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New agents in the Treatment for Malignancies of the Salivary and Thyroid Glands

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INTRODUCTION

The treatment of relatively rare malignancies, such as those of the salivary glands and iodine refractory thyroid cancer has been invigorated by the development of novel molecular targeting agents. Accrual to clinical trials for these disease sites continues to be limited by their relatively low incidence. Nonetheless, multi-center collaborations have contributed greatly to the development of a number of emerging systemic therapies. This review will briefly summarize the epidemiology and pathogenesis of salivary gland and thyroid cancer, and then describe some of the new drugs under evaluation for these malignancies.

MALIGNANT SALIVARY GLAND TUMORS

Malignant salivary gland tumors (MSGT) are relatively rare and encompass a diverse group of histologies and natural histories. The incidence per year is about 1–3 in 100,000 people, accounting for about 6% of head and neck cancers.¹ Surgery is the primary modality for cure of local disease. Treatment for metastatic disease is usually palliative. MSGT often exhibit a notably indolent course, especially the low grade, more differentiated histologies. Thus, given the potential for an unusually long natural history and prolonged periods of stable disease appropriate endpoints in clinical trials need to be chosen. Due to these factors, clinical investigation for this disease group continues to present some unique challenges.

Malignancies in the salivary gland can arise in either the major or minor glands, with about 70% of cases arising in the parotid gland. Unlike squamous cell head and neck malignancies, smoking and tobacco have not been associated with an increased risk of MSGTs. A history of

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radiation exposure, however, is associated with the development of benign and malignant SGT's.²³ Due to the common risk factor of radiation exposure, there can also be coincident MSGTs and thyroid cancers, although the molecular pathogenesis of the 2 diseases varies.^{4, 5} Another potential risk factor for the lymphoepithelial salivary gland carcinoma variant includes Epstein Barr virus exposure, which has especially been noted in East Asia, similar to the epidemiology of nasopharyngeal lymphoepithelioma.^{6, 7, 8, 9} The exact mechanism for pathogenesis remains unknown, but mutations in the LMP1 gene, associated with aberrant transcriptional regulation, have been detected.¹⁰

The histology and clinical course of salivary gland tumors varies greatly.¹¹ For the purposes of this review, we will focus on salivary gland carcinomas, rather than benign tumors that do not have malignant potential and thus do not require systemic therapy. The classification of carcinomas according to the WHO histologic classification is presented in Table 1. It should be noted that as this is a histological classification, it does not provide insight into the molecular pathogenesis of each variant. The more indolent carcinomas include acinic cell carcinoma, low grade mucoepidermoid carcinomas, and epithelial-myoepithelial carcinoma. By contrast, the more aggressive histologies include adenoid cystic carcinoma, high grade mucoepidermoid carcinomas, salivary duct carcinoma, invasive carcinoma in pleomorphic adenoma, and small cell carcinoma.

Management of localized salivary gland tumors primarily involves surgical resection. At times, adjuvant radiation is offered depending on risks factors such as positive surgical margins and perineural invasion, but unlike SCCN there is no role for adjuvant chemoradiotherapy. The use of systemic therapy is reserved for patients with unresectable, locally advanced or metastatic disease. Even in patients with unresectable locally advanced disease there is a major palliative role for local radiation therapy. Given the often indolent disease course (for instance, the median survival for metastatic adenoid cystic carcinoma is three years and can be up to ten years), it is important to consider whether there really is any important role for routine systemic cytotoxic chemotherapy in the management of this metastatic disease.¹² Therefore, watchful waiting is often the most appropriate strategy for many, if not the majority of patients with asymptomatic, indolent disease. For those with rapidly progressing, symptomatic disease, on the other hand, therapeutic options include monotherapy with traditional cytotoxic agents, such as monotherapy with cisplatin, vinorelbine, or paclitaxel (mucoepidermoid and adenocarcinoma) but the benefits are very modest and the potential for toxicity considerable.^{13–15} Combination regimens appear to have higher response rates at the expense of greater toxicity but there are no randomized comparisons to assess a survival benefit vs. monotherapy. Combinations with anti-tumor activity include CAP (cyclophosphamide, doxorubicin, cisplatin) which has been shown to have a modest response rate of 27% in a phase 2 setting.¹⁶ Cisplatin/vinorelbine (ORR 44%) and carboplatin/paclitaxel are other combination regimens with anti-tumor activity, again with unproven impact on survival.^{14, 17}

Molecular Pathogenesis and Novel Targets

With the availability of novel agents directed at molecular targets commonly over-expressed or altered in cancer, including MSGT, most interest to date has focused on the following markers: c-kit, VEGF/VEGFR, EGFR and Her-2/neu. High c-kit expression detected by immunohistochemistry (IHC) has been observed in adenoid cystic, acinic cell, polymorphous low grade adenocarcinoma, epithelia-myoepithelial carcinoma, and carcinosarcoma.^{18–21} Two phase 2 studies were conducted to assess the anti-tumor activity of imatinib, an inhibitor of the c-kit tyrosine kinase, in patients with adenoid cystic carcinoma that over-expressed c-kit.^{22, 23} No objective responses were observed in either study. Other preclinical work has suggested that loss of c-kit is associated with high malignant grade and decreased survival.

²⁰ In a third small clinical study, rapid disease progression was observed with imatinib treatment.²⁴

Increased vascular endothelial growth factor (VEGF) expression by IHC has also been noted in small preclinical studies, and seems to correlate with lymph node metastases, advanced clinical stage, high risk of recurrence, and inferior cause specific survival.^{25, 26} Adenoid cystic carcinoma cell lines with high metastatic potential have demonstrated increased angiogenic ability.²⁷ AEE788, a dual inhibitor of EGFR and VEGFR, has inhibited growth and induced apoptosis in ACC cell lines.²⁸ Multi-kinase inhibitors, such as sorafenib and sunitinib in addition to the monoclonal antibody bevacizumab have been studied widely in oncology and are FDA approved in a variety of solid tumors. Currently, the use of these agents remains investigational for salivary gland tumors, and their effectiveness in for this disease is unknown. Currently, phase 2 trials specifically studying the efficacy of one of these agents in salivary gland malignancies are not available, and appropriate phase 1 studies are reasonable treatment options.

The finding of elevated epidermal growth factor receptor (EGFR/HER1) and Her2/neu expression in MSGTs has logically led to preclinical investigation of EGFR and Her2/neu targeting agents. For instance, the malignant component of carcinoma in pleomorphic adenoma had an increase in the expression of these receptors in comparison to the benign component.²⁹ The more aggressive variant of mucoepidermoid carcinoma has been associated with increased Her-2/neu expression as well.³⁰ In addition to increased protein expression by IHC, increased amplification of the Her-2/neu gene by FISH has been detected in salivary duct carcinomas, but it is not clear if this phenomenon correlates with outcome.^{31, 32} By contrast, Her-2/neu overexpression was only noted in a small number of adenoid cystic carcinoma specimens.³³

In order to attempt to exploit these findings therapeutically, a salivary gland adenocarcinoma cell line was treated with the small molecule tyrosine kinase inhibitor of the EGFR, gefitinib, and resulted in cytostasis with downregulation of cyclin D1, STAT3 and MAPK.³⁴ In the clinic, however, treatment with gefitinib yielded no responses in 29 patients with MSGT (19 ACC, 2 mucoepidermoid).³⁵ Ten patients did have stabilization of disease, but the significance of this will remain unclear in a relatively indolent disease process. A phase 2 trial studying the EGFR targeting monoclonal antibody cetuximab in salivary gland tumors has also been reported.³⁶ Histologies that were treated included predominantly adenoid cystic carcinoma, in addition to mucoepidermoid, myoepithelial and acinic cell. Fifty percent of the twenty-two evaluable patients had stable disease (SD); seven of which had durable stability lasting over six months. There were no partial or complete responses. Clinical benefit (duration of stable disease) did not correlate with the classic EGFR inhibitor associated rash or with EGFR amplification by FISH although several patients with increased EGFR expression by IHC had prolonged stable disease. This study indicated potential activity of this agent in a selected population but again, the finding of prolonged stable disease is hard to interpret in such an indolent disease.

Given the preclinical data regarding Her-2/neu expression, there was interest in testing trastuzumab in the clinical setting. A phase 2 study was initiated in which patients with 2+ and 3+ Her-2/neu IHC staining were to be treated with trastuzumab monotherapy.³⁷ In order to screen potentially eligible patients for this study, 137 tumor specimens were screened. Only fourteen patients were enrolled before the study was terminated due to generally low levels of Her-2 expression in most screened patients. The median time to progression for all patients treated was only 4.2 months.³⁸ The overall frequency of Her-2/neu overexpression was 17%, but among the adenoid cystic tumors the frequency of overexpression was only 4%. Salivary duct tumors on the other hand had a higher rate of overexpression of Her-2/neu of 83%. These

findings led to a study that was conducted by SWOG, in which patients with Her-2/neu overexpression or gene amplification were selected for treatment. Adenoid cystic carcinomas were specifically excluded. (www.clinicaltrials.gov) Unfortunately, a poor funding climate led to withdrawal of financial support and further accrual was discontinued. Thus, there is a lack of clinical data to suggest which criteria might select patients with MSGTs that would respond to trastuzumab.

Lapatinib is a small molecule tyrosine kinase inhibitor that binds to the ATP binding site of both EGFR and Her-2/neu. Given the known potential for cross-talk between these two tyrosine kinase receptors, dual targeting has been of interest. In a recent study of MSGTs, patients were stratified and enrolled according to adenoid cystic (ACC) and non-ACC histologies.³⁹ In the ACC treatment arm, at least one objective response was required after the first twelve patients in order for enrollment to continue. Eligibility criteria included measurable disease with evidence of disease progression and positive IHC staining for EGFR and Her-2/neu. As in prior studies, there were no partial responses in either group. However, tumor stabilization was noted in 75% of the patients with ACC, and in 47% of non-ACC patients. Stable disease lasting over six months was noted in 45% and 21% of patients in the 2 groups, respectively, which is greater than what would be expected based on historical controls. Serial biopsies were done to assess possible biological markers of activity, but there were none that correlated with response with the possible exception of a suggestion that increased EGFR and Her-2/neu expression might serve as markers for patients who would benefit from lapatinib therapy.

Currently, most of the clinical efforts for the study of MSGTs have focused on EGFR and Her-2/neu targeting agents. Future trials will likely incorporate anti-angiogenesis agents, especially multi-targeted tyrosine kinase inhibitors, into treatment regimens as well. Based on recent studies of these agents in other more common cancers the expectation for outcome must be disease stabilization rather than objective responses.

In order to increase the chance of detecting a clinical benefit, it will be important to develop studies that take into account the different histologies and molecular profiles of MSGTs. Given the rarity of these tumors, however, this will continue to present a major challenge and will require multi-institutional collaborations, and study designs based on pre-clinical data of target expression and sensitivity to the molecular therapeutics.

THYROID CANCER

Thyroid cancers, while relatively uncommon at an annual incidence of 34,000 cases, have been increasing in incidence for reasons that remain unclear at a rate of 3% per year.^{1, 40, 41} Known risk factors include prior radiation exposure, reduced iodine intake, lymphocytic thyroiditis, and a family history of thyroid cancer.⁴² In addition, those exposed to nuclear fall-out as a result of nuclear disasters are known to have a higher risk of papillary thyroid cancer.⁴³ The rising incidence of thyroid cancer seems to be mainly due to increased rates of papillary thyroid cancer, as opposed to the other histologies, and appears driven in part by an increase in the detection of small cancers via ultrasound and other imaging technologies.⁴¹ There are two distinct cellular origins. Papillary, follicular and anaplastic thyroid cancers arise from the follicular cells, while medullary cancers arise from the parafollicular C-cells. The majority of thyroid cancers are the differentiated histologies (DTC), with papillary thyroid cancer (PTC) accounting for 80%, follicular cancer/Hurthle cell variant (FTC) accounting for 15%, and anaplastic (ATC) accounting for 2% of diagnoses. The mainstay of treatment for thyroid malignancies is surgical resection. The differentiated thyroid cancers are often amenable to adjuvant treatment for cure with radioactive I-131, and this modality is also the initial preferred treatment for metastatic disease that is iodine-avid. This group of thyroid cancers is also

sensitive to TSH stimulation and they produce thyroglobulin. In contrast, medullary thyroid cancers (MTC) do not have any of these features.

Doxorubicin is currently the only FDA-approved systemic agent for the treatment of advanced, incurable thyroid cancer. Doxorubicin has been shown to induce apoptosis in thyroid cancer cell lines.^{44, 45} While the clinical experience with doxorubicin in thyroid cancer has spanned decades, in practice there has been little enthusiasm to use it as a routine first line option. Historically, numerous small phase 2 studies of doxorubicin with sample sizes ranging from two to nineteen patients have shown response rates ranging from 22–90%.^{46–52} It is widely believed that the small patient numbers and varying criteria for assessing response, especially among the older studies which pre-dated spiral CT scans as well as consensus criteria for response assessment such as RECIST, exaggerated the effectiveness of this agent. Even a small phase 2 study of the combination of cisplatin and doxorubicin only resulted in a response rate of 9%.⁵³ Doxorubicin has been studied in two relatively contemporary trials. In one, seventeen patients were treated with doxorubicin in combination with interferon alpha.⁵⁴ Only one patient had a partial response and ten had stable disease, with a median time to progression (TTP) of 5.9 months. In another study, doxorubicin monotherapy (either given weekly or once every three weeks) was administered.⁵⁵ Among the patients with papillary or follicular cancer, there was a PR rate of 5% with 42% of patients showing SD. Among patients with medullary thyroid cancer, the rates of PR and SD were both 11%. Thus, while doxorubicin has single agent activity, there is an obvious need for a more effective, less toxic therapy.

Molecular Pathogenesis of Thyroid Cancer

Iodine-refractory thyroid cancer arises as a result of tumor cell de-differentiation and accounts for about 2–5% of all thyroid cancers. High risk features for developing eventual iodine refractory disease include tumor necrosis, extrathyroidal extension, older age, male gender, and high grade histology. The majority of deaths from differentiated thyroid cancer occur in patients with iodine refractory disease. In the past treatment options for this unfortunate group of patients have included surgery or external beam radiation for localized disease in the neck and upper thorax, doxorubicin for systemic disease, or referral for experimental therapy, usually phase 1 trials.

Novel molecular therapies are having a potentially dramatic impact on the course of incurable, iodine-refractory thyroid cancer as well as medullary thyroid cancer and are likely to change our treatment paradigms. An understanding of the pathogenesis of thyroid cancer is necessary in order to understand why responses are occurring and also to determine how best to utilize the multi-kinase inhibitors that are currently under evaluation in the clinic. This involves an understanding of the initiating genetic lesions responsible for these diseases, as well as those transformation events that lead to the progressive de-differentiation that result in undifferentiated and anaplastic cancers.

The molecular events associated with the development of papillary thyroid cancer mainly appear to involve alterations of genes encoding effectors of the MAPK pathway. This typically includes non-overlapping activating mutations in one of the following four genes, which are detectable in 70% of papillary thyroid cancers: RET/PTC rearrangements, BRAF, NTRK1 (neurotrophic tyrosine kinase receptor 1) rearrangements, or RAS.^{56, 57} Ret and NTRK1 are both tyrosine kinase receptors, and Raf is a serine/threonine kinase. Numerous RET/PTC rearrangements have been identified in sporadic and radiation exposure related papillary thyroid cancers, with RET/PTC1 and RET/PTC3 being more common.⁵⁸ A somatic mutation in BRAF, (V600E), is one of the more common mutations identified (36–69%), while RAS mutations are more rare in papillary cancers and appear to be more common in follicular cancers.^{57, 59} RAF mutations correlate with adverse clinical features, such as extrathyroidal invasion, lymph node metastases, advanced stage, risk of recurrence, and loss of I-131 avidity.

60, 61 In one series, RAF point mutations have been detected in 38% of papillary carcinomas, 13% of poorly differentiated carcinomas, and 10% of anaplastic carcinomas, but not in follicular or Hurthle cell malignancies. 61 In addition, BRAF mutation has been shown to correlate with low expression of the sodium iodide symporter (NIS), which could provide a molecular explanation of the de-differentiated, non-iodine-avid phenotype of these cancers. 62 Interestingly, the RET/PTC alteration was not associated with NIS expression. Inhibition of the MAPK pathway therefore becomes an obvious therapeutic approach for iodine refractory thyroid cancers. Preclinical data from cell lines with either BRAF, RAS or RET mutations interestingly indicate that only the BRAF mutation predicts for sensitivity to MEK inhibition, the downstream effector of all of these pathways. 63 Raf kinase inhibitors also inhibited the growth of thyroid cancer cells with BRAF or RET/PTC activating mutations. 64

Follicular thyroid carcinomas differ molecularly from papillary cancers and are characterized by RAS mutations and PAX8-PPAR γ rearrangements (t(2;3)(q13;p25)). The fusion of the thyroid transcription factor PAX8 and the steroid nuclear hormone receptor PPAR γ has been detected in up to 50% of follicular thyroid cancers, but not follicular adenomas nor papillary thyroid cancers, and results in a distinct gene expression profile. 65, 66 The rearrangement likely inhibits cell differentiation while stimulating growth, functioning as a dominant negative inhibitor of the wild type PPAR γ receptor, the latter probably serving as a tumor suppressor. 67 In vitro, PPAR γ agonists led to reduced growth of follicular carcinoma tumor cells, and thus the clinical study of PPAR γ modulators in follicular cancers, such as the thiazolidinediones (pioglitazone and rosiglitazone) is warranted. 68

RAS mutations and PAX8-PPAR γ rearrangements are rarely found in the same tumor, suggesting two separate molecular pathogenic pathways for this disease. 69 Point mutations in H-RAS and N-RAS have been detected in follicular thyroid carcinomas. 70, 71 As RAS mutations are also seen in papillary carcinomas, it is possible that these mutations contribute to tumorigenesis in conjunction with other oncogenes, and are not specific to follicular carcinomas and are not serving as the primary instigators of malignancy.

While the genes discussed above have been implicated in the initial pathogenesis of thyroid cancers, other growth factor receptors appear to play a role in the progression and behavior of thyroid carcinomas. For instance, the vascular endothelial growth factor (VEGF) is detected at increased levels in papillary and follicular thyroid cancers compared to hyperplastic or benign thyroid tissue, and is associated with increased risk for recurrence and metastatic disease. 72–75 Targeting angiogenesis in this disease is thus another area of extensive research. The growth of tumors in anaplastic thyroid cancer mouse xenografts, for example, was curtailed by AZD2171, a potent inhibitor of the vascular endothelial growth factor receptors (VEGFR). 76

The EGFR (epidermal growth factor receptor) is also expressed and phosphorylated in thyroid cancer cell lines and tissue. 77 It is overexpressed in human thyroid cancer as well, and is associated with a worse prognosis. 78 EGFR activation may also result in activation of c-met signaling. 79 There are also provocative interactions between the EGFR and the RET/PTC fusion protein. It is known that the RET/PTC oncogene dimerizes, resulting in autophosphorylation of tyrosine kinase motifs and constitutive activation of downstream signaling. 80 Inhibition of EGFR decreases RET autophosphorylation, and the two proteins co-immunoprecipitate from cell lysates, and thus appear to form a complex. 81 In vitro, a role for EGFR activation in thyroid cancer is also supported by the finding that the EGFR and multi-kinase inhibitors, gefitinib, PKI1166 and AEE788 had growth inhibitory effects in cell lines with the RET activating mutation. AEE788 also has activity against VEGFR, and this compound also had inhibitory effects on ATC xenografts. 82 The agent ZD6474 (vandetanib), which targets RET, VEGFR and EGFR, is another attractive compound to explore in this

setting, and in preclinical studies does limit the growth of thyroid cancer cells with the RET/PTC activating rearrangement.⁸³

Activation of Akt, a downstream effector of PI3kinase, has been observed in follicular and papillary thyroid cancer cells.⁸⁴ Inhibition of Akt did result in decreased cell proliferation and increased apoptosis in thyroid carcinoma cell lines in vitro. It is also well known that patients with Cowden's syndrome, who have a loss of PTEN resulting in activation of the Akt pathway, are at increased risk of developing thyroid cancer. A mouse model of follicular thyroid adenoma has been generated by engineering a loss of PTEN in the thyroid follicular cells, but another genetic event is likely required for malignant transformation.⁸⁵

Anaplastic and undifferentiated thyroid cancers are aggressive malignancies that are not responsive to radioactive iodine or other systemic cytotoxic therapies. It is felt that originally differentiated thyroid cancers undergo additional molecular changes resulting in clonal evolution to a less differentiated variant. One such genetic event includes p53 mutations, which have been detected in anaplastic carcinoma cell lines, but not in the more differentiated histologies.^{86, 87} In one series, evidence of p53 mutations was noted in cells which also harbored BRAF mutations, suggesting that both events are important to malignant transformation.⁸⁷ Mutations in the catalytic subunit of PI3K, PIK3CA, have also been observed in ATC cell lines.⁸⁸ Modification of the extracellular matrix likely influences malignant progression and metastatic potential as well. For instance, E-cadherin expression is low in recurrent, metastatic thyroid carcinomas, but is present in less advanced, well-differentiated cancers.^{89, 90} β -catenin, which associates with cadherins, was found to have low expression as well, with increased nuclear localization of this molecule.⁹¹ In the future, further delineation of the molecular events associated with the undifferentiated histologies will aid greatly in the development of more effective therapies for this aggressive and notoriously refractory group of carcinomas.

Medullary thyroid cancer (MTC) is characterized by activating mutations in the RET proto-oncogene with constitutive activity of this tyrosine kinase receptor. The majority, 75%, of MTCs are sporadic, with mutations in RET detected in up 25–66% of this population.⁹² Most of these somatic mutations are in exon 16. In contrast, the remaining 25% of MTCs that are familial as part of the MEN2 (multiple endocrine neoplasia type 2) syndrome nearly all carry RET mutations, often in exons 10 or 11.^{93, 94}

Systemic Therapy for Metastatic Disease

Novel multi-kinase small molecule inhibitors are being actively studied in I-131 non-avid papillary and follicular carcinomas (DTC), as well as medullary thyroid cancers (MTC), with encouraging early results. Table 2 lists these agents, the targets they act upon, and the subtypes of thyroid cancer in which they have been studied. It is clear from the Table that a shared mechanism of action for most of the agents is to inhibit angiogenesis, with most of these molecules binding to VEGF or VEGF receptors. In addition, RET is an obvious target, given its role as an initiating factor in papillary and medullary thyroid cancer. Table 3 summarizes the numerous phase 2 studies that have been conducted in recent years with these agents, several of which will be discussed further below.

Motesanib is an oral inhibitor of the VEGF receptors 1, 2, and 3; PDGF (platelet derived growth factor); KIT; and Ret. An open label, single arm, multicenter phase 2 study was conducted in patients with locally advanced or metastatic differentiated thyroid cancers that were refractory to radioactive iodine therapy.⁹⁵ In total, 93 patients (61% PTC) were treated with 125mg of motesanib once daily. 83% had not received prior chemotherapy. Tumor genotyping was conducted, but was not performed in 52% of samples; 30% had the BRAF(V600E) mutation, and 18% had RAS mutations, but neither finding was clearly associated with response. The

objective response rate was 14%, with stable disease observed in 67% of patients. The median duration of response was 32 weeks, with a median progression free survival (PFS) of 40 weeks. Grade 3 toxicities occurred in 55% of patients, including diarrhea, hypertension, fatigue, nausea and anorexia. Of note, 12 patients discontinued treatment due to adverse events and 5 developed cholecystitis.

Axitinib is also a potent oral anti-angiogenesis agent, with selective inhibition of VEGF receptors 1, 2, 3. An open label phase 2, single arm, multicenter study enrolled 60 patients.⁹⁶ All histologies were included (papillary-50%, follicular-25%, anaplastic-3% and medullary-18%) as long as the disease was not appropriate for treatment with I-131. Therapy was started at a dose of 5 mg orally twice daily, with an option to increase to 7 mg and 10 mg twice daily if there were minimal toxicities. Only 15% of patients had received prior chemotherapy. The objective response rate was 30%, with disease stability greater than 16 weeks in an additional 38%, and a median PFS of 18.1 months. Treatment benefit and response was noted in all histologies. Due to adverse events, 8 patients discontinued therapy. Grade 3 and 4 toxicities occurred in 19 patients (32%) and 3 patients, respectively, and included hypertension, diarrhea, proteinuria and fatigue. A decrease in soluble VEGFR levels was noted in response to treatment, but no conclusions could be made in regards to how this correlated with response.

Sunitinib, an oral tyrosine kinase inhibitor that inhibits RET, PDGFR and VEGFR is an attractive agent to study given its dual actions as an anti-angiogenic agent and a RET inhibitor. A recently presented phase 2 study treated 43 patients with all histologies of thyroid cancer (37 DTC, 6 MTC) with sunitinib at a dose of 50mg orally daily for 4 weeks, followed by 2 weeks off.⁹⁷ Response assessments were as follows: in DTC PR 13%, SD 68% and in MTC the SD rate was 83%. Grade 3–4 toxicities included neutropenia (26%), thrombocytopenia (16%), hypertension (16%), fatigue (14%), palmar-plantar erythrodysesthesia (14%), and gastrointestinal tract events (14%). Preliminary results from two other phase 2 studies with this agent were reported at the 2008 American Society of Clinical Oncology meeting. In the first, 17 patients have been enrolled so far with a PR in 1 and SD in 12.⁹⁸ In another phase 2 trial, a schedule of sunitinib 37.5 mg orally daily was used to treat DTC and MTC. After enrollment of 18 patients, preliminary results indicate 44% of patients had a PET response after 7 days, but further efficacy data are not mature.⁹⁹

Sorafenib, another multi-kinase inhibitor against Raf, VEGFR and PDGFR has also been studied in several phase 2 studies. One open label phase 2 study has treated 36 patients with iodine refractory disease (papillary 61%, follicular 28%, anaplastic 5.5%) and MTC (5.5%).¹⁰⁰ Seven patients had a PR, and an additional 20 had SD. Grade 3 toxicities reported to date include hypertension and palmar-plantar erythrodysesthesia. Early correlative studies show a decrease of pERK and pAKT in post-treatment tissue.¹⁰¹ An additional study has been reported in which 18 patients (10 MTC, 8 DTC) were treated, but it is too early to draw conclusions about response.¹⁰²

Additional agents that have been evaluated include gefitinib and lenalidomide. In a phase 2 study of gefitinib, there were no objective responses noted in the 25 patients treated. Thus, while there are preclinical data regarding EGFR activation in thyroid cancer, EGFR inhibitors may have limited single agent activity.¹⁰³ Preliminary results with the anti-angiogenic agent lenalidomide showed favorable activity in DTC, with a PR of 22% and SD in 44% of the first evaluable 18 patients. However, this is a small number of patients, with only short-term follow-up. Grade 3 toxicities were primarily hematologic.¹⁰⁴

Vandetanib, an oral agent that targets RET, VEGFR and EGFR, has been studied predominantly in hereditary MTC, which would harbor a RET mutation. In one study,

vandetanib was administered at a dose of 100mg orally daily to 19 patients.¹⁰⁵ 16% of patients had a confirmed PR and 63% had SD. Three patients withdrew due to adverse events, and 6 patients had grade 3–4 events. An earlier study had treated 30 patients with hereditary MTC with a higher dose of 300mg daily. A PR was noted in 17%, with SD in 50%.¹⁰⁶

Finally, another interesting agent, XL184, is in the process of being studied for medullary thyroid cancer. This inhibitor of RET, MET and VEGFR2 was evaluated in a phase 1 study in advanced solid tumor patients. In this study, 22 patients with MTC were treated; of interest, this number included patients who had received prior tyrosine kinase inhibitor therapy with either motesanib, vandetanib or sorafenib. Nearly all the MTC patients treated had a treatment benefit with 47% PR and 53% SD. Grade 3 toxicities included low rates of nausea, diarrhea, mucositis and increased liver function tests. This drug is currently being studied further in an ongoing trial in patients with MTC.

Discussion

Many of the agents that were discussed above are still being evaluated in ongoing studies for advanced thyroid malignancies. Additional agents, such as the MEK inhibitor AZD6244 and the anti-angiogenesis small molecule pazopanib, are in trials now. There are a number of obvious challenges. One is patient selection. We have reviewed the principal genetic lesions driving the development and evolution of thyroid cancer. What we do not know is how well any of these lesions predicts response to a given agent or class of agents. For instance, based on preclinical data, a BRAF mutation may predict for responsiveness to agents that target MEK, but this needs to be studied prospectively in clinical trials. As well, the mechanisms of resistance, primary and acquired, to these drugs need to be studied further in order to optimize their use.

A second challenge is be able to determine when a patient should begin treatment with one of these agents. Although less toxic than traditional cytotoxic therapies (including doxorubicin), these drugs nevertheless have a number of very significant toxicities. One must also consider that many patients might end up being treated for prolonged periods of time if not the rest of their lives. Clinical trials designs must therefore take into account that advanced thyroid cancer, even when destined to be fatal, is an indolent metastatic cancer compared to many malignancies. Stable disease is an obvious endpoint that has already emerged from the ongoing trials but the clinical significance of stable disease remains a matter of ongoing scientific and regulatory debate. With so many potentially active agents for a relatively rare disease, designing feasible (completable) phase 3 studies to eventually merit FDA registration will also require an evaluation of patient resources and the creation of effective, likely international, research consortia. An additional relevant question is whether or not these agents need to be or should be compared to current approved FDA drug, doxorubicin, knowing that this approval occurred many years ago in a different therapeutic and regulatory environment. An international registration study for axitinib for patients who had formally failed doxorubicin was planned, but accrual was poor due to the requirement for prior doxorubicin treatment that patients and physicians were hesitant to consider.

While the data to date are preliminary it is clear that we are in a new era in the treatment of advanced thyroid cancer. The new drugs will provide significant insight into the disease itself and likely alter the natural history of what had previously been an untreatable medical illness. The next steps are clear, namely to validate the clinical utility of these agents in well-designed clinical trials, and understand the determinants of clinical response and resistance.

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Table 1
WHO Classification of Salivary Gland Tumors ¹¹

Carcinomas	Features
Low Grade, favorable prognosis	
Acinic Cell Carcinoma	-low grade and low malignant potential -lymphoid infiltrate in supporting stroma
Low grade Mucoepidermoid Carcinoma	- low grade: cystic, mucous producing cells
Polymorphous low grade adenocarcinoma	-arises in minor salivary glands -good prognosis
Epithelial – myoepithelial carcinoma	-predominately in parotid gland -higher incidence in females
Basal cell adenocarcinoma	-low grade with regional recurrence -predominantly in parotid
Sebaceous carcinoma	
Papillary cystadenocarcinoma	
Mucinous adenocarcinoma	
Oncocytic carcinoma	
High Grade, Poor prognosis	
Salivary duct carcinoma	- high grade, poor prognosis
High Grade Mucoepidermoid Carcinoma	- high grade: solid, with hemorrhage and necrosis
Adenoid Cystic Carcinoma	- biologically aggressive
Adenocarcinoma	
Malignant myoepithelioma	
Carcinoma in pleomorphic adenoma (Mixed malignant tumor)	- degree of invasiveness determines prognosis
Squamous cell carcinoma	
Small cell carcinoma	- poor prognosis similar to small cell carcinoma of the lung and other anatomic sites
Undifferentiated carcinoma	- histologically similar to lymphoepithelial carcinoma of the nasopharynx

Table 2

Current small molecule inhibitors in trials for thyroid cancer and their targets

	Subtypes	Targets
Motesanib	DTC	VEGFR 1,2,3, PDGF, KIT, RET
Lenalidomide	DTC	Antiangiogenic properties, anti-TNF-α, immunomodulator
Axitinib	DTC, MTC	VEGFR-1, 2, 3; PDGFR- α,β; KIT (but not RET)
Sunitinib	DTC, MTC	VEGFR, PDGFR, c-kit, RET
Sorafenib	DTC, MTC	VEGFR-2, VEGFR-3, PDGFR-β, Flt-3, C-Kit, RET, RAF and FGFR-1
Vandetanib	MTC	RET, VEGFR, EGFR
XL184	MTC	MET, VEGFR2, and RET
AZD6244	DTC	MEK

Table 3

Response rates in recent phase 2 studies in thyroid cancer

	No. of patients	Partial Response	Stable Disease
Motesanib <i>S. Sherman, 2007</i>	93 DTC	14%	67%
Axitinib <i>E. Cohen, 2007</i>	45 DTC 12 MTC	31% DTC 25% MTC	44% DTC 33% MTC
Sorafenib <i>Brose, 2008</i>	42	21%	59%
Sunitinib <i>E. Cohen, 2008</i>	37 DTC 6 MTC	13% DTC	68% DTC 83% MTC
Gefitinib <i>Pennell, 2007</i>	25	0%	48%
Lenalidomide <i>Ain, 2008</i>	18	22%	44%
Vandetanib <i>Haddad, 2008</i>	19	16%	63%
Vandetanib <i>Wells, 2007</i>	30	17%	50%
XL184 <i>Salgia, 2008</i>	22	47%	53%