CheckMate 73L: A Phase 3 Study Comparing Nivolumab Plus Concurrent Chemoradiotherapy (cCRT) Followed by Nivolumab ± Ipilimumab Versus cCRT Followed by Durvalumab for Previously Untreated, Locally Advanced Stage III Non-Small Cell Lung Cancer

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Background

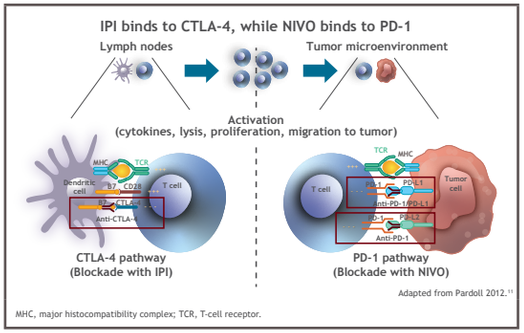
Unmet need in the treatment of locally advanced (LA) non-small cell lung cancer (NSCLC)

- Lung cancer is the leading cause of cancer death worldwide[1]
- Approximately 30% of patients diagnosed with NSCLC present with stage III disease[2]
- Historically, the standard treatment for LA stage III NSCLC not amenable to definitive resection was cCRT, resulting in a 5-year overall survival (OS) rate of 15%-30%[3,4]
- Durvalumab (DURVA) consolidation therapy has recently emerged as the new standard of care for patients with non-progressive disease following cCRT[5,6]
  - The majority of the patients still experience progression or death within 2 years (18-month progression-free survival [PFS] rate of 44%)[7]
  - In Europe, this consolidation therapy is restricted to patients with tumor programmed death ligand 1 (PD-L1) expression ≥ 1%[8]
- Therefore, new therapeutic approaches are needed in this patient population

Immuno-oncology (I-O) therapy with nivolumab (NIVO) and ipilimumab (IPI)

- IPI is a cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitor that blocks the interaction between CTLA-4 on T cells and CD80/CD86 on antigen-presenting cells, inducing anti-tumor immune responses[9-11]
- NIVO is a programmed death-1 (PD-1) inhibitor antibody that blocks the interaction between PD-1 on activated T cells and PD-L1/PD-L2 on tumor cells, restoring anti-tumor immune responses[11-13]
  - NIVO monotherapy is approved in the United States, European Union, and other countries for the treatment of patients with metastatic NSCLC whose disease has progressed on or after chemotherapy, as well as for other types of cancer[13,14]
- NIVO + IPI has demonstrated improved and durable survival benefits in multiple tumor types including melanoma, renal cell carcinoma, metastatic NSCLC, and mesothelioma[15-21]
  - NIVO + IPI is indicated in the United States for the first-line (1L) treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (≥ 1%), with no *EGFR* or *ALK* genomic aberrations[13]
- NIVO and IPI have distinct but complementary mechanisms of action: NIVO restores anti-tumor T-cell function, while IPI induces de novo anti-tumor T-cell responses (**Figure 1**)[22]

Figure 1. NIVO and IPI mechanisms of action



Adapted from Pardoll 2012.[11]

MHC, major histocompatibility complex; TCR, T-cell receptor.

Study Rationale

Anti-PD-1 therapy + cCRT

- cCRT has the potential to prime anti-tumor immunity; however it can also upregulate PD-L1 expression and potentially dampen the immune response. Thus, anti-PD-(L)1 therapy is hypothesized to improve anti-tumor effects of cCRT[23]

cCRT followed by I-O therapy

- PACIFIC, a phase 3, randomized, double-blind, placebo-controlled trial in patients with unresectable, stage III LA NSCLC showed that DURVA following cCRT significantly prolonged PFS and OS versus placebo[24]
  - Median PFS: 17.2 vs 5.6 months (HR, 0.51; 95% CI, 0.41-0.63)[24]
  - Median OS: Not reached vs 28.7 months (HR, 0.68; 99.73% CI, 0.47-0.997)[24]
  - Subgroup analyses showed improved outcomes with initiating DURVA < 14 days versus ≥ 14 days after cCRT[7]
- Combining I-O therapies with different mechanisms of action in the consolidation phase following cCRT offers the possibility of a synergistic anti-tumor response

I-O therapy administered with cCRT

- Results from the single-arm, phase 2 NICOLAS trial demonstrated the safety and feasibility of the addition of NIVO to cCRT in patients with stage III LA NSCLC[25,26]
  - No grade ≥ 3 pneumonitis was observed in the interim safety cohort (n = 21) with 3 months post-radiotherapy follow-up, suggesting that the combination is safe and tolerable[25,26]
  - The 1-year PFS rate was 50.0% (90% exact binomial CI, 40%-60%)[27]

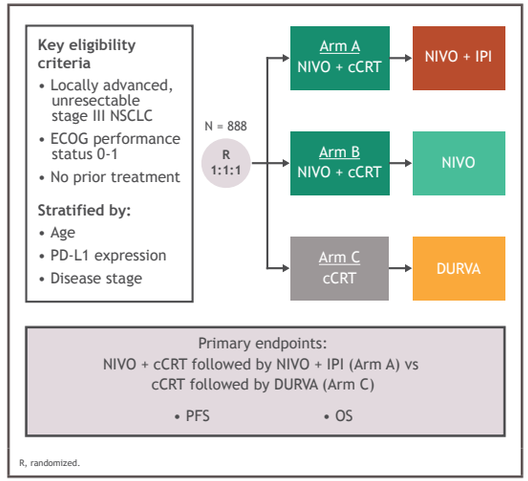
Study Objective

- To compare the efficacy and safety of NIVO + cCRT followed by NIVO + IPI maintenance (Arm A) or NIVO + cCRT followed by NIVO maintenance (Arm B) vs cCRT followed by DURVA (Arm C) in participants with previously untreated LA NSCLC[28]

Study Design

- CheckMate 73L (NCT04026412) is a randomized, open-label, phase 3 trial evaluating the efficacy of NIVO + cCRT followed by maintenance therapy with NIVO ± IPI versus cCRT followed by DURVA in patients with previously untreated LA NSCLC (**Figure 2**)
- cCRT comprises platinum-doublet chemotherapy + radiotherapy
- A total of 888 patients will be randomized (1:1:1) to receive:
  - NIVO + cCRT followed by NIVO + IPI (Arm A)
  - NIVO + cCRT followed by NIVO (Arm B)
  - cCRT followed by DURVA (Arm C)
- Key inclusion and exclusion criteria are in **Table 1**

Figure 2. Study design



R, randomized.

Table 1. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Newly diagnosed NSCLC, with no prior local or systemic anticancer treatment given as primary therapy for LA disease	Prior thoracic radiotherapy
	Active infection requiring systemic therapy 14 days prior to randomization
LA stage IIIA, IIIB, or IIIC histologically confirmed NSCLC per 8th TNM classification according to multidisciplinary assessment at baseline	Conditions including medical, emotional, psychiatric, or logistical that, in the opinion of the Investigator, would preclude the patient from adhering to the protocol or increase risk associated with study participation
ECOG performance status 0-1	History of organ or tissue transplant requiring systemic use of immune suppressive agents

TNM, tumor, node, metastasis.

Key Endpoints

Primary endpoints

- PFS by RECIST v1.1 for Arm A versus Arm C
- OS for Arm A versus Arm C

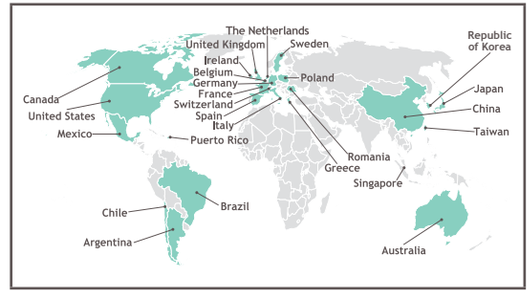
Secondary endpoints

- PFS by RECIST v1.1 for Arm B versus Arm A, or Arm C
- OS for Arm B versus Arm A, or Arm C
- Objective response rate, complete response rate, duration of response, time to response, and time to death or distant metastases by RECIST v1.1
- Safety and tolerability

Study Sites

- 175 study sites in 26 countries (**Figure 3**)
- Study start date: August 20, 2019
- Estimated primary completion date: October 17, 2022
- Estimated study completion date: November 30, 2024

Figure 3. Study sites



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