Current Trial Report

CheckMate 73L: A Phase 3 Study Comparing Nivolumab Plus Concurrent Chemoradiotherapy Followed by Nivolumab With or Without Ipilimumab Versus Concurrent Chemoradiotherapy Followed by Durvalumab for Previously Untreated, Locally Advanced Stage III Non-Small-Cell Lung Cancer

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Abstract

Introduction: The 5 year survival rate for patients with locally advanced non-small-cell lung cancer (NSCLC) not amenable for definitive resection with historical standard-of-care concurrent chemoradiotherapy (cCRT) ranges from 15% to 32%. cCRT primes anti-tumor immunity and also upregulates programmed death ligand-1 (PD-L1), providing a rationale for combining an immune checkpoint inhibitor with cCRT to improve outcomes. In the PACIFIC trial, consolidation therapy with the PD-L1 inhibitor durvalumab improved progression-free survival (PFS) and overall survival (OS) vs. placebo in patients with stage III NSCLC who did not have disease progression after cCRT. CheckMate73L (NCT04026412), a randomized phase 3 study, evaluates the efficacy of nivolumab plus cCRT followed by nivolumab with or without ipilimumab vs. cCRT followed by durvalumab for untreated, stage III NSCLC. **Patients and Methods:** Patients with untreated, stage III NSCLC will be randomized 1:1:1 to nivolumab plus cCRT followed by nivolumab in combination with ipilimumab (Arm A) or nivolumab alone (Arm B); or cCRT followed by durvalumab (Arm C). Primary endpoints are PFS and OS (Arm A vs. Arm C). Secondary endpoints include additional analyses of PFS and OS (Arm A vs. Arm B; Arm B vs. Arm C), as well as objective response rate, complete response rate, time to response, duration of response, time to death or distant metastases, and safety and tolerability. Recruitment began on August 20, 2019, and the estimated primary completion date is October 17, 2022.

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Introduction

Locally advanced stage III non-small-cell lung cancer (NSCLC) constitutes approximately 35% of NSCLC cases.[1] Concurrent chemoradiotherapy (cCRT), the historical standard-of-care for unresectable stage III NSCLC, results in 5 year overall survival (OS), ranging from 15% to 32%.[1,2] cCRT may prime anti-tumor immunity while increasing programmed death ligand-1 (PD-L1) expression in tumor cells, which may augment response to anti-PD-1 (PD-1)/PD-L1 therapies.[3] These mechanisms provide a rationale for combining cCRT with immuno-oncology (IO) therapy to further improve outcomes in patients with stage III NSCLC. The first trial assessing IO therapy after cCRT in stage III NSCLC was the phase 3 PACIFIC trial. The coprimary endpoint of progression-free survival (PFS) with durvalumab after cCRT vs. placebo was met at the interim analysis.[4] Grade 3 to 4 pneumonitis or radiation pneumonitis was reported in 3.4% of patients receiving durvalumab after cCRT and 2.6% of patients in the placebo arm.[4] At the 5 year update, PFS was prolonged and 43% of patients remained alive.[5]

Feasibility of combining anti-PD-1 therapy with cCRT in stage III NSCLC has recently been demonstrated and clinical benefit was favorable. In the single-arm, phase 2 NICOLAS study of nivolumab in combination with cCRT, led by European Thoracic Oncology Platform (ETOP), 9 of the 79 patients (11.4%) experienced pneumonitis of ≥ grade 3. Seven of 9 were resolved completely, one was resolved with sequelae, whereas one reoccured;[6] median PFS was 12.7 months and 1 year PFS rate was 53.7%. Similar findings for efficacy and safety were seen in KEYNOTE 799, a non-randomized phase 2 trial evaluating pembrolizumab plus cCRT in patients with stage III NSCLC which reported a ≥ grade 3 pneumonitis rate between 6.9% and 8.0%.[7] With promising efficacy and acceptable safety profiles, these trials support the continued investigation of combining cCRT with IO therapy in stage III NSCLC.

Nivolumab is a human anti-PD-1 monoclonal antibody that disrupts the interaction between the PD-1 receptor and PD-L1/2. Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 inhibitor with a distinct but complementary mechanism of action to nivolumab. Ipilimumab induces T-cell proliferation and *de novo* anti-tumor T-cell responses (memory T-cell inclusive), while nivolumab restores existing anti-tumor T-cell function. Nivolumab plus ipilimumab has shown durable OS benefit in several tumors, including melanoma,[8] renal cell carcinoma,[9] metastatic NSCLC,[10] and mesothelioma.[11] In CheckMate 227, this combination provided statistically significant and clinically meaningful OS improvements vs. chemotherapy in patients with tumor PD-L1 expression ≥ 1%.[10] A similar benefit was also observed in an exploratory analysis in patients with tumor PD-L1 expression < 1%. This trial led to the approval of nivolumab plus ipilimumab in the United States as a first-line treatment in patients with metastatic NSCLC whose tumors express PD-L1 ≥ 1%, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic aberrations.[12] In CheckMate 9LA, this combination plus 2 cycles of chemotherapy provided statistically significant and clinically meaningful OS improvements vs. chemotherapy regardless of PD-L1 expression. This trial led to the approval of nivolumab plus ipilimumab with 2 cycles of chemotherapy in various countries, including the United States, as a first-line treatment in patients with metastatic NSCLC, with no EGFR or ALK genomic aberrations.[13]

Taken together, these findings support the potential use of nivolumab plus ipilimumab in stage III NSCLC not amenable for definitive resection. CheckMate 73L is evaluating the efficacy of nivolumab plus cCRT followed by nivolumab with or without ipilimumab as maintenance therapy vs. cCRT followed by durvalumab in patients with untreated, stage III NSCLC. Primary endpoints are PFS and OS (nivolumab plus cCRT followed by nivolumab with ipilimumab vs. cCRT followed by durvalumab).

Patients and Methods

Patients

Adult patients with newly diagnosed, treatment-naïve, stage III histologically confirmed NSCLC amenable to definitive cCRT and an Eastern Cooperative Oncology Group performance status of 0 to 1 are eligible. Key eligibility criteria are listed in the Table 1.

Study design and treatment

CheckMate 73L (NCT04026412) is a multicenter, randomized, open-label, phase 3 trial that compares 3 treatment arms in patients with previously untreated stage III NSCLC not amenable for surgical resection (Figure 1). Stratification factors include age, PD-L1 expression, and disease stage. During the cCRT phase, all patients receive histology-based platinum-doublet chemotherapy. Patients are randomized 1:1:1 to nivolumab plus cCRT in Arms A and B or to cCRT alone in Arm C. In Arms A and B, the maintenance treatment phase consists of nivolumab in combination with ipilimumab or nivolumab alone. In Arm C, the consolidation phase consists of durvalumab alone. Durvalumab discontinuation criteria will follow the prescribing information.

Primary endpoints are PFS (according to Response Evaluation Criteria in Solid Tumors, version 1.1, per blinded independent central review) and OS comparing Arms A and C. Secondary endpoints include additional analyses of PFS and OS (Arm A vs Arm B; Arm B vs Arm C), as well as objective response rate, complete response rate, time to response, duration of response, time to death or distant metastases, and safety and tolerability.

The study protocol was developed in collaboration with ETOP. The study is being conducted at 178 locations throughout Asia, Australia, Europe, North America, and South America; participating ETOP sites are also recruiting patients to the study. Study recruitment was initiated on August 20, 2019 and the estimated primary completion date is October 17, 2022.

The study is approved by the institutional review board or ethics committee at each study site and is being conducted in accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization. All patients provide written informed consent. Data from the study will be available in accordance with the data sharing policy of Bristol Myers Squibb, available here.

Statistical analysis

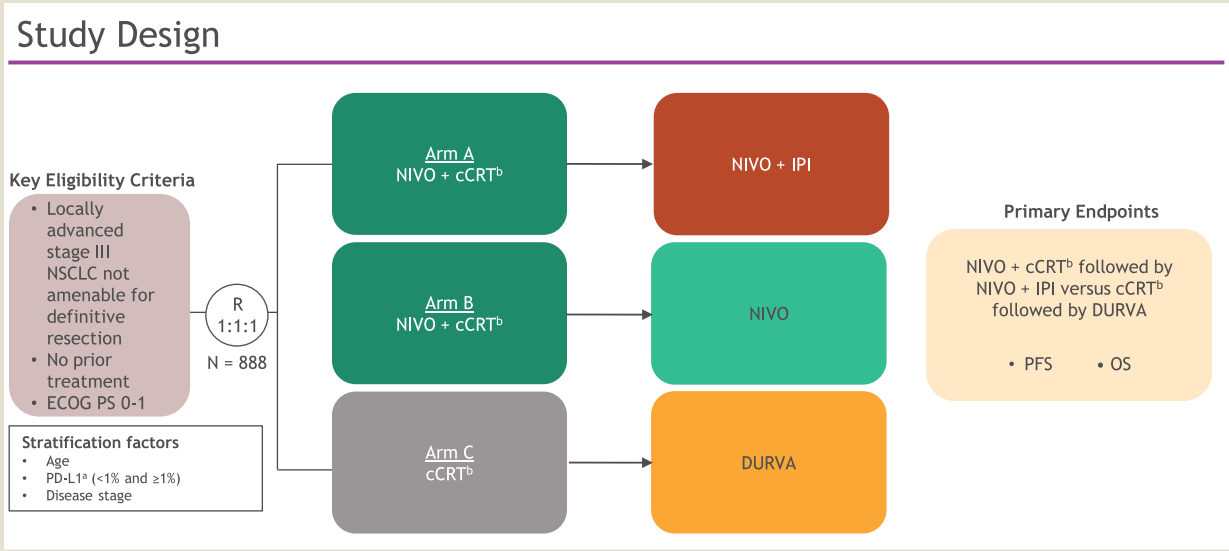
The primary population for efficacy and baseline characteristics consists of all randomized patients, whereas dosing and safety analyses will include all treated patients. Screening of approximately 1400

Table 1 Key Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
• Newly diagnosed NSCLC, with no prior local or systemic anticancer therapy given as primary therapy for LA disease • LA stage IIIA, IIIB, or IIIC histologically confirmed NSCLC per 8th TNM classification according to multidisciplinary assessment at baseline • ECOG PS 0-1	• Prior thoracic radiotherapy • Active infection requiring systemic therapy within 14 days prior to randomization • History of organ or tissue transplant that requires systemic use of immune suppressive agents • Conditions including medical, emotional, psychiatric, or logistical that, in the opinion of the investigator, would preclude the patient from adhering to the protocol or would increase the risk associated with study participation • Any EGFR mutation, ALK translocation, and/or ROS1 rearrangement • Having known or suspected autoimmune disease

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; LA = locally advanced; NSCLC = non-small-cell lung cancer; TNM = tumor nodal metastasis.

Figure 1 Study design of CheckMate 73L Study (NCT04026412).
[a]PD-L1 testing will be performed using the validated Agilent/Dako PD-L1 IHC 28-8 pharmDx assay. [b]Patients with tumors of squamous histology will receive etoposide/cisplatin or paclitaxel/carboplatin. Patients with tumors of non-squamous histology will receive either etoposide/cisplatin, paclitaxel/carboplatin, or pemetrexed/cisplatin. If cisplatin cannot be tolerated, cisplatin may be replaced with carboplatin. If pemetrexed cannot be tolerated, pemetrexed may be replaced with etoposide.
Abbreviations: cCRT = concurrent chemoradiotherapy (histologically based platinum-doublet chemotherapy plus radiotherapy); DURVA = durvalumab; ECOG PS = Eastern Cooperative Oncology Group performance status; IPI = ipilimumab; NIVO = nivolumab; NSCLC = non-small-cell lung cancer; OS = overall survival; PD-L1 = programmed cell death ligand-1; PFS = progression-free survival; R = randomization.



patients is predicted to provide 888 patients for randomization into Arms A and C. The timing of performing analyses is driven by event accrual.

Discussion

The historical standard-of-care for stage III NSCLC has been cCRT for the past decade.[1,14] Recently, the PACIFIC trial showed that cCRT with consolidation therapy with durvalumab provides a significant PFS and OS improvement vs. cCRT alone in patients with stage III NSCLC not amenable for definitive resection. However, there is still a need to improve outcomes for this population of patients, as only approximately 50% of the patients are alive after 4 years of durvalumab initiation.

Both NICOLAS and KEYNOTE 799 trials have shown acceptable safety profiles and promising anti-tumor activity of IO therapies administered with cCRT in patients with stage III NSCLC.[5] Nivolumab plus ipilimumab with or without chemotherapy has demonstrated a survival advantage in multiple phase 3 trials. For example, in CheckMate 227, OS was significantly prolonged for nivolumab plus ipilimumab vs. chemotherapy in patients with untreated advanced NSCLC with a PD-L1 expression of ≥ 1% and a survival benefit was also observed in patients who had tumor

PD-L1 expression < 1% based on a descriptive analysis.[15] The CheckMate 9LA trial of nivolumab plus ipilimumab with 2 cycles of chemotherapy also showed a significant survival benefit compared with chemotherapy for patients with untreated advanced NSCLC, regardless of PD-L1 expression.[13] Furthermore, the efficacy of dual IO therapy in melanoma,[8] renal cell carcinoma,[9,16] and mesothelioma[11] has also been demonstrated, and these trials evaluating nivolumab plus ipilimumab have shown a consistent and acceptable safety profile.[10,15,16]

Of particular relevance to a challenging but potentially curable clinical scenario such as locally advanced NSCLC, this dual IO combination provides an opportunity for durable and long-term OS benefits.[10,15,16] Thus, nivolumab plus cCRT followed by nivolumab in combination with ipilimumab holds promise as a potential treatment for patients with stage III NSCLC not amenable for definitive resection.

Conclusion

The CheckMate 73L study evaluates a novel strategy to improve PFS and OS for patients with stage III NSCLC by integrating nivolumab into cCRT followed by a maintenance phase with nivolumab plus ipilimumab.

Disclosures

D.D. has served as an advisory member and received honoraria from Bristol Myers Squibb, Celgene, Merck/Pfizer, Roche/Genentech, AstraZeneca, MSD, and Seattle Genetics and has received research funding from Boehringer Ingelheim, Bristol Myers Squibb, AstraZeneca, Philips, and Olink. S.R. has served as an advisory member for Amgen, AbbVie, Bristol Myers Squibb, Roche/Genentech, Merck/Pfizer, AstraZeneca, and Takeda, and has received research funds from Tesaro, Merck/Pfizer, AstraZeneca, Advaxis, Bristol Myers Squibb, Amgen, and Takeda. J.U. has nothing to disclose. D.E.G. has served as an advisory member for Catalyst Pharmaceuticals, G1 Therapeutics, BeiGene, and Janssen; has received research funds from AstraZeneca, BerGenBio, Karyopharm, and 3V Biosciences; and owns stock and/or stock options in Gilead. D.S.W.T. has received honoraria from Boehringer Ingelheim, Merck/Pfizer, Roche/Genentech, Novartis, and Takeda; has served as an advisory member for Novartis, Bayer, Boehringer Ingelheim, Celgene, AstraZeneca, Eli Lilly, LOXO, Pfizer, Takeda, and Merrimack; has received research funding from Novartis, Bayer, AstraZeneca, GlaxoSmithKline, and Pfizer; and has received travel accommodation from Merck/Pfizer, Takeda, Boehringer Ingelheim, and Novartis. J.C. and A.L. are employees of Bristol Myers Squibb and own stock and/or stock options in Bristol Myers Squibb. S.P. has served as an advisory member and received honoraria from AbbVie, Amgen, AstraZeneca, Bayer, Biocartis, Bioinvent, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Clovis, Daiichi Sankyo, Debiopharm, Eli Lilly, Roche, Foundation Medicine, Illumina, Janssen, Merck/Pfizer, Merrimack, Novartis, PharmaMar, Regeneron, Sanofi, Seattle Genetics, Takeda, and Vaccibody; has received research funding from Amgen, AstraZeneca, Biodesix, Boehringer Ingelheim, Bristol Myers Squibb, Clovis, Roche, Illumina, Merck/Pfizer, and Novartis; and has received travel accommodation from AstraZeneca, Bayer, Bristol Myers Squibb, Roche, Foundation Medicine, Illumina, Merck/Pfizer, and Seattle Genetics.

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CRediT authorship contribution statement

Dirk De Ruysscher: Conceptualization, Investigation, Resources, Writing – review & editing, Visualization. **Suresh Ramalingam:** Conceptualization, Investigation, Resources, Writing – review & editing. **James Urbanic:** Conceptualization, Writing – review & editing, Visualization. **David E Gerber:** Conceptualization, Writing – review & editing, Visualization. **Daniel S.W. Tan:** Conceptualization, Writing – review & editing, Visualization. **Junliang Cai:** Conceptualization, Validation, Formal analysis, Data curation, Writing – review & editing, Visualization. **Ang Li:** Conceptualization, Validation, Formal analysis, Data curation, Writing – review & editing, Visualization. **Solange Peters:** Conceptualization, Investigation, Resources, Writing – review & editing, Visualization.

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