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MERAIODE: A redifferentiation phase II trial with trametinib followed by radioactive iodine for metastatic radioactive iodine refractory differentiated thyroid cancer patients with a RAS mutation

S. Leboulleux[1], D. Benisvy[2], D. Taieb[3], M. Attard[4], C. Bournaud[5], M. Terroir[6], A. Al Ghuzlan[7], L. Lamartina[8], M.J. Schlumberger[9], Y. Godbert[10], I. Borget[11]

[1] Medecine Nuclear and Endocrine Oncology, Gustave Roussy - Cancer Campus, Villejuif, France, [2] Nuclear Medicine, CLCC Antoine Laccasagne, Nice, France, [3] Nuclear Medicine, CHU Timone, Marseille, France, [4] Radiology, Gustave Roussy - Cancer Campus, Villejuif, France, [5] Nuclear Medicine and endocrinology, Hospices Civils de Lyon, Lyon, France, [6] Nuclear Medicine, Gustave Roussy - Cancer Campus, Villejuif, France, [7] Pathology, Gustave Roussy - Cancer Campus, Villejuif, France, [8] Nuclear Medicine and Endocrine Oncology, Gustave Roussy - Cancer Campus, Villejuif, France, [9] Nuclear Medicine, Institut Gustave Roussy, Villejuif, France, [10] Medical oncology, Institut Bergonie, Bordeaux, France[11] Biostatistic And Epidemiology, Institut Gustave Roussy, Villejuif, France

Background

Two-thirds of metastatic differentiated thyroid cancers (DTC) become refractory to radioactive iodine (RAIR). The inhibition of the MAP-kinase pathway activated in case of *RAS* mutation might increase RAI incorporation into metastatic foci and reverse RAI refractoriness. MERAIODE is a prospective multicentric, open-label, phase II trial, evaluating the efficacy and tolerance of trametinib followed by RAI administration in metastatic RAIR DTC patients.

Methods

Patients with *RAS* mutated RAIR metastatic DTC with RECIST progression within 18 months prior to enrollment and no lesion > 3 cm were included. A rhTSH-stimulated diagnostic whole body scan (dc WBS1) was performed at baseline. Patients were treated with trametinib for 42 days. At day 28, a second rhTSH-stimulated dc WBS2 was performed. After 35 days, a therapeutic activity of RAI (5.5 GBq) was administered independently of the results of dcWBS2. Primary endpoint was objective response rate (ORR) at 6 months according to RECIST v1.1 (central review).

Results

Patients: Among the 11 patients (mean age 67 years, 4 females) *RAS* mutated RAIR DTC included between March 2018 and May 2020 in centers from the TUTHYREF network, 11 received trametinib, 10 received therapeutic activity of RAI, and 10 were evaluable for the primary outcome. Results: Abnormal RAI uptake was present in 3 (30%) patients on the baseline dc-WBS1, in 4 (40%) on the dc-WBS2 and in 6 (60%) on the post-therapeutic WBS; The RECIST 6-months tumor response was partial response (PR) in 20% (95%CI 2-56), stable disease (SD) in 70% (95% CI 35-93) and progressive disease (PD) in 10% (95% CI 0-45). At 6-month, the FDG metabolic PET response was PR in 2/8 (25%), SD in 5/8 (63%) and PD in 1/8 (13%). Decrease in serum thyroglobulin > 50% occurred in 15% of the patients. Most frequent toxicities were diarrhea, asthenia, and cutaneous eruption, all grade 1-2. A grade 3 gamma-GT+ PAL elevation occurred in 1 patient. No grade 4-5 adverse event occurred.

Conclusions

Trametinib in RAS-mutated patients restores RAI uptake in a few patients and is followed by tumor response in 20% with limited adverse events. (PHRC 2015, NCT 03244956).

Clinical trial identification

NCT 03244956.

Legal entity responsible for the study

Institut Gustave Roussy.

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Disclosure

S. Leboulleux: Financial Interests, Personal, Advisory Board: Eisai; Financial Interests, Personal, Advisory Board: Lilly. D. Taieb: Financial Interests, Personal, Principal Investigator: Sanofi Genzyme; Financial Interests, Personal, Advisory Board: Novartis;

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