

Supplementary Material

Supplementary Table S1. Selected recent/ongoing studies of interest investigating questions and controversies related to TKI therapy of RAI-R DTC

<i>Clinical issue</i>	<i>Recent/ongoing studies</i>	<i>Comments</i>
Starting dose: “higher (full recommended dose) versus lower”	E7080-G000-211 (identifier NCT02702388; https://clinicaltrials.gov/ct2/show/NCT02702388 , last accessed 28 October 2020)	Ongoing randomized, double-blind, multicenter Phase 2 study comparing safety profile and efficacy of lenvatinib, 18 mg vs. 24 mg starting dose
Utility of biomarker-guided intermittent versus continuous TKI regimen	“Adaptive Tyrosine Kinase Inhibitor (TKI) Therapy In Patients With Thyroid Cancer” (NCT03630120; https://clinicaltrials.gov/ct2/show/NCT03630120?term=lenvatinib&cond=Thyroid+Cancer&draw=2&rank=17 , last accessed 28 October 2020)	Ongoing randomized, single-center Phase 2 study comparing conventional lenvatinib or sorafenib regimens against respective drug regimen in which patients are treated or not based on thyroglobulin levels

Clinical issue	Recent/ongoing studies	Comments
Utility of using non-TKI adjuncts in combination with TKI in patients with insufficient response to TKI monotherapy	<p>UPCC 36315 (identifier NCT03139747; clinicaltrials.gov/ct2/show/NCT03139747?term=lenvatinib&cond=thyroid+cancer&draw=2&rank=10, last accessed 28 October 2020)</p> <p>Study of Everolimus and Sorafenib in Patients With Advanced Thyroid Cancer Who Progressed on Sorafenib Alone (identifier NCT01263951 (https://clinicaltrials.gov/ct2/show/NCT01263951?term=sorafenib&cond=Thyroid+Cancer&draw=2&rank=2, last accessed 28 October 2020)</p> <hr/> <p>Evaluating the Combination of Everolimus and Sorafenib in the Treatment of Thyroid Cancer (identifier NCT01141309 (https://clinicaltrials.gov/ct2/show/NCT01141309?term=sorafenib&cond=Thyroid+Cancer&draw=2&rank=4, last accessed 15 October 2020)</p> <p>Sorafenib Tosylate With or Without Everolimus in Treating Patients With Advanced, Radioactive Iodine Refractory Hurthle Cell Thyroid Cancer (Identifier NCT02143726; https://clinicaltrials.gov/ct2/show/NCT02143726?term=sorafenib&cond=Thyroid+Cancer&draw=2&rank=7, last accessed 28 October 2020)</p>	<p>Ongoing or just-completed Phase 2 studies evaluating addition of the mTOR inhibitor everolimus to lenvatinib in patients who progressed on lenvatinib monotherapy or to sorafenib in patients who progressed on (NCT01263951) or could be (NCT01141309) or had to be (NCT02143726; Hürthle-cell RAI-R DTC only) naïve to sorafenib monotherapy; NCT02143726 is a randomized, controlled, crossover study</p>

<i>Clinical issue</i>	<i>Recent/ongoing studies</i>	<i>Comments</i>
Utility of TKI + denosumab in treating bone-predominant metastatic RAI-R DTC	LENVOS (Identifier NCT03732495; http://clinicaltrials.gov/ct2/show/NCT03732495?term=lenvatinib&cond=thyroid+cancer&draw=3&rank=12 , last accessed 28 October 2020)	Ongoing open-label, multicenter Phase 2 study evaluating addition of the denosumab to lenvatinib in patients with bone-predominant metastatic RAI-R DTC
Utility of TKI + checkpoint inhibitor combination therapy	Combination Targeted Therapy With Pembrolizumab and Lenvatinib in Progressive, Radioiodine-Refractory Differentiated Thyroid Cancers (ATLEP Study) (Identifier NCT02973997; https://clinicaltrials.gov/ct2/show/NCT02973997?term=lenvatinib&cond=Thyroid+Cancer&draw=3&rank=18 , last accessed 28 October 2020)	Ongoing multicenter Phase 2 study evaluating the combination of lenvatinib with the checkpoint inhibitor pembrolizumab

DTC, differentiated thyroid carcinoma; mTOR, mechanistic target of rapamycin; RAI-R DTC, radioiodine-refractory differentiated thyroid carcinoma; TKI, tyrosine kinase inhibitor