A non-inferiority randomized phase III trial of standard immunotherapy VS. reduced dose intensity in responding patients with metastatic cancer: MOIO study

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BACKGROUND

Immunotherapy (IO) is increasingly used for treating various metastatic cancers.

With respect to the pharmacologically-active levels of IO drugs and their pharmacokinetics features, standard scheduling lead to plasma exposures largely exceeding the thresholds associated with target engagement :

- Phase I studies have shown that saturation of the target can persist far beyond the serum IO drugs half-life.
- *In silico* modeling studies have suggested that alternate scheduling (i.e. 3-monthly dosing) could be performed without compromising efficacy.
- Prolonged IO half-lives, time-varying clearance plus plasma concentrations far above the threshold associated with maximal target-engagement, suggest that the rhythm of IO administration could be slowed down.
- A phase II showed that extending IO dosing intervals did not compromise efficacy, while reducing toxicity in metastatic renal cell cancer.

STUDY DESIGN

MOIO is a non-inferiority, multicenter, randomized, controlled,open label phase III trial of reduced dose intensity of IO versus approved standard IO regimen in patients with metastatic oncologic tumour in partial (PR) or complete response (CR) after 6 months of treatment with standard IO (except melanoma in CR)

Patients will be randomized 1:1 into two arms:

- **Experimental arm: Reduced dose intensity of IO**
  IO will be administered every 3 months (at the same dose levels) until disease progression, unacceptable toxicity, death, patient's choice or investigator's decision.
- **Control arm: Standard IO**
  Continuation of IO at the same dose levels and rhythmicity until disease progression, unacceptable toxicity, death or for patient's choice.

Random allocation will be stratified by:

- **tumour type**
- **response status (**partial response vs complete response)
- **treatment line** (first line vs others)
- **type of IO** (anti-PD-1 vs anti-PD-L1)

INDICATION

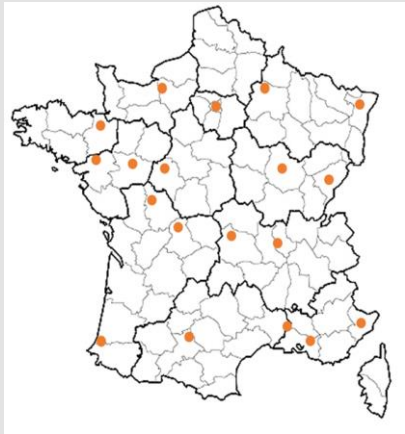
Only patients with oncologic metastatic tumour in partial or complete response after 6 months of standard IO treatment (monotherapy or previously in combination with other immunotherapy (ipilimumab) or chemotherapy or continuous combination with pemetrexed or bevacizumab or TKI).

Tumour types:

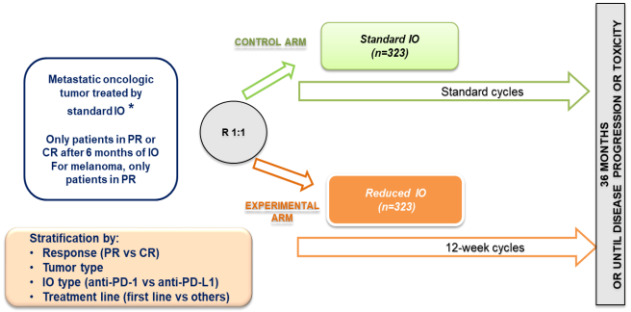
- Lung cancer
- Renal cell cancer (except IMDC favorable-risk treated Tyrosine Kinase Inhibitor [TKI] / immunotherapy [IO] combination)
- Head and neck cancer
- Bladder cancer
- Triple negative breast cancer
- Merkel cancer
- Melanoma (except melanoma in CR)
- Hepatocellular carcinoma

ENROLLMENT

- Nationwide participation
- Planned number of French centers = 36
- Planned number of patients: 646
- FPI = 08/03/2022



TRIAL SCHEMA



IO monotherapy or in combination
**Except mRCC patients with IMDC favourable risk treated TKI/IO combination*

INCLUSION PERIOD: **36 months**

TREATMENT DURATION: Until disease progression, unacceptable toxicity, death, patient's choice or investigator's decision

FOLLOW UP-PERIOD (including treatment period) : 36 months

OVERALL TRIAL ESTIMATED DURATION : 72 months

OBJECTIVES

PRIMARY OBJECTIVE

To demonstrate the non-inferiority in term of Progression-free survival (PFS) of administration of reduced dose intensity of IO versus standard IO for patients in response after 6 months of standard IO.

SECONDARY OBJECTIVES

- Cost-effectiveness,
- Immune progression-free survival using iRECIST,
- Objective response rate at 12 and 24 months post-randomization,
- Overall survival,
- Duration of response at 12 months post-randomization
- Quality of life (self-reported EORTC QLQ-C30, and EQ-5D-5L questionnaires),
- Anxiety and fear of relapse using specific questionnaires,
- Safety profile.

STATISTICAL METHODS

PRIMARY ENDPOINT

Non-inferiority in PFS will be evaluated on the per protocol set and mITT set. Cox's regression analyses including terms for randomization factors will be used to estimate the hazard ratio for treatment arm (reduced IO vs standard IO) with 90% confidence interval.

SECONDARY ENDPOINTS

- The economic evaluation will be based on the entire population of patients included in the trial. An incremental approach will be used with differences in costs and QALYs expressed as an incremental cost-effectiveness ratio (ICER) - cost per additional QALY gained
- Immune progression-free survival (iPFS), duration of response (DoR) and objective response rates (ORR) will be analyzed on the per protocol population and the mITT population.
- Overall survival (OS) will be analyzed in the mITT population.
- Analyses of self-reported questionnaires will be based on the mITT population set.

MAIN ELIGIBILITY CRITERIA

- Patient aged ≥18 years old.
- Initial metastatic disease histologically confirmed
- Patients in partial or complete response after 6 months of standard immunotherapy (whatever the line of therapy) according to the RECIST (confirmed by local radiological assessment). For metastatic melanoma only patients in partial response.
- Eligible to maintain the same standard IO treatment.
- Patient with ECOG performance status ≤1.
- Patients treated by IO previously combined with chemotherapy are allowed.
- Patients with TKI-IO or pemetrexed-IO or bevacizumab-IO are allowed.

ANCILLARY STUDY – MOIO-TR

This ancillary project is divided in 2 specific studies:

- An immune monitoring study,
- A pharmacokinetic study.

FFPE tumour sample and blood samples will be collected for 200 patients (100 patients per arm).

ANCILLARY OBJECTIVES AND ENDPOINTS

Immune monitoring study:
To identify immune biomarkers of long-term response allowing IO dose reduction by comparing soluble forms of immune checkpoints in plasma and immune cells population in PBMC between treatment arms.

Pharmacokinetic study:
To measure the IO's residual concentrations in plasma (trough levels) by comparing IO's residual concentrations in plasma between treatment arms.

Conclusion

Should the hypothesis of non-inferiority with an IO reduced dose intensity be validated, alternate scheduling could preserve efficacy while being cost-effective and allowing a reduction of the toxicity, with an increase in patient's of quality of life.

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