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Progress in Endocrine Neoplasia

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Abstract

Most endocrine tumors are benign, and afflicted patients usually seek medical advice, because of symptoms caused by too much, or too little, native hormone secretion, or the impingement of their tumor on a vital structure. Malignant endocrine tumors represent a more serious problem, and patient cure often depends on early diagnosis and treatment. The recent development of novel molecular therapeutics, holds great promise for the treatment of patients with locally advanced or metastatic endocrine cancer. In this *CCR Focus* expert clinical investigators describe the molecular characteristics of various endocrine tumors, and discuss the current status of diagnosis and treatment.

Introduction

Endocrine tumors are rare, most often occurring sporadically and in women. There are more differences than similarities among the tumors, not only concerning anatomic location and secretory function, but the frequency of hereditary disease - rare in adrenal cortical and differentiated thyroid tumors, uncommon in pituitary tumors, and common in neuroendocrine tumors of the adrenal, the pancreas and the thyroid-, and the frequency of malignant disease - virtually non-existent in pituitary tumors, 10% to 30% in tumors of the adrenal cortex, adrenal medulla, and follicular thyroid, and 50% to 100% in neuroendocrine tumors of the pancreas and thyroid. Except for thyroid tumors, which are usually visible or palpable on physical examination, endocrine tumors are usually occult, and become evident, either because of a secretory malfunction, a space occupancy problem, or their incidental detection on imaging studies. The spectrum of endocrine tumors is almost completely expressed within the Multiple Endocrine Neoplasia syndromes, MEN1 and MEN2. MEN1 includes tumors primarily of the pituitary, parathyroids, and pancreatic islets, and less often the follicular derived thyroid tumors adrenal cortical tumors, and carcinoid tumors. MEN2 includes tumors of the neuroendocrine thyroid, the parathyroids, and the adrenal medulla. The discovery of the genetic mutations causing the MEN1 and MEN2 syndromes has clarified much about the molecular biology of the syndromes and their component tumors, and in many cases has led to improved methods of diagnosis and treatment. As is often the

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case, information gained from the basic and clinical research of rare tumors serves as a guide to investigative strategies of more common neoplasms.

Surgical resection is the treatment for primary endocrine tumors, but molecular targeted therapeutics have replaced chemotherapy as front line therapy for patients with advanced cancers of the pancreas and thyroid. The US Food and Drug Administration (FDA) has approved several molecular targeted therapeutics for these cancers, based on phase III prospective, randomized, placebo controlled, clinical trials, which showed significantly improved progression free survival in patients with metastatic disease (Table 1). Unfortunately, the drugs are expensive and associated with significant toxicities. Most importantly, they have failed to significantly improve overall survival. There is a critical need for new drugs with great specificity for oncogenic targets, and an equally urgent need to understand the mechanisms of resistance to molecular targeted therapeutics - so far lacking for most solid organ malignancies – since this is key to the development of rescue therapy for tumors that become resistant to an initial therapeutic (1, 2).

The Cancer Genome Atlas studies of the National Cancer Institute, and the Human Genome Research Institute, have provided a comprehensive genomic landscape (including: DNA whole exome sequencing, DNA copy number arrays, mRNA sequencing, miRNA sequencing, DNA methylation arrays, and in some tumors, reverse phase protein arrays) of various malignant tumors. The importance of these studies cannot be overemphasized, as they have expanded our knowledge of the molecular biology and pathogenesis of selected tumors, often defining a relationship between genotype and phenotype, and yielding useful information regarding potential diagnostic tests and new therapeutics. Whether The Cancer Genome Atlas studies will lead to a broad array of curative molecular targeted therapeutics, remains an open question. The Cancer Genome Atlas recently reported study results of adrenal cortical carcinoma, papillary thyroid cancer, and pheochromocytoma and paraganglioma. The complete study results are available in publications, either in print form, or online as videos (3–5).

Adrenal cortical carcinoma

Adrenal Cortical Carcinoma (ACC) occurs in a bimodal pattern, developing during childhood or the fourth decade of life (6). The majority of adrenal cortical carcinomas are sporadic, but some occur in a hereditary pattern as a component of diseases such as the Li-Fraumeni syndrome, the Lynch syndrome, and the Beckwith-Wiedemann syndrome (7–9).

In the recently published Cancer Genome Atlas study of 91 patients with ACC, the female to male ratio was 1.8, and 57% of the tumors functioned, most often secreting cortisol (5). Median overall survival was 78 months, and 5-year survival was 59%; however, locally invasive and metastatic ACCs were associated with a 5-year survival of 22% (5). With the increased use of sensitive imaging studies came an increased incidental detection of occult adrenal tumors; the incidence increasing with age, being as high as 10% in the elderly (10). Complete surgical resection is the only cure for ACCs; however, when this is not possible, tumor debulking may relieve symptoms caused by hormonal excess. There is a direct correlation between the size of an adrenal tumor and the presence of malignancy;

approximately 80% of tumors larger than 6 in diameter are malignant (11). Most minimally invasive surgeons limit laparoscopic resection of adrenal tumors to those less than 6 cm in size, and with no evidence of malignancy. In the accompanying article, Payabyab and associates stress the importance of avoiding laparoscopic biopsy, or resection, of potential or proved ACC citing the likelihood of peritoneal seeding, a fatal complication (12).

Mitotane is the only drug approved by the FDA for treatment of advanced ACC; however, prospective trials of mitotane alone in patients with advanced disease showed partial responses of 5 to 30%, with no survival benefit (13). Furthermore, The substantial toxicity of mitotane has limited its use. There have been two multi-center retrospective trials of adjuvant mitotane in patients with ACC. One trial of 177 patients suggested a prolonged recurrence-free survival; however, the second trial of 207 patients showed no improved progression free survival or overall survival (13–15). Phase II trials of combination chemotherapy, with or without mitotane, showed minimal benefit in patients with advanced or metastatic disease (16–18). In a prospective phase III trial, 304 patients with advanced ACC were randomized to receive either a combination of etoposide, doxorubicin, and cisplatin or mitotane plus streptozotocin. The response rate, (23.2% versus 9.2%; $p<0.001$) and the progression free survival (5 months versus 2.1 months; $p<0.001$), were higher in patients receiving the three drug combination, compared to those receiving mitotane and streptozotocin; however there was no improvement in overall survival (19).

The mitotic rate of ACC cells, as is the case for most endocrine and non-endocrine tumor cells, is directly proportional to the clinical behavior of the parent tumor (20–22). Weiss and associates studied the relationship between histological parameters and survival in 41 patients with ACC. Only mitotic rate was significantly associated with survival. Accordingly, ACCs were designated as high grade or low grade based on whether they had greater than, or less than, 20 mitoses per 50 high powered fields (20). The Cancer Genome Atlas study of ACC confirmed and expanded the Weiss classification by integrating tumor subsets identified across the DNA copy-number and mutations, DNA-methylation, mRNA-expression, and miRNA-expression platforms (5). In a Cluster of Cluster (CoC) analysis, they designated three tumor subtypes, CoCI, CoCII, and CoCIII, with respective disease progression rates of 7%, 56% and 97%. At the time of the study the median event - free survival was not yet reached for CoCI, although it was 38 months for CoCII, and 8 months for CoCIII. Loss of large segments of DNA followed by whole-genome doubling was also a maker of tumor progression (5).

Chemotherapy is currently the front line treatment for patients with advanced ACC, and much effort is being devoted to the creation of effective molecular targeted therapies, and immunotherapies. It is hoped that the trove of molecular data generated by TCGA study of ACC, and by other investigators in the field, will lead to the development of curative drugs.

Pheochromocytoma and Paraganglioma

Pheochromocytomas and paragangliomas - referred to collectively as pheochromocytomas - are chromaffin-rich tumors arising from neural crest derived sympathetic lineage cells in the adrenal medulla, or from paraganglia in the thorax, abdomen, or pelvis (23). Sympathetic

derived tumors secrete epinephrine and norepinephrine, whereas parasympathetic derived tumors, arising in the head and neck along the vagus or glossopharyngeal nerves, do not (23, 24). The annual incidence of pheochromocytomas is approximately 2 cases per million individuals, and the tumor occurs in 0.6% of patients with hypertension and in 5% of patients with incidentally discovered adrenal masses (25, 26). Pheochromocytomas are most often sporadic, but an increasing number are reported to be hereditary. The associated age of onset of pheochromocytoma is 43.9 years in sporadic cases and 24.9 years in hereditary cases (27).

The diagnosis of hormonally active pheochromocytomas depends on the detection of increased plasma levels of free metanephrines and metoxytyramine (28, 29). Surgical resection, under careful pharmacological preparation, is the treatment of pheochromocytomas; the procedure is performed either by laparoscopic resection or transabdominal resection. Depending on the anatomic location, from 10% to 40% of pheochromocyctomas are malignant, and the associated 5-year survival is 50% (30). Treatment options for locally advanced or malignant pheochromocytomas include; chemotherapy, radiation therapy, ^{131}IMIBG, and molecular targeted therapeutics. The regimen of cyclophosphamide, vincristine, and dacarbazine is the most often used front line therapy for patients with advanced disease, even though there has been no prospective clinical trial evaluating its efficacy (31). In a retrospective evaluation of temozolomide in 15 patients with metastatic pheochromocytoma the progression free survival was 13.3 months; 5 patients had partial responses, 7 patients had stable disease, and 3 patients had tumor progression. Interestingly, the partial responses only occurred in patients with *SDHB* mutations (32). In a retrospective study of sunitinib in 17 patients with malignant pheochromocytomas, 3 patients had a partial response and 8 patients had stable disease. Most patients who had a clinical benefit carried the *SDHB* mutation (33).

A recent Cancer Genome Atlas study of the genomic landscape of 173 pheochromocytomas found that considering somatic mutations, DNA chromosome breaks, mRNA proliferation, and methylation, pheochromocytomas have a relatively quiet genome; however, they have the highest degree of heritability of any human tumor (34). In twelve familial syndromes, linked to a specific genetic locus, there is an increased risk of developing pheochromocytomas (29). In 65% of pheochromocyctomas, mutations have been discovered in 19 mutually exclusive susceptibility genes. The mutations are either germline (*SDHA, SDHB, SDHC, SDHD, RET, VHL, NF1, MAX, EGLN1*, and *TMEM127*), or somatic (*HRAS, EPAS1, ATRX, CSDE1, GPR128, SETD2, ARNT, FGFR1*, and *BRAF*). *RET, VHL*, and *NFI* occur as both germline mutations and somatic mutations (23, 34, 35).

Pheochromocytomas can be divided into 3 clusters, depending on whether they have mutations in genes that alter proteins constituting the Krebs cycle (*SDHA, SDHB, SDHC, SDHD, SDHAF2, MDH2*, and *FH*), in genes associated with the hypoxic response (*VHL* and *EPAS1*), or in genes linked to signaling in the RAS/RAF, MAPK or mTOR pathways. The mechanisms of oncogenesis remain unknown for a large number of pheochromocytomas.

Pheochromocytoma was the first human tumor shown to be caused by a germline mutation of *SDHD*, a gene that encodes a metabolic enzyme, and also the first human tumor shown to have activating mutations in *HIF2A* (36, 37). Jochmanova and Pacak in the accompanying manuscript focus on the metabolic aspect of pheochromocytomas, describing them as the first metabolic endocrine tumors, and discussing how metabolic alterations generated by genetic mutations suggest avenues for personalized cancer management (38).

Thyroid Cancer

Thyroid cancer is the most common endocrine malignancy, and over 95% of the tumors arise from follicular cells, most often as differentiated thyroid carcinomas; including, papillary (85%) and follicular thyroid carcinomas (2 to 5%), and less often as poorly differentiated (1 to 3%), or anaplastic thyroid carcinomas (1 to 3%). Generally, papillary thyroid carcinomas and follicular thyroid carcinomas are indolent clinically; whereas poorly differentiated and anaplastic thyroid carcinomas are highly aggressive with mean survivals of 3.2 years and 6 months. The incidence of thyroid cancer has tripled over the last three decades, primarily due to the increased detection of small papillary thyroid carcinomas on imaging studies (39, 40). Papillary thyroid carcinomas less than 1 cm in size (papillary microcarcinomas) occur in up to 30% of adults. The majority of microcarcinomas are stable over time, and can be managed expectantly by monitoring tumor growth (41, 42). Approximately 5% of thyroid cancers are derived from the neural crest as medullary thyroid carcinoma.

The encapsulated variant of the follicular variant of papillary thyroid carcinoma accounts for 10 to 20% of all thyroid cancers diagnosed in North America and Europe, and can be dived into invasive and noninvasive subtypes (43). In a recent international study, 109 patients with noninvasive encapsulated follicular variant papillary thyroid carcinoma treated by thyroid lobectomy alone were alive with no evidence of disease at a median of 13 years after treatment. The authors proposed the name “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” for these especially indolent neoplasms, and suggested that they not be considered cancers. This new classification would affect more than 45,000 patients annually world-wide (44).

Compared to other tumors, papillary thyroid carcinoma has a low mutation density, which is consistent with its relatively indolent behavior. Prior work demonstrated mutually exclusive clonal mutations in papillary thyroid carcinoma (*BRAF*; 60%, *RAS*; 15%, and chromosomal rearrangements involving *RET*, and *NTRK1*; 5 to 40%), follicular thyroid carcinoma (*RAS*; 40 to 55%, and rearranged *PPARG1*; 25 to 60%), poorly differentiated thyroid carcinoma (*BRAF*; 0 to 13%, *RAS*; 20 to 30%, *CTNNB1*; 0 to 5%, and *TP53*; 17 to 40%), and anaplastic thyroid carcinoma (*BRAF*; 10 to 35%, *RAS*; 20 to 60%, *CTNNB1*; 66%, and *TP53*; 67 to 90%) (45).

A recent Cancer Genome Atlas study of 496 papillary thyroid carcinomas identified new mutations in *EIFIAX, PPM1D, CHEK2* genes, and novel chromosomal rearrangements of *BRAF, RET, NTRK*, and *ALK*, thereby reducing the number of unknown driver mutations from 25% to 3.5% (3, 46). It is hoped that molecular targeted therapeutics can be developed to effectively target these newly discovered diver mutations. The Cancer Genome Atlas

study investigators were able to divide papillary thyroid carcinomas into 3 molecular subtypes with mutually exclusive mutations and variable degrees of differentiation: (1) recurrent mutations in genes; the most prominent being *BRAF* (59.7%), *NRAS* and *HRAS*, (14.0, (2) gene fusions of *BRAF, RET, PPARG, NTRK1, NTRK3, ALK, LTK, MET, FGFR2*, and *THDA* (15.3%), and (3) somatic copy number alterations. The investigators also found that $BRAF^{V600E}$ mutated PTCs signal preferentially through the MAPK pathway, while *RAS* mutated PTCs signal through either the MAPK pathway or the PI3K pathway (3). These findings support the reclassification of papillary thyroid carcinomas to more accurately define the relationship between genotype and phenotype.

Recent cytological techniques, based either on proprietary gene expression classification, or on next generation sequencing of a panel of oncogenes, have sharpened the diagnosis of inconclusive fine needle aspirates of thyroid nodules (47, 48). Also, phase III prospective, randomized, placebo-controlled clinical trials of the molecular targeted therapeutics, sorafenib and lenvatinib, have shown significant improvement in progression free survival, but not overall survival in patients with advanced differentiated thyroid carcinoma (49, 50). The FDA has approved both drugs for the treatment of advanced differentiated thyroid carcinoma.

Thyroid lobectomy, or total thyroidectomy, with or without resection of cervical lymph node compartments, is the treatment for primary thyroid cancer, the specific operation depending on tumor histology and the extent of disease. Postoperative adjuvant ^{131}I is administered to patients with a high risk of recurrence. Measurement of thyroglobulin in the postoperative period is useful in detecting persistent or recurrent disease

Less than 5% of thyroid cancers are medullary thyroid carcinomas, the majority of which are sporadic; however, 25% are hereditary and present as the major part of the multiple endocrine neoplasia (MEN) syndromes, MEN2A and MEN2B. The tumor cells secrete the polypeptide calcitonin, which serves as an excellent tumor marker for detecting recurrent or persistent disease following thyroidectomy, and especially for determining disease progression, as judged by the rate at which the level of serum calcitonin doubles over time. Approximately 50% of sporadic medullary thyroid carcinomas have somatic *RET* mutations, and a lesser number have *RAS* mutations. Virtually all hereditary medullary thyroid carcinomas have germline *RET* mutations, and there is a strong genotype-phenotype relationship in patients with MEN2A and MEN2B, not only regarding the range of disease expression, but also the severity of disease. Based on phase III prospective, randomized, placebo - controlled, trials that showed significant improvement in progression free survival, the FDA approved vandetanib and cabozantinib for the treatment of patients with advanced medullary thyroid carcinoma (51, 52) (Table 1).

The treatment of patients with metastatic thyroid cancer has evolved, since 1974 when the FDA approved doxorubicin for the treatment of advanced thyroid cancer (53). Unfortunately, most chemotherapeutics, whether administered alone or in combination with other agents, have shown low response rates of short duration; understandably, the FDA has approved no other chemotherapeutic agent since doxorubicin. Until recently, suppression of thyroid stimulating hormone and the administration of radioactive iodine were the primary

treatments for patients with metastatic differentiated thyroid carcinoma. For patients who failed this therapy, and for patients with advanced medullary thyroid carcinoma, poorly differentiated thyroid carcinoma, or anaplastic thyroid carcinoma, chemotherapy, with or without radiation therapy was the only option. The advent of molecular targeted therapeutics has opened a new era of therapy for patients with advanced differentiated and medullary thyroid carcinoma, and even though the new drugs provide no overall survival benefit, they have significantly improved progression free survival, and often a patient's cancer will remain in remission for several months, and sometimes years.

In the accompanying article Raue and Frank-Raue provide a succinct overview of the histological types of thyroid cancer (54). In differentiated thyroid carcinomas they define patients with low, intermediate, and high risk disease, stressing the importance of dynamic risk assessment, based on several variables, to define both an initial treatment plan for primary thyroid cancer, and a management strategy to evaluate and treat patients with recurrent or persistent disease following thyroidectomy (55).

Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors arise from the islets of Langerhans and range from islet cell hyperplasia or adenomas to poorly differentiated neuroendocrine carcinomas. Less than 5% of all pancreatic tumors are neuroendocrine in origin, and their incidence - 0.4 cases per 100,000 - has increased over the last three decades, partly due to the aging population and to their incidental detection on imaging studies (56). The prevalence of pancreatic neuroendocrine tumors at autopsy is approximately10% (57, 58). Sporadic pancreatic neuroendocrine tumors appear around the sixth or seventh decade of life, but hereditary tumors develop at a younger age. Most pancreatic neuroendocrine tumors are nonfunctional and malignant, and over half of them have metastasized at the time of diagnosis. Nonfunctional pancreatic neuroendocrine tumors have a worse prognosis compared to functional tumors, and among the functional tumors the prognosis varies according to the histological subtype (59). The World Health Organization grading system for neuroendocrine carcinomas (Gi, G2, or G3) is based on an increasing Ki-67 index or mitotic count (<2% to >20%), TNM stage, and functional activity (60).

Larsson's report that the MEN1 gene is located on chromosome 11, and is most likely a tumor suppressor gene, was confirmed by Chandrasekharappa and associates, who cloned the *MEN1* gene and named the gene product menin (61, 62). No *MEN1* mutation is found in 10 to 30% of typical MEN1 kindreds (probably the result of current DNA sequencing strategies) and 10% of the mutations are de novo, there being no family history (63). *MEN1* is also the most common mutation in sporadic pancreatic neuroendocrine tumors, followed by mutations in *DAXX/ATRX (Death-Domain Associated Protein/Mental Retardation Syndrome X-Linked Genes)* and the mTOR (*Molecular Target of Rapamycin*) pathway (64). There is no genotype phenotype relationship in patients with MEN1, unlike MEN2, where specific *RET* mutations are associated with clinical phenotypes. Furthermore, unlike MEN2, genetic screening in kindreds with MEN1 does not lead to a recommendation regarding medical or surgical intervention.

The primary treatment of pancreatic neuroendocrine tumors is surgical resection, although the procedure fails to cure most patients with malignant tumors. Cytoreductive surgery for bulky regional disease or accessible metastases may reduce morbid symptoms caused by hormone excess (65). Arterial embolization, chemoembolization, radioembolization, and radiofrequency ablation may be effective in some patients with hepatic metastases (66–68).

In the accompanying manuscript, Maxwell and associates provide an excellent overview of the diagnosis and treatment of pancreatic neuroendocrine tumors, stressing the importance of the clinical trials that led to FDA approval of effective therapeutics for the treatment of advanced pancreatic neuroendocrine tumors (69). Until recently, streptozotocin was the only approved treatment for pancreatic neuroendocrine tumors; however the effectiveness of this agent alone, or combined with other chemotherapeutics remains controversial (70, 71). The majority of pancreatic neuroendocrine tumors have G protein-coupled somatostatin receptors (SSTRs), and a reduction in receptor density is associated with increased tumor dedifferentiation (72). Somatostatin acts through a family of five receptors (SSTR1 to SSTR5).

Somatostatin analogues were introduced to control symptoms associated with the excess secretion of hormones from pancreatic neuroendocrine tumors. The short and long-acting synthetic somatostatin analogues octreotide and lanreotide have a strong binding affinity for SSTR2, SSTR3, and SSTR5 (expressed in brain, anterior pituitary gland and, gastrointestinal tract; SSTR2 is also expressed in the pancreas) (73). Both drugs have shown efficacy in clinical trials of patients with midgut neuroendocrine malignancies (74, 75). (Table) In the PROMID study, a long-acting release octreotide, compared to placebo, showed a significantly prolonged time to recurrence, and a marked risk reduction in tumor progression (74). In the CLARINET trial, lanreotide, compared to placebo, showed an improved progression free survival in patients with gastrointestinal neuroendocrine tumors (75). Based on the PROMID and CLARINET trial results, the FDA approved octreotide and lanreotide for the treatment of advanced neuroendocrine tumors. The recently developed somatostatin analogue, pasireotide, binds primarily to all SSTRs except for SSRT4, and is more effective than octreotide in inhibiting GH, IGF1, and ACTH (76). The drug, however, inhibits insulin secretion, and treated patients are at risk for glucose intolerance, which is reversible following cessation of therapy. Recently, the FDA also approved the angiogenesis inhibitor, sunitinib, based on a phase III, prospective, randomized trial that showed improved median progression free survival in the treatment group compare to placebo (77). The RADIANT I, II, and III trials evaluated the mTOR inhibitor everolimus in patients with GP-NETs (78–80). Based on the prolonged progression free survival (but not overall response rate) compared to placebo (RADIANT III) the FDA also approved everolimus for the treatment of advanced pancreatic neuroendocrine tumors. Even though these new molecular targeted therapeutics have shown efficacy, responses are almost always transient and the tumor ultimately progresses.

Pituitary Tumors

The incidence of symptomatic pituitary tumors in the general population is 1:1000, although recent radiological and autopsy studies suggest a prevalence as high as 22% (81).

Functioning endocrine tumors, including: prolactinomas (25 to 40%), somatotroph adenomas (1 to 15%), adrenocorticotrophic adenomas (~10%), and TSH producing adenomas (~1%) are associated with recognizable clinical syndromes. Five to 10% of pituitary tumors secrete excess gonadotrophins (LH/FSH), often causing hypogonadism (82). From 30 to 40% of pituitary tumors have no endocrine function, but become symptomatic when they enlarge and compress adjacent structures, or destroy normal pituitary cells, causing hypopituitarism (83, 84).

Pituitary tumors are monoclonal, and although they are aneuploid, only 0.2% are malignant (85, 86). Less than 5% of pituitary tumors occur as a benign component of hereditary syndromes, such as MEN1, MEN4, the Carney Complex, and familial isolated pituitary adenoma (87–90). The term, MEN4, applies to rare patients with the MEN1 phenotype, who have germline mutations in *CDKN1B*, not *MEN1*. The Carney complex, characterized by multiple skin lesions cardiac myxoma, acromegaly, schwannoma, thyroid tumors, and pigmented nodular adrenocortical disease, is caused by germline mutations in *CNC1* which encodes the regulatory subunit of the protein kinase A (PRKAR1A). Approximately 65% of patients have mutations in *PRKARIA* and 20% have mutations in the putative CNC2 gene located on chromosome 2; however, the specific gene has not been identified. Dominant germline mutations in the aryl hydrocarbon-receptor interacting protein gene, *AIP*, occur in about 20% of patients with familial isolated pituitary tumors; however, no tumors are found in 80% of family members, who carry the mutation, indicating that there are other undiscovered genetic causes of the syndrome.

The large majority of pituitary tumors are sporadic, and not associated with any known syndrome; however, germline *AIP* mutations are found in 4% of them; the incidence being higher in children and in young adults with macroadenomas or gigantism. Sporadic tumors with *AIP* mutations, compared to those without *AIP* mutations, are more common in males, are larger and invasive, and secrete growth hormone, or prolactin. Germline mutations in *MEN1* are found in 0.6 to 2.6% of very young patients with isolated pituitary tumors (82, 91). There are few reports of *CDKN1B* mutations, and no reports of *PRKAR1A* mutations in sporadic pituitary tumors (92).

Although the subject of intense investigation, the role of epigenetic regulation on the pathogenesis of pituitary adenomas, is unclear and merits further investigation.

In their article on the genetic background of pituitary adenomas, Caimari and Korbonits discuss non-syndromic and syndromic pituitary adenomas (93). They also describe a number of somatic mutations associated with sporadic pituitary tumors, but note that the role of these mutations in tumor pathogenesis and progression is unclear.

Conclusions

Although recent discoveries in molecular medicine have led to a deeper understanding of endocrine neoplasia, much remains unknown. Novel molecular targeted therapeutics have improved progression free survival in patients with some endocrine cancers, yet they have failed to improve overall survival. With the development of molecular therapeutics that

specifically target causative mutations, and the design of combinatorial drug regimens based on an understanding of mechanisms of drug resistance, there is hope of curative therapy. At present curative therapy depends on the age-old, yet important, principle of establishing the diagnosis of malignancy at an early stage when treatment is curative.

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TABLE 1

RECENT PHASE III CLINICAL TRIALS OF FDA APPROVED NOVEL THERAPEUTICS FOR TREATMENT OF THYROID CANCERS AND PANCREATIC NEUROENDOCRINE TUMORS

DRUG TRIAL	RANDOMIZATION	HISTOLOGY	PFS	DR/DD/DTH
Sorafenib (DECISION)[52]	207 Soraf 210 Placebo	DTC	10.8 mos. Soraf 5.4 mos. Placebo HR 0.59 (95% CI; 0.39–0.61), P < 0.0001	64.3%/18%/12, 1, drug related
Lenvatinib (SELECT)[53]	261 Lenvat 131 Placebo	DTC	18.3 mos. Lenvat 3.6 mos. Placebo HR 0.21 (99% CI; 0.14–0.31), P< 0.001	67.8%/14.2%/ 20, 6 drug related
Vandetanib (ZETA)[54]	231 Vand 100 Placebo	MTC	30.5 mos. Vand 19.3 mos. Placebo HR 0.46 (95% CI; 0.31–0.69), P< 0.001	35%/12%/ 5,1 possibly drug related
Cabozantinib (EXAM)[55]	219 Cabo 111 Placebo	MTC	11.2 mos. Cabo 4.0 mos. Placebo HR 0.28 (95% CI, 0.19–0.40) P <0 .001	79%/22%/12, 9 drug related
Octreodide LAR (PROMIDE)[73]	42 LAR 43 Placebo	NETs	14.3 mos. LAR * 6.0 mos. Placebo HR 0.34 (95% CI,0.20 to 0.59) P< 0.0007)	NA/12%/None
Lanreotide (CLARINET)[74]	101 Lanreotide 103 Placebo	EPNT	MPFS not reached Lanreotide 18.0 mos. Placebo HR 0.47 (95% CI, 0.30–0.73) P<0.001	NA/3%/2
Sunitinib[76]	86 Sunitinib 85 Placebo	PNET	11.4 mos. Sunitinib 5.5 mos. Placebo HR 0.42 (95% CI, 0.26–0.66) P<0.001)	NA/NA/ 5, 1 drug related.
Everolimus (Radiant 3)[79]	207 Everolimus 203 Placebo	PNET	11.0 mos. Everolimus 4.6 mos. Placebo HR 0.35 (95% CI, 0.27–0.45) P< 0.001	NA/13%/12, 1 drug related

* = Time to tumor progression