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Randomized Phase 2 study evaluating efficacy and safety of inupadenant, an investigational drug which inhibits the adenosine A2A receptor, in combination with carboplatin and pemetrexed in adults with nonsquamous non-small cell lung cancer who have progressed on immunotherapy

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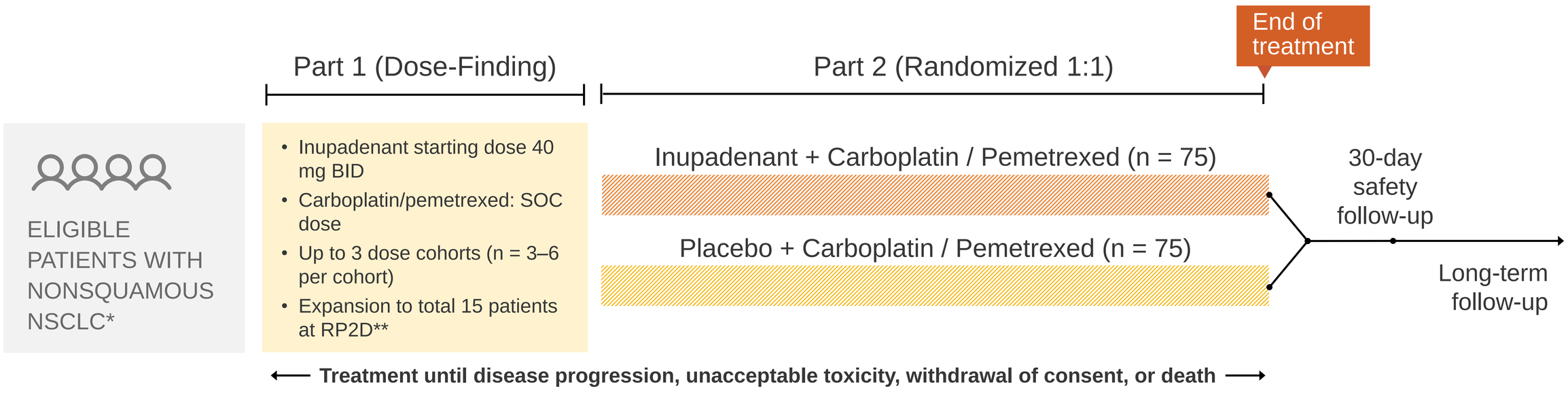
Background

Solid tumors, such as adenocarcinomas of the lung and colon, are frequently hypoxic and are, therefore, likely to exhibit increased adenine nucleotide breakdown yielding adenosine. This accumulation of adenosine in the tumor microenvironment (TME) mediates immune suppression mainly via the high affinity A2A receptor (A2AR), causing dysregulation of innate and adaptative immune cell subsets and dampening the antitumor immune response. This results in increased tumor cell survival and immune escape (Blay 1997; Merighi 2003; Muller-Haegele 2014). Therefore, inhibiting A2AR could reverse immunosuppression and re-establish immune surveillance in the tumor microenvironment.

Inupadenant is an antagonist of the A2AR that maintains high potency even at the high concentrations of adenosine present in the tumor microenvironment and is non-brain penetrant. Ongoing clinical studies have established inupadenant as a molecule with a favorable safety profile. Preliminary evidence of clinical activity has been shown in multiple tumor types, including durable PRs in patients who have exhausted standard treatment options (Buisseret 2020, Buisseret 2021).

The standard treatment for NSCLC patients without a driver mutation who progress on first-line immunotherapy (IO) in Stage IV or on durvalumab in Stage III is a platinum-based doublet chemotherapy regimen. Carboplatin plus Pemetrexed (C+P) is the preferred chemotherapy in nonsquamous NSCLC. Study A2A-005 will evaluate the efficacy and safety of inupadenant in combination with C+P in adult patients with nonsquamous NSCLC (post-IO). A successful outcome from study A2A-005 could support further investigation of this combination in this patient population and help address a high unmet need for these patients.

Open-Label Study to Evaluate the Efficacy & Safety of Inupadenant in Combination with C+P in Adult Patients with Nonsquamous NSCLC



Study Population

Key eligibility criteria include:

1) Metastatic NSCLC (Stage IV) or locally advanced, unresectable (Stage III) NSCLC of nonsquamous pathology that has relapsed or progressed after prior anti-programmed death (PD)-ligand (L)1 therapy*,
2) Measurable disease as defined by RECIST v1.1 criteria, and
3) Eastern Cooperative Oncology Group status ≤1

* *Stage IV patients should have received only 1 line of anti-PD-(L)1 therapy in the metastatic setting, without concomitant chemotherapy (IO/IO combination therapy is allowed).*

* *Stage III patients should have received single-agent durvalumab therapy post-chemoradiation.*

Key Study Objectives

Primary Objective for Part 1: Evaluate safety and tolerability of inupadenant in combination with carboplatin and pemetrexed, and to identify the inupadenant recommended Phase 2 dose (RP2D) to be used in combination with carboplatin and pemetrexed in Part 2 of the study.

Primary Objective for Part 2: Compare progression-free survival (PFS) between the active arm (inupadenant and C+P) and the control arm (placebo and C+P).

Secondary objectives include evaluation of change in tumor size, ORR, and adverse events.

Exploratory objectives include evaluation of biomarkers in the tumor and in peripheral blood.

Statistical Considerations

The sample size for the randomized Part 2 of the study (N = 150) is to demonstrate superiority of inupadenant versus placebo in increasing the PFS, the primary study objective. Participants will be stratified prior to randomization by PD-L1 expression status, duration of prior anti-PD-(L)1, and primary diagnosis before coming to this study.

References

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Clinical trial information: EudraCT 2021-005487-22