**RACIN**

**A phase I study of the combination of low-dose radiation, aspirin, metronomic cyclophosphamide, ipilimumab and nivolumab in patients with advanced, TIL-negative solid tumors (NCT03728179)**

**Inclusion criteria**

1) Patients with locally advanced or metastatic incurable solid tumors (any histology), who progress after at least one standard therapy.

2) Signed main study Informed Consent Form.

3) Absence of tumor infiltrating intraepithelial CD8+ T cells by immune histochemistry on baseline biopsy defined as <5 CD8+ cells per high power field of tumor.

4) At least one lesion accessible to biopsy without putting patient at risk.

5) Number of metastatic lesions viewed on CT scan and irradiated: all metastatic lesions observed in the baseline CT scan can be irradiated. It is at the discretion of the investigator to exclude a metastatic site from the radiation field that, due to the radiotherapy volume, dose or location too close to a healthy organ, may put the patient at risk of suffering from radiation induced toxicity. If this would be the only metastatic site to be irradiated, the concerned patient will be excluded from the study.

6) Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol.

7) Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment:

a) ANC ≥1.5 G/L (without granulocyte colony-stimulating factor support within 2 weeks prior registration)

b) WBC counts ≥2.5 G/L and <15 G/L

c) Lymphocyte count ≥0.5 G/L

d) Platelet count ≥ 100 G/L (without transfusion within 1 week prior registration)

e) Hemoglobin ≥90 g/l (Patients may be transfused to meet this criterion but it should not be done within 1 week prior registration)

f) AST, ALT, and alkaline phosphatase ≤2.5 x ULN (with the exception for patients with documented liver metastases: AST, ALT and alkaline phosphatase ≤ 5 x ULN)

g) Serum bilirubin ≤1.5 x ULN (with the exception for: patients with known or suspicion of Gilbert disease who have serum bilirubin level ≤ 3 x ULN may be enrolled)

h) Coagulation: International Normalized Ratio or Prothrombin Time ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants; Activated Partial Thromboplastin Time ≤ 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.

i) Serum albumin > 25 g/l

j) Serum creatinine ≤1.5 X ULN or creatinine clearance ≥40 ml/min on the basis of Cockcroft-Gault Formula

8) No prior radiation therapy in areas of desired radiation

9) Patients may have had prior therapy provided a washout period of 4 weeks prior to registration is allowed. Exception: hormone therapy for breast and prostate cancer is allowed to be continued during the study. The introduction of a new line of hormonal therapy during the 6 months that proceed the study or during the study is not allowed

Patients who have received prior treatment with anti-PD1, anti-PD-L1 or anti-CTLA-4 may be enrolled, provided at least 5 half-lives (approximately 75 days) have elapsed from the last dose to the registration and there was no history of severe immune-mediated adverse effects from such therapy (NCI CTCAE v3.0 Grade 3 and 4)

10) Recovery from any toxic effects of prior registration to ≤ Grade 1 per the NCI CTCAE v4.03 except fatigue or alopecia.

11) For women of childbearing potential (sexually mature women who have not undergone a hysterectomy, have not been naturally post- menopausal for at least 12 consecutive months or have a serum follicle-stimulating hormone < 40 mIU/ml):

a. Agreement to use 2 acceptable methods of contraception during participation in the trial and for 6 months after last study combined treatment and after 5 months of maintenance treatment

b. Women must have a negative urine pregnancy test within 7 days before registration. A positive urine test must be confirmed by a serum pregnancy test, or menopausal as per NCCN guidelines.

12) For men: agreement to use 2 acceptable methods of effective contraception during participation in the trial and for 7 months after last study treatment (combined or maintenance treatment). Female partners of men who take part in this trial must also use at least one method of effective contraception during the trial and 7 months after last study treatment (combined or maintenance)

Abbreviations: TIL: tumor infiltrating lymphocytes, CT: computed tomography scan, ANC: absolute neutrophil count, WBC: white blood cells, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ULN: upper limit of normal, NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events, NCCN: National Comprehensive Cancer Network