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# Novel concepts for initiating multitargeted kinase inhibitors in radioactive iodine refractory differentiated thyroid cancer

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Multitargeted kinase inhibitors have been shown to improve progression-free survival in patients with structurally progressive, radioactive iodine refractory differentiated thyroid cancer. While the inclusion criteria for phase 3 clinical trials and clinical practice guidelines provide guidance with regard to the minimal requirements that need to be met prior to initiation of a multitargeted kinase inhibitor, a better way to integrate the rate of

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structural disease progression with the size of the metastatic foci to more precisely define the optimal time to recommend initiation of therapy for individual patients is needed. In this manuscript we describe how to use assessments of tumor size and growth rates (structural disease doubling times) to define the critical point in time when the volume and rate of progression of metastatic structural disease merits consideration for initiation of systemic therapy (the inflection point).



## Introduction

A structural incomplete response to initial therapy (persistent or recurrent structural disease) is seen in up to 30% of patients with differentiated thyroid cancer who have been treated with total thyroidectomy and radioactive iodine (RAI) remnant ablation [1–3]. While the majority of structural incomplete responses will have persistent disease only in the neck, as many as 5%–10% may have distant metastasis at presentation, with an additional 5%–10% developing distant metastases during follow up [4]. The majority of distant metastases are located in the lungs, with a smaller number located in the bones or in other sites [4]. While many distant metastases remain asymptomatic, disease progression can be associated with a wide variety of symptoms, including pain and dyspnea on exertion.

Although two-thirds of patients with metastatic disease demonstrate substantial uptake of RAI, only 42% demonstrate complete structural resolution of their disease, and fewer than 10% demonstrate complete resolution of both biochemical and structural evidence of disease [5–7]. While 10-year survival rates of >95% have been documented in young patients with distant metastases, a median 10-year overall survival rate of <50% can be expected in older patients with either papillary or follicular thyroid cancer presenting with distant metastases [8,9]. Unfortunately, long-term overall survival drops to 10% when distant metastases are not responsive to RAI therapy [5]. Further, overall survival is significantly worse in patients with bone or brain metastases [6,10]. While traditional chemotherapy is associated with short-term response rates of $\leq$25% [11], multitargeted kinase inhibitors have demonstrated much better results with documented improvements in progression-free survival associated with a tolerable side-effect profile [12–15].

In a recently described cohort of 199 patients with pulmonary metastases, an increase in the size and/or number of metastatic foci was documented by Sabra and colleagues in 68% of patients despite repeated doses of RAI therapy (Fig. 1) [6]. For the entire cohort, the median time to progression was 3.7 years, with 17% of patients progressing by the end of year 1, 35% by year 2, 55% by year 5, and 65% by year 10. However, disease progression occurred sooner and more often in RAI refractory patients (Table 1). Further, progression-free survival was significantly worse in patients with aggressive histologies (poorly differentiated thyroid cancer, hurthle cell cancer), fluorodeoxyglucose-positron emission tomography (FDG-PET) avid disease, metastatic lesions > 1 cm in diameter, bone metastasis, and in patients over 45 years of age at the time the metastatic disease was identified [6].

With the approval of two oral multitargeted kinase inhibitors (lenvatinib and sorafenib) for the treatment of RAI refractory thyroid cancer, the clinician and the patients are now faced with the challenging decision of when to initiate multitargeted kinase inhibitor therapy. Both agents are approved for progressive or symptomatic RAI refractory thyroid cancer that is not amenable to localized therapies. However, in clinical practice, it is quite common to see patients with RAI refractory disease that is either stable or slowly progressive. Further, in some patients, the pace of clinical disease progression appears to increase as the metastatic lesions increase in size. Therefore, the precise time point in the clinical course of disease progression to initiate therapy for an individual patient can be difficult to identify. As such, treatment of advanced thyroid cancer is optimally undertaken in the context of a functional, integrated, disease-management team because management of these patients may require extensive surgery, external beam irradiation, radiofrequency ablation, embolization, or metastasectomy either in addition