

Thymic Malignancies: From Clinical Management to Targeted Therapies

Ronan J. Kelly, Iacopo Petrini, Arun Rajan, Yisong Wang, and Giuseppe Giaccone

All authors: National Cancer Institute, National Institutes of Health, Bethesda, MD.

Submitted March 17, 2011; accepted August 3, 2011; published online ahead of print at www.jco.org on November 21, 2011.

Supported by the National Cancer Institute (NCI), National Institutes of Health (NIH) and by the NIH Intramural Research Program, Center for Cancer Research, NCI.

The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services nor does mention of trade names, commercial products, or organization imply endorsement by the US Government.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Giuseppe Giaccone, MD, PhD, National Cancer Institute, 10 Center Dr, Room 12N226, Bethesda, MD 20892-1457; e-mail: giaccone@mail.nih.gov.

© 2011 by American Society of Clinical Oncology

0732-183X/11/2936-4820/\$20.00

DOI: 10.1200/JCO.2011.36.0487

ABSTRACT

Purpose

A key challenge in the treatment of thymoma and thymic carcinoma (TC) is in improving our understanding of the molecular biology of these relatively rare tumors. In recent years, significant efforts have been made to dissect the molecular pathways involved in their carcinogenesis. Here we discuss the results of large-scale genomic analyses conducted to date and review the most active chemotherapies and targeted treatments.

Methods

We reviewed the literature for chemotherapeutic trials in the last 20 years and trials involving targeted therapies between 1999 and 2010. The search was supplemented by a review of abstracts presented at the annual meetings of the American Society of Clinical Oncology (from 1999 to 2010), at the first International Conference on Thymic Malignancies in 2009, and at a follow-up meeting of the newly formed International Thymic Malignancies Interest Group in 2010.

Results

Surgery remains the treatment of choice for operable tumors, whereas chemotherapy is standard in locally advanced and metastatic disease. Thus far, targeted therapies have been developed empirically. Histone deacetylase inhibitors have shown some activity in thymoma whereas sunitinib may be active in TC. There are no data to support the use of HER2- or EGFR-targeted therapies in thymic malignancies.

Conclusion

Drug development for the treatment of thymic malignancies is difficult because of the rarity of these tumors. Ethnic differences are becoming apparent, with aggressive subtypes being observed in Asians and African Americans. Incremental improvements in our understanding of tumor biology suggest that molecular profiling-directed therapies may be the preferred route of investigation in the future.

J Clin Oncol 29:4820-4827. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Thymic epithelial tumors (TETs) are divided into two broad categories: thymomas and thymic carcinomas (TCs). As the site of maturation for T cells, the thymus plays a central role in adaptive immunity. A wide spectrum of autoimmune disorders, including myasthenia gravis (30%), are seen in patients with thymomas, whereas patients with TC rarely if ever have autoantibody-induced phenomena.¹ The risk of second malignancies, in particular, non-Hodgkin's lymphoma, and a possible protective effect in the presence of myasthenia gravis suggests inherent immune differences among patients with regard to immune surveillance and autoimmunity.²⁻⁴ Surgical resection forms the cornerstone of therapy for early-stage tumors, and approximately 90% of patients with encapsulated thymomas are cured

with complete surgical extirpation of disease.⁵ In advanced or recurrent TETs, a multimodality approach incorporating surgery, radiation, and chemotherapy is required. The rarity of this tumor has precluded it from large phase II and III clinical trial investigations, and new drugs have been slow in development. In the last decade, several targeted agents have been investigated with varying success rates. The cause of thymoma remains unknown; however, our understanding of the aberrant pathways involved is improving. Herein, we summarize the molecular biology of thymic malignancies that defines molecular subsets with potential clinical and therapeutic relevance. We highlight the most important new trends in the treatment of these tumors with respect to current standard-of-care chemotherapeutic regimens and discuss ongoing research involving targeted therapies.

Table 1. Masaoka Staging of Thymic Malignancies¹¹ With Modifications by Koga et al¹² and WHO Classification of Thymic Malignancies¹³

Stage/Type	Definition
Stage	
I	Grossly and microscopically completely encapsulated
II (a)	Microscopic transcapsular invasion
II (b)	Macroscopic invasion into thymic or surrounding fatty tissue or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion of neighboring organs (ie, pericardium, great vessel, or lung)
IV (a)	Pleural or pericardial dissemination
IV (b)	Lymphatic or hematogenous metastasis
Histologic type	Description
A	Neoplastic oval or spindle cells; no atypia; no lymphocytes
AB	Type A with foci of lymphocytes
B1	Plump epithelioid cells resembling normal thymic medulla
B2	Scattered foci of atypical epithelial cells with lymphocytes
B3	Round or polygonal epithelial cells with mild atypia with minor component of lymphocytes
Thymic carcinoma (C)	Histologic subtyping required

meeting of the newly formed International Thymic Malignancies Interest Group (ITMIG) in 2010 in New York were reviewed.

Incidence and Epidemiology

Although thymic malignancies are relatively rare (0.2% to 1.5% of all malignancies or 0.13 per 100,000 person-years in the United States⁶), they are among the most common mediastinal primary tumors with up to 50% of anterior mediastinal masses proving to be of thymic descent.⁷ Males have a slightly higher risk of developing thymomas than females, and the risk rises with age, reaching a peak in the seventh decade of life, which is in direct contrast to the progressive involution of the thymus with age.² Data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program collected for Hispanic and Asian/Pacific Islander subgroups have been available only since 1992 and 1998, respectively. Thymoma incidence in the United States is higher in African Americans and especially Asian/Pacific Islanders than among whites or Hispanics. Furthermore, thymoma arises at a younger age among African Americans than among whites (median age at diagnosis, 48 v 58 years; SEER data). Similarly, myasthenia gravis may be more common in African Americans than in whites.⁸ Compared with controls, patients with thymoma are more likely to have an autoimmune disease at some point during their lives (32.7% v 2.4%; *P* < .001), most frequently myasthenia gravis (24.5%), systemic lupus erythematosus (2.4%), or red cell aplasia (1.2%).⁹ Ethnic variations in terms of higher incidence rates and younger age at diagnosis suggest a role for genetic factors. The distribution of alleles at the HLA locus on chromosome 6 varies markedly across racial groups.² Both class I and class II HLA proteins are highly expressed on thymic epithelial cells.¹⁰ Further research is needed to understand whether particular genetic variants (at HLA or other loci) predispose to thymoma.

Staging and Histology

The Masaoka staging (Table 1) focuses on the integrity of the thymic capsule, the presence of micro or macroscopic invasion into adjacent structures, and metastatic spread.¹¹ The WHO histologic classification¹³ focuses on thymic epithelial cell morphology (spindle or epithelioid), the degree of the lymphocytic component, and the presence or absence of epithelial atypia (Table 1). Epithelial morphology corresponds to medullary or cortical differentiation. The classification reports a continuum of tumors from type A, AB, B1, B2, B3, and thymic carcinomas. Thymic epithelial neoplasms have been the subject of much controversy over the years because of difficulties in predicting prognosis and behavior. As a result of the complexity of these tumors, several attempts at classification have been presented in the literature. Moran

METHODS

Information for this review was derived from searching the PubMed database for all significant chemotherapeutic clinical trials that have occurred in the last 20 years and trials in the last decade that involve targeted agents. Our search limits included thymic malignancies and clinical trials. The search was supplemented by a review of abstracts presented at the American Society of Clinical Oncology (ASCO) annual meetings from 1999 to 2010. In addition, all abstracts presented at the first International Conference on Thymic Malignancies (held in 2009 at the National Institutes of Health) and a follow-up

Table 2. Molecular Abnormalities in Thymic Malignancies

Oncogene/Molecular Change	Thymoma (%)	Thymic Carcinoma (%)	Reference
<i>EGFR</i>			
Gene amplification (FISH)	20	25	Lonescu et al ¹⁸
Overexpression (IHC)	23	67-100	Suzuki et al, ¹⁹ Henley et al, ²⁰ Hayashi et al ²¹
<i>HER2</i>			
Overexpression (IHC)	6	53	Pan et al ²²
<i>c-KIT</i> (CD117)			
Overexpression (IHC)	< 5	73-86	Nakagawa et al, ²³ Pan et al ²⁴
<i>BCL2</i>			
Overexpression (IHC)	14	100	Pan et al ²²
Tumor suppressor genes			
<i>TP53</i>			
LOH	0	38	Penzel et al ²⁵
Mutation	0	11-30	Tateyama et al, ²⁶ Chen et al, ²⁷ Pich et al, ²⁸ Weirich et al ²⁹
Overexpression (IHC)	12-100	80-100	Tateyama et al, ²⁶ Weirich et al, ²⁹ Hirabayashi et al ³⁰
<i>P16INK4A</i>			
LOH	0	25	Penzel et al ²⁵
Loss of expression	40-50	70	Hirabayashi et al ³⁰

Abbreviations: FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; LOH, loss of heterozygosity.

Table 3. Major Prospective Chemotherapy Trials in Extensive-Stage Inoperable Thymoma

Reference	Regimen	Stage	No. of Patients	CR + PR (%)	Median Survival (years)
Anthracycline-containing regimens					
Loehrer et al ⁵⁷	Cisplatin, doxorubicin, cyclophosphamide	IV	30	50	3.2
Fornasiero et al ⁵⁸	Doxorubicin, cisplatin, vincristine and cyclophosphamide	III/IV	32	90	1.25
Non-anthracycline-containing regimens					
Giaccone et al ⁵⁹	Cisplatin and etoposide	IV	16	56	4.3
Highley et al ⁶⁰	Ifosfamide	III/IV	13	46	N/R
Loehrer et al ⁶¹	Etoposide, ifosfamide, cisplatin	IV	28	32	2.5
Grassin et al ⁶²	Etoposide, ifosfamide, cisplatin	IV	16	25	N/R
Lemma et al ⁶³	Carboplatin, paclitaxel	IV	44	35	N/R
Loehrer et al ^{64,65}	Pemetrexed	IV	23	17	2.4

Abbreviations: CR, complete response; N/R, not recorded; PR, partial response.

and Suster¹⁴ examined more than 600 thymoma cases to determine morphologic heterogeneity. They concluded that proper evaluation of histology and aggressive potential in thymoma should be based on ample sampling (cutoff number of five sections is required) and assessment of capsular integrity.

Although tumor stage is the single most important prognostic factor in thymoma, a combination of stage and histologic subtype should be considered in predicting survival. Types A, AB, and B1 have an excellent overall survival rate of more than 90% to 95% at 10 years.¹⁵ Five-year survival for types B2, B3, and C are 75%, 70%, and 48%, respectively.¹⁶ TCs account for less than 1% of thymic malignancies and have a different molecular and clinical profile when compared with thymoma¹⁷ (Table 2). A variety of histopathologic subtypes of TC—some being more aggressive than others—have been reported, including squamous cell, lymphoepithelioma-like, sarcomatoid, clear-cell, basaloid, mucoepidermoid, papillary, and undifferentiated carcinoma. Thymomas rarely metastasize, whereas TCs display a more aggressive phenotype, with distant metastases in liver, lymph nodes, and bones.

Molecular Biology

The molecular biology of thymic malignancies is poorly understood because of the availability of only a few cell lines, the rarity of the disease, and the lack of specific preclinical animal models. A multistep accumulation of genetic and epigenetic aberrations in thymic epithelial cells is thought to drive neoplastic transformation. Cytogenetic studies¹⁶ have revealed chromosomal abnormalities in all histologic subtypes, including t(15;19) translocations and 6p22-p25 deletions, which are the only recurrent abnormalities found in TETs. The t(15;19)(q13;p13.1) translocation generates the fusion gene *BRD4-NUT*, which has been described in a rare subtype of undifferentiated thymic carcinomas.¹³ A relatively large body of data exists from comparative genomic hybridization (CGH)^{31,32} and microsatellite/loss of heterozygosity studies.^{33,34} The most frequent genetic alterations identified across the spectrum of thymomas occur on chromosome 6p21.3 (major histocompatibility complex locus) and 6q25.2 to 25.3.^{31,33,35} Interestingly, the identification of 6q25 as a common genetic alteration across all histologic subtypes suggests the presence

of an as yet undefined tumor suppressor gene which may be absent in the more aggressive phenotypes. In TC, CGH has demonstrated frequent copy number gains of 1q, 17q, and 18 and loss of 3p, 6, 16q, and 17p.^{31,32} Although TCs are a distinct entity in the WHO classification scheme, they do share some similarities with type B3 thymoma, most notably gain of 1q and loss of chromosome 6.³¹ The frequency, extent, and number of genomic aberrations increases from type A thymoma to TC.³²

Transgenic mice expressing SV40 large T-antigen and small t-antigen under L-pyruvate kinase promoter develop TETs,³⁶ suggesting the importance of *RB* and p53 during TET development. Variable expression of p53 has been reported in TETs^{21,22,26-30,37-44} with p53 being more frequently expressed in invasive thymomas and TCs. p53 expression is a poor prognostic marker in TETs,^{28,29,39,40} and inactivating mutations have been described with variable frequency.^{26,29,30,32,38,41} Both *RB* and P16INK4 have been implicated in TET; P16INK4, through inhibition of CDK4 and CDK6, prevents *RB* phosphorylation leading to G1 → S block. Methylation of the P16INK4 promoter has been observed in 3% to 13% of TETs, which correlates with p16 downregulation albeit in a minority of cases.^{30,45} No P16INK4 mutations have been described in TETs to date, but deletion of the gene locus is related to invasive phenotypes in rat animal models⁴⁶ (Table 2).

Autoimmune Disease and the Autoimmune Regulator Gene

Failure to induce self-tolerance may be a key factor leading to the export of autoreactive T-cell clones that subsequently circulate systemically and lead to autoantibody development in the spleen, lymph nodes, and bone marrow.⁴⁷ Approximately 40% of patients with thymoma develop an autoimmune condition, half of which will be myasthenia gravis.⁴⁸ Autoimmune regulator gene (*AIRE*) is important for ectopic expression of peripheral self-antigen and, as such, it is critical for central thymic T-cell education and deletion of autoreactive clones.^{47,49} This regulatory role is achieved through the activation of nuclear transcription of ectopic tissue-specific autologous antigens in medullary epithelial cells and in their presentation to medullary thymocytes; peptide recognition by self-reactive thymocytes causes their negative selection.^{47,50} The molecular basis underlying the defective expression of *AIRE* in most thymomas is enigmatic; however, it has been identified as the gene responsible for autoimmune polyendocrinopathy syndrome type 1, candidiasis, and ectodermal dystrophy (APECED), a rare autosomal recessive disorder characterized by organ-specific autoimmunity affecting the parathyroid and adrenal glands.^{51,52} The *AIRE* gene is located on chromosome 21q22.3 and encodes a 58-kDa protein involved in nuclear transcription.⁵³ Defective expression of *AIRE* in thymoma may play a crucial role in the pathogenesis of autoimmune diseases by favoring the development of self-reactive T-cell clones within the thymus leading to the export of a CD4+ progeny without tolerogenic myoid cells that are actively autoimmunized against autoantigens (eg, acetylcholine receptors). High rates of autoantibodies to cytokines have been described in patients with thymic malignancies. A luciferase immunoprecipitation system panel for autoantibodies against 39 different cytokines⁵⁴ showed a statistically increased but highly heterogeneous immunoreactivity against 16 of the 39

Table 4. Targeted Therapies in Thymic Malignancies

Reference	Drug	No. of Patients	Thymoma	Thymic Carcinoma	RR	SD	PD
Kurup et al ⁶³	Gefitinib	26	19	7	1	14	—
Bedano et al ⁷⁰	Erlotinib + bevacizumab	18	11	7	0	11	7
Giaccone et al ⁷¹	Imatinib	7	2	5	0	2	5
Salter et al ⁷²	Imatinib	11	0	11	0	3	4
Giaccone et al ⁷³	Belinostat	41	25	16	2	25	13

Abbreviations: PD, progressive disease; RR, response rate; SD, stable disease.

cytokines in patients with thymoma. The suggestion that *AIRE* expression may be altered in thymic tumors provides a fascinating link between autoimmunity and malignancy, as demonstrated by patients with thymomas.

Chemotherapy

Chemotherapy is offered to patients with advanced thymomas (stages III to IV) on the basis of evidence from small phase II studies in either the neoadjuvant or refractory/recurrent disease setting. No validated biomarkers exist to predict response to chemotherapy.^{55,56} Here we discuss treatment options for patients with inoperable refractory or recurrent disease.

Platinum-based combinations. Cisplatin-based chemotherapy remains the standard of care (Table 3). In the early 1990s, the ADOC regimen (doxorubicin, cisplatin, vincristine and cyclophosphamide) was tested in first-line treatment with an overall response rate (ORR) of 92% and a median survival (MS) of 15 months.⁵⁸ An intergroup trial⁵⁷ investigated a three-drug combination—cisplatin, doxorubicin and cyclophosphamide (PAC)—with an ORR of 50% and an MS of 38 months. Another three-drug regimen consists of cisplatin, doxorubicin, and methylprednisone (CAMP). This regimen was administered in the neoadjuvant setting and demonstrated an ORR of 93% with a 5-year overall survival (OS) of 81% in a small phase II trial of 17 patients.⁶⁶ The European Organisation for Research and Treatment of Cancer (EORTC) investigated cisplatin and etoposide in 16 patients who demonstrated an ORR of 56% and an MS of 4.3 years.⁵⁹ The addition of ifosfamide to this doublet (VIP) demonstrated a partial response rate of 32% and an MS of 32 months.⁶¹ Carboplatin and paclitaxel demonstrated a modest clinical benefit in patients with thymic malignancies with an ORR of 33% and progression-free survival of 19.8 months and 6.2 months for thymomas and TCs, respectively.⁶³ In 2011, the PAC regimen is considered standard first-line chemotherapy in most centers.

Pemetrexed. A phase II study⁶⁴ evaluated pemetrexed 500 mg/m² every 3 weeks for a maximum of six cycles in 27 patients with previously treated unresectable stage IVA (n = 16) or stage IVB (n = 11) recurrent thymic malignancies. In 23 fully evaluable patients, two complete responses (CRs) and two partial responses (PRs) were noted. All four responding patients had stage IVA thymoma. The median time to progression (TTP) for all patients was 45 weeks (thymomas, 45.4 weeks v TC, 5.1 weeks), and the MS was 29 months for all patients.⁶⁵ Overall, single-agent pemetrexed is an active agent in a heavily pretreated population of patients with recurrent thymomas, but it has limited activity in TC.

Targeted Therapy

Epidermal growth factor receptor signaling pathway. Somatic activating epidermal growth factor receptor (*EGFR*) mutations are extremely rare in thymic malignancies except for a few isolated case reports in Asian patients.^{67,68} *EGFR* gene amplification by fluorescent in situ hybridization occurs in approximately 20% of thymomas, in particular type B3 thymomas, and in TCs and is associated with more advanced stage and capsule invasion.¹⁸ *EGFR* protein overexpression by immunohistochemistry (IHC) is present in 46% to 85% of thymomas^{19,20}; however, no clear association with clinicopathologic features has been determined. Twenty-six previously treated patients with metastatic thymoma (n = 19) or TC (n = 7) received gefitinib 250 mg orally daily (Table 4).⁶⁹ There were no CRs, one PR lasting 5 months, and 14 patients with stable disease (SD). Median TTP was 4 months. None of the patients analyzed (including one PR) had evidence of *EGFR* or *KRAS* mutations. A phase II trial studied the combination of erlotinib and bevacizumab in 18 pretreated patients (thymomas, 11; TCs, 7) with progressive TETs. Erlotinib 150 mg orally once daily and bevacizumab 15 mg/kg intravenously was repeated every 21 days.⁷⁰ Eleven patients achieved SD, and seven had progressive disease. The MS has not been reported, but it appears that this combination has limited activity. Cetuximab has been reported to have activity in two case reports: one patient overexpressed *EGFR* by IHC and the other did not.^{74,75} *Ras* mutations have been detected in three of 63 thymic tumors analyzed: one TC (*KRAS* mutation, G12V), one type B2 thymoma (*KRAS* mutation, G12A), and one type A thymoma (*HRAS*, G13V), respectively.³² No occurrences of *HER2* gene amplification by fluorescent in situ hybridization have been detected.²² Overall results from *EGFR* tyrosine kinase inhibitors have been disappointing in patients with thymic malignancies and, at present, these therapies cannot be recommended.

Angiogenesis inhibition. VEGF-A, VEGFR-1, and VEGFR-2 are overexpressed in thymoma and TC,^{76,77} and microvessel density and VEGF expression levels have been shown to correlate with both tumor invasion and clinical stage.⁷⁸ However, there are limited data regarding the efficacy of angiogenesis inhibitors in thymic malignancies. A phase I trial⁷⁹ reports a PR to the combination of aflibercept and docetaxel in a patient with thymoma. Sorafenib and sunitinib have not been assessed in formal clinical trial settings, and case reports have described evidence of the activity of these agents in TC. A PR has been reported in a patient receiving sorafenib who had a missense mutation in

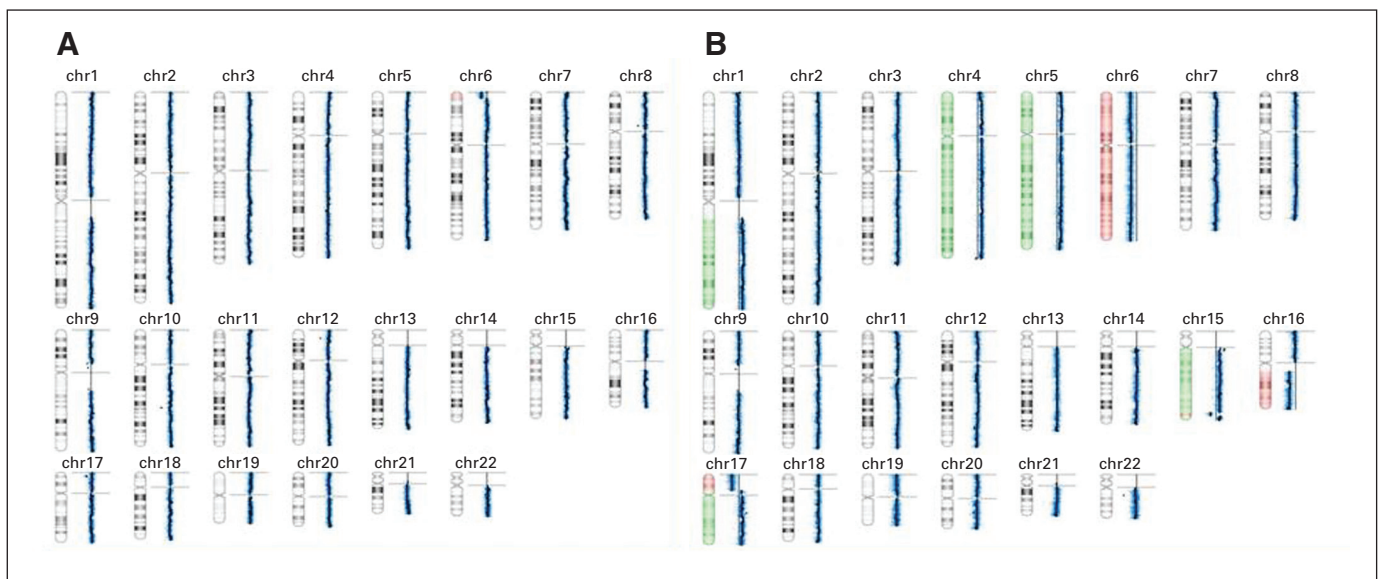


Fig 1. Summary of array comparative genomic hybridization results for autosomic chromosomes of two patients with thymic epithelial tumors. Regions highlighted in red represent copy number (CN) losses and regions highlighted in green represent CN gains. Blue dots represent the array probes, and their respective positions aligned to the chromosomes are shown on the left. The divergences from the median axis of the blue dots indicate regions of CN aberrations. Tumor DNA was cohybridized with commercially available normal reference DNA on Agilent 180K Sure Print array (Agilent, Palo Alto, CA). Data were collected from the Agilent microarray scanner (Agilent) and analyzed by using Nexus 5.1 software (Biodiscovery, La Jolla, CA). (A) Type A thymoma exhibits a much less aberrant karyotype than (B) thymic carcinoma.

exon 17 (D820E) of the *c-KIT* gene,⁸⁰ and a second patient has demonstrated prolonged SD (> 9 months) in a nonmutated but high IHC expressing tumor for KIT, p53, and VEGF.⁸¹ Of four patients with TC who were treated with sunitinib, three had PRs (2 to 18+ months) and one had prolonged SD (22 months), with OS ranging from 4 to 40+ months.⁸² In a phase I trial of SU14813,⁸³ a multitargeted tyrosine kinase inhibitor (VEGFRs, PDGFRs, *KIT*, and *FLT-3*), four patients with thymoma were treated and two had PRs with progression-free survival of 15.3 and 9.0 months, respectively. From the limited data to date, it appears that multikinase inhibitors may be of interest in targeting angiogenesis with some benefit, especially in TC.

***c-KIT* signaling pathway.** Thymic malignancies have shown *c-KIT* positivity by IHC in 73% to 86% of TCs, but there is limited to no overexpression in thymoma, with approximately 2% of patients demonstrating positivity.^{20,24} Despite a high frequency of *KIT* expression in TC, the rate of *KIT* mutations remains low at 9%. From the observed mutations, the two V560 deletions^{32,84} and the L576P substitution⁶⁷ are sensitive to imatinib,⁸⁵ the D820E to nilotinib, and H697Y to sorafenib.⁸⁶ A small phase II trial evaluated imatinib in seven patients with either type B3 thymomas (two patients) or TC (five patients). *c-KIT* expression was found in one of four samples by IHC; no mutations in *c-KIT* or *PDGFRA* genes were demonstrated in three tumors examined, and no responses were seen.⁷¹ A second trial⁷² investigated imatinib in 11 patients with previously treated, advanced, unresectable TC. IHC expression was confirmed for *c-KIT* in nine patients and *PDGFR* in two patients, and there were no objective responses in this study. Future studies should consider selecting patients on the basis of the presence of *c-KIT* mutations, although

they are rare. Second-generation *KIT* inhibitors currently undergoing clinical trial evaluation would be preferable because *KIT* mutations in TC are not uniformly sensitive to imatinib.⁸⁴

Histone deacetylase inhibitors. Belinostat is a pan-histone deacetylase inhibitor. In a phase I study⁸⁷ of this agent, a patient with thymoma had some tumor reduction that lasted for 17 months on treatment. We performed a phase II trial of belinostat, given by intravenous infusion at 1 g/m² on days 1 through 5 of a 21-day cycle until progression or intolerance.⁷³ In total, 41 patients were enrolled, 25 with thymoma and 16 with TC. Treatment was well tolerated, with nausea, vomiting, and fatigue as the major adverse effects. There were two PRs in patients with thymoma, 25 patients with SD, and 13 with progressive disease. There were no responses in TC. TTP and OS were 174 days and 575 days, respectively. This study is one of the largest phase II trials of a targeted agent performed in thymic malignancies to date. An ongoing phase II trial is investigating belinostat in combination with PAC as first-line therapy in patients with advanced thymic malignancies (NCT 01100944).

Octreotide. Somatostatin (SST) receptors belong to a superfamily of G-protein-coupled receptors with several transmembrane-spanning domains.⁸⁸ SST receptors are found in TET tissue, and SST receptor scintigraphy that uses radiolabeled octreotide can be used to identify locally advanced and metastatic disease.⁸⁹ Indium-111 diethylenetriamine pentaacetic acid (¹¹¹In-labeled DTPA)-octreotide scintigraphy has been evaluated in 18 patients with thymic masses.⁹⁰ Uptake was increased in patients with thymoma compared with patients who had thymic hyperplasia or other benign disorders. Small metastatic pleural or pericardial metastases can be missed, but lesions larger

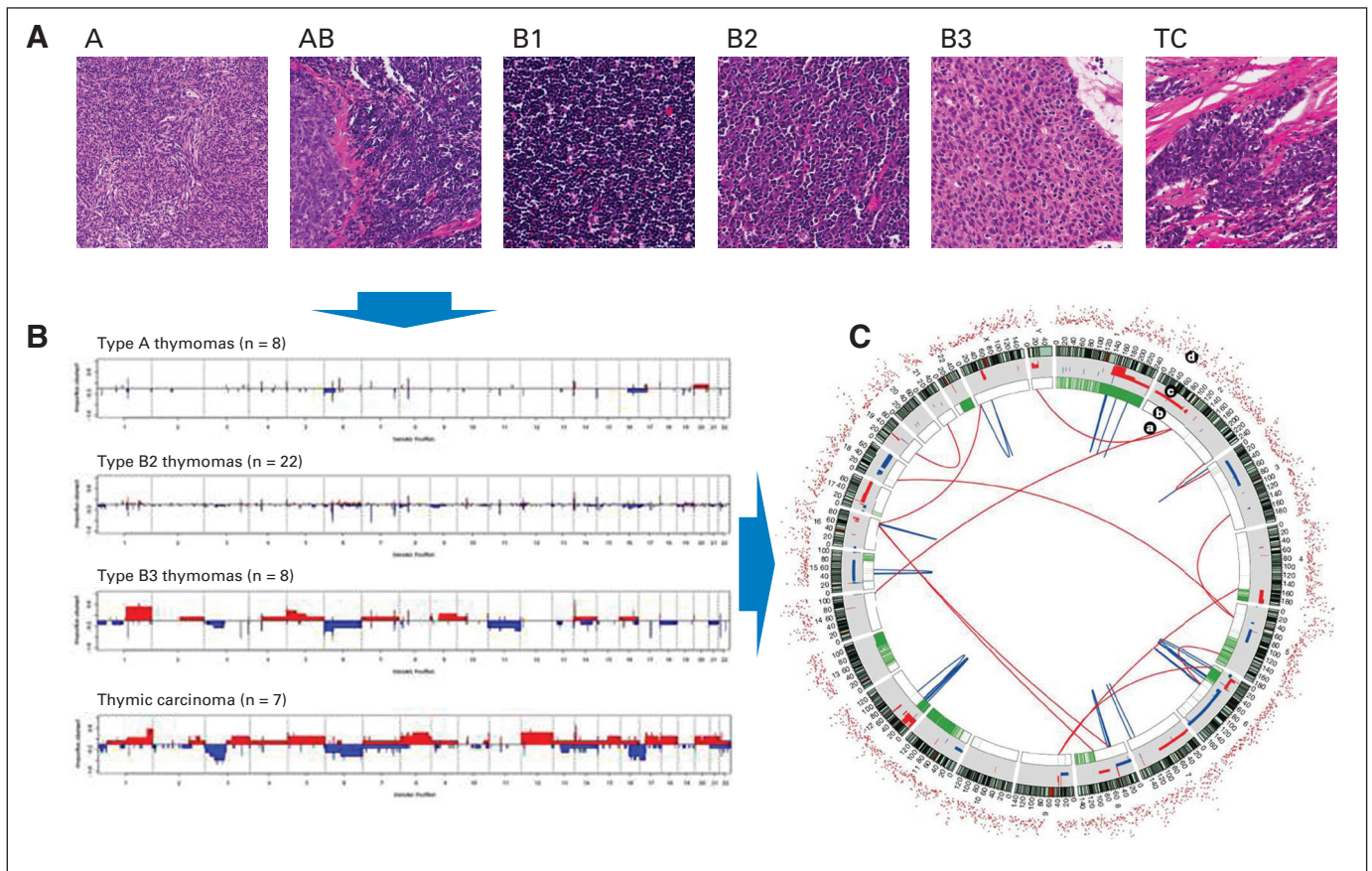


Fig 2. (A) Thymic epithelial tumors are classified according to their histologic appearance into type A, AB, B1, B2, B3, and TC (thymic carcinoma) groups. (B) Correlation of thymic epithelia histotypes with specific genomic abnormalities. Comparative genomic hybridization diagram is derived from Girard et al,³² reprinted by permission from Clinical Cancer Research. Red represents the frequency of copy number (CN) gain, and blue represents the frequency of CN loss for eight type A thymomas, 22 type B2 thymomas, eight type B3 thymomas, and seven thymic carcinomas. (C) Modified chromosome ideograms (Reprinted by permission from Macmillan Publishers Ltd: Lee et al: Nature 465:473-477, 2010) depict complete genome sequencing from a lung adenocarcinoma. Next-generation sequencing technology allows genome-wide identification of single nucleotide mutations (d, red dots), CN aberrations (c, red, regions of CN gain; blue, regions of CN loss), loss of heterozygosity and allelic imbalance (b, green), and somatic structural variations (a, red lines, interchromosomal variations; blue lines, intrachromosomal variations).

than 1.5 cm may be detected. Octreotide, an octapeptide SST analog, has high affinity for a selective SST subtype (SST₂) receptor and has been demonstrated to have an in vitro inhibitory effect in thymic epithelial cells, perhaps through blockage or inhibition of the insulin-like growth factor 1 (IGF-1) and endothelial growth factor.⁹¹ It has also been suggested that an interaction between thymic tissue and SST has an impact on T-lymphocyte development through paracrine mechanisms.⁹² The Eastern Cooperative Oncology Group (ECOG) conducted a phase II trial⁵ of octreotide with or without prednisone in patients with advanced, unresectable, octreotide scan–positive thymic malignancies. Thirty-eight patients (32 thymomas, five TCs, and one thymic carcinoma) received octreotide 0.5 mg subcutaneously three times daily for up to 1 year. Two CRs (5.3%) and 10 PRs (25%) were observed (four PRs with octreotide alone). None of the six patients without pure thymoma responded. The 1- and 2-year survival rates were 86.6% and 75.7%, respectively, indicating that octreotide alone has modest activity in patients with octreotide scan–positive thymomas but can be considered for treatment of recurrent disease in selected patients. Prednisone improves the overall response rate but is associated with increased toxicity. An ongoing clinical trial is currently studying the efficacy of octreotide in patients with primary inoperable thymomas.

IGF-1 receptor signaling pathway. Increased IGF-1 receptor (IGF-1R) expression in TET has a poor prognostic value for OS⁹³ and in primary tumors for TTP.⁹⁴ We evaluated IGF-1R expression by IHC in 132 operable thymic tumors and demonstrated that 22 (20%) of 111 samples were positive.⁹⁴ In this study, IGF-1R was less common in type A, AB, and B1 thymomas compared with B2, B3, and C subtypes (3.4% v 37.2%; $P < .001$). A second study⁹³ evaluated 63 thymic tumors and confirmed a higher degree of IGF-1R expression by IHC in TC versus thymoma (83% v 43%, respectively; $P = .039$). Figitumumab, an anti-IGF-1R antibody demonstrated clinical activity in a patient with refractory thymoma⁹⁵ lasting more than 1 year. We are currently performing a phase II trial (NCT00965250) investigating cixutumumab (IMC-A12; ImClone Systems, Bridgewater, NJ), an IGF-1R monoclonal antibody, in advanced and refractory thymoma and TC following at least one platinum-containing chemotherapy treatment. Cixutumumab 20 mg/kg is administered on day 1 of a 21-day cycle until progression and treatment is well tolerated.⁹⁶ At present, no major signs of activity have been observed in TC trials in which accrual has been halted, whereas major responses have been seen in patients with thymoma in trials in which accrual is still ongoing.

Tropomyosin receptor kinase A and cyclin-dependent kinase A inhibitor. The tropomyosin receptor kinase (Trk) family comprises three isoforms (TrkA, TrkB, and TrkC), which have an intrinsic tyrosine kinase activity. TrkA is the specific receptor for nerve growth factor; TrkB for brain-derived neurotrophic factor, NT-4, and NT-5; and TrkC for NT-3.⁹⁷ Decreased expression of cell-cycle proteins p21 and p27, both of which are natural inhibitors of cyclin-dependent kinases (CDKs), predict for a poor response to neoadjuvant chemotherapy in invasive thymoma.⁹⁸ TrkA activation promotes tumor growth, probably through MAPK pathway activation. The expression of Trk receptors was evaluated in 99 patients with TET by using IHC staining.⁹⁹ All tumors except one TC demonstrated cytoplasmic TrkA immunostaining, and no tumors showed TrkB or TrkC immunoreactivity. Our laboratory has analyzed 60 paraffin-embedded samples from patients diagnosed with TET. We found copy number gain of TrkA in 45% of all thymoma samples analyzed and 72% of TC samples (unpublished data). Another group has shown that CDK proteins that control the cell cycle G1→S phase transition may be altered through p16INK4 loss in thymoma.³⁰ On the basis of these results, we believe TrkA could potentially be an important therapeutic target in thymic tumors. The pyrazoloquinazoline PHA-848125-AC is an oral compound that is a potent inhibitor of the CDK2/cyclin A complex and TrkA. Preliminary results from a phase I trial demonstrated PRs in two of three patients with thymic malignancies (type B3 and type C). Two phase II studies (NCT01011439 and NCT01301391) in advanced TC are currently investigating PHA-848125-AC. The first is an international study in patients with TC for whom one line of prior treatment has failed, and the second is a single-center study by the National Cancer Institute in patients with type B3 and TC with progressive disease after more than one line of therapy.

Src inhibitors. The Src family of tyrosine kinases and its ligands are considered important components in thymocyte development.¹⁰⁰ A phase II

trial investigated saracatinib (AZD0530), a small-molecule inhibitor of Src in patients with previously treated advanced thymic malignancies. A total of 21 patients (14 thymomas and seven TCs) received 175 mg of saracatinib daily. The trial was terminated because of lack of clinical activity.¹⁰⁰

DISCUSSION

Although surgery remains the mainstay treatment in thymic malignancies, tumors are often large and require preoperative chemotherapy. Despite radical resection, recurrence is not unusual, especially in more aggressive histologic tumor types. Preliminary data suggest that the expression of some biologic markers may be of prognostic or predictive value.^{101,102}

A better understanding of the biology of these tumors through the integration of results obtained with advanced technologies, such as array CGH, expression array analysis, and next-generation sequencing, will likely help identify potential markers for prognosis and treatment of advanced cases (Figs 1 and 2). Gene expression profiling and genomic clustering studies performed to date indicate that thymic tumors as defined histologically by the current 2004 WHO classification do have different molecular features.³² Type B2 thymoma, which has a distinctly more lymphocytic component can be separated from the other subgroups in which epithelial cells predominate. Genomic profiling also distinguishes type B3 thymoma and TC from type A and type B2 thymomas. The presence of *KIT* mutations in TC further strengthens the notion of subtypes existing among the spectrum of thymic malignancies.

The rarity of these tumors is a major limitation in researching thymic malignancies and, for many years, it has prevented us from performing large randomized clinical trials. Rare diseases may, however, lend themselves perfectly to investigation via molecular profiling–directed therapies. Individual case reports that highlight advanced thymic tumors responding to targeted agents suggest that thymic malignancies may comprise clinically relevant subsets that can be defined at the molecular level. We are currently conducting a molecular profiling study (NCT01306045) in which patients with thymic malignancies have a repeat biopsy to enable genome-wide sequencing. Therapy is assigned depending on the molecular profile of the tumor. It is hoped that this protocol may herald a new paradigm of therapies for thymic malignancies and will facilitate a rapid translation of preclinical findings to the clinic.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: All authors

Collection and assembly of data: Ronan J. Kelly, Iacopo Petrini, Yisong Wang, Giuseppe Giaccone

Data analysis and interpretation: Ronan J. Kelly, Iacopo Petrini, Yisong Wang, Giuseppe Giaccone

Manuscript writing: All authors

Final approval of manuscript: All authors

REFERENCES

1. Margaritora S, Cesario A, Cusumano G, et al: Thirty-five-year follow-up analysis of clinical and pathologic outcomes of thymoma surgery. *Ann Thorac Surg* 89:245-252, 2010; discussion 252
2. Engels EA, Pfeiffer RM: Malignant thymoma in the United States: Demographic patterns in incidence and associations with subsequent malignancies. *Int J Cancer* 105:546-551, 2003
3. Evoli A, Punzi C, Marsili F, et al: Extrathymic malignancies in patients with thymoma. *Ann Oncol* 15:692-693, 2004
4. Pan CC, Chen PC, Wang LS, et al: Thymoma is associated with an increased risk of second malignancy. *Cancer* 92:2406-2411, 2001
5. Loehrer PJ Sr, Wang W, Johnson DH, et al: Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: An Eastern Cooperative Oncology Group Phase II Trial. *J Clin Oncol* 22:293-299, 2004
6. Engels EA: Epidemiology of thymoma and associated malignancies. *J Thorac Oncol* 5:S260-S265, 2010 (suppl 4)
7. Strollo DC, Rosado de Christenson ML, Jett JR: Primary mediastinal tumors: Part 1. Tumors of the anterior mediastinum. *Chest* 112:511-522, 1997
8. Phillips LH 2nd, Torner JC, Anderson MS, et al: The epidemiology of myasthenia gravis in central and western Virginia. *Neurology* 42:1888-1893, 1992
9. Gadalla SM, Rajan A, Pfeiffer R, et al: A population-based assessment of mortality and morbidity patterns among patients with thymoma. *Int J Cancer* 128:2688-2694, 2011
10. Vukmanović S, Bevan MJ, Hogquist KA: The specificity of positive selection: MHC and peptides. *Immunity* 135:51-66, 1993
11. Masaoka A, Monden Y, Nakahara K, et al: Follow-up study of thymomas with special reference to their clinical stages. *Cancer* 48:2485-2492, 1981
12. Koga K, Matsuno Y, Noguchi M, et al: A review of 79 thymomas: Modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. *Pathol Int* 44:359-367, 1994
13. Kuo TT: Tumours of the thymus, in Travis WD, Brambilla E, Muller-Hermelink HK, et al (eds): *World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart*. Lyon, France, IARC Press, 2004, pp 146-248
14. Moran CA, Suster S: On the histologic heterogeneity of thymic epithelial neoplasms: Impact of sampling in subtyping and classification of thymomas. *Am J Clin Pathol* 114:760-766, 2000
15. Chen G, Marx A, Chen WH, et al: New WHO histologic classification predicts prognosis of thymic epithelial tumors: A clinicopathologic study of 200 thymoma cases from China. *Cancer* 95:420-429, 2002
16. Herens C, Radermecker M, Servais A, et al: Deletion (6)(p22p25) is a recurrent anomaly of thymoma: Report of a second case and review of the literature. *Cancer Genet Cytogenet* 146:66-69, 2003
17. Kuhn E, Wistuba II: Molecular pathology of thymic epithelial neoplasms. *Hematol Oncol Clin North Am* 22:443-455, 2008
18. Ionescu DN, Sasatomi E, Cieply K, et al: Protein expression and gene amplification of epidermal growth factor receptor in thymomas. *Cancer* 103:630-636, 2005
19. Suzuki E, Sasaki H, Kawano O, et al: Expression and mutation statuses of epidermal growth factor receptor in thymic epithelial tumors. *Jpn J Clin Oncol* 36:351-356, 2006
20. Henley JD, Cummings OW, Loehrer PJ Sr: Tyrosine kinase receptor expression in thymomas. *J Cancer Res Clin Oncol* 130:222-224, 2004
21. Hayashi Y, Ishii N, Obayashi C, et al: Thymoma: Tumour type related to expression of epidermal growth factor (EGF), EGF-receptor, p53, v-erb B and ras p21. *Virchows Arch* 426:43-50, 1995
22. Pan CC, Chen PC, Wang LS, et al: Expression of apoptosis-related markers and HER-2/neu in thymic epithelial tumours. *Histopathology* 43:165-172, 2003
23. Nakagawa K, Matsuno Y, Kunitoh H, et al: Immunohistochemical KIT (CD117) expression in thymic epithelial tumors. *Chest* 128:140-144, 2005
24. Pan CC, Chen PC, Chiang H: KIT (CD117) is frequently overexpressed in thymic carcinomas but is absent in thymomas. *J Pathol* 202:375-381, 2004
25. Penzel R, Hoegel J, Schmitz W, et al: Clusters of chromosomal imbalances in thymic epithelial tumours are associated with the WHO classification and the staging system according to Masaoka. *Int J Cancer* 105:494-498, 2003
26. Tateyama H, Eimoto T, Tada T, et al: p53 protein expression and p53 gene mutation in thymic epithelial tumors: An immunohistochemical and DNA sequencing study. *Am J Clin Pathol* 104:375-381, 1995
27. Chen FF, Yan JJ, Jin YT, et al: Detection of bcl-2 and p53 in thymoma: Expression of bcl-2 as a reliable marker of tumor aggressiveness. *Hum Pathol* 27:1089-1092, 1996
28. Pich A, Chiarle R, Chiusa L, et al: p53 expression and proliferative activity predict survival in non-invasive thymomas. *Int J Cancer* 69:180-183, 1996
29. Weirich G, Schneider P, Fellbaum C, et al: p53 alterations in thymic epithelial tumours. *Virchows Arch* 431:17-23, 1997
30. Hirabayashi H, Fujii Y, Sakaguchi M, et al: P16INK4, pRB, p53 and cyclin D1 expression and hypermethylation of CDKN2 gene in thymoma and thymic carcinoma. *Int J Cancer* 73:639-644, 1997
31. Zettl A, Ströbel P, Wagner K, et al: Recurrent genetic aberrations in thymoma and thymic carcinoma. *Am J Pathol* 157:257-266, 2000
32. Girard N, Shen R, Guo T, et al: Comprehensive genomic analysis reveals clinically relevant molecular distinctions between thymic carcinomas and thymomas. *Clin Cancer Res* 15:6790-6799, 2009
33. Inoue M, Marx A, Zettl A, et al: Chromosome 6 suffers frequent and multiple aberrations in thymoma. *Am J Pathol* 161:1507-1513, 2002
34. Zhou R, Zettl A, Ströbel P, et al: Thymic epithelial tumors can develop along two different pathogenetic pathways. *Am J Pathol* 159:1853-1860, 2001
35. Inoue M, Starostik P, Zettl A, et al: Correlating genetic aberrations with World Health Organization-defined histology and stage across the spectrum of thymomas. *Cancer Res* 63:3708-3715, 2003
36. Nabarra B, Pontoux C, Godard C, et al: Neoplastic transformation and angiogenesis in the thymus of transgenic mice expressing SV40 T and t antigen under an L-pyruvate kinase promoter (SV12 mice). *Int J Exp Pathol* 86:397-413, 2005
37. Stefanaki K, Rontogianni D, Kouvidou CH, et al: Expression of p53, mdm2, p21/waf1 and bcl-2 proteins in thymomas. *Histopathology* 30:549-555, 1997
38. Oyama T, Osaki T, Mitsudomi T, et al: p53 alteration, proliferating cell nuclear antigen, and nucleolar organizer regions in thymic epithelial tumors. *Int J Mol Med* 1:823-826, 1998
39. Mineo TC, Ambrogio V, Mineo D, et al: Long-term disease-free survival of patients with radically resected thymomas: Relevance of cell-cycle protein expression. *Cancer* 104:2063-2071, 2005
40. Khoury T, Arshad A, Bogner P, et al: Apoptosis-related (survivin, Bcl-2), tumor suppressor gene (p53), proliferation (Ki-67), and non-receptor tyrosine kinase (Src) markers expression and correlation with clinicopathologic variables in 60 thymic neoplasms. *Chest* 136:220-228, 2009
41. Hino N, Kondo K, Miyoshi T, et al: High frequency of p53 protein expression in thymic carcinoma but not in thymoma. *Br J Cancer* 76:1361-1366, 1997
42. Gilhus NE, Jones M, Turley H, et al: Oncogene proteins and proliferation antigens in thymomas: Increased expression of epidermal growth factor receptor and Ki67 antigen. *J Clin Pathol* 48:447-455, 1995
43. Engel P, Francis D, Graem N: Expression of bcl-2 in fetal thymus, thymomas and thymic carcinomas: Association with p53 expression and review of the literature. *APMIS* 106:449-455, 1998
44. Comin CE, Messerini L, Novelli L, et al: Ki-67 antigen expression predicts survival and correlates with histologic subtype in the WHO classification of thymic epithelial tumors. *Int J Surg Pathol* 12:395-400, 2004
45. Hirose Y, Kondo K, Takizawa H, et al: Aberrant methylation of tumour-related genes in thymic epithelial tumours. *Lung Cancer* 64:155-159, 2009
46. Tsuji T, Ikeda H, Tsuchikawa T, et al: Malignant transformation of thymoma in recipient rats by heterotopic thymus transplantation from HTLV-I transgenic rats. *Lab Invest* 85:851-861, 2005
47. Scarpino S, Di Napoli A, Stoppacciaro A, et al: Expression of autoimmune regulator gene (AIRE) and T regulatory cells in human thymomas. *Clin Exp Immunol* 149:504-512, 2007
48. Okumura M, Fujii Y, Shiono H, et al: Immunological function of thymoma and pathogenesis of paraneoplastic myasthenia gravis. *Gen Thorac Cardiovasc Surg* 56:143-150, 2008
49. Anderson MS, Venanzi ES, Klein L, et al: Projection of an immunological self shadow within the thymus by the aire protein. *Science* 298:1395-1401, 2002
50. Anderson MS, Venanzi ES, Chen Z, et al: The cellular mechanism of Aire control of T cell tolerance. *Immunity* 23:227-239, 2005
51. Finnish-German APECED Consortium: An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. *Nat Genet* 17:399-403, 1997
52. Kekäläinen E, Tuovinen H, Joensuu J, et al: A defect of regulatory T cells in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J Immunol* 178:1208-1215, 2007
53. Nagamine K, Peterson P, Scott HS, et al: Positional cloning of the APECED gene. *Nat Genet* 17:393-398, 1997
54. Burbelo PD, Browne SK, Sampaio EP, et al: Anti-cytokine autoantibodies are associated with opportunistic infection in patients with thymic neoplasia. *Blood* 116:4848-4858, 2010
55. Liu JM, Wang LS, Huang MH, et al: Topoisomerase 2alpha plays a pivotal role in the tumor biology of stage IV thymic neoplasia. *Cancer* 109:502-509, 2007

56. Sasaki H, Fukai I, Kiriya M, et al: Thymidylate synthase and dihydropyrimidine dehydrogenase mRNA levels in thymoma. *Surg Today* 33: 83-88, 2003
57. Loehrer PJ Sr, Kim K, Aisner SC, et al: Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: Final results of an intergroup trial—The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. *J Clin Oncol* 12:1164-1168, 1994
58. Fornasiero A, Daniele O, Ghiotto C, et al: Chemotherapy for invasive thymoma: A 13-year experience. *Cancer* 68:30-33, 1991
59. Giaccone G, Ardizzoni A, Kirkpatrick A, et al: Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma: A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol* 14:814-820, 1996
60. Highley MS, Underhill CR, Parnis FX, et al: Treatment of invasive thymoma with single-agent ifosfamide. *J Clin Oncol* 17:2737-2744, 1999
61. Loehrer PJ Sr, Jiroutek M, Aisner S, et al: Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: An intergroup trial. *Cancer* 91: 2010-2015, 2001
62. Grassin F, Paleiron N, Andre M, et al: Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma. A French experience. *J Thorac Oncol* 5:893-897, 2010
63. Lemma GL, Loehrer PJ, Lee JW, et al: A phase II study of carboplatin plus paclitaxel in advanced thymoma or thymic carcinoma: E1C99. *J Clin Oncol* 26:428s, 2008 (suppl; abstr 8018)
64. Loehrer PJ, Yiannoutsos CT, Dropcho S, et al: A phase II trial of pemetrexed in patients with recurrent thymoma or thymic carcinoma. *J Clin Oncol* 24:383s, 2006 (suppl; abstr 7079)
65. Schmitt J, Loehrer PJ Sr: The role of chemotherapy in advanced thymoma. *J Thorac Oncol* 5:S357-S360, 2010 (suppl 4)
66. Yokoi K, Matsuguma H, Nakahara R, et al: Multidisciplinary treatment for advanced invasive thymoma with cisplatin, doxorubicin, and methylprednisolone. *J Thorac Oncol* 2:73-78, 2007
67. Yoh K, Nishiwaki Y, Ishii G, et al: Mutational status of EGFR and KIT in thymoma and thymic carcinoma. *Lung Cancer* 62:316-320, 2008
68. Yamaguchi H, Soda H, Kitazaki T, et al: Thymic carcinoma with epidermal growth factor receptor gene mutations. *Lung Cancer* 52:261-262, 2006
69. Kurup A, Burns M, Dropcho S, et al: Phase II study of gefitinib treatment in advanced thymic malignancies. *J Clin Oncol* 23:381s, 2005 (suppl; abstr 7068)
70. Bedano PM, Perkins S, Burns M, et al: A phase II trial of erlotinib plus bevacizumab in patients with recurrent thymoma or thymic carcinoma. *J Clin Oncol* 26:713s, 2008 (suppl; abstr 19087)
71. Giaccone G, Rajan A, Ruitjer R, et al: Imatinib mesylate in patients with WHO B3 thymomas and thymic carcinomas. *J Thorac Oncol* 4:1270-1273, 2009
72. Salter JT, Lewis D, Yiannoutsos PJ, et al: Imatinib for the treatment of thymic carcinoma. *J Clin Oncol* 26:452s, 2008 (suppl; abstr 8116)
73. Giaccone G, Rajan A, Berman A, et al: Phase II study of belinostat in patients with recurrent or refractory advanced thymic epithelial tumors. *J Clin Oncol* 29:2052-2059, 2011
74. Farina G, Garassino MC, Gambacorta M, et al: Response of thymoma to cetuximab. *Lancet Oncol* 8:449-450, 2007
75. Palmieri G, Marino M, Salvatore M, et al: Cetuximab is an active treatment of metastatic and chemorefractory thymoma. *Front Biosci* 12:757-761, 2007
76. Cimpean AM, Raica M, Encica S, et al: Immunohistochemical expression of vascular endothelial growth factor A (VEGF), and its receptors (VEGFR1, 2) in normal and pathologic conditions of the human thymus. *Ann Anat* 190:238-245, 2008
77. Sasaki H, Yukiue H, Kobayashi Y, et al: Elevated serum vascular endothelial growth factor and basic fibroblast growth factor levels in patients with thymic epithelial neoplasms. *Surg Today* 31: 1038-1040, 2001
78. Tomita M, Matsuzaki Y, Edagawa M, et al: Correlation between tumor angiogenesis and invasiveness in thymic epithelial tumors. *J Thorac Cardiovasc Surg* 124:493-498, 2002
79. Isambert N, Freyer G, Zanetta S, et al: A phase I dose escalation and pharmacokinetic (PK) study of intravenous aflibercept (VEGF trap) plus docetaxel (D) in patients (pts) with advanced solid tumors: Preliminary results. *J Clin Oncol* 26:177s, 2008 (suppl; abstr 3599)
80. Bisagni G, Rossi G, Cavazza A, et al: Long lasting response to the multikinase inhibitor bay 43-9006 (Sorafenib) in a heavily pretreated metastatic thymic carcinoma. *J Thorac Oncol* 4:773-775, 2009
81. Li XF, Chen Q, Huang WX, et al: Response to sorafenib in cisplatin-resistant thymic carcinoma: A case report. *Med Oncol* 26:157-160, 2009
82. Ströbel P, Bargou R, Wolff A, et al: Sunitinib in metastatic thymic carcinomas: Laboratory findings and initial clinical experience. *Br J Cancer* 103:196-200, 2010
83. Fiedler W, Giaccone G, Lasch P, et al: Phase I trial of SU14813 in patients with advanced solid malignancies. *Ann Oncol* 22:195-201, 2011
84. Ströbel P, Hartmann M, Jakob A, et al: Thymic carcinoma with overexpression of mutated KIT and the response to imatinib. *N Engl J Med* 350:2625-2626, 2004
85. Heinrich MC, Maki RG, Corless CL, et al: Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. *J Clin Oncol* 26:5352-5359, 2008
86. Girard N: Thymic tumors: Relevant molecular data in the clinic. *J Thorac Oncol* 5:S291-S295, 2010 (suppl 4)
87. Steele NL, Plumb JA, Vidal L, et al: A phase 1 pharmacokinetic and pharmacodynamic study of the histone deacetylase inhibitor belinostat in patients with advanced solid tumors. *Clin Cancer Res* 14:804-810, 2008
88. Reisine T, Bell GI: Molecular biology of somatostatin receptors. *Endocr Rev* 16:427-442, 1995
89. Krenning EP, Kwekkeboom DJ, Bakker WH, et al: Somatostatin receptor scintigraphy with [¹¹¹In-DTPA-D-Phe1]- and [¹²³I-Tyr3]-octreotide: The Rotterdam experience with more than 1000 patients. *Eur J Nucl Med* 20:716-731, 1993
90. Lastoria S, Vergara E, Palmieri G, et al: In vivo detection of malignant thymic masses by indium-111-DTPA-D-Phe1-octreotide scintigraphy. *J Nucl Med* 39:634-639, 1998
91. Ferone D, van Hagen PM, van Koetsveld PM, et al: In vitro characterization of somatostatin receptors in the human thymus and effects of somatostatin and octreotide on cultured thymic epithelial cells. *Endocrinology* 140:373-380, 1999
92. Fuller PJ, Verity K: Somatostatin gene expression in the thymus gland. *J Immunol* 143:1015-1017, 1989
93. Girard N, Teruya-Feldstein J, Payabyab EC, et al: Insulin-like growth factor-1 receptor expression in thymic malignancies. *J Thorac Oncol* 5:1439-1446, 2010
94. Zucali PA, Petrini I, Lorenzi E, et al: Insulin-like growth factor-1 receptor and phosphorylated AKT-serine 473 expression in 132 resected thymomas and thymic carcinomas. *Cancer* 116:4686-4695, 2010
95. Haluska P, Shaw HM, Batzel GN, et al: Phase I dose escalation study of the anti insulin-like growth factor-I receptor monoclonal antibody CP-751,871 in patients with refractory solid tumors. *Clin Cancer Res* 13:5834-5840, 2007
96. Rajan A, Berman AW, Kelly RJ, et al: Phase II study of the insulin-like growth factor-1 receptor (IGF-1R) antibody cixutumumab (C) in patients (pts) with thymoma (T) and thymic carcinoma (TC). *J Clin Oncol* 28:e17525, 2010 (suppl)
97. Bothwell M: Functional interactions of neurotrophins and neurotrophin receptors. *Annu Rev Neurosci* 18:223-253, 1995
98. Mineo TC, Mineo D, Onorati I, et al: New predictors of response to neoadjuvant chemotherapy and survival for invasive thymoma: A retrospective analysis. *Ann Surg Oncol* 17:3022-3029, 2010
99. Kim DJ, Yang WI, Kim SH, et al: Expression of neurotrophin receptors in surgically resected thymic epithelial tumors. *Eur J Cardiothorac Surg* 28: 611-616, 2005
100. Wakelee HA, Gubens MA, Burns M, et al: A phase II study of saracatinib (AZD0530), a SRC inhibitor, administered orally daily to patients with advanced thymic malignancies. Presented at International Thymic Malignancy Group Conference, New York, NY, May 5-6, 2010
101. Mineo TC, Ambrogi V, Baldi A, et al: Recurrent intrathoracic thymomas: Potential prognostic importance of cell-cycle protein expression. *J Thorac Cardiovasc Surg* 138:40-45, 2009
102. Aisner SC, Dahlberg S, Hameed MR, et al: Epidermal growth factor receptor, C-kit, and Her2/neu immunostaining in advanced or recurrent thymic epithelial neoplasms staged according to the 2004 World Health Organization in patients treated with octreotide and prednisone: An Eastern Cooperative Oncology Group study. *J Thorac Oncol* 5:885-892, 2010