BACKGROUND

We raise the hypothesis that a 'stop and go' strategy with induction by double immunotherapy Nivolumab + Ipilimumab combination during 6 months, followed by observation in patients with disease control (DC) at 6 months, would not be inferior to immunotherapy combination continuation until progression or unacceptable toxicity, in terms of progression-free survival, allowing lower toxicities cumulative rates, better quality of life and lower costs. Such strategy should not penalize overall survival, provided resuming immunotherapy at disease progression before second-line platinum-based chemotherapy.

OBJECTIVES

- Primary objective
  
  According to a non-inferiority design, the primary objective will be to observe not significantly different median 1st Progression-Free Survival (PFS) from the date of randomization (thus in disease controlled patients) for the 'stop' and 'go' arm A, as compared to the standard arm A with immunotherapy until progression or unacceptable toxicity, followed by cisplatin-based chemotherapy at progression.

- Secondary objectives
  
  Quality of life
  Overall survival
  Safety and Tolerability

ELIGIBILITY CRITERIA

Inclusion Criteria

- Histologically-proven NSCLC (squamous or non-squamous)
- Stage IV (M1, including M1a pleural involvement) disease (8th classification TNM, UICC 2015)
- ECOG PS ≤ 1
- Measurable tumor disease by CT or MRI per RECIST 1.1 criteria
- Available tumor samples for centralized PD-L1 immunohistochemistry analysis
- PD-L1 tumor content ≥ 1% and < 50% tumor cells as assessed locally by the investigator center

Exclusion Criteria

- Known EGFR activating tumor mutation (deletion LREA in exon 19, L858R or L861X mutations in exon 21, G719A/S mutation in exon 18) or HER 20 insertion (either tissue or plasma ctDNA mutation).
- Known ALK or ROS1 gene rearrangement as assessed by IHC, FISH or NGS sequencing

OBJECTIVES

- Primary objective
  
  The primary objective is to compare the estimated median Progression-Free Survival (PFS) of the two arms (A and B) from the date of randomization, until progression or unacceptable toxicity, during the first line treatment.

- Secondary objectives
  
  Quality of life
  Overall survival
  Safety and Tolerability

ELIGIBILITY CRITERIA

Inclusion Criteria

- Histologically-proven NSCLC (squamous or non-squamous)
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STATISTICAL METHODS

Randomized Phase III study (Fleming-two-stage method), with a 2.5% unilateral alpha risk, and a power of 80%.

Assuming an estimated median PFS duration of 20 months from randomization, and a pre-specified non-inferiority limit for the hazard ratio (HR) of 1.25 to be excluded, it was estimated that a total of 868 patients (651 events needed) would be needed to be randomized (1:1). Non-inferiority will be concluded if the upper limit of the 95% confidence interval (CI) of the HR will be ≤ 1.25.

TREATMENTS

- INDUCTION: Patients are treated by nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks during 24 weeks.
- ARM A: Patients are treated by nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks until progression or unacceptable toxicity.
- ARM B: Patients are observed until progression then are treated by nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks until progression or unacceptable toxicity.

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