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Therapeutic options for advanced thyroid cancer

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Abstract

Thyroid cancer can be largely classified as well-differentiated, poorly differentiated, medullary and anaplastic. Differentiated thyroid cancer (DTC) includes follicular and papillary subtypes, with the incidence of papillary thyroid cancer (PTC) on the rise. The mainstay of treatment for DTC includes a combination of surgery, radioactive iodine (RAI) and levothyroxine suppression. DTC portends a favorable prognosis, even in the presence of distant metastases, with a 50% rate of 5-year survival largely due to tumor cell's sensitivity to RAI therapy influencing disease outcome. In radioactive iodine refractory differentiated thyroid cancer (RAI-refractory DTC) there is a lower survival rate prompting the use of other therapeutic options available. RAI refractoriness is more common in older patients (age >40), large metastases and lesions that are fluorodeoxyglucose (FDG) avid on position emission tomography (PET). Over the past decade, Identification of genetic mutations in the signaling pathway involved in thyroid tumorigenesis has led to the approval of tyrosine kinase inhibitors (TKIs); Sorafenib and Lenvatinib in RAI-refractory DTC. Similarly, metastatic medullary thyroid cancer (MTC) implies an unfavorable 10-year survival rate of only 20% as the principal treatment options focuses on loco regional control via surgical and/or non-surgical options. The approval of TKIs such as Cabozantinib and Vandetanib has introduced an encouraging, novel, systemic therapeutic option for metastatic MTC. Lastly, anaplastic thyroid cancer (ATC) carries the worst prognosis with high recurrence rates. Treatment includes surgery, chemotherapy and external beam radiation. The FDA recently approved Dabrafenib plus trametinib for BRAF V600E mutated ATC.

Considering the modality of chemotherapy and the expanding field of targeted therapies, the role of the oncologist and interaction with endocrinologist in the management of thyroid cancer needs further clarification aiming at collaborative management plans more than ever. This review summarizes the key phase III trials that led to the approval of TKIs in the treatment of DTC and

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metastatic MTC. Additionally, the review aims to clarify the patient selection criteria for initiation of TKIs and examine the implications, considerations and adverse effects prior to utilizing targeted therapy. Clinical trials are ongoing with promising results and may contribute to the addition of several targeted molecules and immune check point inhibitors to the therapeutic armamentarium for RAI-refractory DTC, medullary and anaplastic thyroid cancer.

Introduction

Thyroid cancer is the most common endocrine malignancy with its incidence on the rise. Differentiated thyroid cancer comprises of follicular and papillary subtypes and accounts for 95% of the thyroid cancer [1]. Medullary and Anaplastic thyroid cancers make up 4% of the thyroid cancers [1]. DTC is typically managed by endocrinologists as it responds favorably to the conventional treatment which includes surgical resection, RAI, TSH suppression therapy with monitoring. There is no role for RAI therapy in MTC and ATC [1]. Surgery and other means of loco regional control are therapeutic options in MTC [2]. The role of chemotherapy is limited in the management of all thyroid cancers, with the most significant role being in ATC.

This report explores the circumstances in which differentiated thyroid cancer (DTC) management deviates from the standard therapy, specifically describing the indications for targeted therapy and updates within the field. In addition, we aim to further describe the role of the oncologist in the management of medullary as well as anaplastic thyroid cancer.

Differentiated thyroid cancer

Differentiated thyroid cancers constitute about 95% of thyroid cancers [1]. This constitutes cancers arising from the thyroid follicular epithelial cells; namely papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). PTC accounts for 85% of diagnosed cases of DTC with 12% being FTC [2]. Both PTC and FTC generally exhibit a desirable response to initial therapy, therefore DTC is considered to have a good prognosis. A robust initial approach to a patient with DTC is aimed at improving overall and disease specific outcomes, reducing the risk of persistent or recurrent disease and reducing morbidity [1]. The initial management of DTC emphasizes on complete surgical resection of primary tumor and loco-regional nodal metastases [3]. The extent of surgical resection and preoperative staging is beyond the scope of this review. While surgical resection remains the primary management, RAI and suppressive thyroid hormone remains integral to the postoperative management of DTC. RAI is the mainstay therapy for all patients with DTC. It is used to ablate residual normal thyroid tissue (remnant ablation), adjuvant therapy or therapy for persistent disease [1,4,5].

The role of chemotherapy in DTC

Doxorubicin was FDA approved in 1974 for the treatment of thyroid cancer. Chemotherapy regimens with doxorubicin have shown 31%–45% partial response [6–8]. The proposed utility of neo-adjuvant chemotherapy in inoperable primary thyroid cancer and loco-regional control in DTC were presented in a non-randomized, retrospective trial by Basic [9,10]. The results showed comparable response rates with a decrease in tumor size in both FTC and

PTC (45% and 44% respectively) [9,10]. Dang et al., reviewed the effects of neoadjuvant chemotherapy in reducing morbid or complicated surgical resection [11]. Despite a few trials which showed beneficial results in locally invasive disease, the data had several limitations and neoadjuvant chemotherapy is not currently recommended [11]. Doxorubicin with cisplatin did not result in additional overall response compared to doxorubicin alone [12,13]. Several other combination chemotherapy regimens have not yielded any encouraging results either [14–16]. Per American Thyroid Association (ATA) guidelines, systemic adjuvant therapy referencing systemic chemotherapy or targeted inhibitor therapies are not routinely indicated in DTC [1]. Furthermore, the poor response rates, short duration of response and toxic effects of chemotherapy deems it inadvisable in patients with DTC [17].

RAI- refractory DTC

DTC typically portends a favorable prognosis with a 10-year survival rate greater than 90% with a 10%–20% risk of recurrence [18]. In the event of recurrence, standard treatment is typically reconsidered. Even in the setting of metastatic DTC, 40% of patients remain disease free at 5 years [18,19]; this is largely attributed to RAI avidity in the majority of DTCs. The most common sites of distant metastases are lung, bone, brain, liver and skin [18]. There is a subset of DTC which shows an inherent resistance to RAI therapy, termed radioiodine (RAI)-refractory differentiated thyroid cancer. The 5-year disease specific survival rate of RAI-refractory DTC is 66% [20] with the 10-year survival rate being only 10% [21].

There are four classes of RAI-resistance as defined in the 2015 ATA guidelines [18], these include

- i.** The malignant/metastatic tissue does not ever concentrate RAI (no uptake outside the thyroid bed at the first therapeutic whole-body scan),
- ii.** The tumor tissue loses the ability to concentrate RAI after previous evidence of RAI-avid disease (in the absence of stable iodine contamination)
- iii.** RAI is concentrated in some lesions but not in others
- iv.** Metastatic disease progresses despite significant concentration of RAI. The development of RAI-resistance which occurs later during the disease, specifically following initial RAI treatment is particularly associated in patient with multiple, large metastases [22]. The theory exists that the initial RAI therapy leads to the selected survival of poorly differentiated cells with an inherent RAI resistance. The likelihood of progression of these lesions remain higher specifically when 18FDG uptake is seen [22,23].

A lack of a defined consensus makes identification of RAI refractory DTC challenging. A more in-depth definition of RAI refractory DTC which considers variables such as progression based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria, appropriate imaging modality and tumor markers is needed [24,25]. For now, a carefully weighed decision to determine the utility of RAI should be made in those patients who demonstrate the latter criteria. RAI should be continued to be used only when a clear benefit is shown since ongoing RAI therapy does carry a risk of secondary malignancies [26,27].

The role of targeted therapy in differentiated cancer

In recent years, the identification of genetic alterations in thyroid carcinogenesis has shifted the focus on exploring the role of targeted therapies in thyroid cancer [28]. Mutations in the intracellular signaling pathways involving RAS, BRAF and PI3K/Akt play a key role in thyroid tumor cell growth and survival [29–31]. Additionally, vascular endothelial growth factor (VEGF) and its receptors (VEGFR) are also implicated in aggressive thyroid carcinoma [32,33]. Studies have shown RET/PTC and BRAFV600E mutations to commonly occur in PTC while RAS point mutations are largely seen in FTC and poorly differentiated thyroid carcinoma [33,34]. Therapeutic options in RAI-refractory DTC has expanded with the advent of tyrosine kinase inhibitors.

Randomized control trials

Several phase II trials with VEGF inhibitors have showed promising results in progression free survival [35–38].

Two randomized placebo-controlled phase III clinical trials (DECISION, SELECT) have led to US Food and Drug Administration (FDA) approval of TKIs for treatment of progressive RAI-refractory DTC [39–43]. In the DECISION trial, Sorafenib, an MKI which has an inhibitory effect on VEGF-1, -2 and -3, platelet-derived growth factor receptor (PDGFR), BRAF and RET demonstrated a benefit in median progression free survival (PFS) over the placebo group (10.8 vs 5.8 months) [39]. The SELECT trial reported significantly longer median PFS with Lenvatinib vs placebo (18.3 versus 3.6 months) [40]. These results were demonstrated across all subgroups, including those previously treated with a tyrosine kinase inhibitor [41]. Despite encouraging results demonstrating superior PFS in these key trials, there is no conclusive data regarding overall survival due to lack of data points at the end of the trial and crossover which occurred during the trial. There were also increased reports of adverse effects in the TKI group.

Adverse events

The significant side effects associated with VEGFR TKIs ranging from minor, temporary side effects to potentially life threatening adverse events govern in part the decision to pursue treatment with these agents [44]. In the SELECT trial, 75% of the patients treated with Lenvatinib experienced grade 3 or higher side effects [40,45]. The most common adverse effects reported include hypertension (necessitating initiation of an antihypertensive), diarrhea, anorexia. Side effects should be promptly recognized and managed either by implementing appropriate treatment, dose reduction or treatment cessation. TKI therapy is a long-term therapy and treatment duration is determined based on treatment response and side effects. TKI therapy is discouraged in patients with preexisting co-morbidities due to the increased risk of adverse events [45,46] (Table 1).

Candidacy of treatment

Prior to initiation of a kinase inhibitor, the patient and the physician must make a well-informed decision, with careful consideration of the risks including adverse events and lower quality of life weighed against the individualized benefits obtained from these therapies [47].

Albeit, there is still a need for a more robust, evidence-based approach to determine appropriate time for referral to an oncologist and the ideal time to initiate a TKI.

When a patient is initially diagnosed with metastatic RAI refractory DTC, if the patient is asymptomatic, or the spread disease remains stable or indolent without a risk for encroachment on vital structures, close monitoring along with TSH suppressive therapy is advised [47,48].

In patients with single or oligometastatic disease who are symptomatic and carry a high risk for complications, directed therapy aimed at local control such as surgery, stereotactic radiation, External beam radiation therapy (EBRT), thermal ablation (radiofrequency ablation and cryoablation) and chemoembolization should be considered prior to initiation of systemic therapy (such as a TKI) [49–52]. These treatment modalities aim to achieve local disease control and delay the need for systemic therapy.

The ATA currently recommends “Kinase inhibitor therapy should be considered in RAI refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches [1].”

In conclusion, initiation of a TKI should occur in consultation with an oncologist and should be tailored to each patient to achieve stable disease, minimize progression and aid with symptom management. It is indicated based on tumor burden, tumor progression utilizing the RECIST criteria and imminent threat to vital structures [53]. For patients with slow tumor growth (less than 20%) increase in a year, observation may be indicated. Sabra et al., suggest a potential role for volume doubling time (VDT) to aid in determining the decision to initiate targeted therapy [54].

Additionally, while there has been improvement of PFS, there is no evidence on OS with TKIs. Stable disease appears to be the most likely outcome. Furthermore, the data from the cross over trials can be best interpreted as no difference in outcomes when TKI therapy was delayed [55].

With continued use, secondary resistance to a TKI is a well know phenomenon, often necessitating salvage therapy [56,57]. Failure of therapy with an initial TKI justifies consideration of a second TKI if not limited by side effects. The choice of TKIs is currently only guided by data provided by randomized control trials or in the context of clinical trials. A retrospective review by Dadu et al., demonstrated longer median overall survival (OS) salvage therapy compared with sorafenib alone (58 vs 28 months, $P = .013$) in patients with advanced RAI refractory DTC [58]. Based on these trials, it can be recommended that if disease progression or intolerance to sorafenib is experienced, salvage therapy with an alternative TKI is warranted [58]. Another large retrospective trial reported stable disease in DTC patients treated with a second-line therapy but with similar median PFS [59]. Interestingly, another retrospective study at MD Anderson, while it corroborated the clinical benefit of first-line and second-line TKIs in metastatic RAI refractory DTC, it additionally identified differential responses at various metastatic sites. The study revealed that

regression of lung metastases was most common, with the least response and even progression of disease seen in previously non-irradiated bony metastases [60].

Future therapies in DTC

Given the poor outcomes in RAI-refractory thyroid cancer, several clinical trials are ongoing to study the efficacy of targeting the various tumor mutations associated with DTC including BRAF, ALK, mTOR or PAX8/PPAR γ rearrangements [61]. Given that RAI therapy has such a crucial role in the treatment of DTC, a promising field in RAI refractory DTC research explores iodine re-sensitization therapies. RAI refractoriness occurs due to the down regulation of the sodium-iodide symporter gene [62]. A phase II trial with a MEK inhibitor, selumetinib demonstrated increased iodide uptake in 12 out of 20 patients, specifically in patients with RAS mutations [63]. A phase II trial with Dabrafenib (BRAF inhibitor) showed increased RAI uptake in 60% of the patients [64]. Other areas of interest include check point inhibitors such as pembrolizumab and combination therapies with other MKIs to counteract the escape mechanism [65].

Medullary thyroid cancer (MTC)

Medullary thyroid cancer (MTC) accounts for 3%–5% of the thyroid cancer diagnosis of which 75% are sporadic and 25% are familial, typically MEN2A and MEN2B [66]. The systemic approach to the management of MTC hinges on identifying the stage of MTC. Total thyroidectomy with compartment-oriented lymph node dissection is the initial treatment in localized MTC [66,67]. There is no role for radioactive iodine in MTC [66].

The decision to treat metastatic MTC is pursued to improve quality and quantity of life. In advanced progressive MTC, further spread endangers vital structures which mandates treatment for survival. Pain and hormonal manifestations impose significant burdens on quality of life, making it imperative to pursue control of disease either by loco regional control or systemic therapies [68]. Measures such as tumor burden, rate of progression on sequential imaging as defined by the RECIST criteria and tumor marker doubling times (DT) such as serum calcitonin DT) are used as objective markers of progression [66].

Per ATA recommendations, loco-regional control via surgery, EBRT, radiofrequency ablation must be the mainstay in metastatic MTC whenever possible, such as in oligometastatic disease or single organ involvement [66,69,70]. Systemic therapy may be indicated for advanced progressive MTC with large tumor burden and progression in <1 year [71].

The role of chemotherapy in MTC

Cytotoxic chemotherapy has a limited role in the treatment of persistent or recurrent MTC due to the poor response rates (10%–15% partial response) and there is no data on survival benefit [72,73]. Combination chemotherapy based on dacarbazine, doxorubicin has been described in clinical trials, albeit with limited results [72,73]. Following the approval of TKIs, the revised ATA guidelines recommends chemotherapy as a last line, only after considering other systemic therapies.

The role of targeted therapies in MTC

Germline RET mutations are present in MEN2A and MEN2B. The identification of somatic RET mutations in sporadic MTC have led way to a preclinical and clinical trials to investigate the utility of targeted therapy [74,75]. Additionally, 18–80% of patient without somatic RET mutations have somatic RAS mutations [75]. VEGF receptors are also over expressed in MTC [76].

Multikinase inhibitors targeting RET and VEGFR2 showed promising results in phase II trials prompting phase III trials involving Vandetanib and Cabozantinib [77–79]. In 2011, the FDA approved these drugs for symptomatic or progressive MTC.

In the prospective, randomized, double-blind, phase III ZETA study, patients with unresectable, progressive metastatic MTC were randomized to vandetanib (300mg per day) or placebo. The results demonstrated a significant PFS prolongation of 11 months compared to placebo (HR: 0.46, $p < 0.0001$) [80]. Partial responses were observed in 45% of patients treated with vandetanib, with a predicted median duration of response of 22 months [80]. The results were similar for patients with sporadic and hereditary MTC with and without RET mutations. However, a further subgroup analysis of PFS by M918T (RET) mutation positive showed higher response to vandetanib [81]. Notably, patients in the vandetanib arm also demonstrated improved quality of life and biochemical response. Adverse events (AEs) were mostly grade 1–2 with 35% requiring a dose reduction [81].

In a double-blind, phase III (EXAM) trial comparing cabozantinib with placebo, estimated median PFS was significantly higher with 11.2 months for cabozantinib versus 4.0 months for placebo (hazard ratio, 0.28; $p < 0.001$) [82]. Response rate was 28% with an estimated duration of response of 14.6 months [82]. Patients in the cabozantinib arm experienced a higher incidence of grade 3–4 AEs with discontinuation of drug in 16% of patients and a dose reduction in 79% of the patients [82,83]. The most frequent grade 3 or 4 AEs were diarrhea, palmar-plantar erythrodysesthesia, GI fistulas and fatigue [84]. In 2017, a final analysis of overall survival (OS) of the phase III EXAM trial was carried out. There was a 5.5-month numerical increase in median OS with cabozantinib versus placebo (26.6 versus 21.1 months) [85]. However, this difference did not reach statistical significance (stratified HR, 0.85; 95% CI, 0.64–1.12; $P = 0.24$) [85]. In exploratory analyses, the most significant OS benefit was observed in patients with RETM918T- positive mutation with 44.3 months [85].

Currently, there is no evidence-based guide for the initial selection of a TKI in the treatment of MTC. Until then, consideration should be given to underlying patient characteristics and past medical history with identification of factors that may predispose to certain adverse events [86]. (Table 2). For instance, Vandetanib is known to cause QT prolongation is therefore contraindicated in patients with a history of torsades de pointes and underlying cardiac pathology [87].

Future therapies in MTC

Other multikinase inhibitors, specifically those targeting RET and VEGF such as sunitinib, sorafenib and lenvatinib have shown benefit in phase II trials [88,89]. Combination

therapies, second line TKIs and other therapeutically targetable mutations in MTC are being investigated [90].

Anaplastic thyroid cancer (ATC)

Anaplastic thyroid cancer has an incidence of 1.7% with a mortality rate of 33%–50%. The median survival is 5 months with a high rate of recurrence [91]. ATC can result from dedifferentiation as result of multistep mutations or can arise de novo [92].

Given the aggressive nature of the disease, patients are regarded as Stage IV on diagnosis with Stage IVC defined by the presence of distant metastases [91]. Due to the dismal prognosis and poor response to standard therapies, the oncologist's involvement tends to be upfront in the therapeutic management of ATC. The goals of therapy whether curative or palliative should be defined in advance [91,93]. The standardized treatment for curative intent ATC is a multimodal approach and involves timely surgery, external beam radiation with radiosensitizing chemotherapy [92]. The initial intent should be loco-regional control of the disease despite the presence of distant metastases. Stage IVC disease is seen in 1/3 of the patients with ATC [93]. It is reasonable to consider systemic therapy initially on presentation in these patients [93].

The role of chemotherapy in ATC

Doxorubicin, taxanes (paclitaxel or docetaxel) and platins (cisplatin or carboplatin) have demonstrated activity in ATC with response rates ranging from 15%–25% [93]. A US national cancer registry study showed longer median survival rates for stage IVA and IVC in patients who received chemotherapy in addition to surgery and radiation [94].

Apart from the previously defined role of radiosensitizing chemotherapy [95], a few studies have also demonstrated the utility of neoadjuvant chemotherapy in patients with stage IVA and IVB tumors allowing them to undergo successful resection [96–98]. A study by Kumar et al., explores the multimodality therapy for patients who desire and for whom aggressive treatment is feasible [99].

Future therapies in ATC

Over the last decade, the identification of the various genetic and molecular mutations which occur in ATC have led to several clinical trials to explore the efficacy of targeted therapy. However, no single agent has yet provided promising results with further preclinical and clinical studies underway. The most common mutation identified in ATC is TP53 tumor suppressor gene [100]. Two signaling pathways including PI3K/Akt/mTOR and RAF/MEK/ERK pathways also play a key role in dedifferentiation and tumor cell growth in ATC [101,102].

The 2012 ATA guidelines do not currently recommend routine molecular profiling however based on limited case reports and clinical trials, this information may be a critical guide for targeted therapies in the near future.

In separate clinical trials, fosbretabulin and crolibulin; tubular binding proteins which impair neovascularization of the tumors through mitotic arrest and cell death in endothelial cells,

were administered in combination with standardized chemotherapy; both produced disappointing results [103,104].

Multikinase inhibitors: Within the realm of MKIs, phase II trials involving sorafenib, sunitinib and pazopanib did not yield positive results [105–107]. Based on promising results from a Japanese phase II trial, lenvatinib is currently being investigated () [108]. Imatinib also appears to show activity in ATC however further validation is needed [109].

Immune check point inhibitors: A high expression of anti-programmed death 1/ programmed death-ligand 1 (PDL1) was seen in ATC [110]. Two clinical trials investigating the role of Pembrolizumab () and Atezolizumab plus various targeted therapies based on genetic mutations () are currently underway.

In 2018, a phase II, open-label trial investigated Dabrafenib plus trametinib in patients with *BRAF*V600E mutations in ATC [111]. The overall response rate (the primary endpoint) was 69% [111]. Based on these findings, the FDA approved Dabrafenib plus trametinib for treatment of BRAF V600E- mutated ATC.

Conclusion

RAI refractory DTC responds poorly to conventional therapy due to the lack of RAI avidity leading to progressive disease. Therefore, the oncologist's involvement is largely only in the treatment of RAI resistant tumors and as a last approach in metastatic DTC. Progressive metastatic disease in both RAI refractory DTC and metastatic MTC, especially single or oligometastatic disease, should be addressed whenever possible with loco regional control measures such as radiation, RFA or chemoembolization etc. In the setting of asymptomatic or indolent metastases, a watch and wait method is also recommended. The need for systemic therapy arises when disease progression leads to development of symptoms, increased tumor burden, encroachment on vital structures and when loco regional therapeutic options have failed or are limited. With the approval of targeted therapies, chemotherapy has an even less significant role in the systemic treatment of RAI-refractory DTC and metastatic MTC. Prior to the initiation of TKIs, patient comorbidities should be considered and an open discussion with the patient regarding the implications of therapy including adverse events and potential for a lower quality of life is needed. Failure of one TKI does not preclude from the use of second line agents. There are no new recommendations or advances in the treatment of ATC. Intent of treatment should be established. Treatment of ATC includes combination chemotherapy, surgery and radiation whenever possible. Additionally, thyroid cancers may occur due to NTRK fusion driven oncogenes. The approval of Larotrectinib provides yet another option for NTRK fusion thyroid cancer. Clinical trials further exploring the role of targeted therapies, radio iodine re-sensitization and immunotherapy are ongoing for thyroid cancer.

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Table 1:

Common molecular mutations found in thyroid cancer [29–34,75,76,100–102].

Follicular	RAS (HRAS, NRAS, KRAS), PIK3CA/B, EGFR, PAX8- PPAR- γ , VEGFR, TERT promoter, IDH1
Papillary	BRAF V600E, RET (RETPTC1, RETPTC3), RAS PIK3CA/B, EGFR, PAX8- PPAR- γ , VEGFR, TERT promoter, IDH1
Medullary (Hereditary) Medullary (Sporadic)	RET RET (40%–60%), RAS (KRAS, HRAS, NRAS), MET, VEGF2, 3, FGFR
Anaplastic	Tp53, PTEN, RAS, RET/PTC-1, BRAF, PAX8-PPAR- γ , PIK3CA, ALK, AKT

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Table 2:

Showing common side effects, serious adverse events and laboratory abnormalities associated with FDA approved targeted multi kinase inhibitors [40–45,80–82,89].

<u>Sorafenib</u>	<u>Lenvatinib</u>
<u>Common adverse effects</u>	<u>Common adverse effects</u>
Hand-foot skin reaction	Hypertension
Diarrhea	Diarrhea
Alopecia	Fatigue/Anorexia/Weight loss
Rash or desquamation	Nausea
Fatigue/anorexia/weight loss	Stomatitis
Hypertension	Palmar-plantar erythrodysesthesia
Oral mucositis	
<u>Serious/ noteworthy side effects</u>	<u>Serious/noteworthy side effects</u>
Secondary malignancy (squamous cell carcinoma, acute myeloid leukemia, bladder cancer)	Arterial thromboembolic events
Dyspnea	Venous thromboembolic effects
Pleural effusion	Renal failure
	Hepatic failure
	Gastrointestinal fistulas
	Corrected QT prolongation
<u>Common Laboratory abnormalities</u>	<u>Common Laboratory abnormalities</u>
Serum thyroid stimulation hormone (TSH) increase	Increased serum thyrotropin levels
Hypocalcemia	
Increased ALT, AST	
<u>Vandetanib</u>	<u>Cabozantinib</u>
<u>Common adverse effects</u>	<u>Common adverse effects</u>
Diarrhea	Diarrhea
Rash	Palmar plantar erythrodysesthesia
Nausea	Weight loss/Anorexia
Hypertension	Nausea
Headache	Fatigue
Fatigue/Anorexia	Dysgeusia
Acne	Hypertension
<u>Serious/noteworthy side effects</u>	<u>Serious/noteworthy side effects</u>
Diarrhea	Diarrhea
Hypertension	Palmar plantar erythrodysesthesia
QTc prolongation (black box warning)	Fatigue
Palmar plantar erythrodysesthesia	Hypertension
Dysgeusia	Fistula, perforations (black box warning)
Hemorrhage	Hemorrhage (black box warning)
	Weight loss/Anorexia

<u>Common Laboratory abnormalities</u>	<u>Common Laboratory abnormalities</u>
Hypocalcemia	Increased AST, ALT
Increased ALT	Increased alkaline phosphatase
Hypoglycemia	Hypocalcemia

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