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The INCA trial: an open label, randomized, phase II trial evaluating Ipilimumab plus Nivolumab versus chemotherapy in non-small cells lung cancer

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Abstract:

Non-small cell lung cancer is a highly prevalent malignancy, whose social and economic burden have raised substantially in the previous decades. Novel progresses in the biological field have allowed the development of treatments aiming at regulatory check-points of our immune system. These new developments are shedding a hope towards an improvement in the quality of life and prognosis of affected individuals. Importantly, phase II studies have brought first evidences that a combination of two immune check points regulators, Ipilimumab and Nivolumab, could improve the overall prognosis of this disease. Therefore, in order to collect evidences on this therapeutic approach we aim to structure a well-defined clinical trial design. We describe a study design for a multicenter, randomized, phase II, open-label clinical trial which aims to compare the superiority of the combination Ipilimumab and Nivolumab versus chemotherapy (Pemetrexate-Cisplatin) in patients with advanced non-squamous non-small cell lung cancer naive to treatment. Over 24 months, we plan to evaluate progression-free survival as primary outcome, and relevant secondary outcomes as overall survival, objective response rate, quality of Life and adverse effects. Our trial design has the potential to collect relevant evidence on the safety and efficacy of the combined therapy Ipilimumab and Nivolumab in non-small cell lung cancer patients and open this therapeutic prospective for targeting other forms of tumors.

Keywords: Nivolumab; Ipilimumab; Clinical Trial, Phase II; Carcinoma, Non-Small-Cell Lung

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BACKGROUND AND RATIONALE

Primary lung cancer remains a leading cause of worldwide cancer-related death and non-small cell lung cancer (NSCLC) represents 85-90% of these cases (Leventakos & Mansfield, 2016). The American Joint Committee on Cancer defines the staging for NSCLC based on the primary tumor size and whether it has grown or spread to nodes and metastasized. Computer tomography, magnetic resonance imaging, and positron emission tomography are used to identify tumor dimensions, metastasis, and nodal involvement. Treatment decision on this type of cancer depends primarily on its staging. Platinum based therapy has been the first-line treatment for advanced stage NSCLC in the

past three decades. However, this treatment shows moderate-to-severe toxicities and few improvements in clinical outcomes. The proportion of patients who achieve a response to chemotherapy is limited to 30%; additionally, responses are rarely durable, and nearly half of patients die within 1 year (Hellmann et al, 2017).

Nivolumab (Opdivo®) is an antibody that target programmed cell death ligand 1 (PD-L1) and it was the first PD-L1 inhibitor to gain regulatory approval. It is currently used in patients with non-resectable NSCLC. (3) PD-L1 is a T-cell immune checkpoint involved in decreasing autoimmunity in the peripheral effector phase of T-cell activation, subsequently leading to immune tolerance of cells expression. Brahmer et al. suggested

that patients with the PD-L1 positive rate above 1% treated with Nivolumab showed better overall survival at one year compared with Docetaxel (42% (95% CI, 34 to 50) versus 24% (95% CI, 17 to 31), respectively), and a higher rate of confirmed objective response (20% (95% CI, 14 to 28) vs. 9% (95% CI, 5 to 15), respectively).(4)

Ipilimumab (Yervoy®) is cytotoxic T lymphocyte antigen-4 (CTLA-4) immune-checkpoint inhibitor antibody. It is a protein expressed in activated lymphocytes and conducted with T-cell-mediated cytotoxicity (Camacho, 2015). It received approval by the Federal and Drug Administration for the treatment of non-resectable stage III and metastatic melanoma in 2011. The mechanism of action suggests that Ipilimumab, alone or in combination, may be beneficial in treating different types of cancer (Antonia et al., 2016; Camacho, 2015).

Phase I/II trials in NSCLC demonstrated that a combination of Nivolumab plus Ipilimumab has tolerable safety profile and clinical activity characterized by a durable and high response rate; only a small number of participants discontinued treatment due to adverse events (13%) and no treatment related deaths were reported (Hellmann et al., 2017). First promising data are also emerging in the treatment of other forms of tumor as metastatic renal cell carcinoma (Motzer et al., 2018). Combined monoclonal antibody treatment against standard treatment for advanced non-squamous NSCLC has never been tested before. Therefore, the aim of this study is to assess over 24 months if combined therapy of Ipilimumab plus Nivolumab is superior to chemotherapy (cisplatin plus pemetrexed) in improving the time to tumor progression or death (Progression-Free Survival) in patients with advanced non-squamous NSCLC naive to treatment. Secondary end points will include overall survival, objective response rate, frequency and severity of each adverse event up to 100 days after the last dose of drugs, and Quality of Life evaluated by questionnaire at baseline and every tumor assessment until progression of disease or death (Abernethy et al., 2015).

METHODS

Research question

Is Ipilimumab plus Nivolumab superior to standard chemotherapy (cisplatin plus pemetrexed), in terms of progression free survival, in patients with advanced non-squamous non-small cell lung cancer?

- P (population) - Patients aged 18 years or older with chemotherapy naive non-squamous NSCLC and histological or cytological confirmation for stage IIIb or stage IV.

- I (intervention) - Ipilimumab plus Nivolumab.
- C (control) – Cisplatin plus pemetrexed.
- O (outcome) – Primary outcome: progression-free survival; secondary outcome: overall survival, objective response rate, quality of Life and adverse effects.
- T (time) – 24 months.

Hypotheses

Null hypothesis (H0): treatment of non-squamous NSCLC with “Ipilimumab plus Nivolumab” is equal to the standard treatment with “cisplatin plus pemetrexed”, in terms of PFS.

Alternative hypothesis (H1): treatment of non-squamous NSCLC with “Ipilimumab plus Nivolumab” is superior to the standard treatment with “cisplatin plus pemetrexed”, regarding PFS.

Primary and Secondary Aims

The primary aim is to determine whether the treatment of non-squamous NSCLC with “Ipilimumab plus Nivolumab” is superior to the standard treatment with “cisplatin plus pemetrexed” for stage IIIb and IV patients regarding PFS, with defined as in time in months between the date of randomization and the first date of documented tumor progression or death.

The secondary aim is to evaluate the difference between both treatments mentioned above regarding: i) overall survival, defined as the time from randomization to death from any cause; ii) overall response rate iii) adverse effects and iv) quality of Life.

Trial Design

This is a phase II, superiority trial, open label, randomized, and parallel group. Our primary outcome will be assessed by an independent radiologist following the modified Response Evaluation Criteria In Solid Tumors guideline (RECIST) (Fournier, Ammari, Thiam, & Cuénod, 2014). The participating sites will be located in the US and will have to meet the following to selection criteria: i) to recruit at least 30 patients, ii) to assign a committed principal investigator, iii) to have a dedicated clinical research team, and iv) to obtain institutional review board approval.

Randomization - sequence generation and allocation concealment

Randomization sequence will be created using Stata 9.0 (StataCorp, College Station, TX, USA) statistical software and will be stratified by center with a 1:1 allocation proportion. All patients who give consent for participation and fulfill the inclusion criteria will be

randomized. Randomization will be requested by the staff member responsible for recruitment and the sequence allocation will be generated by an Interactive Voice Response System. The randomization list remains with the Coordination Centre of Clinical Trials for the whole duration of the study. Therefore, there will not be any influence from main investigators, evaluators, or therapists during the conducted randomizations.

Blinding

This trial will be open-label, due to the complexity, well known adverse effects and difference in the treatment schemes (different pre-medication, infusion times and cycles periods) make it impossible to perform an adequate blindness.

Eligibility Criteria

Inclusion criteria:

Signed written Informed Consent; men and women ≥ 18 years of age; women of childbearing potential must have a negative serum or urine pregnancy test and must use a highly effective method(s) of contraception (failure rate of less than 1% per year); histological or cytological confirmation of advanced non-squamous NSCLC naive to treatment; stage IIIB or stage IV disease; at least one measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1); PD-L1 expression at least 1%; no previous chemotherapy for advanced disease; no previous treatment with immunological therapy; performance Status Eastern Cooperative Oncology Group (ECOG) of 0 or 1, or Karnofsky score $> 70\%$; life expectancy at least 3 months; all baseline laboratory requirements within -14 days of randomization; WBCs $\geq 2000/\mu\text{L}$ o Neutrophils $\geq 1500/\mu\text{L}$ o Platelets $\geq 100 \times 10^3/\mu\text{L}$ o Hemoglobin ≥ 9.0 g/dL. o Serum creatinine of $\leq 1.5 \times$ Upper Limit of Normal (ULN) o AST and ALT $\leq 2.5 \times$ ULN, or $\leq 5 \times$ ULN if liver metastasis is present o Total bilirubin $\leq 1.5 \times$ ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL).

Exclusion criteria:

Pregnant or breastfeeding women; subjects with active, known or suspected autoimmune disease (e.g. rheumatoid arthritis, progressive systemic sclerosis (scleroderma), systemic lupus erythematosus, vasculitis (e.g. Wegener granuloma); subjects with carcinomatous meningitis; subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization; prior therapy with anti-PD-1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including Ipilimumab or any other

antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways); subjects with a history of interstitial lung disease; other active malignancy requiring concurrent intervention; all toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) (U.S. Department of health and human services. National Institutes of Health National Cancer Institute, 2010) or baseline before administration of study drug; subjects positive for human immunodeficiency virus (HIV); subjects positives for Hepatitis B and/or C; history of severe hypersensitivity reactions to other monoclonal antibodies; history of severe hypersensitivity reaction to prior drug in the study; ongoing or planned administration of anti-cancer therapies other than those specified in this study; treatment with any investigational agent within 28 days of first administration of study treatment.

Recruitment Strategy

Time of recruitment: 2 years. We created a Recruitment and Adherence Coordination Center (RACC), responsible to reach the sample size and maintain the adherence all long the study. The RACC will contact, by e-mail, phone call or personally, many specialized hospitals in oncology and pulmonology, with emphasis on lung cancer. They will receive invitation letters to participate in the study, explaining all the purpose's project, benefits, and safety control to oncologists for the treatment of NSCLC. Once the hospital accepts participating in the study, the research team will visit the center in order to present the study and train the doctors and other professionals to guarantee the accuracy of data collection. Considering that the majority of the patients with advanced lung cancer presents to many hospitals to get a treatment, the doctor, who has received the training, will identify potential patient for the study and communicate the RACC. We will create a channel communication by e-mail and phone with doctors in case of new patients. The research recruitment coordinator will analyze all responses and verify compliance with the inclusion and exclusion criteria, responding to each contact.

Adherence

Adherence deviations will be reported for the intention to treat population. To present a good study adherence to the protocol, some adherence strategies will be taken, such as:

- Reminders (phone call with subjects and phone application to remind the patients about each appointment).

Table 1

Outcomes and their assessment intervals.

Outcome	Assessment Interval
Primary outcome	
Progression free survival	12 weeks
Secondary outcome	
Overall survival	At discontinuation or End of study
Objective response rate	At discontinuation or End of study
Adverse events	At every tumor assessment visit, or patient reported
Quality of life score	At every tumor assessment visit

- Specific training for the site staff to provide the effective communication with the subjects.
- Schedule of regular study visits. Research visits will be organized conceiving patients and trial timelines, to avoid missing follow-ups in the study schedule.
- Upon patient consent, family members will be contacted to help the patient in correctly following the study schedule.
- A person of the research team will be responsible for 20 patients and will be available 24h on a specific phone number, where patients can call every time they have issues, problems or want to quit the study.
- Additionally, there will be a group meeting out of 20 patients to exchange problems. - There will be a psycho-oncologist available all the time to overview and help patients.
- \$20 will be handed out for each visit of every patient.

Interventions

Eligible patients will be randomized in equal proportions between intervention and control groups. Intervention group will receive Nivolumab 3mg/kg, 60 min infusion, every 15 days, and Ipilimumab 1mg/kg, 90 min infusion, every 6 weeks. Control group will receive vitamin B12 and folic acid supplementation seven days prior to chemotherapy as well as dexamethasone three days prior to the intervention. On day 1 of the cycle patients will receive 30 minutes of pemetrexed infusion, followed by a 6-hours cisplatin infusion. The number of cycles for the control group will be 6, according to the most recent National Comprehensive Cancer Network (NCCN) guidelines (Ettinger et al., 2017), Figure 1a. In the setting of adverse events classified as grade 3 or 4 the drug administration should be discontinued. According to National Cancer Institute common terminology criteria

for adverse events version 4.0, grade 3 is classified as severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ADL), while grade 4 is classified as life-threatening consequences; urgent intervention indicated (U.S. Department of health and human services. National Institutes of Health National Cancer Institute, 2010).

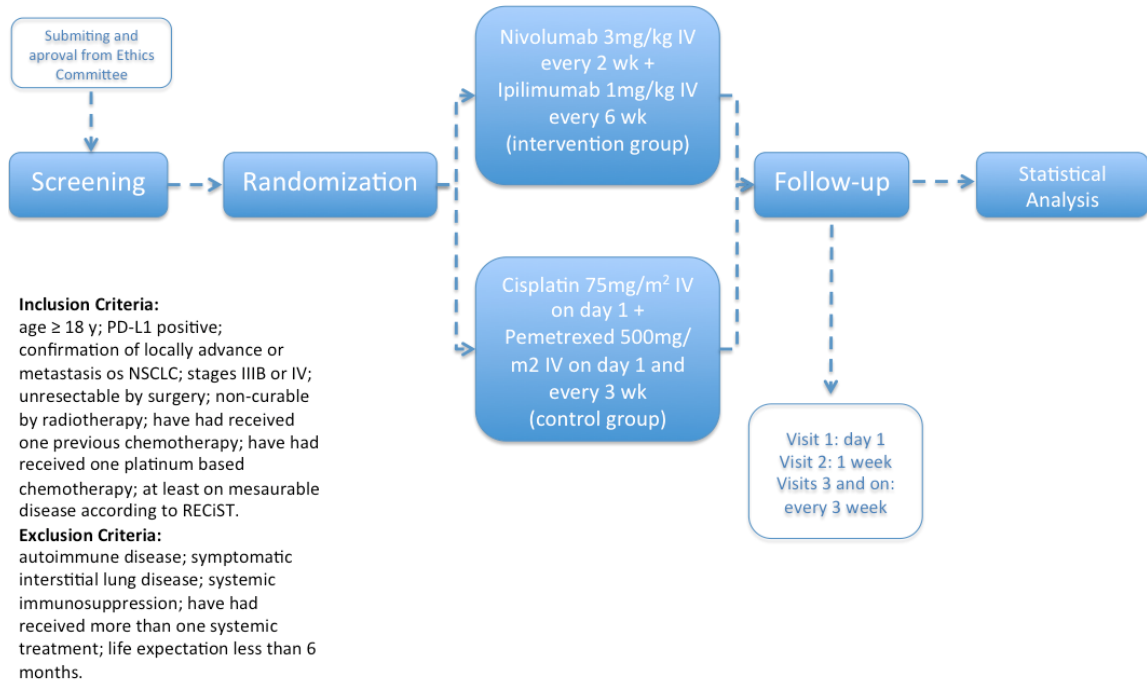
Outcomes

The primary outcome will be Progression-Free Survival, which is defined as the time (in months) between the date of randomization and the first date of documented tumor progression. The event that indicates a tumor progression is defined as by the RECIST criteria or by death due to any cause, whichever occurs first. Participants who do not progress or die will be censored on the date of their last evaluable tumor assessment (Eisenhauer et al., 2009; Sun et al., 2010; Van Persijn Van Meerten, Gelderblom, & Bloem, 2010). The primary outcome will be Progression-Free Survival, which is defined as the time (in months) between the date of randomization and the first date of documented tumor progression according to RECIST guideline or death due to any cause, whichever occurs first. PFS is going to be assessed every 12 weeks. Participants who do not progress or die will be censored on the date of their last evaluable tumor assessment (Eisenhauer et al., 2009; Sun et al., 2010; Van Persijn Van Meerten et al., 2010). Secondary end points will include (Table 1):

- Overall survival, which is defined as the time from randomization to death from any cause
- Objective response rate, which is defined as the percentage of patients with a confirmed complete or

a)

Nivolumab and Ipilimumab combination in Stage IIIB/IV Non small-cancer lung cancer (NSCLC) (Nivo+100)



b)

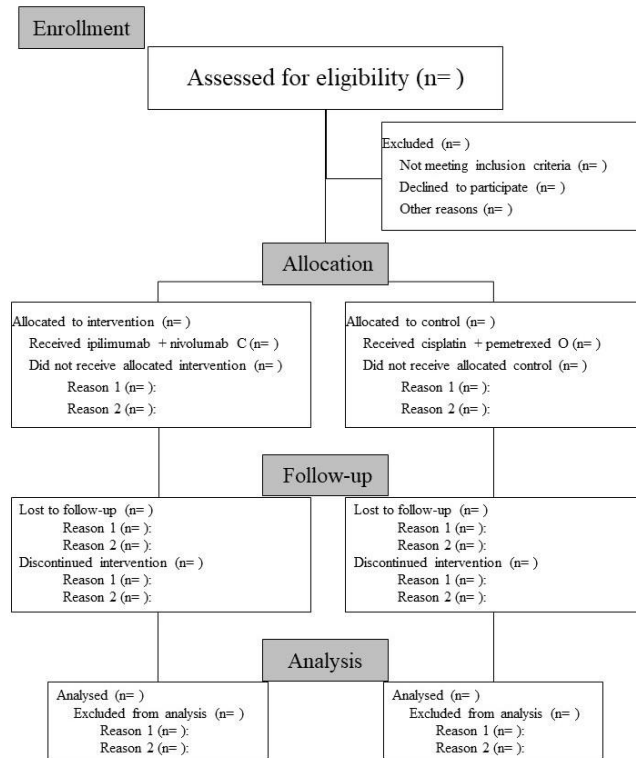


Figure 1. a) Proposed timeline for the study, b) Diagram flow of the

partial response according to RECIST guideline (Motzer et al., 2018).

- The frequency and severity of each adverse event reported will be assessed up to 100 days after the last dose of drugs (with causal association with intervention determined by investigators and based on phase 1/2 study) (Hellmann et al., 2017) (U.S. Department of Health and Human Services Food and Drug Administration, 1996).
- Quality of Life Score, that will be evaluated by the quality of life questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30), Version 3, at baseline and at every tumor assessment until progression of disease or death (Abernethy et al., 2015).

Data Management and Monitoring

The software tool ORACLE CLINICAL will be used in data management. Each site will be responsible for recording all clinical data for each patient. The Coordinating site will compile these data. Monitoring will be followed to comply with the Good Clinical Practice guidelines (U.S. Department of Health and Human Services Food and Drug Administration, 1996). Adverse events will be monitored according to the Data and Safety Monitoring Board Guidelines (National Institutes of Health. Data and Safety Monitoring Board Guidelines, 2014). In case of the intervention is interrupted in greater than 25% of patients due to adverse events grade 3 or 4, the trial will be evaluated for its continuity (Carbone et al., 2017; Hellmann et al., 2017).

Sample Size Calculation

To perform the sample size calculation, the effect sized was calculated using input from different references. The program used was “Small Stata 14”, and statistic method was Log-rank test, Freedman method. In a first step, it was considered the PFS probability in the control group and in the intervention group. The PFS at 6 months was about 47% in patients receiving Nivolumab + Ipilimumab and about 25% in patients receiving cisplatin plus Pemetrexed (Hellmann et al., 2017; Kawano et al., 2013). It was considered the following parameters to calculate the sample size: $\alpha = 5\%$, $\beta = 20\%$, withdrawal percentage = 5%. The number of patients required per group is 75 resulting in a total sample size of 150 subjects. In a second step, it was used the Hazard Ratio (HR) of 0.62 for disease progression, published by previous studies comparing immunotherapy and chemotherapy for squamous non-small cell lung cancer, considering that this hazard ratio could provide a minimally clinically relevant effect on lung cancer (Brahmer et al., 2015). Immunotherapy has

shown very similar response rates in squamous and non-squamous non-small cell lung cancer (Gettinger et al., 2015). Based on the hazard ratio of 0.62 and using the same parameters ($\alpha = 5\%$, $\beta = 20\%$, and withdrawal percentage = 5%), the number of patients required per group is 76 resulting in a total sample size of 152 subjects. After that analysis, it was chosen the most conservative approach with the total sample size of 152.

Statistical Analysis for primary and secondary outcomes

Our data will be presented as mean and standard deviation (\pm) or as median (25th–75th percentile) for continuous variables or as percent and frequencies for categorical variables. The PFS and overall survival will be analyzed using a two-sided log rank test and the rates will be derived from the Kaplan–Meier estimates. Hazard ratios and corresponding confidence intervals will be estimated with the use Cox proportional-hazards model, with randomized group as a single covariate. Objective response rates will be compared using the Chi-square test. Safety analyses by Peto odds ratio method will include all the treated patients (those who received at least one dose of study drug). The quality of life will be described as percentage change from baseline and calculation of p-value will be based on an independent t-test. For all tests, it will be considered a p-value with $\alpha < 0.05$ as level of significance.

Missing Data

We will report reasons for withdrawal for each randomization group and compare the reasons qualitatively. The effect that any missing data might have on results will be assessed via sensitivity analysis of augmented data sets. Dropouts (essentially, participants who withdraw consent for continued follow-up) will be included in the analysis by modern imputation methods for missing data (Figure 1b).

CONCLUSION

We will conduct a randomized multicenter and parallel group phase II trial. The participation sites will be located in the US and will be capable to recruit at least 30 patients aged 18 or older with histological or cytological confirmation of stage IIIb or stage IV, chemotherapy naive non-squamous NSCLC with positive PD-L1 protein. A successful recruitment of at least 152 participants, with a drop-out at follow up below 5%, would allow us to detect a significant superiority in our primary outcome between the two study arms. Finally, the described protocol would enable the collection of strong evidence supporting or not

the use of Ipilimumab plus Nivolumab as combination therapy in non-small cell lung cancer.

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Disclosures

Opinions expressed in this paper do not necessarily reflect the views or policies of the Brazilian Health Regulatory Agency (ANVISA)

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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