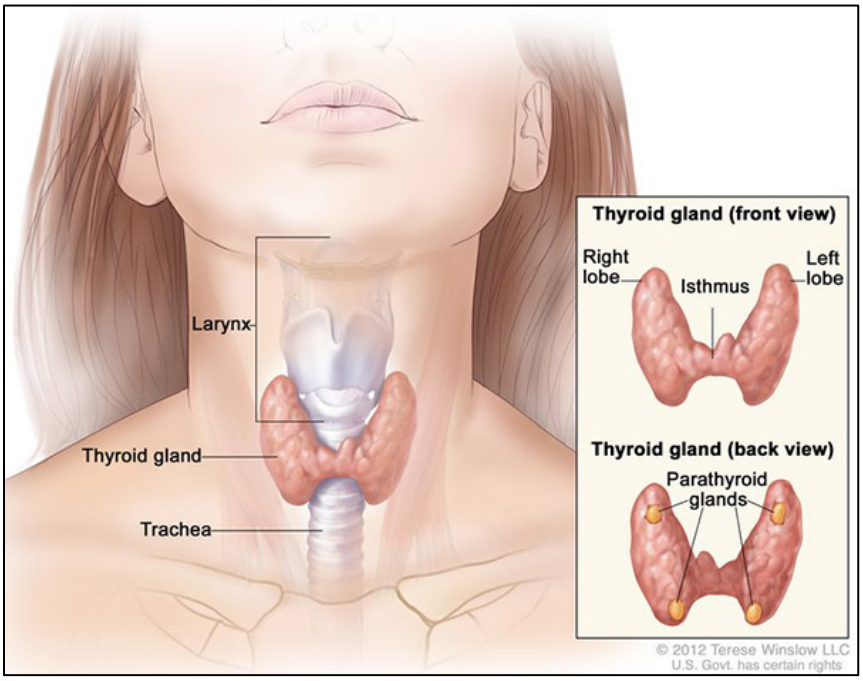
Thyroid cancer Screening and treatment



Saad A. Khan, MD
Assistant Professor of Medicine
Hematology and Oncology

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Live-tweet questions/comments: @smakface #ThyroidCancerUTSW

Purpose and overview: Thyroid cancer is an increasing health problem all over the world, with tremendous advances in screening and treatment. One challenge is determining the optimal time to act on thyroid cancer, not intervening may be an option both in early disease and often even after the development of metastases. Understanding the biology of thyroid cancer will help us not only to predict the natural history of the disease, but also to target the mutations that lead to its malignant behavior.

Saad A. Khan, MD is an assistant professor of medicine in hematology and oncology who focuses on treating head and neck cancer. He completed his postgraduate training at the Fox Chase Cancer Center, Temple University, UMass and the Mayo Clinic after graduating from Punjab Medical College, Pakistan. His research interests are clinical trials of targeted agents in head and neck squamous and thyroid cancer. He also works on early drug development, and is developing a portfolio of effective clinical trial options for his patients as co-leader of the head and neck team at UTSW.

Objectives:

1. Understand the molecular mechanisms underlying thyroid cancer

2. Understand the seriousness and urgency of a rapidly enlarging thyroid mass suspicious for undifferentiated thyroid cancer.

3. Review new systemic therapies that delay progression of differentiated thyroid cancer

4. Learn about the impact of a national ultrasound screening program in thyroid cancer

Check out these links for more information on clinical trial options for thyroid cancer at UTSW:

Intensity-Modulated Radiation Therapy and Paclitaxel With or Without Pazopanib Hydrochloride in Treating Patients With Anaplastic Thyroid Cancer
https://clinicaltrials.gov/ct2/show/NCT01236547

Ceritinib (LDK378) in Mutation and Oncogene Directed Therapy in Metastatic or Locally Advanced Anaplastic/Undifferentiated Thyroid Cancer
https://clinicaltrials.gov/ct2/show/NCT02289144

Introduction:

Thyroid cancer is an increasing public health issue, with recent developments regarding treatment, screening and potentially over-diagnosis. In 2014, over 62,000 new cases were projected to have been diagnosed, mostly in women [3]. Thyroid cancer increased at an annual rate of more than 5% between 2006 and 2010, and that trend is continuing.

Thyroid cancer can be differentiated which is often indolent, or undifferentiated which is exceptionally aggressive. Treatment of thyroid cancer involves surgery, hormonal suppression, chemotherapy, external radiation, radioactive iodine and targeted therapy.

Epidemiology and subtypes

The incidence of thyroid cancer has risen faster than any other malignancy [4]. The causes of this increase may be environmental or improved detection. There are over half a million survivors of thyroid cancer in the US, and 1890 deaths in 2014 [5]. 1.1% of men and women will be diagnosed with thyroid cancer in their lifetime, compared to 6.8% for lung cancer.

Differentiated thyroid cancer is much more common in women than men (45,000 vs 15,000 in 2013), while undifferentiated thyroid cancer is evenly distributed.

Thyroid cancer can develop from the follicular epithelium, leading to papillary/follicular when it is differentiated. Undifferentiated or anaplastic cancer also originates from the thyroid epithelium but is very aggressive. Medullary thyroid cancers are neuroendocrine tumors that arise from the para-follicular C cells and are associated with familial syndromes like MEN2.

Thyroid lymphomas are rare tumors that often develop in the setting of existing chronic autoimmune (Hashimoto's) thyroiditis. The risk of developing thyroid lymphoma is 60 times greater in patients with Hashimoto's [6] and appears to be associated with iodine supplementation [7].

Gender disparity in thyroid cancer.

Though we are accustomed to gender disparity in many diseases, in thyroid cancer it is very pronounced and difficult to explain. The traditional two-hit "theory" of cancer is that over many years, cells accumulate genetic abnormalities that lead to uncontrolled growth and metastasis. That is one reason why cancers in older people are more common; their cells have had greater time to accumulate genetic abnormalities.

Empiric observations of risk factors have a tremendous role to play in medicine, even when the exact mechanism is unknown. This has been apparent for centuries, for example Semmelweiss who in the 1840's noted that puerperal sepsis was more common in clinics where the delivering practitioner had contact with cadavers. Though the germ theory of infection had not yet been proposed thus the mechanism by which chlorine hand-washing reduced mortality was unknown, nevertheless his empiric observations saved many lives.

Similarly, the observation that thyroid cancer is more common in females may lead to a better understanding of the biology of thyroid cancer. It is unclear whether this is a result of different exposures or hormonal/genetic factors [8]. Thyroid cancer is the 7th most common cancer in women, and but is not even in the top 15 cancers in men.

The subtypes of thyroid cancer also show gender disparity. Aggressive, less differentiated thyroid cancers like anaplastic or medullary thyroid cancer are equally common in women and men. Differentiated thyroid cancers such as papillary thyroid cancer are much more common in general and more commonly seen in women. The papillary thyroid cancer subtype represents 80% of all thyroid cancer, and is nearly 3 times more common in women.

Hepatocellular cancer is another cancer with gender disparity, one with a marked male predominance. In this disease, high estrogen levels are thought to play a role. IL-6 is often found to be elevated in patients with HCC. Estrogen has the effect of inhibiting IL-6 secretion, which in animal models both decreases and prevents liver carcinogenesis.

The risk of women developing thyroid cancer varies with age. Age specific incidence rises sharply at the beginning of the reproductive years, peaks at ages 40-49, and then in later years the risk of developing thyroid cancer is equivalent for man and women. This has led to the hypothesis that fluctuating sex hormones contribute to carcinogenesis. Varying sex hormone levels are seen during the menstrual cycle, during pregnancy and as women approach menopause. However, no causal relationship has yet been identified. Past pregnancies, age of menarche and menopause do not show consistent correlation with thyroid cancer risk. Even when an association with late age of menarche, late age of first child, first pregnancy miscarriage and induced menopause was found it was weak risk factor.

Other causes of the gender differences between men and women have been sought. Differences in dietary intake have been evaluated. Iodine deficiency is a risk factor for developing follicular cancer and iodine excess has been implicated in the development of follicular cancer [9]. Some food items such as fish and cruciferous vegetables have high iodine content, but no nutritional factors have been found to explain the difference.

Molecular abnormalities in thyroid cancer

In 2/3 of patients with thyroid cancer, genetic alterations that likely contribute to malignant behavior can be identified. The most common abnormality is found in BRAF, roughly 60% followed by RAS in 13% and RET/PTC in 6.3%.

The actual impact of these mutations is the subject of much study. They do lead to aberrant regulation of various signaling pathways such as the MAP kinase, RASSF1A and NF–κB pathways. One of the effects of this is uncontrolled growth and translation/transcription of proteins. It also results in upregulation of pro-oncogenic molecules and downregulation of tumor suppressor genes [10]. BRAF mutations are especially associated with reduced expression of the sodium-iodide transporter, partially explaining the ineffectiveness of RAI in these patients.

BRAF mutations are very common in papillary thyroid cancer, but in only seen in 1% of follicular cancer [11]. In a retrospective analysis [12], BRAF V600E mutations initially appeared to be associated with poorer prognosis but currently that is less clear. BRAF mutations do appear to predict for a response to BRAF inhibitors such as vemurafenib [13, 14].These are less common in undifferentiated/anaplastic thyroid cancer, though there are case reports of cancers with mutations in BRAF V600E and ALK being identified and successfully treated with targeted therapy.

RET/PTC was first discovered to cause constitutive expression of tyrosine kinase. It is rarely found in advanced differentiated thyroid cancer including those that are RAI-refractory. It is however more commonly found in radiation induced thyroid cancers, and in patients with loco-regionally disease rather than metastatic [15].

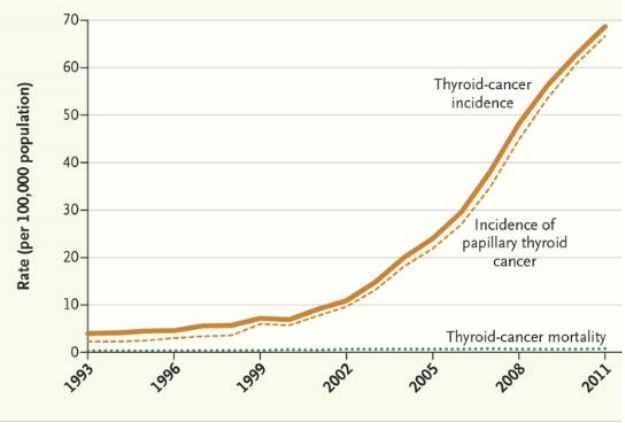
Thyroid cancers are very vascular, and papillary thyroid cancer strongly expresses vascular endothelial growth factor (VEGF). Unchecked tumor growth leads to hypoxia, and VEGF signaling leads to development of new blood vessels to allow even greater tumor growth [16]. Targeting VEGF as a strategy for disease control reduces growth of the tumors, but may promote tumor invasion and metastatic potential [17]. Resistance to anti-VEGF therapy develops through Fibroblast Growth Factor (FGF), and FGFR blockade is being evaluated in combination with VEGF.

BRAF mutations are found in various forms in thyroid cancer. BRAF mutations do not appear to be prognostic for more aggressive disease [12], but do appear to predict for a response to BRAF inhibitors such as vemurafenib [13].

Medullary thyroid cancer has a unique familial predilection. Germline mutations in RET are responsible for an array of symptoms in MEN2. These polymorphisms can be seen in different codons, but most appear to involve the extracellular tyrosine kinase domain [18]. In patients who develop medullary thyroid cancer without a germline mutation, RET is mutated 60% of the time [19]. Germline testing is recommended for all new cases of MTC.

Ultrasound Screening of Thyroid Cancer

Results from years of thyroid cancer screening in the Republic of Korea have been reported [1]. Incidence and mortality related to thyroid cancer were evaluated. Though the screening ultrasound procedure itself is of relatively low cost and morbidity, however it leads ultimately to interventions that are not always benign. Ultrasound appears to detect cancers at a relatively early stage, often with such a small size and low growth rate that it is unclear that they would eventually have had any clinical impact.



Impact of ultrasound screening on thyroid cancer incidence and mortality[1]

Many young people who are otherwise healthy then have these cancers are then surgically removed rather than observed. These treatments often lead to increased psychosocial/financial stress as well as complications from surgery, radiation and thyroid replacement. On a national level, over the decade of thyroid cancer screening, the incidence of thyroid cancer increased significantly. However, there was not a noticeable impact on mortality. For this purpose, routine ultrasound screening of an asymptomatic population cannot be recommended at this time.

Treatment of Advanced Thyroid cancer

Radioactive iodine

Radioactive iodine is a mainstay of treatment of differentiated thyroid cancer. Undifferentiated cancers, like anaplastic and medullary, generally do not respond to radioactive iodine. Radioactive iodine therapy exploits the unique ability of thyroid tissue to accumulate and concentrate iodine from the blood, through a membrane sodium-iodine transporter [20] . Thyroid cancer cells may have reduced expression of this transporter and as result have reduced sensitivity to radioactive iodine.

Radioactive iodine consists of a radioactive isotope I-131, which has a half-life of 8 days. It is a common product of nuclear fission. It is also released into the air as a result of nuclear accidents such as Chernobyl and Fukushima. Airborne nuclear tests led to fallout that produced I-131 and was linked to thousands of excess deaths, mostly as a result of thyroid cancer [21].

Mechanism of action:

After absorption of radioactive iodine, I-131 leads to cell death by production of beta radiation with a range of 1-2 mm. One benefit of this is that surrounding cells can be affected by radiation, even if they did not take up iodine, a so-called bystander effect.

Radioactive iodine can be given after surgery to ablate any remaining thyroid tissue, or if there is distant disease present. I-131 injected into the blood is absorbed by both benign and malignant tissue. This can be effective in eradicating any residual cancer after surgery. By destroying any non-malignant thyroid tissue it makes subsequent I-131 scanning for diagnostic purposes more effective, because all non-malignant thyroid tissue has been destroyed. Similarly, measurement of thyroglobulin becomes more accurate for surveillance of cancer after surgical resection and RAI ablation.

Indications:

RAI is commonly given to patients who have unresectable disease in the neck or metastases. A risk adaptive approach is used for the administration of RAI after surgery. From the American Thyroid Association guidelines, RAI is recommended for the following indications:

TABLE 5. MAJOR FACTORS IMPACTING DECISION MAKING IN RADIOIODINE REMNANT ABLATION

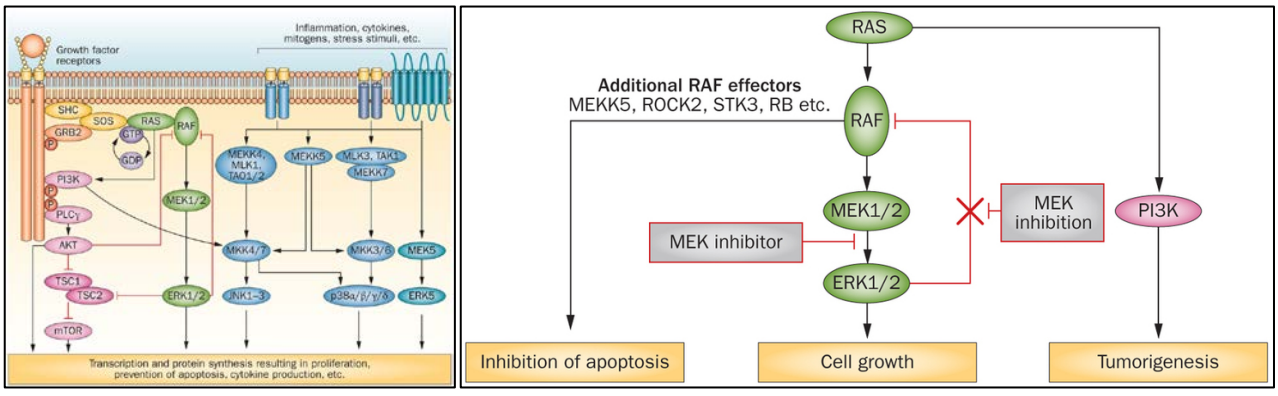
Factors	Description	Expected benefit: Decreased risk of death	Expected benefit: Decreased risk of recurrence	Expected benefit: May facilitate initial staging and follow-up	RAI ablation usually recommended	Strength of evidence
T1	1 cm or less, intrathyroidal or microscopic multifocal	No	No	Yes	No	E
	1–2 cm, intrathyroidal	No	Conflicting data[a]	Yes	Selective use[a]	I
T2	>2–4 cm, intrathyroidal	No	Conflicting data[a]	Yes	Selective use[a]	C
T3	>4 cm					
	<45 years old	No	Conflicting data[a]	Yes	Yes	B
	≥45 years old	Yes	Yes	Yes	Yes	B
	Any size, any age, minimal extrathyroidal extension	No	Inadequate data[a]	Yes	Selective use[a]	I
T4	Any size with gross extrathyroidal extension	Yes	Yes	Yes	Yes	B
Nx,N0	No metastatic nodes documented	No	No	Yes	No	I
N1	<45 years old	No	Conflicting data[a]	Yes	Selective use[a]	C
	>45 years old	Conflicting data	Conflicting data[a]	Yes	Selective use[a]	C
M1	Distant metastasis present	Yes	Yes	Yes	Yes	A

[a]Because of either conflicting or inadequate data, we cannot recommend either for or against RAI ablation for this entire subgroup. However, selected patients within this subgroup with higher risk features may benefit from RAI ablation (see modifying factors in the text).

Table from the American Thyroid Association guidelines for differentiated thyroid cancer [22].

Selumetinib as a means of resensitizing RAI refractory differentiated thyroid cancer

The development of metastatic disease is the most common cause of death in thyroid cancer. 10-year survival declines to 10% in patients with RAI-refractory disease, compared to 60% for RAI-avid thyroid cancer [23]. There is still no curative option for metastatic differentiated thyroid cancer, and newer targeted agents must be taken daily for the remainder of a patient's life. They are also associated with serious, sometimes fatal, side effects. Therefore any approach that maximizes the effectiveness of existing therapy such as RAI would be critically helpful in improving patient outcomes.



MEK inhibitors allow for resumption of iodine uptake in DTC that was previously refractory to RAI, as well as slow down growth [2].

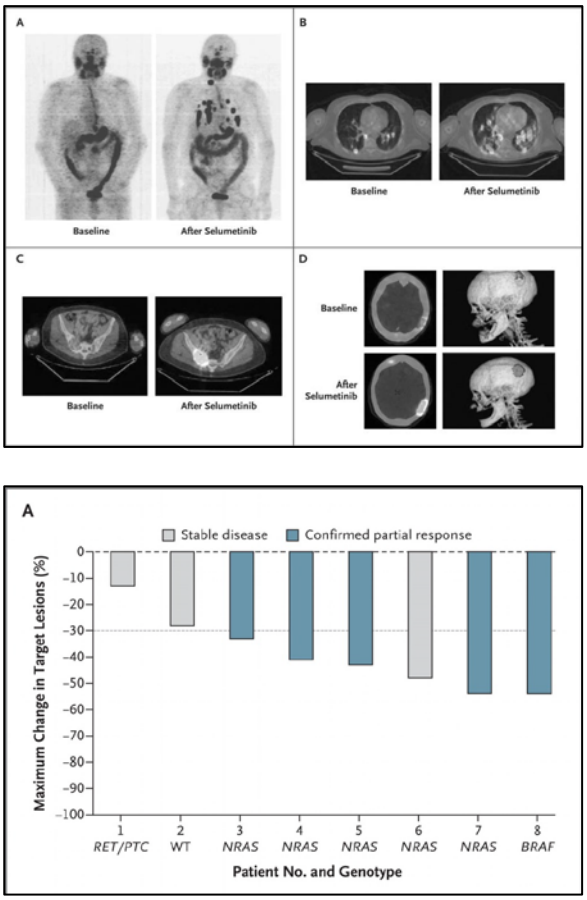
The mutational status of differentiated thyroid cancer is increasingly being understood, especially in explaining the development of lack of response to radioactive iodine.

The common gene mutations in differentiated thyroid cancer are those of RAS, BRAF, RET and NTRK1. Activation of these proteins leads to stimulation of the mitogen-activated protein kinase (MAPK) signaling. In thyroid cancers, this leads to reduced expression of genes for the sodium-iodide transporter and thyroid peroxidase. As a result thyroid cancer cells become less susceptible to the effects of radioactive iodine. Mice models of thyroid cancer with BRAF mutations do not accumulate iodine, and inhibition of BRAF restores iodine uptake in these cells [24]. This effect is seen both in genetic inactivation of BRAF and also with BRAK/MAPK inhibitors.

The approach of blocking MAPK as a means of restoring sensitivity to radioactive iodine in thyroid cancer has been tested. 20 patients with differentiated thyroid cancer who would normally not have been considered candidates for further therapy with radioactive iodine were enrolled. Patients had to have had an iodine-avid lesions that progressed even after treatment with radioactive iodine, PET-avid lesions (which commonly are iodine refractory) or thyroid cancer that did not show evidence of uptake on iodine scan.

The study agent was selumetinib, a selective inhibitor of MEK1 and MEK2. PET with iodinated contrast agents (I-124), was used to determine change in iodine avidity in target lesions at specific time-points in the study.

In a study [25], 12 out of 20 patients with iodine refractory disease demonstrated increased iodine uptake on I-124 PET after 4 weeks of selumetinib 75 mg taken twice daily. 8 patients had sufficient uptake to receive treatment with RAI. The uptake was most consistently seen in patients with NRAS mutations. Though increased uptake was seen in patients with BRAF mutations, few of those could get treated as the required dose of I-131 was too high.



Increased I-124 uptake after selumetinib (top), and responses in patients after I-131 (bottom)

5/8 patients demonstrated partial responses and 3 had stable disease, suggesting a further role for this approach in resensitizing patients to RAI. Though this approach will not replace other therapies such as tyrosine kinase inhibitors due to the cumulative toxicity of RAI, it proves the value of small, rationally designed clinical trials where the mechanism of action is clearly understood. A Phase 3 placebo controlled trial is currently under way (NCT01843062), to confirm the findings and to determine if this is

an approach that can be used prior to initiation of TKI therapy such as sorafenib or lenvatinib.

Tyrosine kinase inhibitors:

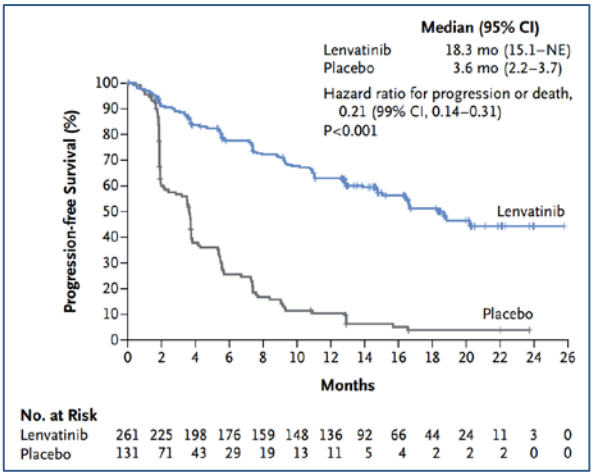
Sorafenib is a small molecule tyrosine-kinase inhibitor that also targets VEGF, PDGFR, RET/PTC and BRAF [26]. The DECISION trial was a Phase 3 trial for patients with progressive, iodine refractory metastatic differentiated (follicular/papillary) thyroid cancer. 417 patients were randomized to either placebo or 400 mg twice daily of sorafenib [27].

Upon completion of the trial, patients on the placebo arm had a PFS of 5.8 months compared to those patients on the sorafenib arm who had a PFS of 10.8 months. Tumor shrinkage was seen in only ~10% of patients, with disease stability being more common. As a result, this drug is now FDA approved for use in this patient population. Sorafenib is associated with significant side effects, including the potential for serious hypertension, stroke and cardiovascular effects. In the trial 20% of patients had to permanently discontinue sorafenib and almost all required dose reductions.

Lenvatinib

A newer tyrosine kinase inhibitor, lenvatinib, received FDA-approval on February 13th, 2015. Lenvatinib has similar targets to sorafenib; VEGFR, FGFR, PDGFR, RET, KIT. The SELECT trial [28] enrolled and randomized patients with progressive, RAI refractory differentiated thyroid cancer to either 24 mg daily of lenvatinib (n=261) or placebo (n=131).

93 patients on this trial had received one prior treatment with a TKI. The primary endpoint was Progression Free Survival, which was 3.6 months in the placebo arm and 18.3 months in the lenvatinib arm.



Progression free survival on the SELECT trial, comparing patients on lenvatinib vs placebo

There were 63% partial responses and 1.5% complete responses with lenvatinib, compared to 1.5% and 0% respectively in the placebo arm. However, lenvatinib is a drug with potentially very serious adverse effects, and in this trial there were 6 (2.3%) treatment related deaths.

The benefit of lenvatinib was similarly pronounced in patients who had previously been treated with sorafenib. This second drug dramatic delay of progressive thyroid cancer gives great hope for long-term disease control for patients.

Medullary thyroid cancer:

Over the last 4 years 4 drugs have been approved for thyroid cancer. One of the first targeted therapies approved was for medullary thyroid cancer, vandetanib. This is an oral inhibitor of VEGFR, RET/PTC and EGFR. A Phase 3 trial [29] enrolled advanced MTC patients (both sporadic and inherited) and were treated with vandetanib (n=231) or placebo (n=100). PFS was 19.3 months in the placebo group and predicted to be 30.5 months in the vandetanib group. Due to serious side effects of the drug including hypertensive crisis, sudden death and QT-prolongation, vandetanib is available only via a Risk Evaluation Mitigation Strategy (REMS) program.

Cabozantinib is a small molecule TKI that acts against VEGFR, c-MET and RET. A randomized trial of 140 mg of cabozantinib daily or placebo was done in 330 patients with advanced MTC[30]. The PFS for cabozantinib was 11.2 months vs 4 months for the patients on the placebo arm.

Overview of Anaplastic Thyroid Cancer pathogenesis, epidemiology and current treatment

Anaplastic Thyroid Cancer

Anaplastic thyroid cancer (ATC) is an undifferentiated tumor of thyroidal follicular epithelium. Though not as common as differentiated thyroid cancers, ATC has much higher disease specific mortality; approaching 100% [31]. Though ATC accounts for less than 5 % of all thyroid cancer diagnoses [32], it leads to more than half of the 1200 deaths from thyroid cancer every year in the US [33].

46% of patients present with distant metastases, and almost 70% demonstrate metastases at some stage of the disease [33]. All staging for anaplastic thyroid cancer is as stage IV [33], given its aggressive nature and propensity for metastasis. Even with the most aggressive existing multimodality therapy involving surgery, radiation and chemotherapy, most patients do not derive consistent, sustained benefit in outcomes and survival. Median overall survival is still reported as 3-4 months, with 90% of patients dead at 1 year from diagnosis [33]. Patients often suffer from distant metastases even after local therapy is completed, demonstrating the inadequacy of treatment. Lung and bone metastases are common as well as significant airway compromise and suffocation even after tracheostomy.

Doxorubicin is the only approved chemotherapy for anaplastic thyroid cancer [34], and is often combined with radiation or surgery as part of multi-modality therapy. No randomized trial has demonstrated improved statistically significant survival or better quality of life in patients treated with any current therapy [34].

Clinical trials for this disease are also extremely rare, leaving patients with very limited treatment options. Patients diagnosed with anaplastic thyroid cancer have a dismal prognosis even with aggressive surgery and radiotherapy, with near-complete certainty

of dying within a few months because of their disease. As such there is a clear need for improving therapy for anaplastic thyroid cancer in a rational, patient selective manner.

Given the poor prognosis, guidelines from the American Thyroid Association as well as the National Comprehensive Cancer Network recommend all patients should be treated as part of a clinical trial regardless of stage [34, 35].

UTSW is will offer targeted, biomarker driven therapy for anaplastic thyroid cancer patients who would otherwise have very poor treatment options and outcome. This clinical trial will also have the major goals collecting information about the genetic mutations found in thyroid cancer

Targeted therapies in ATC

There are currently no approved and no commonly employed targeted therapies in Anaplastic Thyroid Cancer. This is an area of urgent need for patients, not just for approved treatments but also rationally-designed clinical trials designed specifically for ATC.

Newer agents have been tested, but are currently not approved for any stage of therapy for patients in the US. Fosbretabulin is a novel tubulin binding compound that showed activity in ATC [36]. A Phase III trial treated ATC patients after surgical resection with carboplatin and paclitaxel and were randomized to fosbretabulin or placebo [37]. The arm containing the experimental drug had 33.3% survival at one year vs 7% for the carboplatin and paclitaxel alone arm. Though not powered to detect differences in survival, the median survival for the standard arm was reported as 4 months on the control arm versus 8.4 months on the fosbretabulin arm.

Sorafenib has demonstrated some activity in small studies. In 20 patients treated with sorafenib, 2 patients demonstrated a partial response [38]. Sorafenib is currently not listed as a recommended regimen in the NCCN guidelines for anaplastic thyroid cancer, nor in the ATA guidelines for Anaplastic Thyroid Cancer.

The goal of the UTSW multi-center, multi-arm trial is to measure the impact of treating metastatic anaplastic thyroid cancer patients with targeted therapy selected for these patients by the presence of a genetic mutation or other aberration. This trial will serve as a framework by which new genetic abnormalities as well as biomarker-drug combinations can be identified and added as new arms.

Other abnormalities have been reported and sporadically targeted in anaplastic thyroid cancer. These include *braf* which is found in 14-25% of anaplastic thyroid cancer [13, 39]. This has also been associated with dramatic responses to targeted therapy in one case report. These anecdotal results remain to be confirmed in larger studies.

Other mutations commonly found in ATC include PI3KCA (24%), PTEN (16%), RAS (60%) and TP53 (48%) [40]. Additional arms will be added to this protocol as promising biomarker/mutation and drug combinations are identified. Currently, further arms are expected to finalized that will encompass approximately 50% of patients with ATC.

ALK positive tumors in other organs

ALK is a receptor tyrosine kinase, part of the insulin receptor family. The *ALK* gene abnormalities have been identified in several cancers as driving malignant behavior. It has been identified in non-small cell lung cancer, lymphoma and neuroblastoma.

Non-small cell lung cancer: *ALK* becomes constitutively when fused with other proteins. In approximately 5% of non-small lung cancer, a translocation on chromosome 2 fuses exons 1-13 fuses Echinoderm Microtubule-Associated protein like-4 (EML-4) with exons 20-29 of *ALK* and the resulting EML4-*ALK* fusion product induces tumor formation in transgenic mice [41]. Lung adenocarcinoma with *ALK* rearrangements is more commonly seen in never smokers or light smokers.

Experience of *ALK* inhibitors in malignancies with *ALK* abnormalities

Crizotinib is an oral inhibitor of *ALK* tyrosine kinase that has shown remarkable results in the ALK positive non-small cell lung cancer. Patients with advanced non-small cell lung cancer who developed progressive disease but had EML4-*ALK* rearrangements have been treated with crizotinib. In these trials, high response rates have been seen along with improvement in survival [42-44].

Ceritinib is a second generation ALK inhibitor with 20 times greater potency than crizotinib. It demonstrated response rates of greater than 55%, even in patients who had previously received crizotinib. As a result, ceritinib is FDA-approved for ALK-positive lung cancer after crizotinib.

Next generation DNA sequencing of ATC:

Part of the difficulty in treating ATC arises from our limited understanding of the underlying biology of this rare disease. One of the goals of this trial is to collect tissue from 100 patients with anaplastic thyroid cancer, and analyze their tumors for the presence of mutations or other genetic abnormalities. The goal is to create a catalog of commonly found mutations in ATC, and allow for rapid addition of new arms of therapy as they become available.

ALK aberrations in anaplastic thyroid cancer

Experiments have been done to determine the genetic drivers of malignancy in aggressive thyroid cancer. In anaplastic thyroid cancer (ATC) collected from patient samples, mutations in the kinase domain of *ALK* have been characterized in 11% [45]. In this study of ATC, two exons in the tyrosine kinase domain were sequenced and novel mutations were found in both exon 23 and 25. Both mutations led to increased tyrosine kinase activity of *ALK*.

These mutations were associated with activation of the PI3kinase pathway as well as high phosphorylation levels of Akt and ERK, suggesting that they contributed to malignant behavior. These novel *ALK* mutations were transfected into wild type *ALK* cells, and stimulated cell transformation and invasion as possible mechanism of malignancy.

This study looked at two exons in the tyrosine kinase domain of *ALK*, exon 23 and 25, based on their data in neuroblastomas. They did not sequence the entire *ALK* gene, which suggests the potential exists of discovering other oncogenic mutations within the gene of other patients with anaplastic thyroid cancer. Within just these two exons, the frequency of *ALK* mutations was 11%.

There is limited published experience of *ALK* inhibitors in anaplastic thyroid cancer. In one 71 year old patient with anaplastic thyroid cancer, *ALK* overexpression was seen [46]. Further analysis demonstrated the presence of a rearrangement and the patient was treated with the *ALK*-inhibitor crizotinib. This resulted in a dramatic response and reduction of the lung metastases by 90%.

The dramatic response of *ALK* inhibitors in the setting of *ALK* abnormalities suggests that this is a very promising target in anaplastic thyroid cancer, but requires further study.

The paucity of effective treatment options for patients with the disease prognosis of anaplastic thyroid cancer means there is an urgent need for any effective therapy. Though the biomarker may only have currently been detected in a small number of patients, the mutation rate may increase as the remainder of the *ALK* gene is sequenced. For even the small number of patients that harbor *ALK* mutations, any effective treatment is likely to make a major impact on their disease.

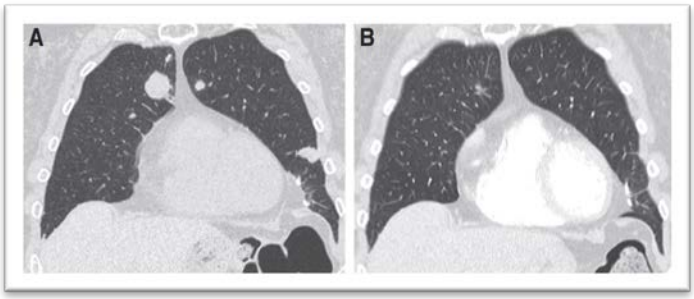
The presence of actionable mutations in ATC offers an option for treatment for these patients. This is consistent with the oncologic concept of targeting the driver mutation with rational therapy. Given the limited treatment options for ATC, targeting *ALK* mutations is a reasonable option for disease control. This trial will treat ATC patients with ceritinib, a 2nd generation ALK inhibitor. This drug is currently approved for use in non-small cell lung cancer.

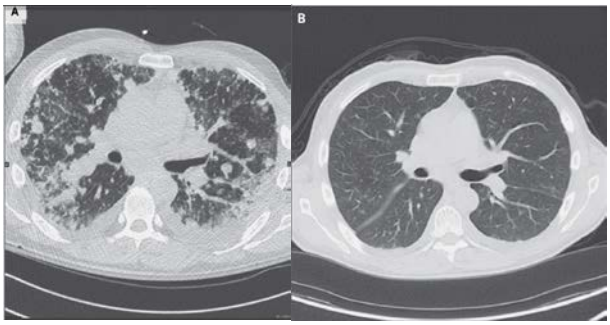
Study rationale and purpose

Mutations form the basis of targeted therapy in lung cancer. Although *ALK* rearrangements have only been identified with a frequency of 2-8%, *ALK* inhibitors have demonstrated a therapeutic advantage over traditional chemotherapy, yielding response rates of >60% in *ALK* positive non-small cell lung cancer [42, 43, 47]. The NCCN guidelines recommend crizotinib therapy as first line treatment for non-small cell lung cancer that demonstrates *ALK* gene rearrangement [48].

Although a small percentage of all lung cancer patients, the discovery of a biomarker predicting efficacy of a targeted agent has revolutionized therapy for those patients. Similarly, discovery of a biomarker predicting efficacy of a targeted agent in anaplastic thyroid cancer would also have a major impact, not least due to the very poor state of current therapy. The goal is to target the mutation driving the cancer.

Recently *ALK* rearrangements have also been identified in a patient with anaplastic thyroid cancer [46]. This patient with rearranged *ALK* was then treated with an *ALK* inhibitor and had a dramatic response to therapy. This suggests that ceritinib therapy may be a very effective therapeutic option for patients with *ALK* abnormalities, but this requires further study.





Therapy targeting molecular pathways in anaplastic thyroid cancer

Left: ALK-mutated ATC before and after ALK inhibitor Right: ATC with BRAF V600E before and after BRAF inhibitor

Even in the small number of exons sequenced in the *ALK* gene, mutations were found in 11% of patient samples [45]. By sequencing the entire tyrosine kinase domain additional mutations may be found. It is likely that any mutations in *ALK* in a cancer specimen are those that contribute to the malignant behavior rather than those mutations conferring resistance to ALK inhibitors. In addition, rearrangements are a common genetic mechanism for up regulating *ALK* expression in human tumors. Therefore FISH and IHC defined *ALK*-positive tumors will be included to accommodate other mechanisms leading to *ALK* positivity. Tumors that are positive for *ALK* rearrangement by FISH and IHC are sensitive to *ALK*-inhibitors.

Pre-clinical data suggest that mutations in the kinase domain are associated with increased malignant behavior. Applying an *ALK* inhibitor to these tumor samples may slow down their growth to the point that it would translate into a meaningful clinical outcome. Unfortunately patients with anaplastic thyroid cancer have very limited treatment options, so any response to a targeted agent is likely to have a profound clinical impact.

For these ATC/UTC patients with no good treatment options, this trial will test the role of ceritinib. This will be designed to determine the effectiveness of therapy in *ALK* mutated anaplastic thyroid cancer in anticipation of a larger trial if a promising signal is seen. Currently there is no effective chemotherapy for metastatic or locally recurrent anaplastic thyroid cancer.

This trial will also define the frequency of mutations in tyrosine kinase domain of *ALK*. In previously published reports it was 11% in two exons, 23 and 25. There are no published reports on the frequency of mutations in *ALK* in the entire tyrosine kinase domain. This will offer an opportunity for further therapy for these patients while we better understand the biology of this deadly disease.

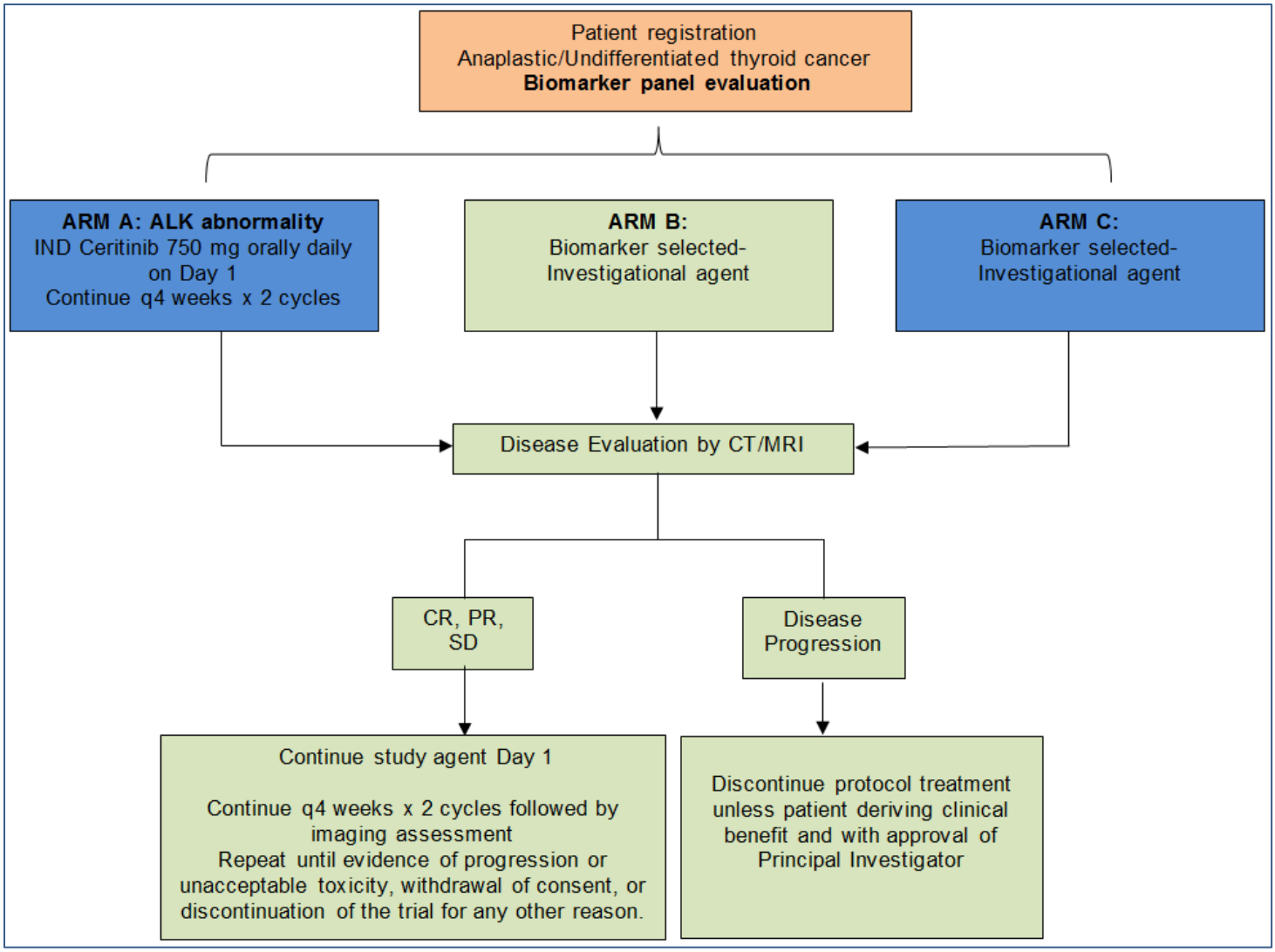
This trial will be open to all patients with pathologically confirmed diagnosis of Anaplastic Thyroid Cancer. Due to the extremely rare nature of this disease, it is often a difficult diagnosis for pathologists to make, and requires extra time. In many cases the diagnosis is delayed and may be listed as poorly differentiated or undifferentiated thyroid cancer. As a result, these cases are actually anaplastic thyroid cancer that has yet to be diagnosed. These patients will be considered eligible for the screening portion

of the trial. If they are subsequently found to have mutations in the *ALK* gene, they will be eligible for the therapeutic portion of the trial if they meet eligibility criteria.

Trial design:

Screening: An estimated 100 anaplastic thyroid cancer or undifferentiated thyroid cancer specimens will have had biomarker analysis performed as part of standard of care at their institutions.

ARM A: analysis of the ALK gene by sequencing/IHC/FISH will be performed.
ARM B and ARM C: will be added as new biomarker-drug combinations are identified.



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