Dual CD39 and PD-L1 inhibition: Interim results from the phase 2 MATISSE trial of IPH5201 plus durvalumab and platinum-based chemotherapy in patients with resectable NSCLC

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Disclosure information

Professor Fabrice BARLESI, MD, PhD

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None

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MATISSE study background and rationale

- Approximately **25%** of patients with Non-Small Cell Lung Cancer (NSCLC) are diagnosed at a resectable early-stage and potentially curable
- Neoadjuvant chemo-immunotherapy (PD-(L)1) has become the new **standard of care** (NCCN V5.2026*, ESMO 2025 guidelines**)
- In Phase 3 studies with chemo/PD-(L)1 inhibitors, **only ~25%** of patients achieve **pathologic complete response (pCR)**, associated with increased Overall Survival***
- Developing **next-generation strategies** to notably improve the pCR rate and the potential of cure of chemo-immunotherapy is therefore needed

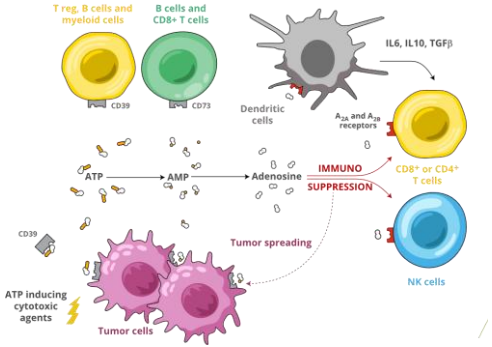
**NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer; Version 5.2026, March 13, 2026*

***Zer et al.: Early and locally advanced non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up; Ann Oncol. 2025; 36(11): 1245-1262.*

**** Rocco et al.: Neoadjuvant therapy of NSCLC: a review of the use and impact of monoclonal antibodies; Exp Op Bio Ther 2025; 25(9): 979-988.*

IPH5201 CD39 inhibitor MoA

Adenosine pathway



✓ **CD39 is an extracellular enzyme over-expressed in the tumor microenvironment**. Upstream CD39 degrades immunostimulatory extracellular ATP released by dying cells into AMP, which is further degraded into immunosuppressive adenosine by downstream **CD73***

*Allard et al. Immunol.l Rev.. 2017; Vigano et al. Front. Immunol. 2019; Kepp et al. EMBO J. 2021
**Perrot et al. Cell Reports, 2019; Paturel et al., ESMO-IO, 2022 ;
*** Powderly et al., Cancer Res com, 2025

IPH5201 CD39 inhibitor MoA

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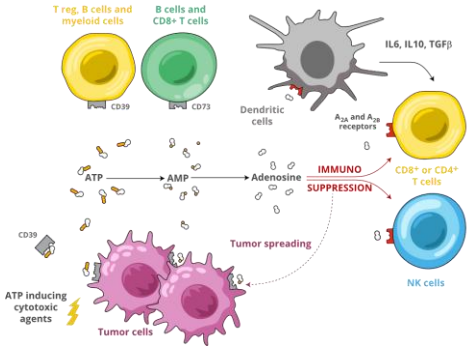
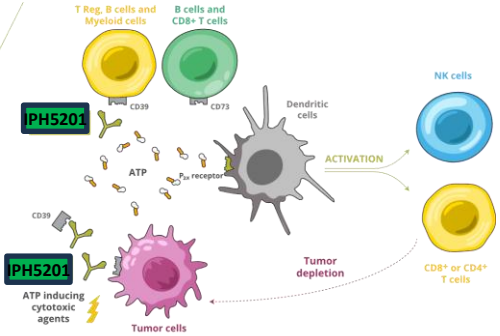
Adenosine pathway



IPH5201 blocking CD39 antibody



- IPH5201 is a **humanized Fc-silent IgG1** inhibiting **both membrane and soluble CD39**
- IPH5201 improves antitumor activity of durvalumab+chemo in preclinical models, turning anti-PD-(L)1 resistant into sensitive tumors**
- IPH5201 as monotherapy or in combination with durvalumab was well tolerated and pharmacodynamically active***

✓ **CD39 is an extracellular enzyme over-expressed in the tumor microenvironment**. Upstream CD39 degrades immunostimulatory extracellular ATP released by dying cells into AMP, which is further degraded into immunosuppressive adenosine by downstream **CD73***

✓ Blocking CD39 **enhances Dendritic Cells** activation through ATP accumulation but also **restores T cell stimulation** by reducing adenosine levels**

**Allard et al. Immunol.l Rev.. 2017; Vigano et al. Front. Immunol. 2019; Kepp et al. EMBO J. 2021*
***Perrot et al. Cell Reports, 2019; Paturel et al., ESMO-IO, 2022 ;*
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MATISSE study design

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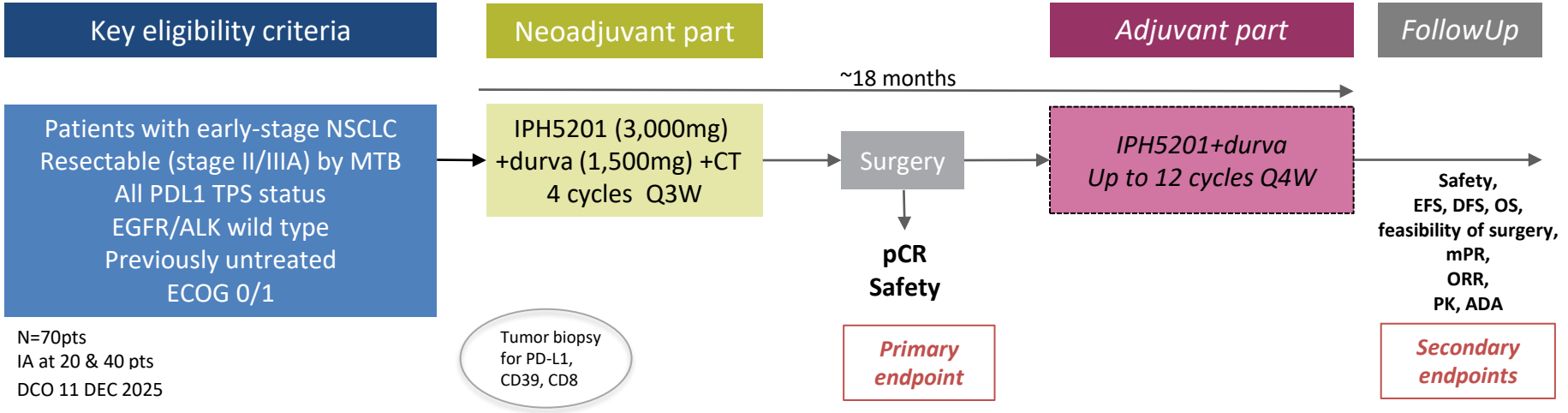
MATISSE is an open-label, **single-arm phase 2 study** evaluating IPH5201 in combination with neoadjuvant CT and perioperative durvalumab in resectable, early-stage NSCLC



FPI: Jun 2023
The trial recruited patients in France, Hungary, Poland, Greece and USA

ADA: anti-drug antibody; ALK: Anaplastic Lymphoma Kinase; CT: chemotherapy (carboplatin/paclitaxel or cisplatin/pemetrexed or carboplatin/pemetrexed); DCO: Data Cut Off; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group performance status; EGFR: Epithelial Growth Factor Receptor; EFS: event-free survival; FPI: First Patient In; IA: interim analysis; mPR: major pathological response; NSCLC: non-small cell lung cancer; OS: overall survival; ORR: overall response rate; pCR: pathological complete response; PK: Pharmacokinetics; Q3W: every 3 weeks; Q4W: every 4 weeks; TPS: Tumor PD-L1 score;

Patient baseline characteristics & disposition

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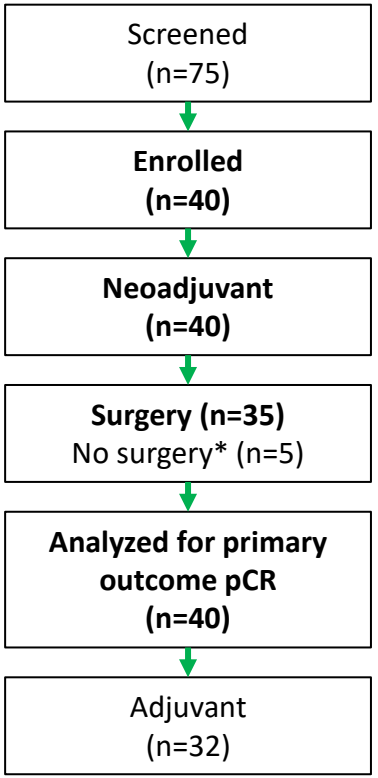
Baseline characteristics (N=40)	N (%)
Median age (range)	**64.7** (48, 83)
Females/Males	13 (32.5) / 27 (67.5)
ECOG 0/1	32 (80.0) / 8 (20.0)
PD-L1 ≥1% / PD-L1 <1%	28 (70.0) / 12 (30.0)
Clinical Preoperative Stage (TNM 8th)	
Stage IIA	4 (10.0)
Stage IIB	16 (40.0)
Stage IIIA	20 (50.0)
Histology	
Adenocarcinoma	19 (47.5)
Squamous cell carcinoma	16 (40.0)
Other	5 (12.5)
Backbone Chemotherapy	
Carboplatin/Paclitaxel	16 (40.0)
Carboplatin/Pemetrexed	12 (30.0)
Cisplatin/Pemetrexed	12 (30.0)



Number of chemo/CD39/Durva cycles: 1, 2 pts; 2, 2 pts; 3, 3 pts; 4, 33 pts

*1 patient disqualified from lung surgery by the surgeon, 1 inadequate lung function, 1 consent withdrawn, 2 progressive disease

Safety

Safety overview	N (%)
TEAE (any grade)	**39 (97.5)**
related to any drug	36 (90.0)
related to chemotherapy	32 (80.0)
related to IPH5201	29 (72.5)
related to durvalumab	29 (72.5)
grade ≥3	**22 (55.0)**
grade ≥ 3 related to any drug	13 (32.5)
permanent discontinuation of any drug	9 (22.5)
permanent discontinuation of chemotherapy	3 (7.5)
permanent discontinuation of IPH5201*	7 (17.5)
permanent discontinuation of durvalumab	7 (17.5)
AESI	27 (67.5)
SAE (any)	**14 (35.0)**
SAE related to any drug	7 (17.5)
TEAE **Grade 5**	1** (2.5)

**In the event that an AE is considered related only to durvalumab, both IPH5201 and durvalumab must be discontinued*
***postoperative pneumonia*

AESI: adverse event of special interest; SAE: serious adverse event;
TEAE: Treatment emergent adverse event

TEAE ≥ 15%	N (%)
Patients with at least one TEAE	**39 (97.5)**
Asthenia	16 (40.0)
Constipation	12 (30.0)
Nausea	12 (30.0)
Anemia	11 (27.5)
Thrombocytopenia	10 (25.0)
Arthralgia	10 (25.0)
Neutropenia	10 (25.0)
Weight decreased	9 (22.5)
Rash	8 (20.0)
Hypothyroidism	8 (20.0)
Alopecia	7 (17.5)
Neuropathy peripheral	7 (17.5)
Procedural pain	7 (17.5)
Decreased appetite	6 (15.0)

TEAE ≥ 10% related to at least IPH5201	N (%)
Patients with at least one IPH5201 related TEAE	**29 (72.5)**
Asthenia	8 (20.0)
Arthralgia	5 (12.5)
Hypothyroidism	5 (12.5)
Thrombocytopenia	4 (10.0)

Efficacy

Radiological Response to systemic treatment

Radiological response per RECIST V1.1	% [95% CI] or N (%)
ORR, % [95% CI]	**62.5 [45.8, 77.3]**
CR, n (%)	3 (7.5)
PR, n (%)	22 (55.0)
SD, n (%)	14 (35.0)
PD, n (%)	1 (2.5)

Surgery

Surgery	N (%)
Surgery	
Subjects underwent surgery	**35 (87.5)**
Subjects underwent surgery within 40 days	28 (75.7)
Subjects with surgery delayed (>40 days) Logistic reasons (surgeon planning) Other: 1 investigator decision, 3 AEs (delay range 3-15 days)	 3 (7.5) 4 (11.4)
Outcome of surgery R0 R1 R2	 **31 (88.6)** 4 (11.4) 0 (0.0)
Subjects did not undergo surgery*	**5 (12.5)**

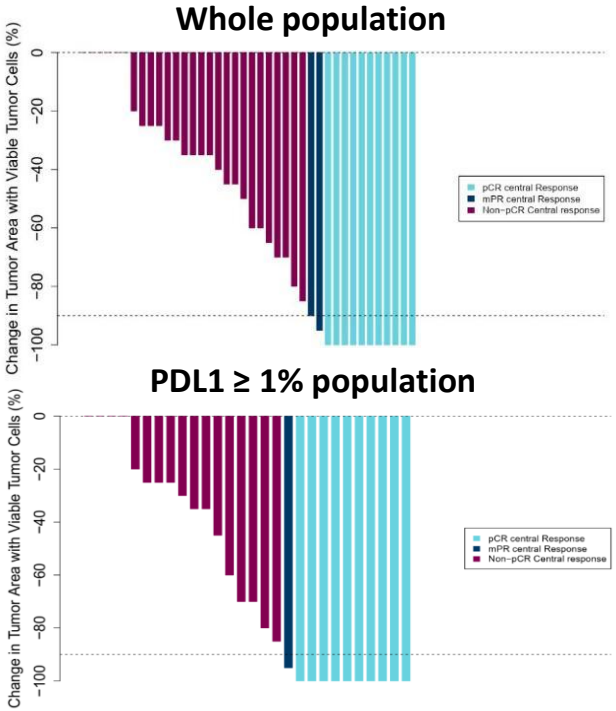
**1 investigator decision (patient disqualified from lung surgery by the surgeon), 1 inadequate lung function, 1 consent withdrawn before surgery, 2 progressive disease before surgery (1 PD per RECIST, 1 judged clinically progressive before surgery)*

Efficacy

Pathological response, N=40*	% [95% CI]
Overall pCR, % [95% CI]	**27.5** [14.6, 43.9]
MPR, % [95% CI]	32.5 [18.6, 49.1]
pCR by PD-L1 expression	
PD-L1 <1% (N=12)	8.3 [0.2, 38.5]
PD-L1 ≥ 1% (N=28)	**35.7** [18.6, 55.9]
PD-L1 ≥ 50% (N=14)	50.0 [23.0, 77.0]

**include all patients treated (who received at least one dose of study treatment and who received surgery (n=35) or were unable to receive surgery (n=5)*

Improved pCR rate / PD-L1 tumor TPS (PD-L1≥1%)



Waterfall plots present treated population patients with no change in tumour area (patient who discontinued treatment prior surgery or patients with non evaluable tumour area viable cells) are set to 0.

Pathological complete response (pCR) 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) as per IASLC 2020 (Travis W, et al. IASLC Multidisciplinary Recommendations for Pathologic Assessment of Lung Cancer Resection Specimens After Neoadjuvant Therapy. J Thorac Oncol 2020;15(5);709–740).

NSCLC: non small cell lung cancer; pCR: pathological complete response; mPR: major pathological response

Tumor CD39+ cell density as an emerging biomarker

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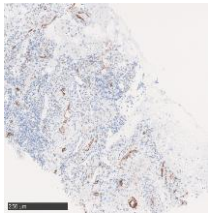
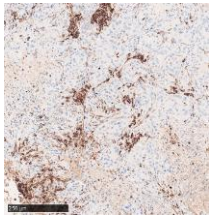
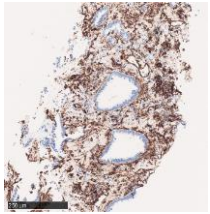
CD39 expression profiles
Representative images of the MATISSE study



CD39+ cell density in tumor =126 cells/mm²



CD39+ cell density in tumor =466 cells/mm²



CD39+ cell density in tumor =2124 cells/mm²

- In treatment naive early-stage NSCLC patients, CD39 expression is mainly localized at the **tumor stroma** (Koppensteiner, 2023*)
- High expression of CD39 in the tumor stroma is associated with **poor recurrence-free survival (RFS)** rate at 5 years, while density of CD39+CD103+CD8+ T cells in the tumor predicts improved RFS at 5 years (Koppensteiner, 2023*)

** Koppensteiner et al., Location of CD39+ T cell subpopulations within tumors predict differential outcomes in non-small cell lung cancer, J Immunother Cancer 2023 Aug;11(8)*

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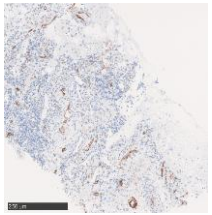

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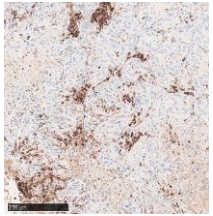

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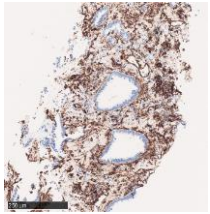
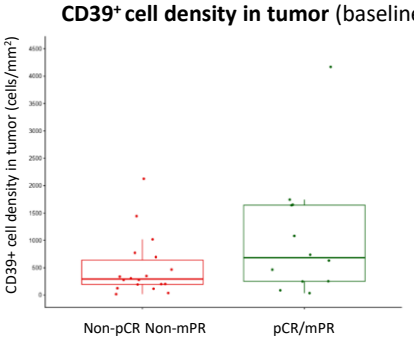
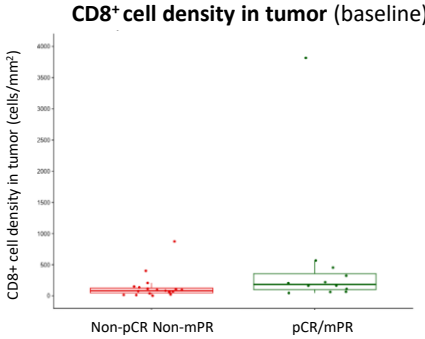


CD39+ cell density in tumor =2124 cells/mm²

Higher baseline CD39+ and CD8+ cell density in tumor of patients with mPR/pCR





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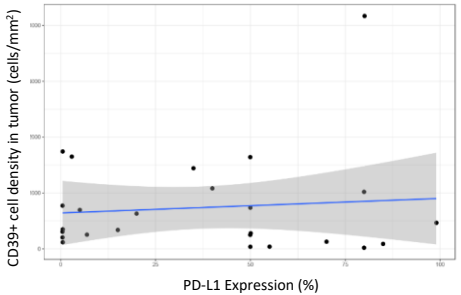
** Koppensteiner et al., Location of CD39+ T cell subpopulations within tumors predict differential outcomes in non-small cell lung cancer, J Immunother Cancer 2023 Aug;11(8)*

No correlation between CD39 cell density in tumor and PD-L1 expression



DCO 24 Oct 2024 (n=38 patients)

Conclusions

- MATISSE is the first clinical study to show feasibility and preliminary activity of **preoperative CD39 blockade** by IPH5201 in combination with platinum-based chemotherapy and PD-L1 inhibition for patients with resectable early stage NSCLC with:
  - The majority of patients reaching **surgery (87.5%)**
  - A **safety profile comparable** to preoperative platinum-based chemotherapy/durvalumab
  - A promising overall **pCR rate of 27.5%**
- Prediction of response to [IPH5201+durvalumab] might be related to:
  - **PDL1 expression status**, with 35.7% and 50% of the patients achieving **pCR** when tumor expressed PD-L1≥1% and 50%, respectively
  - **CD39 expression** as a potentially emerging biomarker trending to higher intratumoral density in patients reaching pCR/mPR
- MATISSE paves the way for **CD39/Adenosine pathway inhibition** in early-stage NSCLC
- MATISSE **continues with the recruitment of PD-L1≥1%** patients to further enrich the dataset

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