib is already under investigation in combination with pembrolizumab in a phase 1b/2 study described in further detail later in this article.

The planned enrollment for the phase 3 study is 735 patients with advanced clear cell RCC who have not received any prior systemic therapy.



FGFR, fibroblast growth factor receptor; VEGF, vascular endothelial growth factor.

Figure 2 | The activity of lenvatinib in combination with everolimus in renal cell carcinoma appears to involve the synergistic dual inhibition of the fibroblast growth factor (FGF) pathway, as well as dual inhibition of the mTOR-S6K-S6 pathway.



Number at risk:

Lenvatinib + everolimus	51	41	27	23	16	10	5	1	0
Lenvatinib	52	41	29	20	11	6	4	1	0
Everolimus	50	29	15	11	7	3	1	0	

CI, confidence interval; HR, hazard ratio; VEGF, vascular endothelial growth factor.

Figure 3 | Lenvatinib in combination with everolimus significantly improved progression-free survival compared with everolimus as a single agent in patients with advanced renal cell carcinoma who had received one prior VEGF-targeted therapy. *Reprinted from* The Lancet Oncology, *Vol 16, Motzer RJ* et al, *Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label multicentre trial, pp1473–1482, Copyright (2015), with permission from Elsevier.*[15]

Patients will be randomized to receive either sunitinib 50 mg/day for 4 weeks followed by 2 weeks without treatment, lenvatinib 20 mg/day plus pembrolizumab 200 mg every 3 weeks, or lenvatinib 18 mg/day plus everolimus 5 mg/day until disease progression or unacceptable toxicity. Patients will be stratified by geographic region and risk according to Memorial Sloan-Kettering Cancer Center criteria. The primary objective of this study will be to evaluate progression-free survival. Secondary endpoints will include objective response rate and overall survival. The results of this trial will be an important addition to our current understanding of the treatment options for advanced clear cell RCC in the first-line setting. The hope underlying this phase 3 study is that combination therapy may provide an improved treatment option for patients with RCC.

A phase 2 study of lenvatinib in combination with everolimus for non-clear cell RCC

The previously published study of lenvatinib in combination with everolimus enrolled patients with clear cell RCC, the most common type of RCC. Non-clear cell RCC, a distinct histologic entity, comprises about 30% of RCC cases[2]. Despite the sizeable proportion of patients, data are limited regarding the activity of the agents approved for clear cell RCC in patients with non-clear cell RCC because most clinical trials of the approved agents have not included these patients[19]. As such, it is important to also determine optimal treatment strategies for patients with non-clear cell RCC, and investigations are underway to evaluate lenvatinib in combination with everolimus in this patient population. An additional study, which has not yet begun recruiting, is planned to enroll approximately 31 patients with unresectable, advanced or metastatic non-clear cell RCC who have not received any prior systemic therapy in two stages. In the first stage of the study, 16 patients will receive lenvatinib 18 mg/day combined with everolimus 5 mg/day until disease progression or unacceptable toxicity. If fewer than two patients respond to treatment, the study will end. If, however, 2 or more patients respond to the combination, an additional 15 patients will be enrolled and receive treatment. The primary endpoint of the study will be the objective response rate. Secondary objectives will be safety of the combination, progression-free survival, overall survival and pharmacokinetics. This study will provide necessary insight as to whether the combination of lenvatinib and everolimus is a treatment option for patients with non-clear cell RCC.

A study in combination with everolimus with a different starting dose of lenvatinib

The combination of lenvatinib and everolimus was shown to improve progression-free survival in patients with progressive clear cell RCC who received one prior VEGF-targeted treatment in the phase 2 study described above. Nearly all patients in this trial experienced a treatment-related adverse event. These adverse events were generally managed by dose interruptions, dose reductions and discontinuations[13]. It is important to ensure that patients gain the maximum benefit from treatment while minimizing adverse events.

To potentially identify whether an alternative dose regimen of lenvatinib exists

SPONSOR FEATURE

that demonstrates the same efficacy as in the phase 2 trial that led to the approval of the combination but with reduced toxicity, a protocol is in development for a postmarketing requirement study. This study is planned to enroll 306 patients with clear cell RCC who had disease progression following one VEGF-targeted treatment. Eligible patients may also have received prior PD-1 treatment. These patients will be randomized 1:1 to receive either lenvatinib 18 mg/day plus everolimus 5 mg/day or lenvatinib 14 mg/day plus everolimus 5 mg/day. The study is planned to last approximately 48 months. In the lenvatinib 14 mg/day group, the lenvatinib dose will be increased to 18 mg/day if no intolerable grade 2 or grade 3/4 adverse events are observed in the first 4 weeks. Dose reductions for toxicity will be used as in all other lenvatinib trials. Patients will be stratified by risk according to Memorial Sloan-Kettering Cancer Center criteria and prior PD-1 targeted treatment. This study will provide additional information regarding the dosing of lenvatinib in combination with everolimus for patients with clear cell RCC following prior VEGF-targeted treatment. Furthermore, this study will provide important information about how patients respond to lenvatinib and everolimus combination therapy after they have received immunotherapy.

Phase 1b/2 study of lenvatinib in combination with pembrolizumab

In addition to the phase 3 study in patients with RCC mentioned earlier, another study (NCT02501096) is underway to evaluate the efficacy and safety of lenvatinib in combination with pembrolizumab in patients with selected solid tumours. This phase 1b/2 study is enrolling patients with metastatic non-small cell lung cancer, endometrial cancer, urothelial cancer, squamous-cell carcinoma of the head and neck, melanoma or RCC. Patients must have had disease progression after approved treatment, if effective treatment is available for their disease.

The study will be performed in two parts. In the phase 1b part of the study, which has concluded, the maximum tolerated dose of lenvatinib in combination with pembrolizumab 200 mg administered every 3 weeks was determined to be 20 mg/day. In the phase 2 expansion part of the study, patients will be assigned by tumour type to up to 6 cohorts of up to 20 patients each. Objective response rate as of week 24 will be evaluated for each cohort as the primary objective for this part of the study. Secondary objectives for both parts of the study include evaluation of safety and tolerability of the combination, objective response rate, progression-free survival, overall survival, duration of response, disease control rate and pharmacokinetics. This study will provide new insight into possibilities for the combination of VEGF-targeted treatment and immunotherapy as a potential treatment option for a variety of patients with metastatic disease, including those with metastatic RCC.

Our perspective

Treatment options for patients with RCC have grown dramatically over the past ten years and new therapies continue to emerge at a rapid pace. Despite these advances, the challenge remains to ensure that patients receive the best possible treatment for their individual needs. Given the discovery of promising new agents with different mechanisms of action for the treatment of patients with advanced disease, it is anticipated that the focus of the coming years will be on combination trials to increase efficacy and reduce drug resistance. With that comes the complex task of identifying the optimal combinations, dose and timing of therapy. The ongoing clinical trials described here are one part of the global effort to tackle these challenges. Eisai is dedicated to this mission to determine effective combination therapies for RCC and to make them commercially available to the patients who need them.

REFERENCES

1. American Cancer Society. *Cancer Facts & Figures 2015. Atlanta: American Cancer Society*, <http://www.oralcancerfoundation.org/facts/pdf/Us_Cancer_Facts.pdf> (2015).
2. Kabaria, R., Klaassen, Z. & Terris, M. K. Renal cell carcinoma: links and risks. *Int. J. Nephrol. Renovasc. Dis.* **9**, 45-52 (2016).
3. Incorvaia, L. *et al.* Beyond evidence-based data: scientific rationale and tumor behavior to drive sequential and personalized therapeutic strategies for the treatment of metastatic renal cell carcinoma. *Oncotarget* **7**, 21259–21271 (2016).
4. Schlumberger, M. *et al.* Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N. Engl. J. Med.* **372**, 621-630 (2015).
5. Yamamoto, Y. *et al.* Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell* **6**, 18 (2014).
6. Matsui, J. *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. *Int. J. Cancer* **122**, 664-671 (2008).
7. Okamoto, K. *et al.* Antitumor activities of the targeted multi-tyrosine kinase inhibitor lenvatinib (E7080) against RET gene fusion-driven tumor models. *Cancer Lett.* **340**, 97-103 (2013).
8. *Lenvima (lenvatinib) [prescribing information]*. Eisai Inc., Woodcliff Lake, NJ, 2015.
9. Adachi, Y. *et al.* Lenvatinib in combination with everolimus demonstrated enhanced antiangiogensis and antitumor activity in human RCC xenograft models [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; Apr 16-20, 2016; New Orleans, LA. Philadelphia (PA): AACR; 2016. Abstract nr 3264.
10. Mitsuhashi, K. *et al.* Effects of lenvatinib mesilate in combination with everolimus on VEGF and FGF-driven angiogenesis and tumor growth [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; Apr 16-20, 2016; New Orleans, LA. Philadelphia (PA): AACR; 2016. Abstract nr 3262.
11. Rosell, R. *et al.* Adaptive resistance to targeted therapies in cancer. *Transl. Lung Cancer Res.* **2**, 152-159 (2013).
12. Stjepanovic, N. & Capdevila, J. Multikinase inhibitors in the treatment of thyroid cancer: specific role of lenvatinib. *Biologics* **8**, 129-139 (2014).
13. Motzer, R. J. *et al.* Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. *Lancet Oncol.* **16**, 1473-1482 (2015).
14. Hutson, T. E., Dutcus, C. E., Ren, M., Baig, M. & Fishman, M. Subgroup analyses and updated overall survival from the phase II trial of lenvatinib (LEN), everolimus (EVE), and LEN+EVE in metastatic renal cell carcinoma (mRCC) [abstract]. *J. Clin. Oncol.* **34 Suppl**, Abstract 4553 (2016).
15. Bottsford-Miller, J. N., Coleman, R. L. & Sood, A. K. Resistance and escape from antiangiogenesis therapy: clinical implications and future strategies. *J. Clin. Oncol.* **30**, 4026-4034 (2012).
16. Arjaans, M. *et al.* VEGF pathway targeting agents, vessel normalization and tumor drug uptake: from bench to bedside. *Oncotarget* **7**, 21247–21258 (2016).
17. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Kidney Cancer. Version 3.2016*, <http://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf> (2016).
18. Medina, P. J. & Adams, V. R. PD-1 pathway inhibitors: ommuno-oncology agents for restoring antitumor immune responses. *Pharmacotherapy* **36**, 317-334 (2016).
19. Valenca, L. B., Hirsch, M. S., Choueiri, T. K. & Harshman, L. C. Non-clear cell renal cell carcinoma, part 2: therapy. *Clin. Adv. Hematol. Oncol.* **13**, 383-391 (2015).