A Phase II multicenter, open label, non-randomized study of neoadjuvant and adjuvant treatment with IPH5201 and durvalumab in patients with resectable, early-stage (II to IIIA) non-small cell lung cancer (MATISSE)

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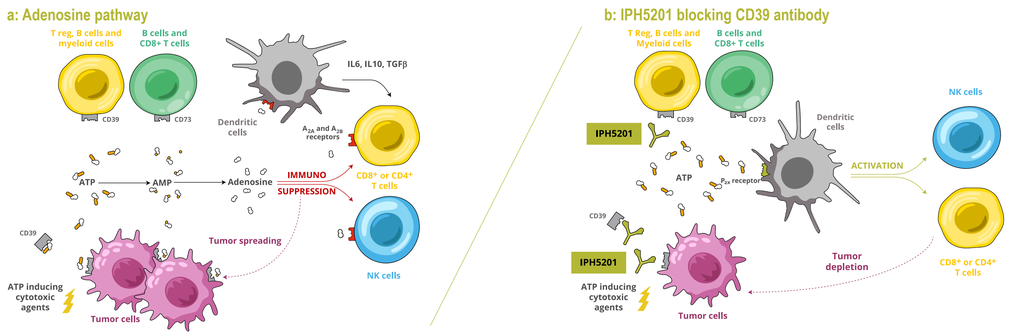
Background

- Neoadjuvant or perioperative immunotherapy targeting programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) combined with neoadjuvant platinum-based chemotherapy (CT) has led to improved outcomes and recent approval for patients with resectable, early-stage non-small cell lung cancer (NSCLC).[1,2,3]
- In particular, recent interim data from the Phase III AEGEAN study (NCT03800134) showed that perioperative durvalumab (anti-PD-L1) plus neoadjuvant CT significantly improved both pathological complete response (pCR) rate (17.2% in the durvalumab-based regimen arm vs 4.3% in the CT arm) and Event-Free Survival (EFS) (median not reached in the durvalumab-based regimen arm vs 25.9 months in the CT arm) in patients with resectable, Stage IIA–IIIB[N2] NSCLC.[3]
- Despite significant improvements in EFS and pCR rates achieved by the combination of PD-(L)1 blocking agents and CT, a large proportion of patients do not achieve a pCR, and patients with low tumor PD-L1 expression are least likely to respond to current therapy options.[1,2,3]
- Many trials are ongoing in this perioperative setting, including combination with drugs targeting new pathways, such as the adenosine pathway (NeoCOAST-2, NCT05061550).
- The open-label, Phase II MATISSE study (NCT05742607) was initiated to evaluate neoadjuvant therapy with durvalumab (Imfinzi®) plus CT and IPH5201, followed by surgery and adjuvant durvalumab plus IPH5201, in treatment-naive patients with resectable early-stage (II to IIIA) NSCLC.

Figure 1: Mode Of Action of IPH5201 CD39 blocking antibody



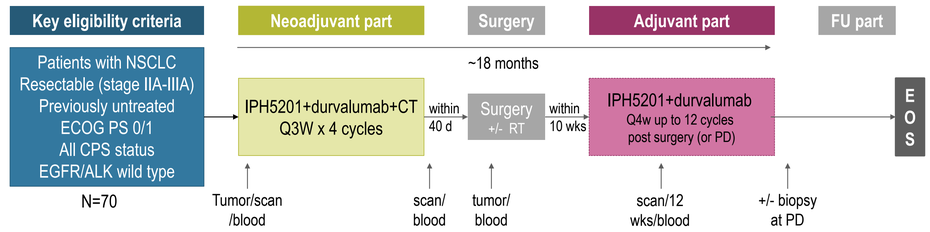
IPH5201

- CD39 is an extracellular ectonucleotidase that is highly expressed in the tumor microenvironment in several cancer types, on both tumor infiltrating cells and stromal cells.
- Extracellular immunostimulatory adenosine triphosphate (ATP) is released by dying cells, upon chemotherapy.
- CD39 inhibits the immune system by degrading ATP into adenosine monophosphate (AMP), that is then further degraded into immunosuppressive adenosine by CD73 (**figure 1a**).
- IPH5201 blocking antibody targeting CD39 enhances dendritic cells activation through ATP accumulation, but also reduces adenosine levels, leading to restoring T cell proliferation and stimulation (**figure 1b**).[4]
- Moreover, IPH5201 improved the efficacy of CT + Durvalumab in preclinical models.[5]
- In a Phase I clinical trial, IPH5201 + Durvalumab were well tolerated and pharmacodynamically active.[6]

Methods

- Patients will receive neoadjuvant IPH5201 + Imfinzi® (durvalumab) in addition to platinum-doublet CT for 4 cycles of treatment every 3 weeks.
- Surgical resection should occur within 40 days of the last dose of neoadjuvant therapy.
- Patients will thereafter receive, within 10 weeks post-surgery, adjuvant IPH5201+ Imfinzi® (durvalumab) every 4 weeks for up to 12 cycles post-surgery or until recurrence (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) or unacceptable toxicity.
- A Safety Review Committee will conduct safety evaluations on an ongoing basis and two interim analyses will be performed for efficacy after enrollment of 20 and 40 patients respectively.
- Up to 70 patients will be enrolled.
- The study design is shown in **figure 2**.

Figure 2: Study Design



CPS: Combined positive score; CT: chemotherapy (carboplatin/paclitaxel or cisplatin/gemcitabine or carboplatin/pemetrexed); ECOG: Eastern Cooperative Oncology Group; EOS: End of Study; FU: Follow-up; NSCLC: Non Small Cell Lung Carcinoma; Q3w = every 3 weeks; Q4w = every 4 weeks; PD: Progressive disease; PS: performance status; RT: radiotherapy

Study Objectives

Primary Objectives

- pCR[a]
- Safety and tolerability

Secondary Objectives

- Event-Free Survival, Disease-Free Survival, Overall Survival
- Feasibility to planned surgery
- mPR[b]
- Objective response rate (per RECIST v1.1)
- Pharmacokinetics, Immunogenicity

Exploratory Objectives: Assessment of exploratory biomarkers

a) pCR (pathological complete response) is defined as lack of any viable tumor cells after complete evaluation in the resected lung cancer specimen and all sampled regional lymph nodes as determined by central independent pathological review (CIPR) and described by IASLC 2020.[7]

b) mPR (major pathological response) is defined as ≤ 10% viable tumor cells in resected tumor after complete evaluation in the resected lung cancer specimen as determined by CIPR as described by IASLC 2020.[7]

Patient Population

Key Inclusion Criteria

- Aged ≥18 years
- Newly diagnosed and previously untreated patients with histologically or cytologically confirmed, resectable, Stage IIA–IIIA (per AJCC 8th edition) NSCLC
- Planned surgery of lobectomy, sleeve resection, or bilobectomy
- WHO or ECOG performance status of 0 or 1
- Adequate organ and marrow function
- Life expectancy ≥12 weeks
- Provision of tumor samples available for PD-L1, *EGFR/ALK* status and biomarker analyses

Key Exclusion Criteria

- Sensitizing *EGFR* mutations or *ALK* translocations
- History of allogeneic organ transplantation
- Active or prior documented autoimmune or inflammatory disorders
- Uncontrolled intercurrent illness
- History of any grade of venous or arterial thromboembolic event
- Small-cell lung cancer or mixed small-cell histology
- Active infection (including tuberculosis, hepatitis B or C)
- Prior radiotherapy
- Moderate or severe cardiovascular disease

Study status

- Enrollment began in June 2023
- The trial is currently recruiting patients across the USA & Europe (France, Greece, Hungary, Poland)

References

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Disclaimer: Speaker Pr Fabrice Barlesi and co-authors: please refer to ESMO website.

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