SUMMARY

TITLE	An academic phase II trial coordinated by Lyon university hospital to assess the safety and the efficacy of the IMMUNOtherapy with Domvanalimab + Zimberelimab combination in patients with anaplastic thyroid cancer
ACRONYME	IMMUNORARE[5] :
N° EUCT	2024-517254-99-00
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UNMET NEED IN ANAPLASTIC THYROID CARCINOMA	With an incidence of 0.1-0.2/10^5/year, anaplastic thyroid carcinomas represent 2-3 % of thyroid carcinomas, but are responsible for 15-40% of thyroid cancer mortality. Their median OS was 6.8 months in a recent analysis of the French database of the TUTHYREF network. Survival rates at 12 months were 32.7% (27.8–37.7%). Most cases (> 90%) are diagnosed with advanced unresectable disease. In such patients carrying the BRAFV600 mutation (20-30%), the standard 1st-line treatment relies on dabrafenib & trametinib. In patients without BRAF mutation, the 1st line treatment is chemoradiation. There is no validated 2nd line treatment. Immunotherapy efficacy was promising in these refractory cancers. For example, in DUTHY trial (Durvalumab + Tremelimumab), the 6month-OS was 65.6% in anaplastic cancers. TIGIT is expressed on ATC in 55% of cases, and this is correlated with poor prognosis. Moreover, TIGIT expression increased during ICI treatment, suggesting potential synergistic effects by simultaneous blockade of TIGIT and PD-1.
HYPOTHESIS	Domvanalimab (AB154) is a humanized IgG1 mAb that targets human TIGIT. Domvanalimab comprises 2 heavy chains of the IgG1 isotype and 2 light chains. The 4 chains are stabilized by multiple disulfide bonds, with a single glycosylation site located on each heavy chain. The molecular weight of Domvanalimab is 145 kilodaltons (kDa) (deglycosylated mass). Zimberelimab is a fully human IgG4 mAb that targets human PD-1. Zimberelimab comprises 2 heavy chains of the IgG4 isotype and 2 light chains. The 4 chains are stabilized by multiple disulfide bonds, with a single glycosylation site located on the heavy chain. The molecular weight of Zimberelimab is 144 kDa (deglycosylated mass). We assume that the combination of Domvanalimab and Zimberelimab is more effective than historical standard treatments in patients with 5 types of advanced rare cancers (peritoneal mesotheliomas, gestational trophoblastic tumors, B3 thymomas / thymic carcinomas, anaplastic thyroid carcinomas, and GEP-NET/TCT/UP-N)
OBJECTIVES	**Primary objective:** The primary objective is to assess the **efficacy** of the combination of Domvanalimab and Zimberelimab in patients with anaplastic thyroid carcinoma in progression/resistance after at least one standard line of treatmen.t **Secondary objectives**: To assess the **efficacy** according to overall response rate. To assess the efficacy according to progression-free survival (RECIST) To assess the **tolerability** of the combination of Domvanalimab and Zimberelimab given alone (cohorts 1-4)
ENDPOINTS	**Primary endpoint :** The primary endpoint for anaplastic thyroid carcinomas will be the survival rate at 24 weeks after the start of study treatment. Proportion of patients alive at 24 weeks (%). **Secondary endpoints** 1) **Overall response rate** defined as the proportion of patients experiencing complete or partial radiological response as the best radiological tumor response on the study period according to RECIST 1.1**;** 2) **Progression-free survival (PFS)** defined as the time elapsed between inclusion and disease progression/death whichever occurs first, according to RECIST criteria Patients alive without progression will be censored at the last date of imaging assessment. **3) Adverse events** and grades according to NCI-CTCAE v 5 criteria.

TUTHYREF CENTERS	Hospices Civils de Lyon Institut Gustave Roussy, Villejuif Institut Curie, Paris Centre Hospitalier Universitaire de Lille Institut Bergonié, Bordeaux ONCOPOLE Claudius Regaud, IUCT-Oncopole, Toulouse Institut de Cancerologie de l'Ouest AP-HM, Hopital TIMONE Institut Paoli-Calmettes Marseille Insitut de Cancérologie Strasbourg Europe
STUDY TYPE	Open-label national multicenter single-arm phase II trials in 5 rare cancers, sponsored by Lyon University Hospital, led in collaboration with the corresponding French national reference centers, with a centralized coordination by a dedicated team. Each phase II trial is designed as a two-stage Simon design, with early termination for futility. Qualification: clinical trial for a medicinal product for human use. IMMUNORARE will comprise 5 independent cohorts of patients treated with Domvanalimab + Zimberelimab Cohort 4 is dedicated to anaplastic thyroid carcinomas Synthetic historical arm: The data from the corresponding French reference centers will be investigated to build synthetic historical arms representative of the efficacy of the standard treatments in similar populations of patients in each cohort. The efficacy of Domvanalimab + Zimberelimab in terms of 6-month disease progression-free rate (cohorts 1, 3, 4, 5) and hCG normalization (cohort 2) will be compared to those of the synthetic historical arms in each cohort. Cohorts will be investigated as independent studies, and will be the objects of separate submissions to health authorities.
NUMBER OF PATIENTS	The numbers of patients were calculated according to a two-stage phase II trial design based on the Simon et al approach (Control Clin Trials. 1989 Mar;10(1):1-10), with a null hypothesis (H0) and an alternative hypotheses (H1) regarding the percentages of patients with success, with 5% one-sided alpha level and 80% power. The efficacy interim analysis may stop inclusions for futility. Treatment would not be considered interesting if the percentage of patients free from events at 6 months is lower than 25% (H0). It is expected that 50% will be free from events at 6 months (H1). At the first step, 9 patients will be included. If the interim analysis does not conclude to futility, 15 additional patients will be included, for a total of 24 assessable patients with at least one full cycle of study treatment (minimax design). Taking into account a 10% of patients not assessable at 6 months or that changed treatment for another reason than progression, 27 patients with at least one full cycle of study treatment will be necessary for evaluation. At most 5% additional patients will be included to achieve 29 patients with at least one full cycle of study treatment. So at most 30 patients will be included. The patients candidates will be identified during the twice a month national multidisciplinary board organized by the French network TUTHYREF where all ATC patients with a discussion of second line treatment are presented. If a patient is identified, the coordinating group will contact the closest French recruiting center to the patient home, so a participation can be proposed to the patient. The expected enrolment rate is 1-2 patients/year/center, for a completed recruitment in 36 months.
DURATION	**Duration of the inclusion period**: The recruitment is planned on a 3 year time period. Each cohort will be led independently. **Duration of participation for each subject (treatment + follow-up)**: Patients will continue to be treated until disease progression, or alternatively 2 years in case of complete response (upon discussion with the coordinator of the study, the coordinator of the cohort and the investigator).

	After treatment discontinuation the patients will be asked to participate to two safety follow-up visits, respectively at 1 and 5 months after the end of treatment. Patients will then enter a long-term follow-up period, where subsequent disease progressions, subsequent treatments, and vital status will be collected through medical records consultation, contacts with the hospitals in which the patients are followed up for further care, or phone calls to the patients. The long term follow up will last up to the end of the trial, and for minimum one year after the initial safety follow up visit. **Total duration of the study: up to 6 years and 1 month.** IMMUNORARE will end one year after the last visit scheduled for safety follow up.
INCLUSION CRITERIA	**General inclusion criteria for all cohorts** 1) Histologically proven advanced solid tumors that progressed/resisted after minimum one line of standard systemic treatment, or resisted during the first-line of treatment 2) No indication of curative surgery for this disease at inclusion 3) Evaluable lesions (target or non-target lesions) for radiological response according to RECIST 1.1 4) Patients older than 18 years 5) Patients with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 6) Patients must be willing to provide an archival tumor tissue block or slides, or undergo procedure to obtain a new biopsy in absence of medical contraindication *If either a fresh biopsy or archival material is not available, patient inclusion has to be discussed and validated with the coordinator of the cohort* 7) Patients with adequate bone marrow function measured within 28 days prior to administration of study treatment : • Absolute Neutrophil count > 1x 109/L • Platelets count ≥ 75 X 109/L • Hemoglobin ≥ 8 g/dL 8) Patients with adequate renal function: Calculated creatinine clearance ≥ 30 ml/min according to the local institutional standard method (MDRD preferred) 9) Serum bilirubin ≤ 1.5 x UNL (≤ 3 x ULN for patients with known Gilbert's syndrome), AST/ALT ≤ 2.5 X UNL (≤ 5 X UNL for patients with liver metastases) 10) Life expectancy ≥ 16 weeks 11) Highly effective contraception for men and childbearing age women. Effective contraceptive methods and guidelines can be found in the Annex 1 of this protocol 12) Signed informed consent prior to participating in any study related procedures. 13) Patients affiliated to the French social security system 14) Patient able to comply with the protocol, including follow-up visits and examinations **Specific inclusion criteria for ATC:** ○ Anaplastic thyroid carcinoma with non-mutated or mutated B-RAF, histologically or cytologically-confirmed by a referent pathologist of the Tuthyref network

	○ In B-RAF non-mutated anaplastic thyroid carcinomas: Persistent disease at the first evaluation after chemoradiation or disease progression/relapse after the end of chemoradiation ○ In B-RAF mutated anaplastic thyroid carcinoma: evidence of progression after a standard B-RAF inhibitor
EXCLUSION CRITERIA	- Previous treatment with immune checkpoint inhibitors (including anti-TIGIT, anti-PD1, anti-PD-L1, anti-CTLA4,), or other types of immunotherapy - Active or prior documented autoimmune or immune-related disorders (Stevens-Johnson syndrome, immune-related myocarditis, immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune mediated dermatologic adverse reactions, immune-mediated nephritis). - Medical condition that requires chronic systemic steroid therapy, or any other forms of immunosuppressive medication. - Uncontrolled intercurrent illness, including but not limited to, congestive heart failure; respiratory distress; liver failure; allergy; psychiatric illness/social situations that would limit compliance with study requirement according to the investigator, or that substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent. - Patients with a second primary cancer, except for: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other hematological or solid cancers curatively treated with no evidence of disease for ≥ 3 years. - All subjects with meningeal involvement. - Untreated or symptomatic Central nervous system (CNS) metastases. *Patients are eligible if the following criteria are met:* • *CNS lesions are asymptomatic and previously treated.* • *Patient does not require ongoing steroid treatment* • *Imaging demonstrates stability of disease 28 days from last treatment for CNS metastases.* - Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 6 weeks from the last dose prior to study treatment (or at least 5 half-lives depending on the defined characteristics of the agents used). The patient can receive a stable dose of bisphosphonates for bone metastases, before and during the study as long as these were started at least 4 weeks prior to treatment with study drug. - Treatment with other investigational agents prone to interact with outcomes of the trial upon to investigator opinion. - Bowel occlusive syndrome, inflammatory bowel disease, immune colitis, or other gastro-intestinal disorders that do not allow oral medication such as malabsorption. - Active HIV, HBV or HCV infection. - Prior organ transplantation, including allogeneic stem cell transplantation (excluding autologous bone marrow transplant). - Ongoing participation in any other clinical trial who may interfere with the present study in the judgment of the investigator - Patients under tutorship or guardianship.
CONDUCT OF THE STUDY	***Inclusion*** Initial assessment including: - Patient interview: - Demographic data - Medical history - Histological subtype - Treatment history

	- Duration of the previous line of treatment (last cycle – first cycle, in months) - Disease control duration during the previous line treatment (progression/first cycle, months) - Concomitant treatments Clinical examination including ECOG (Eastern Cooperative Oncology Group) performance status Electrocardiogram Measurement of LVEF Urine dip stick Biological tests: - CBC: red blood cells, hemoglobin, hematocrit, platelets, leukocytes, neutrophils, reticulocytes for cohort 3) - Serum chemistry: creatinine clearance according to local institutional standard method, creatinine, basic electrolytes (phosphor, calcium, sodium, potassium, and magnesium); troponin; C reactive protein; creatine kinase ; LDL-cholesterol, HDL-cholesterol, triglycerides, fasting glycaemia; - Liver function: albumin, ALT, AST, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase (GGT), prothrombin time (PT)/INR, alkaline phosphatase; - Serological testing for hepatitis B and C and HIV; - Antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), rheumatoid factor (RF), anti RACh antibodies for cohort 3. - Hormones : Thyroid function with TSH, T4L; 8h (8 :00 am) cortisol, adrenocorticotropic hormone (ACTH) at 8:00 am ; FSH, LH, estradiol (women) or testosterone (men) - Pregnancy test for child bearing age women - Samples collection for translational research - Archival or tumor tissue retrieval, blood, saliva and stools. **Specific baseline criteria for ATC** Histopathological review by a referent pathologist of the Tuthyref network, BRAF status must be available at inclusion Radiological evaluation of tumor extension at inclusion: Contrast enhanced thoracic-abdominal pelvic CT scan at arterial time of the 3 levels (or MRI thoracic scan and Gadolinium abdomino-pelvic MRI in the case of contraindication to contrast dye or unassessable target lesion with CT-scanner). A brain CT-scanner or a brain MRI, in the case of symptoms compatible with brain metastases. ***Treatment period*** Treatment cycle durations will last for 3 weeks **At day 1 of EACH CYCLE,** the following assessments will be performed including**:** Patient interview: - Adverse events - concomitant treatments Clinical examination including ECOG (Eastern Cooperative Oncology Group) performance status, Urine dip stick Biological tests: - CBC: red blood cells, hemoglobin, hematocrit, platelets, leukocytes, neutrophils - Serum chemistry: creatinine clearance by local institutional standard method, creatinine, basic electrolytes (phosphor, calcium, sodium, potassium, and magnesium); troponin; C reactive protein; creatine kinase; LDL-cholesterol, HDL-cholesterol, triglycerides. - Liver function: albumin, ALT, AST, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase (GGT), prothrombin time (PT)/INR, alkaline phosphatase; - Fasting glycaemia and hormones (TSH, T4L and Cortisol at 8:00 am): at every cycle until cycle 8 - ECG: every cycle until cycle 4; and then every 3 cycles **Additional tests:** **At Cycle 2 Day 1:** Blood, saliva and stool samples for translational research **Every two cycles during treatment:**

	Pregnancy test for child bearing age women **Every three cycles during treatment:** ECG (at every cycle up to cycle 4, then every 3 cycles) Fasting glycaemia and hormones (TSH, T4L and Cortisol at 8:00 am): at every cycle until cycle 8 and then every 3 cycles. **At 6 months and/or progression (for patients who have not progressed):** Blood, saliva and stools samples for translational research (see chapter 9.3 for details) **Efficacy assessments during treatment:** Tumor imaging assessment will be performed with the same tests as baseline at week 6 (+/- 1 week), then every 9 weeks (+/-1 week). Radiological evaluations must be carried out using the same type of test throughout the study. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. All participants who discontinue study intervention for reasons other than disease progression (eg, AEs) will continue tumor assessments according to the protocol guidelines (i.e. at week 6 +/- 1 week, then every 9 weeks +/- 1 week for cohorts 1-4 and every 8 weeks +/- 1 week for cohort 5) until death, disease progression, initiation of another systemic anticancer therapy, lost to follow-up, withdrawal of consent, or study termination, whichever occurs first.
STATISTICS	***Analysis population*** - All the patients who will have received at least a first dose of either study treatment (Domvanalimab and/or Zimberelimab;), will be evaluable for safety analyses. As a consequence, the patients who will not have started the treatment will be screen-failed, they will not be assessable for safety and efficacy, and will have to be replaced. - All the patients who will have received at least one full cycle of either study drug (Domvanalimab and Zimberelimab), equivalent to 3 weeks that did not change treatment for another reason than progression, and with status available at 6 months, will be evaluable for efficacy analyses. As a consequence, the patients who will discontinue the study treatment before reaching this time window will still be followed-up according to the protocol, and described in the study final report, but will be replaced for efficacy analyses considering the treatment will not have enough time to induce anti-cancer effect, as well as patients that changed treatment for another reason than progression, or patients not assessable at 6 months. - A per protocol population will be defined if other major deviations are encountered in the study (for the primary endpoint). ***Statistical methods*** The quantitative variables will be described by the following parameters: number of patients, number of missing values, mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3), minimum and maximum. Categories could be defined if applicable using a cut-off threshold from literature or quantiles. The qualitative variables will be described by the following parameters: number of patients, number of missing values, frequency and percentage of each modality (missing values will not be included in the denominator used for frequency computation). **For the primary endpoint**, a 5% one-sided alpha level will be used; 90% two-sided confidence intervals will be provided. **For secondary endpoints**, 95% two-sided confidence intervals will be provided. For time to events endpoints, Kaplan-Meier curves will be provided, using interval censoring approach (if necessary). Estimates will be provided at different time-points, with the associated 95% confidence intervals.
CALENDAR	The study should be activated during the 1st trimester of 2025
DATE DE PRESENTATION	Journées nationales TUTHREF 2024 et 2025