Thyroid

THYROID CANCER AND AUTOIMMUNITY

MERAIODE: A Redifferentiation Phase II Trial With Trametinib and Dabrafenib Followed by Radioactive Iodine Administration for Metastatic Radioactive Iodine Refractory Differentiated Thyroid Cancer Patients With a BRAFV600E Mutation (NCT 03244956)

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Background: Two-thirds of patients with metastatic differentiated thyroid cancer (DTC) become refractory to radioactive iodine (RAIR). The inhibition of the MAP-kinase pathway that is activated in case of *BRAFV600E* mutation might increase RAI incorporation into metastatic foci and reverse the RAI refractoriness. MERAIODE is a prospective multicentric open-label phase II trial, using a one-stage Fleming design, evaluating the efficacy and tolerance of trametinib (a MEK inhibitor) and dabrafenib (a BRAF inhibitor) treatment followed by the administration of RAI in metastatic RAIR DTC patients.

Methods: Patients with *BRAFV600E* mutated RAIR metastatic DTC with RECIST progression within 18 months prior to enrollment and no lesion > 3 cm were included. A baseline rhTSH-stimulated diagnostic whole body scan (dc WBS) was performed prior to treatment initiation. Patients were treated with dabrafenib (150 mg bid) and trametinib (2 mg per day) for 42 days. At day 28, a second rhTSH-stimulated dc WBS was performed. After 35 days, a therapeutic activity of RAI (5.5 GBq) was administered. Primary endpoint was objective response rate (ORR) at 6 months according to RECIST v1.1 (central review).

Patients: Among the 24 patients (mean age 67 years, 15 females) with a *BRAFV600E* mutated RAI refractory papillary DTC included between March 2018 and January 2020 in 8 French centers from the TUTHYREF netwok, 24 patients were treated and 21 patients were evaluable for the principal outcome at 6 months.

Results: Abnormal RAI uptake was present in only 1 of the 21 patients (5%; 95%CI 0-24%) on a RAI diagnostic whole body scan (dc-WBS) performed prior to treatment initiation, in 11 patients, 11/17 (65%; 95%CI 38-86) on a dc-WBS performed 4 weeks after dabrafenib-trametinib initiation and in 20/21 (95%; 95%CI 76-100) on the post-therapeutic WBS performed after 5.5 GBq of RAI. The RECIST 6-months tumor response (central review) was partial response (PR) in 38% (95%CI 18-61), stable disease (SD) in 52% (95% CI 30-74) and progressive disease (PD) in 10% (95% CI 1-30). The median change in the sum of target lesions was -22% (range: -79 to +46) at 6 months after baseline. The 6-month fluorodesoxyglucose metabolic PET response was PR in 11/17 (65% 95%CI 38-86), SD in 4/17 (23%) (95% CI 7-50) and PD in 2/17 (12%; 95% CI 1-36). Among the 15 patients without Tg antibodies, 7 (47%) patients had a decrease of serum thyroglobulin level on T4 treatment by more than 50%All patients experienced at least one grade 1-2 adverse event, mainly asthenia, nausea, fever, diarrhea and cutaneous eruption. Nine grade 3 toxicities occurred in 6 treated patients. No grade 4-5 adverse event occurred

Conclusion: The association of dabrafenib and trametinib in BRAFV600E mutated patients is effective for restoring RAI uptake and is followed by a tumor control in 90% of patients and by tumor response in 38% with limited adverse events. (PHRC 2015, NCT 03244956)

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Phenotypic Differences in Thyroid Immune Related Adverse Events Following Treatment With Immune Checkpoint Inhibitors

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Background: Thyroid toxicity is common following immune checkpoint inhibitor (ICI) treatment. Published studies estimate the incidence at 10-20%, although rates vary widely between different ICIs. The etiology of ICI-associated thyroid immune related adverse events (irAEs) is unknown & not all patients develop a classic thyroiditis-like presentation of transient hyperthyroidism followed by a hypothyroid phase. Only small observational cohorts have been reported & the clinical & biochemical features of thyroid irAEs have not been well characterized. The current study aimed to describe thyroid irAEs in a large cohort of patients with melanoma. **Methods:** We reviewed outcomes in a prospective cohort of adult patients undergoing ICI treatment for advanced melanoma. Thyroid function was measured at baseline & at regular intervals during treatment. Thyroid irAEs were defined as new biochemical thyroid dysfunction developing over the course of routine follow-up. **Results:** Thyroid irAEs occurred in 518 of 1246 (42%) patients. Median follow-up was 11.3 months. Multiple patterns of thyroid-irAEs were observed, such as hyperthyroidism (subclinical or overt) in 31%, hypothyroidism in 8%, & euthyroid hyperthyroxinemia, hypothyroxinemia & isolated low FT3 syndrome each in 1% of participants. Thyroid irAEs were more frequent following combination (CTLA-4 + PD-1) ICI treatment (56%) than following PD-1 (38%) or CTLA-4 (25%) based monotherapies (p=0.001). The severity of thyroid irAEs differed by ICI, with higher rates of overt (vs. subclinical) thyroid dysfunction following combination ICI treatment (47%) relative to PD-1 (37%) & CTLA-4 (19%) monotherapies (p=0.001). Younger age (OR