Alliance A091302: Randomized Phase II Study of Sorafenib with or without Everolimus in Patients with Radioactive Iodine Refractory Hürthle Cell Thyroid Cancer

Eric J. Sherman

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Rationale

We have recently completed a phase II study evaluating the efficacy of sorafenib and everolimus in RAI-refractory thyroid cancer. The phase II study used the recommended dose of sorafenib 400 mg twice a day with everolimus 5 mg daily37. In the phase II study of thyroid cancer at Memorial Sloan Kettering Cancer Center, a total of 41 patients were enrolled onto the study of which 36 are currently eligible for evaluation of the primary endpoint of response. Data updated in September of 2013 (unpublished) now shows nine of these patients had Hürthle cell RAI-refractory thyroid cancer. Of these 9 patients, 7 (78%) had either a confirmed or unconfirmed partial response and 2 had stable disease (both patients with stable disease have remained on study for greater than 1 year). Only 2 of the 9 patients came off study in less than a year (one for progression of disease and one for protocol-defined toxicity). As of September 2013, the median time on study has been 500 days (ranging from 76 to 791 days). Both the response rate and the time on study are impressively higher than reported in the Ohio State study (i.e., 0% partial response rate; median progression free survival of 4.5 months). The reason for this increase in response with the addition of everolimus to sorafenib in the Hürthle Cell subgroup has yet to be elucidated, and further investigations are ongoing at Memorial Sloan Kettering Cancer Center.

Based on these impressive results in a single arm phase II study, along with the lack of proven efficacious agents for the treatment of Hürthle cell RAI-refractory thyroid cancer, we have decided to proceed with a randomized phase II study in this uncommon cancer.

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Objective

Primary

- To compare the progression-free survival (PFS) between sorafenib and everolimus vs. sorafenib alone in patients with radioactive iodine refractory Hürthle cell thyroid cancer.

Secondary

- To compare the confirmed response rate, overall survival (OS), and adverse event rates between sorafenib and everolimus vs. sorafenib alone.

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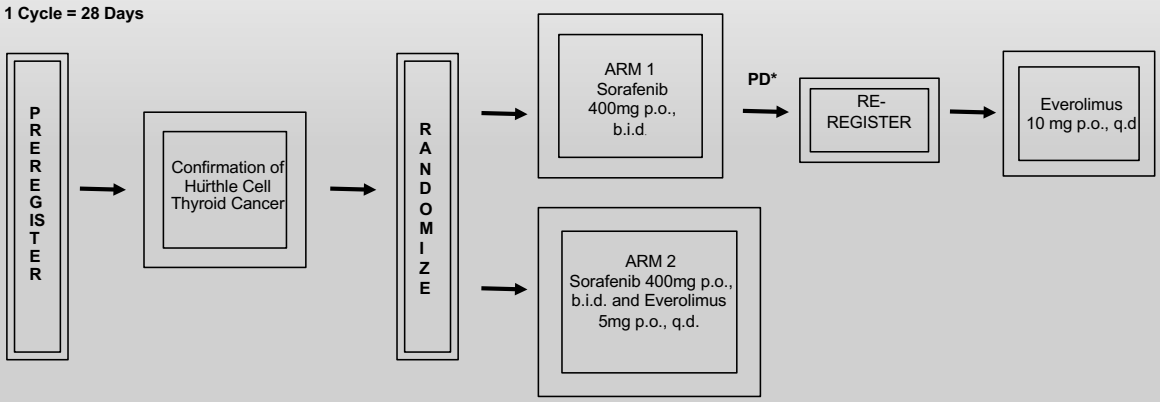
Study Schema



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*PD = Progression of Disease

Treatment is to continue until disease progression or unacceptable adverse event. Patients will be followed for 5 years or until death, whichever comes first. Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

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Treatment Plan

ARM 1

Agent	Dose and Route	Frequency	Cycle Length (ReRx)
Sorafenib*	400 mg PO	Twice daily	28 days

ARM 2

Agent	Dose and Route	Frequency	Cycle Length (RxRx)
Sorafenib*	400 mg PO	Twice daily	28 days
Everolimus**	5 mg PO	Once daily	28 days

Crossover for ARM 1

Agent	Dose and Route	Frequency	Cycle Length (ReRx)
Everolimus**	10 mg PO	Once daily	28 days

* Sorafenib should be taken twice daily on an empty stomach one hour before or two hours after eating. This tablet should be swallowed whole and cannot be crushed or chewed.
** Everolimus should be administered once daily at approximately the same time each day with or without food. Tablets should be swallowed whole with a glass of water. The tablets must not be chewed or crushed and grapefruit juice or grapefruit should be avoided.

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Key Eligibility Criteria

Pre-Registration

Central pathology review submission:

- Patients must have 10 representative H&E stained thyroid tissue slides OR tumor block available for submission to central pathology review. This review is mandatory prior to registration to confirm eligibility.

Registration

- Patients must have measurable disease by RECIST criteria, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan; CT must be performed within 28 days of registration.
- RAI-refractory disease defined in the protocol.
- Progressive disease defined by RECIST criteria < 14 months.
- Patients must have metastatic disease or locally advanced unresectable disease.

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