PROTOCOL

A) CLINICAL TRIAL IDENTIFICATION			
Title:	EDHITO		
Short title:	Randomized controlled trial evaluating the impact of therapeutic patient education on the toxicity of immune checkpoint inhibitors in oncology		
Coordonnateur:	Nathalie Beaumont		
Methodologiste:	Dr Valérie Seegers		
Estimated number of centers:	17	**Number of patients:**	411

B) SPONSOR IDENTIFICATION	
Name:	ICO, Service Promotion de la Recherche Clinique
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C) GENERAL INFORMATION ABOUT THE TRIAL	
Indication:	The study population may include patients with: • Melanoma, whether metastatic or not, or cutaneous squamous cell carcinoma • Non–Small Cell Lung Cancer (NSCLC) • Renal Cell Carcinoma (RCC) • Head and Neck Squamous Cell Carcinoma (HNSCC) Urothelial carcinoma • Any tumor location for which treatment with immune checkpoint inhibitors (ICIs) is indicated (authorized via marketing approval, early access program, or clinical research framework)
Design:	The study has the following characteristics: • National multicenter study • Controlled study • Randomized study (2:1 ratio) • Open-label study
Primary objective:	The primary objective of this study is to compare the number of patients experiencing at least one grade ≥ 3 immune-related adverse event (irAE) within the 25 weeks following the initiation of Immune Checkpoint Inhibitor (ICI) treatment between the experimental group receiving Patient Therapeutic Education (PTE) and the control group receiving standard information
Secondary objectives:	The secondary objectives of this study are as follows: 1. Characterize the toxicity of Immune Checkpoint Inhibitors (ICI): a. Description and timeline of onset of grade ≥ 2 immune-related adverse events (irAEs) b. Description of grade ≥ 3 non-immune-related adverse events (AEs) 2. Quantify the ICI treatment received 3. Assess the prevalence of immunosuppressive treatment use during ICI therapy 4. Measure the patient's quality of life and anxiety/depression status according to their treatment arm 5. Evaluate Patient Therapeutic Education (PTE):

	a. Acquisition of knowledge b. Development of skills c. Behavioral changes d. Patient satisfaction 6. Evaluate the effectiveness of PTE compared to standard information on response to ICI treatment and overall survival
Inclusion criteria:	To be included in the trial, the patient must meet all of the following criteria: 1. Patient with melanoma, cutaneous squamous cell carcinoma, non-small cell lung cancer, renal cell carcinoma (clear cell or papillary), upper aerodigestive tract cancer, or urothelial carcinoma, who is scheduled to receive ICI treatment as part of the approved indication (MA—Marketing Authorization) 2. Any patient with an indication for ICI treatment under a new MA, from the time of inclusion on the additional reimbursement list, within the framework of a Temporary Authorization for Use (ATU) or a Hospital Temporary Recommendation for Use (RIPH) 3. Patient who is naïve to any prior ICI treatment (the upfront combination of two ICIs is permitted for inclusion in the study) 4. Patient who has been informed and has signed the consent form 5. Age ≥ 18 years 6. Patient covered by a social security scheme
Non inclusion criteria:	Conversely, the patient will not be included in the study if they meet any of the following criteria: 1. Patient on systemic corticosteroids or immunosuppressive therapy less than 14 days before inclusion 2. Immunocompromised patient (HIV, transplant, graft, etc.) 3. Clinically uncontrolled brain metastases 4. Patient refusing Patient Therapeutic Education (PTE) 5. Individuals deprived of liberty or under guardianship (including curatorship) 6. Inability to comply with PTE follow-up for social or psychiatric reasons
Primary endpoint:	The primary endpoint is the number of patients experiencing at least one grade ≥ 3 immune-related adverse event (irAE, CTCAE v5.0) within the 25 weeks following the start date of ICI treatment.
Secondary endpoints :	1. Characterization of ICI Toxicity a) **Autoimmune Toxicity:** All grade ≥ 2 immune-related adverse events (irAEs, CTCAE v5.0) will be described in each arm (location, date of onset, and progression over 12 months following the start of treatment). Toxicities will be classified as: • Early (< 2 months during treatment) • Late (≥ 2 months during treatment) • Occurring after ICI discontinuation b) **Non-Autoimmune Toxicity:** Only grade ≥ 3 adverse events (AEs, CTCAE v5.0) will be described in each arm over the 12 months following the start of treatment. 2. Quantification of ICI Treatment Received For each patient, the total cumulative dose of ICI, the number of cycles, and the number of temporary suspensions and permanent discontinuations in each arm will be recorded, along with the reasons for these events. 3. Immunosuppressive Treatments

	Concomitant immunosuppressive treatments for irAEs (corticosteroids, anti-TNFα, tacrolimus, etc.) administered during patient follow-up will be described. 4. Quality of Life and Anxiety/Depressive State a) **Quality of Life**: The QLQ-C30 questionnaire will be completed at the first injection, at visits V3, V4, V5, and 12 months after the start of ICI treatment. b) **Anxiety and Depression Scores**: The Hospital Anxiety and Depression Scale (HADS) scores will be measured at the first injection, at visits V3, V4, V5, and 12 months after the start of ICI treatment. 5. Evaluation of Patient Therapeutic Education (PTE) In the experimental arm only, the acquisition of knowledge, development of skills, and behavioral changes/adaptations will be measured using questionnaires administered at the first (V1) and second (V2) injections, then at V3 (if needed), V4 (if needed), and V5. Patient satisfaction will be evaluated simultaneously. 6. Efficacy of ICI Treatment a) **Response**: The evaluation of response to ICI will follow the standard monitoring in the center. The best response within 25 weeks will be recorded. Since the Response Evaluation Criteria In Solid Tumors (RECIST 1.1) may underestimate the response to immunotherapy, specific criteria for the kinetics of response to immunotherapy have been developed, including bi-dimensional measurement of targets [Wolchok et al., 2009; Seymour et al., 2017]. iRECIST criteria will be collected if available. If the patient's response was evaluated using RECIST 1.1, the investigator will be asked to re-evaluate it using the adapted iRECIST criteria for ICI. b) **Overall Survival**: Given the possibility of pseudo-progression and the emergence of new lesions under ICI, progression-free survival may not be a reliable indicator of response. Overall survival will be evaluated as the time between the start of treatment and the date of death from any cause or the date of the last follow-up if the patient is censored.

D) DESCRIPTION OF STUDY INTERVENTIONS
Experimental arm In the experimental arm, patients will benefit from ETP (Patient Therapeutic Education) sessions as part of a program that will be submitted to the Regional Health Agency (ARS). The ETP program delivered to patients will be identical (structure, tools, and evaluations) for all patients in the experimental arm, regardless of the study site. **Initial Shared Educational Assessment**: Patients will first undergo a Shared Educational Assessment to identify their specific needs and knowledge gaps. **ETP Workshops**: Patients will attend two mandatory ETP workshops focused on managing immune-related adverse events (irAEs), self-monitoring, and treatment adherence. Additional ETP workshops may be offered based on individual patient needs during follow-up. **Final Shared Educational Assessment:** At 25 weeks after the start of ICI treatment, patients will undergo a final Shared Educational Assessment to evaluate progress, knowledge retention, and behavioral changes.
Control Arm In the control arm, patients will receive the standard care routinely provided at the institution.

Follow-up Plan	Screening Visit (Inclusion Visit): Within 28 days prior to randomization, the screening visit will allow the study to be proposed to the patient. If the patient agrees and after signing the informed consent form, randomization will be performed. The randomization visit may be conducted at the latest on the day of Visit 1 (V1). For the baseline assessment, the following information will be collected for all patients: **Clinical Examination** • Review of eligibility criteria • Informed consent signature • Performance Status (PS) • Medical history collection • Concomitant medication review No other specific tests for this trial will be performed. **Data Collection in the Experimental Arm (ETP) and Control Arm** Patients in both arms will undergo the following assessments during visits V1 (Week 1), V2 (Week 3 or 4), V3 (Week 7), V4 (Week 13), V5 (Week 25), and at 12 months from the start of the ICI: **a) Quality of Life Questionnaires** ○ Simplified PRO-CTCAE (except at V2, V3, and V5) ○ EORTC QLQ-C30 (except at V2) ○ HADS (except at V2) **b) Clinical Examination** ○ Toxicity assessment ○ Concomitant treatment review (including immunosuppressive treatments) **Data Collection in the Experimental Arm (ETP)** After randomization, patients will undergo a Shared Educational Assessment (BEP). The BEP must be completed no later than the day of the first ICI injection. **a) Visit 1 (V1) – Week 1** - Workshop: "Understanding the Disease and Treatment" - Assessment questionnaires - Educator evaluation **b) Visit 2 (V2) – Week 3 or 4** - Workshop: "Preventing and Managing Immunotherapy Adverse Effects" - Assessment questionnaires (satisfaction and knowledge) - Educator evaluation **c) Visit 2 (V2) – Week 3 or 4** - Workshop: "Preventing and Managing Immunotherapy-Related Adverse Events" - Assessment questionnaires: Patient satisfaction and knowledge - Educator Evaluation

	d) Visit 3 (V3) – Week 7 and Visit 4 (V4) – Week 13 - ETP Workshop: Conducted based on the patient's needs - Assessment Questionnaires: Patient satisfaction and knowledge (administered if an ETP session is held) - Educator Evaluation **e) <u>Visit 5 (V5) – Week 25</u>** - Final Shared Educational Assessment (BEP) - Assessment Questionnaires: Patient satisfaction and knowledge - Educator Evaluation - <u>Optional</u>: An ETP adjustment session may be conducted based on the results of the final Shared Educational Assessment Timing of Visit 5 (V5): Visit 5 must be conducted at the time of ICI treatment discontinuation, no later than 25 weeks after the start of ICI therapy. Between Visits: Telephone contact may be initiated as needed.
Treatment duration	The duration of the experimental intervention is 25 weeks, and the follow-up period is 12 months. The minimum participation time for a patient is 12 months.

E) STATISTICAL CONSIDERATION	
Sample Size Calculation:	**Hypothesis:** We hypothesize that therapeutic patient education (ETP), by enabling earlier detection of toxicities, will facilitate rapid therapeutic management and limit their worsening. Therefore, the number of patients experiencing at least one episode of grade ≥3 autoimmune toxicity during the first 25 weeks of treatment is expected to be lower in the ETP arm compared to the standard information arm. Assumptions for Sample Size Calculation: In the control group (standard information), the expected percentage of patients experiencing at least one grade ≥3 autoimmune toxicity during the first 25 weeks of ICI treatment is 15% (Eigentler et al., 2016). In the experimental arm (ETP), the expected percentage is 5%. To detect this difference with a 2:1 randomization ratio, an alpha risk of 5%, and a power of 80%, the study requires 228 patients in the ETP arm and 114 patients in the control arm, totaling 342 patients. Accounting for a 20% dropout or non-evaluable rate, the total number of patients to be included is 411 (274 in the ETP arm and 137 in the control arm). **Statistical Analysis:** The primary analysis will be conducted using a modified intention-to-treat (mITT) approach, including all randomized patients with available primary endpoint data. No imputation will be performed for missing primary endpoint data. In the event of missing primary endpoint data, a table comparing baseline characteristics of these patients with those included in the analysis will be provided to identify potential selection bias.

	A per-protocol analysis will also be performed for all randomized patients in the experimental arm who received at least three therapeutic education interventions (BEP and two workshops).
Statistical Analysis Plan	**Data Presentation** Patient baseline characteristics will be presented for all included patients and by treatment arm. Characteristics of the educational intervention (experimental arm) will also be described, including the number of ETP sessions, type of sessions (individual or group), and patient and educator questionnaire responses. Quantitative data will be summarized using means, standard deviations, medians, and interquartile ranges (25th–75th percentiles) and compared using a **t-test** or **Wilcoxon rank-sum test** for non-Gaussian distributions. Qualitative data will be summarized using frequencies and percentages and compared using a **chi-square test** or **Fisher's exact test**, as appropriate. Censored data will be presented for both randomization arms using the **Kaplan-Meier method**, and survival times will be compared using the **log-rank test**. Median survival times and their **95% confidence intervals** will be reported. **Primary Endpoint Analysis** The primary objective is to compare the proportion of patients experiencing at least one **grade ≥3 autoimmune toxicity (immune-related Adverse Events, irAEs, per CTCAE v5.0)** during the first 25 weeks of ICI treatment between the experimental arm (ETP) and the control arm (standard information). **Null Hypothesis (H0):** The proportion of patients with grade ≥3 autoimmune toxicity does not differ between the two arms. This proportion is defined, for each arm separately, as the ratio of patients with at least one grade ≥3 irAE during the first 25 weeks of ICI treatment to the total number of patients included in the analysis for that arm. **Alternative Hypothesis (H1):** There is a difference in the proportion of patients with grade ≥3 autoimmune toxicity between the two arms. To test this comparison, a **chi-square test** will be used to compare the proportions of patients with grade ≥3 autoimmune toxicity. The null hypothesis (H0) will be rejected at an **alpha level of 5%** if the **p-value is less than 0.05**.

STUDY CALENDAR

Number of patients expected :	411
Duration of inclusion:	48 months
Duration of treatment / Duration of follow up:	25 weeks / 12 months
Minimum Participation Time per Patient:	12 mois
Overall Trial Duration:	60 mois
Start Date of the Clinical Trial:	11/12/2019
End Date of the Clinical Trial:	Last Patient Last Visit

Expected Duration Until Primary Objective Analysis:	66 months
Intermediate analysis	No

STUDY ASSESSMENTS SCHEDULE

VISITS	INCLUSION PERDIO	RANDOMIZATION	TREATMENT PERIOD (ICI) (6 months)					FOLLOW UP PERIOD (6 months)
DATES	Between D-28 and randomization (g)		V1 1rst week	V2 3e or 4e weeks (a)	V3 At 7 weeks (a)	V4 At 13 weeks (a)	V5 At the end of ICI treatment and maximum at 25e weeks	12 months after the start of ICI treatment
Inclusion / Exclusion criteria	X							
Informed consent	X							
Randomization		X	Ou X (g)					
ICI TREATMENT								
ICI in D15			1re infusion	2e infusion	4e infusion	7e infusion	13e infusion	
ICI in D22			1re infusion	2e infusion	3e infusion	5e infusion	9e inje infusion ction	
CLINICAL EXAM (b)								
Clinical examn including PS	X							
Comorbidity	X							
Efficacy assessments				At each cycle			X	
Toxicity according to CTCAE v5.0			X	At each cycle			X	X (c)
Concomitant treatments	X		X	At each cycle			X	X
QUALITY OF LIFE AND ANXIETY/DEPRESSION QUESTIONNAIRES								
PRO-CTCAE s			X			X		X (postal)
QLQ-C30			X		X	X	X	X (postal)
HADS			X		X	X	X	X (postal)
ONLY ARM ETP								
Initial Shared Educational Assessment		X	Or X (h)				X	
ETP Workshops			Workshop 1 (d)	Workshop 2 (e)	X (if needed) (f)	X (if needed) (f)	X (if needed) (f)	
Assessment questionnaires			X	X	X (if ETP)	X (if ETP)	X	
Educator evaluation			X	X			X	
Telephone contact (if needed)				Between each infusion				

(a) Visits must be performed on the day of the injections, even in case of postponement. The week numbers are provided for guidance only.
(b) Data collection from the patient's medical record.
(c) Collection of toxicities at 12 months from treatment initiation; causality to be assessed by the investigator.
(d) Workshop 1 (individual or group session) must be completed no later than before the 2nd ICI injection.
(e) Workshop 2 (individual or group session) must be completed no later than before the 3rd ICI injection, regardless of the injection schedule.
(f) Adjustment session according to the patient's needs.
(g) Randomization may be performed on the day of Visit 1