

THYROID CANCER

Ann W. Gramza, MD
NIH/NCI Medical Oncology Branch
Thyroid Oncology Program

Objectives

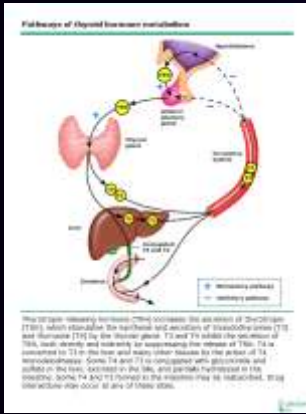
- Understand thyroid cancer types
- Understand thyroid cancer epidemiology and risk factors
- Understand thyroid cancer presentation
- Understand thyroid cancer staging
- Understand thyroid cancer treatment

Thyroid Anatomy and Physiology

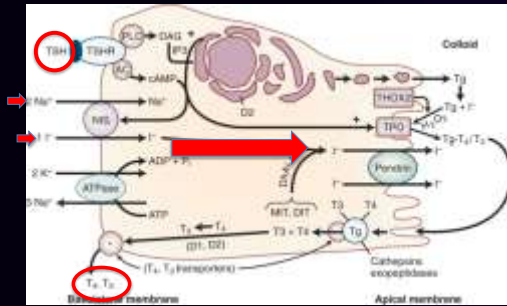


Thyroid function:

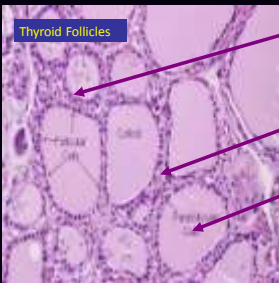
- Thyroid critical for brain and somatic development
- Affects nearly all organs
- Regulates metabolism
- Calcium and phosphorus homeostasis



Thyroid Follicular Cell



Thyroid Histology



Follicular Cells: stimulated by TSH to convert thyroglobulin to T4

Parafollicular (C) cells: synthesize calcitonin

Colloid: storage material for thyroglobulin

Thyroid Malignancies

- Cancers of Follicular Epithelial Cells**

Differentiated Thyroid Cancer

- Papillary Thyroid Carcinoma
- Follicular Thyroid Carcinoma
- Hurthle Cell Carcinoma

Poorly Differentiated Thyroid Cancer

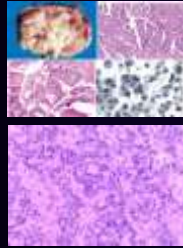
- Derived from Follicular or Papillary Thyroid Carcinomas?

Undifferentiated Thyroid Cancer

- Anaplastic Thyroid Carcinoma

- Cancer of Parafollicular (C) Cells**

Medullary Thyroid Carcinoma



Thyroid Malignancies

Tumor type	Prevalence	Age	Distant Metastases	Survival rate (5yr)
Papillary thyroid carcinoma	85-90%	20-50	5-7%	>90%
Follicular thyroid carcinoma	<10%	40-60	20%	>90%
Poorly differentiated thyroid carcinoma	Rare-7%	50-60	30-80%	50%
Undifferentiated thyroid carcinoma	2%	60-80	20-50%	1-17%
Medullary thyroid carcinoma	3%	30-60	15%	30-80%

Nature Reviews Apr 2006 p 292-306.

Thyroid Cancer Epidemiology

- Thyroid Cancer is the **most common endocrine malignancy**
 - **Papillary Thyroid Cancer** most common thyroid cancer
- age and gender adjusted incidence has increased faster than that of any other malignancy
 - 23,500 cases in 2005
 - 37,200 cases estimated in 2009
 - 48,020 cases estimated in 2011
- Prevalence is high and increasing
 - 2004: 366,000 men and women alive with history of thyroid cancer
 - 2008: 458,403



N S N N AM K 100 M N V L N A P W D W A M B F K Y C B A I J J N Z O H M A E M P L O R O H H G F
 EA C KA ES d BK AU SEER C S w R w 120 2008 H C M d n w MD A p g w 120 2008 B d
 N d 2010 SEER d B w P H d h SEER d h 2011

DIFFERENTIATED THYROID CANCER

(Papillary and Follicular)

Differentiated Thyroid Cancer (DTC) Epidemiology

- Gender: female: male 2.5:1
- Race: Caucasian: African Americans 2:1
- Median age at diagnosis for PTC:
 - Women: 40-41 years
 - Men: 44-45 years
- Median age at diagnosis for FTC:
 - Women: 48 years
 - Men: 53 years

Differentiated Thyroid Cancer (DTC) Risk Factors

- Radiation exposure
 - Survivors of atomic fall out
 - Children exposed to external beam radiation
 - Children living in Chernobyl (nuclear accident)
- Younger age at exposure: Higher risk
 - Controversial whether exposure after age 15 confers increased risk
 - Risk persists for 40 years



- Fukushima??
- After nuclear accident
 - Potassium iodide can protect thyroid from I 131
 - Give as soon as possible
 - Risk of hyper/hypothyroidism

Differentiated Thyroid Cancer (DTC) Risk Factors

- Genetic

Component of several inherited syndromes:

- Familial adenomatous polyposis, Gardner syndrome, Cowden disease, Turcot syndrome, Carney complex

Familial nonmedullary thyroid carcinoma"

- Appears to be low penetrance, heterogeneous
- Case control study (n=339)
10 fold increased risk of thyroid cancer in relatives of thyroid cancer patients
- Swedish retrospective analysis (n=1953 cases)

Familial risk:

- 3.2 when a parent is diagnosed
- 6.2 when a sibling is diagnosed
- 11.2 if a female has a sister diagnosed

Pa T; J C n Endocr nol Metab 2001
Hemm nk K; J C n Endocr nol Metab 2005

Prognosis of Differentiated Thyroid Cancer

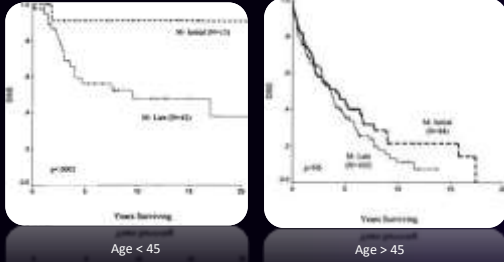
- One of the least morbid solid tumors
- Regional lymph node metastasis
 - < 45 No effect on overall survival
 - > 45 increased risk of death by 46%
- 2/3 of patients have local disease at dx
- 33 61% of patients with PTC have clinically apparent cervical lymph node involvement at dx
- 1 2% PTC have distant mets at dx
- 2 11% FTC have distant mets at dx
- Distant mets at dx: 43-90% of patients will die of thyroid cancer

TNM Stage and Prognosis

Stage	Recurrence (%)	Death (%)
I	15.4	1.7
II	22	15.8
III	46.4	30
IV	66.7	60.9

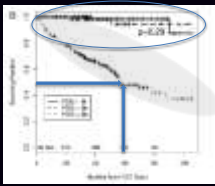
N 700 (PTC=620, FTC=80)
Median follow up duration = 10.6 yrs
Loh et al JCEM 1997

Age and Prognosis in Metastatic Differentiated Thyroid Cancer

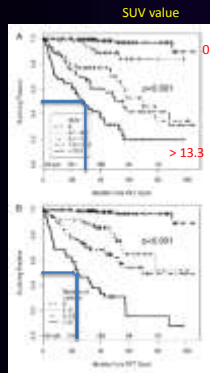


Shoup, et al. JCAS 2003

PET and Prognosis



SUV and number of PET avid lesions influences prognosis in differentiated thyroid cancer



Robbins et al. JCEM Feb 2006 91 (2) 498-505

Diagnosis

- FNA is standard diagnostic procedure when a thyroid nodule is found
- Most thyroid nodules are benign

5-10% chance of malignancy

Higher rate of cancer in:

- Men
- Age < 20 or > 70
- History of childhood neck radiation:
 - 33-37% chance malignancy
- Enlarging nodule
- Fixed nodule/vocal cord paralysis
- h/o Graves disease
- Familial h/o PTC, MTC, MEN 2



Up to 90% of women > 70 and up to 60% men > 80 have nodular goiter

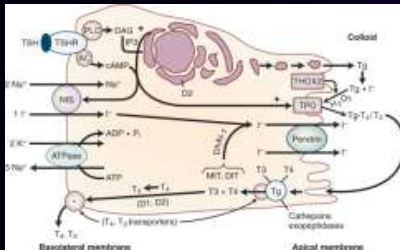
Surgical Resection



Postoperative Radioiodine

- Recommended for nearly all patients who get a total or near total thyroidectomy in the USA
 - Stages III and IV disease
 - All Stage II disease if < 45 yo, most if > 45
 - Selected patients with stage I disease
 - Multifocal disease
 - Nodal mets
 - Extra thyroidal or vascular invasion
 - More aggressive histologies

Thyroid Follicular Cell



Postoperative treatment and surveillance are based on differentiated thyroid cancer maintaining characteristics of normal thyroid follicular cells

Postoperative Radioiodine

- Goals:

Eliminate post surgical thyroid remnant

- Decrease local recurrence
- Facilitate long term surveillance with RAI (radioiodine) scans and/or stimulated thyroglobulin measurements

Destroy micrometastatic disease



- No prospective studies have been done to determine which patients benefit
- Requires TSH stimulation
 - Can be done by stopping thyroid hormone replacement and allowing endogenous TSH levels to rise
 - For low risk patients, can give rTSH (thyrotropin)

TSH Suppression Therapy

- Differentiated thyroid cancer cells express the thyrotropin receptor on the cell membrane

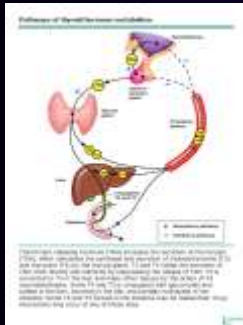
Responds to TSH stimulation

- Increases rates of cell growth

- Use suprathreshold doses of LT4
 - TSH suppression to < 0.1mU/L may improve outcomes in high risk patients
 - TSH 0.1-0.5 is appropriate for low risk patients

- Adverse effects of TSH suppression subclinical thyrotoxicosis:

Exacerbation of angina, increased risk of atrial fibrillation, increased risk of osteoporosis in post menopausal women



Management of Recurrent Disease

- Surgical resection if neck disease +/- post op TSH stimulated Tg, DxWBS, and RAI therapy
- If more extensive disease:
 - Radioiodine if uptake on WBS
 - NOTE: IV contrast SHOULD NOT BE GIVEN for CT scans if RAI is still a potential option
 - Treatment of choice, can result in CR
 - Young patients, small pulmonary nodules
 - External beam radiotherapy
 - Systemic chemotherapy?



RAI-Refractory Thyroid Cancer

- PET avidity is inversely proportional to RAI uptake
- 25-50% metastatic thyroid cancers lose iodine concentrating ability
- Standard chemotherapy has disappointing response rates, significant toxicity

Doxorubicin is only FDA approved therapy

PFS 2 months

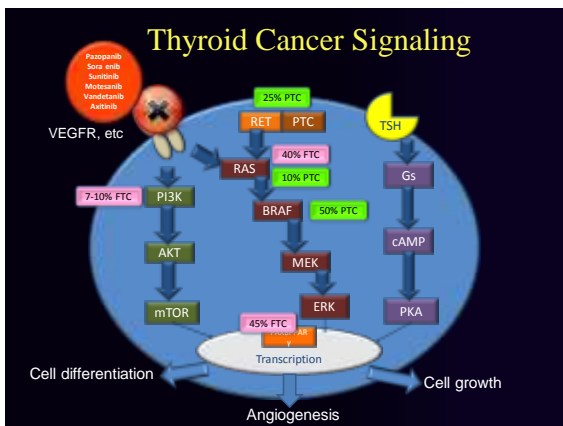
OS 8 months

Shimaoka, et al. Cancer 56, 1985

Systemic Chemotherapy in Advanced Thyroid Cancer

Study	Subtype (N)	ORR	OS
Doxorubicin (Gottlieb and Hill. 1974 NEJM 290(4): 193-197)	Differentiated (15) Medullary (5) Anaplastic (9)	37%	4-11 months
Doxorubicin vs. Doxorubicin + Cisplatin (Shimaoka et al, 1985 Cancer 56 (9): 2155-60)	Differentiated (35) Medullary (10) Anaplastic (39)	17 vs. 26%	5 vs. 7 months
Doxorubicin + Cisplatin (Williams et al, 1986 Can Treat Rep 70(3): 405)	Differentiated (7) Medullary (6) Anaplastic (7)	9.1%	11.8 months
Doxorubicin + Cisplatin + Bleomycin (De Besi, et al, 1991 J Endo Invest 14: 475-480)	Differentiated (8) Medullary (9) Anaplastic (5)	42%	11 months

Thyroid Cancer Signaling

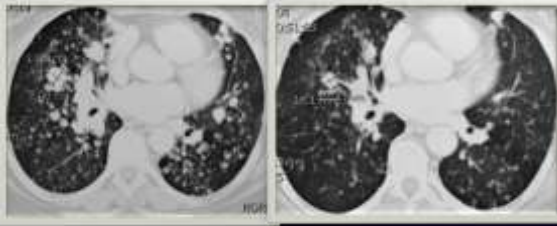


Efficacy of pazopanib in progressive, radioiodine-refractory, metastatic differentiated thyroid cancers: results of a phase 2 consortium study

Wang J, et al. J Clin Oncol. 2011;29:1511-1517. doi:10.1200/JCO.2010.34.2000. Epub 2011/05/11. PMID: 21540000

RECIST RESPONSE	N= 37	Histologic subtype	N 37
Complete Response (CR)	0	Papillary	15
Partial Response (PR)	18 (49%)	Follicular	11
Papillary	5 (33%)	Hurthle Cell	11
Follicular	8 (73%)		
Hurthle Cell	5 (45%)		
Stable Disease (SD)	3 (43%)		
Progression	1 (14%)		

DC after 12 weeks of sorafenib



5/08 CT

10/08 CT

NCCN Recommendation for Advanced/Metastatic DTC

for clinically progressive or symptomatic disease: clinical trials for non radioiodine responsive tumors: consider small molecule kinase inhibitors (such as sorafenib, sunitinib, or pazopanib) or systemic therapy

ANAPLASTIC THYROID CANCER

Anaplastic Thyroid Cancer

- **Rare**
incidence: 1-2 cases/million annually
2-5% of all thyroid cancer
(600-1000 patients in US/year)
- **Aggressive**
Median survival 3-6 months
90% with regional/distant metastases at diagnosis
- **Lethal**
Nearly 100% disease specific mortality
Papillary thyroid cancer has \leq 10% disease specific mortality



Clinical Presentation

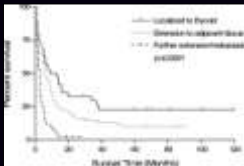
- **Patient characteristics:**
Median age: 65
60-70% occur in women
20% of patients have history of differentiated thyroid cancer (DTC)
20-30% have concurrent DTC
- **Symptoms**
Related to neck mass in most patients
 - Pain, compression of airway, dyspnea, dysphagia, hoarseness, cough
 Constitutional symptoms can occur
- **Diagnosis**
FNA or core biopsy
Imaging studies
 - CT of neck and chest

Prognosis

- good prognostic factors
 - Disease confined to the thyroid
 - Local or regional metastases (rather than distant)
 - Tumor size < 6 cm
- bad prognostic factors
 - Male
 - Older age
 - Dyspnea
 - Tumor > 6 cm
 - Distant mets at diagnosis

Pichardo Lowden, et al. *Thyroid* 2009; 19:775-778
 Kebebew, et al. *Cancer* 2005;103:1330-1335

Survival by Extent of Disease



- Retrospective review
- SEER Database (1983-2002)
- 261 patients
- included those eligible for surgical resection who lived at least one month (omitted 203 patients)

Extent	Median Survival	2 year Survival %	5 year Survival %
Confined to thyroid	9 months	33	23
Local extension	6 months	16	10
Distant mets	3 months	2	---

Chen, et al. *Am J Clin Oncol* 2008; 31:460-464

Goals of Therapy

- Quality of life
- Symptom management
- End of life care
- Prevent asphyxiation?
 - death most often caused by airway compromise (50-60%)
- No therapy has been shown to clearly improve overall survival
 - No randomized trials
 - Selection bias



Anaplastic Thyroid Cancer Treatment

- Surgery: ONLY if tumor appears localized to the thyroid
 - Lobectomy with wide margins
 - Total thyroidectomy does not prolong survival and has higher complication rate
- Adjuvant therapy:
 - No data other than uncontrolled observation
 - Most will treat with concurrent chemoradiotherapy

Metastatic or Advanced ATC

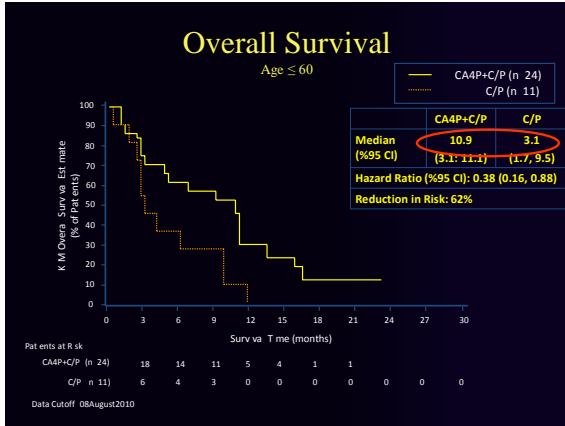
- No effective therapy, uniformly fatal
- Median survival: 3-7 months
- One year survival: 20-35%
- Five year survival: 5-14%
- Death most often due to airway compromise (50-60%)
- Chemotherapy and/or radiation do not prolong survival
- Patients should participate in clinical trials

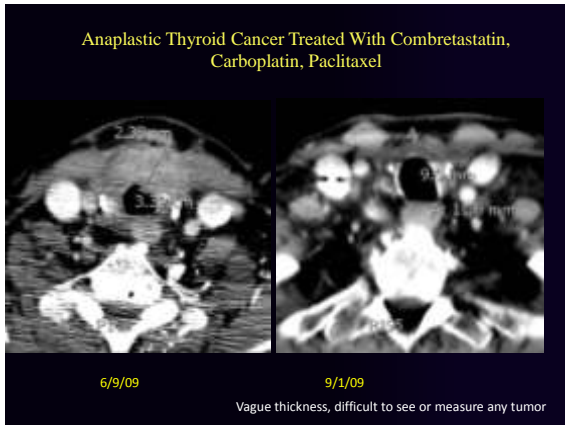


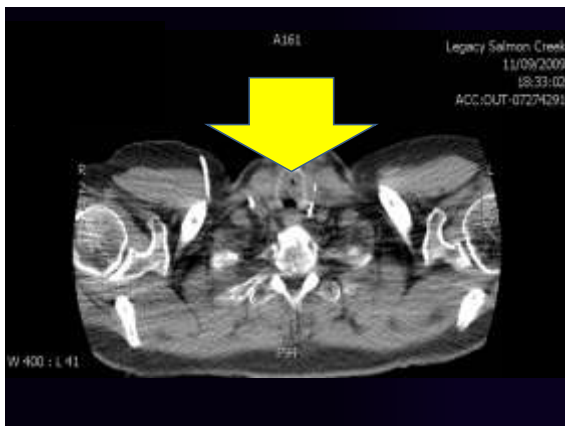
FACT Trial (Fosbretabulin + Carboplatin/Paclitaxel vs. Carboplatin/Paclitaxel Alone in ATC)

- Results reported September 2010
- Phase II/III Randomized Trial
- 80 patients
 - Largest ATC trial
 - First randomized trial
 - Combretastatin/Carbo/Taxol: 55 pts
 - Carbo/Taxol alone: 25 pts
- Improved OS with HR 0.71
- For patients < 60, OS 10.9 vs. 3.1 months with addition of combretastatin
- Larger trial is planned

	CA4P+C/P	C/P
Median (%95 CI)	5.1 (3.1, 9.2)	4.1 (2.8, 8.9)
Hazard Ratio (%95 CI): 0.71 (0.42, 1.22)		
Reduction in Risk: 29%		
6 month survival	48%	37%
1 year survival	23%	9%







MEDULLARY THYROID CANCER

Medullary Thyroid Cancer

- Neuroendocrine tumor of the parafollicular (C cells)
- Produce calcitonin
- 80% are sporadic
- 20% are familial: MEN type 2 syndromes
- Sporadic MTC presents 50s 60s
- Familial MTC (MEN2) presents younger (30s)
 - Children with MEN 2B undergo thyroidectomies in infancy
 - Children with MEN 2A undergo thyroidectomies by ages 5 or 6

Medullary Thyroid Cancer

- Clinical presentation:
 - Thyroid nodule
 - 50% have cervical lymph node involvement
 - 15% have symptoms dysphagia, hoarseness
 - 5% have distant metastases
- Systemic symptoms:
 - Secretes calcitonin: diarrhea, facial flushing
 - Can secrete corticotrophin (ACTH): Cushing s syndrome

Inherited MTC Autosomal Dominant Syndromes

MEN 2A	MEN 2B	FMTC (Familial Medullary Thyroid Cancer)
MTC (100%)	MTC (100%)	MTC
pheochromocytoma	pheochromocytoma	
Primary parathyroid hyperplasia (hyperparathyroidism)	Mucosal neuromas	
RET C634A	RET M918T	RET exon 11



Did he have a pheochromocytoma when assassinated?
 thinner, he fainted while getting up quickly from a chair, he had periodic severe headaches and cold hands and feet.

Did 2 of his sons, Willie and Tad, also have MEN 2B?
 Photographs of them show somewhat irregular lips.
 Willie died at 11, probably of typhoid fever
 Tad at 18, reportedly of tuberculosis
 His mother died at 34

Doubtful...he had already lived to 56

Inherited MTC

- Kindred can be screened for medullary thyroid cancer with calcitonin levels
 Screening of MEN 2A families found 80% of cases most had no thyroid abnormalities on exam
- Kindred are now screened for point mutations in the RET proto oncogene
 Allows for earlier diagnosis and prophylactic thyroidectomies

Clinical Evaluation

- CTs of neck, chest, abdomen, pelvis
- Bone scan
- PET/CT imaging controversial can often miss metastases
- Serum calcium level
- 24 hour excretion of metanephrines, norepinephrine, and epinephrine
- RET mutation
- Calcitonin level

Prognosis

- Postoperative calcitonin doubling time:
 - < 6 months: 10 yr survival 8%
 - 6-24 months: 10 yr survival 37%
 - > 2 yrs: 10 yr survival 100%
- Age at diagnosis:
 - < 40: 10 yr survival 65%
 - > 40: 10 yr survival 50%
- RET M918T mutation

Treatment of Medullary Thyroid Cancer

- Cured only by complete resection of tumor and lymph node mets
- Total thyroidectomy
 - Up to 30% have bilateral or multifocal disease
- Start thyroxine (T4) immediately post op
 - Maintain euthyroid state
 - C cells are not TSH responsive
 - No role for radioiodine
- Measure serum calcitonin and CEA 6 months after surgery
 - Detect residual disease
 - If undetectable, 5% 5 yr recurrence rate

Residual/Recurrent MTC

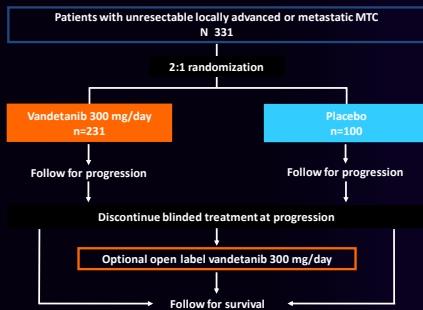
- Surgical resection
- Radiation?
 - No prospective data
 - May prolong disease progression interval
- Chemotherapy
 - Not effective
- Clinical trials with targeted agents
- Vandetanib approved for advanced, progressive or symptomatic disease on 4/6/11

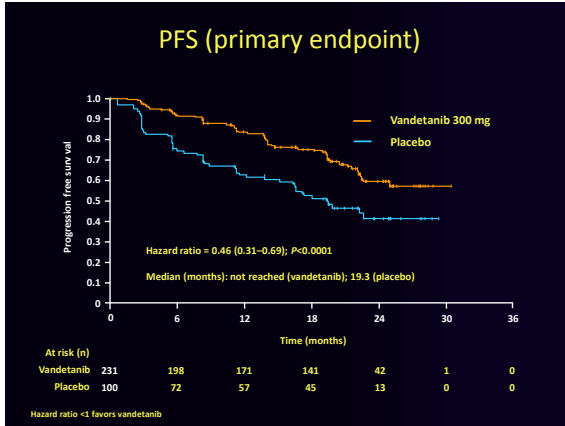
Vandetanib in locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind Phase III trial (ZETA)

SA Wells,¹ BG Robinson,² RF Gagel,³ H Dralle,⁴
 JA Fagin,⁵ M Santoro,⁶ E Baudin,⁷ J Vasselli,⁸
 J Read⁹ and M Schlumberger⁷

¹Medical Oncology Branch, National Cancer Institute, NIH, Bethesda, MD
²Kolling Institute of Medical Research, University of Sydney, Australia
³University of Texas MD Anderson Cancer Center, Houston, TX
⁴Martin Luther University Halle-Wittenberg, Halle, Germany
⁵Memorial Sloan-Kettering Cancer Center, New York
⁶Universita' di Napoli Federico II, Naples, Italy
⁷Institut Gustave Roussy, Villejuif, France
⁸AstraZeneca, Wilmington, DE
⁹AstraZeneca, Macclesfield, UK

Study design





Objective tumor assessments

	Vandetanib 300 mg (n=231)	Placebo (n=100)
ITT analysis*		
Objective response rate	45% (104)	13% (13)
Odds ratio (95% CI)	5.48 (2.99-10.79), P<0.0001	
Excluding open-label scans		
Objective response rate	44% (101)	1% (1)
Odds ratio (95% CI)	76.91 (16.68-1366), P<0.0001	

- 24 patients randomized to placebo received open-label therapy before progression according to central read
 - 12 (50%) had an objective tumor response
- Objective responses were durable; median duration of response not reached at 24 months of follow-up

Odds ratio >1 favors vandetanib
* according to central read

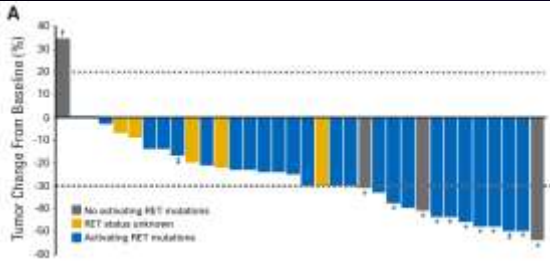
Phase I study of XL184

RECIST RESPONSE	N=35
Complete Response	0
Partial Response	10 (29%)
Stable Disease (≥ 6 months)	15 (41%)
Progressive Disease	

Median response duration not yet reached

Kurzrock, et al. JCO 29 (19): 2660-6

Phase I Study of XL184



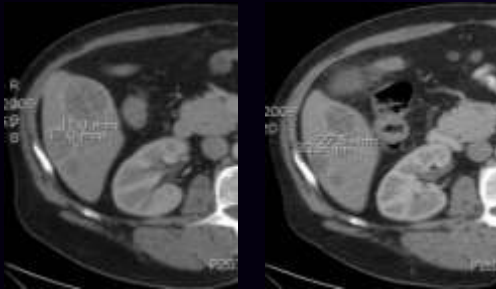
Kurzrock, et al. JCO 29 (19): 2660-6

Sorafenib in MTC

Response	Hereditary N=3 (%)	Sporadic N=16 (%)
Partial Response	1 (33)	1 (6)
Stable Disease	2 (67)	14 (87)
> 20-29% decrease	0	2
>10-20% decrease	1	7
>0-10% decrease	1	5
Stable Disease > 6 months	1 (33)	10 (62)
Median Duration Stable Disease months	5 (4-6+)	12 (2-22+)
Progressive Disease	0	1 (6)

AACR 2009 Abs 4513

AEE After 6 Weeks of Sorafenib



8/25/09

11/04/09

NCI Clinical Trials in Advanced Thyroid Cancer

STATUS	MALIGNANCY	TITLE
OPEN	Medullary Thyroid Cancer	A Targeted Phase I/II trial of ZD6474 (Vandetanib;ZACTIMA)plus the proteasome inhibitor, Bortezomib (Velcade), in advance or metastatic Medullary Thyroid Cancer (MTC)
OPEN	Anaplastic Thyroid Cancer	Phase 1/ 2 Trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)

Phase I/II trial of ZD6474 (Vandetanib;ZACTIMA) plus the Bortezomib (Velcade), in MTC

- Phase I
 - Study Design:
 - assess the safety, efficacy and toxicity of daily oral vandetanib and Bortezomib on days 1, 4, 8 and 11 every 21 days in MTC.
 - Eligibility for phase I:
 - diagnosis of recurrent, metastatic or primary unresectable solid tumor that does not have curative standard treatment.
- Phase II:
 - Study Design:
 - Compare the activity of the combination of bortezomib plus vandetanib or vandetanib alone using a 2:1 randomization
 - Eligibility for phase II:
 - Previously untreated recurrent or metastatic medullary thyroid cancer

COMPLETE

Phase I/II trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)

- Crolibulin (EPC2407):
- microtubule inhibitor that has been shown to have direct antitumor effects in vivo and in vitro
 - disruption of endothelial cells with disruption of blood flow to the tumor

Phase I/II trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)

Phase I Eligibility:

- Adults ≥ 18 with diagnosis of recurrent, metastatic or primary unresectable solid tumor that does not have curative standard treatment.

Phase II Eligibility:

- Adults ≥ 18 with a diagnosis of recurrent, metastatic or primary unresectable ATC

Phase I/II trial of EPC2407 (Crolibulin) plus Cisplatin in Adults with Solid Tumors with a Focus on Anaplastic Thyroid Cancer (ATC)

Phase I Study Design:

- Dose escalation of Cisplatin Day 1 + Crolibulin Days 1,2,3 q 21 days

Phase II Study Design:

- Randomization 2:1 of patients receiving MTD of Cisplatin/Crolibulin vs. Cisplatin alone.

QUESTIONS?

