

Rationale and Design for a Multicenter, Phase II Study of Durvalumab Plus Concurrent Radiation Therapy in Locally Advanced Non-Small Cell Lung Cancer: The DOLPHIN Study (WJOG11619L)

Motoko Tachihara,¹ Kayoko Tsujino,² Takeaki Ishihara,³ Hidetoshi Hayashi,⁴ Yuki Sato,⁵ Takayasu Kurata,⁶ Shunichi Sugawara,⁷ Isamu Okamoto,⁸ Shunsuke Teraoka,⁹ Koichi Azuma,¹⁰ Haruko Daga,¹¹ Masafumi Yamaguchi,¹² Takeshi Kodaira,¹³ Miyako Satouchi,¹⁴ Mototsugu Shimokawa,¹⁵ Nobuyuki Yamamoto,⁹ Kazuhiko Nakagawa⁴

On behalf of members of the West Japan Oncology Group (WJOG)

¹Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe City, Japan; ²Department of Radiation Oncology, Hyogo Cancer Center, Akashi City, Japan; ³Division of Radiation Oncology, Kobe University Graduate School of Medicine, Kobe City, Japan; ⁴Department of Medical Oncology, Kindai University, Osakayama City, Japan; ⁵Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe City, Japan; ⁶Department of Thoracic Oncology, Kansai Medical University Hospital, Hirakata City, Japan; ⁷Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai City, Japan; ⁸Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka City, Japan; ⁹Internal Medicine III, Wakayama Medical University, Wakayama, Japan; ¹⁰Division of Respiratory, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Fukuoka City, Japan; ¹¹Department of Medical Oncology, Osaka City General Hospital, Osaka, Japan; ¹²Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka City, Japan; ¹³Departments of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya City, Aichi, Japan; ¹⁴Department of Thoracic Oncology, Hyogo Cancer Center, Akashi City, Japan; ¹⁵Department of Biostatistics, Yamaguchi University Graduate School of Medicine Yamaguchi, Ube City, Japan

Correspondence: Motoko Tachihara
Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe City, 650-0017, Japan
Tel +81-78-382-5660
Fax +81-78-382-5661
Email mt0318@med.kobe-u.ac.jp

Abstract: Durvalumab (anti-programmed cell death ligand-1) administration after concurrent chemoradiotherapy (cCRT) has improved the survival of patients with unresectable, locally advanced (LA) stage III non-small cell lung cancer (NSCLC). Some patients are unable to complete cCRT and cannot receive immunotherapy due to poor performance status based on adverse events after cCRT. Immunotherapy plays an important role in anti-programmed cell death ligand-1 (PD-L1)-positive advanced NSCLC and is replacing chemotherapy. In addition, radiotherapy and immunotherapy have been reported to have a synergistic effect. This Phase II, multicenter study (DOLPHIN, WJOG11619L, JapicCTI-194840) is designed to assess the efficacy and safety of durvalumab plus concurrent curative radiation therapy for PD-L1-positive unresectable LA-NSCLC without chemotherapy. Unresectable LA stage III NSCLC patients aged 20 years or older with a World Health Organization/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and PD-L1 positivity are enrolled. The patients will receive curative radiation therapy (60 Gy) plus durvalumab 10 mg/kg every 2 weeks (q2w) for up to 12 months until there is evidence of disease progression (PD) or unacceptable toxicity. The primary endpoint is the 12-month progression-free survival rate as assessed by an independent central review. The secondary endpoints are progression-free survival, overall survival, objective response rate, treatment completion rate, and safety. Recruitment began in September 2019.

Keywords: clinical study, locally advanced non-small cell lung cancer, immunotherapy, programmed cell death ligand-1, durvalumab, radiation

Introduction

Approximately one-third of non-small-cell lung cancers (NSCLCs) are found in locally advanced (LA) disease, stage III at diagnosis. LA-NSCLC is considered potentially curable, but The 5-year survival rate was reported to be approximately 20%.¹⁻³ The former standard care for patients with LA-NSCLC was concurrent chemoradiotherapy (cCRT). However, the median progression-free survival (PFS) was approximately 9 months.²

The PACIFIC study has demonstrated significant PFS prolongation by consolidation with the anti-programmed cell death ligand-1 (PD-L1) agent durvalumab compared to placebo after cCRT (median PFS: 16.8 months, HR: 0.52).⁴ cCRT followed by durvalumab consolidation is now the standard of care, but only patients with good performance status (PS) can move on to consolidation therapy after cCRT. There are

no clear data on how many patients could receive durvalumab consolidation. The data on consolidation therapy using chemotherapy show that only approximately 70% of patients receive consolidation therapy.^{2,5,6} In the exploratory analysis from PACIFIC, administration of durvalumab immediately after completion of cCRT (≤ 14 days) has been shown to provide increased benefit. Basic research has established that radiation enhances the antitumour immune response and that the combination of immune checkpoint inhibitors (ICIs) and radiation has a synergistic effect.⁷ In addition, the concurrent administration of a PD-1 inhibitor and radiation has been shown to increase immune activation compared to other treatment timings in mouse models.⁸ Therefore, combination therapy of concurrent ICI and radiotherapy is expected to have a synergistic effect. Presently, several Phase I–II clinical trials with combined ICI and cCRT were reported (Table 1).^{9–11} The treatment strategy may be intriguing, but there are some questions and problems. Chemotherapy causes bone marrow suppression and organ damage as AEs. In particular, neutropenia ($\geq$ grade 3) and febrile neutropenia develop in approximately 18–53% and 3–8% of cases, respectively, under cCRT.^{5,6} Radiation therapy has to be interrupted due to those AEs. Moreover, we must take into account that chemotherapeutic agents and their premedication, such as glucocorticoids, can affect the immune system and response to immunotherapy when combined with ICIs. Also, radiotherapy combined with immunotherapy may increase the incidence of pneumonitis.

On the other hand, in advanced NSCLC, the PD-1 inhibitor pembrolizumab significantly prolongs overall survival (OS) in PD-L1-positive patients compared to

platinum-based chemotherapy.¹² Therefore, it is no exaggeration to say that ICIs are replacing chemotherapy in PD-L1 positive lung cancer.

From the above background, the key drug used in combination with radiotherapy seems to be ICIs. It is unclear whether chemotherapy is essential for the treatment of LA-NSCLC. Thus, we designed this phase II study to assess the efficacy and safety of durvalumab plus concurrent curative radiation therapy for LA-NSCLC without chemotherapy.

Materials and Methods

Study Design and Objective

DOLPHIN is a prospective, multicenter, single-arm, phase II study that is designed to evaluate the efficacy and safety of durvalumab plus concurrent curative radiation therapy for PD-L1-positive unresectable LA-NSCLC.

Endpoints

The primary endpoint is the 12-month PFS rate assessed by independent central review.

The secondary endpoints are PFS, OS, the objective response rate, the disease control rate, time to death or distant metastasis, the treatment completion rate, and safety.

Treatment

Patients receive durvalumab 10 mg/kg every 2 weeks (q2w) for up to 12 months until evidence of disease progression (PD) or unacceptable toxicity, whichever comes first. Radiation is started on day 1 of durvalumab

Table 1 Reported Studies of Combination Immune Checkpoint Inhibitors with CRT for Locally Advanced NSCLC

Trial	Phase	n	Type of Radiation	Treatment	Median PFS (Months)	1-Year PFS Rate (%)	Median OS (Months)	Gr $\geq$ 3 Pneumonitis (%)
NICOLAS (ETOP) ⁹	II	79	Conventional	Three cycles of cCRT with nivolumab then nivolumab up to 1 year	12.7	53.7	38.8	11.7
DETERRED ¹⁰ Part I	II	10	IMRT, Proton	cCRT $\rightarrow$ chemo-atezolizumab X2 $\rightarrow$ atezolizumab up to 1 year	18.6	–	22.7	0.0
DETERRED ¹⁰ Part II	II	30	IMRT, Proton	cCRT with atezolizumab $\rightarrow$ chemo-atezolizumab X2 $\rightarrow$ atezolizumab up to 1 year	13.2	–	Not reached	3.0
Rutgers ¹¹	I	30	Conventional, IMRT, Proton	Pembrolizumab added in 3+3 cohort from consolidation to cCRT	18.7	69.7	29.4	10.0

Abbreviations: IMRT, intensity modulated radiation therapy; cCRT, concurrent chemoradiotherapy; PFS, progression free survival; OS, overall survival.

treatment. Planned radiation is performed by 3-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT), either of which can be selected for each case. Patients will be scheduled to receive 60 Gy in 30 fractions 5 days per week (prescribed to D95% of the planning target volume [PTV]) administered to involved fields (without elective nodal irradiation).

Key Eligibility Criteria

This study consists of two stages of registration (Figure 1). The main eligibility criteria for the primary registration include 1) age of 20 years or older; 2) Eastern Cooperative Oncology Group PS 0 or 1; 3) histologic evidence of NSCLC; and 4) suspected unresectable stage III disease or postoperative recurrent disease that was curable by radiation (Table 2). The main eligibility criteria for the secondary registration include 5) confirmed unresectable stage III disease or postoperative recurrent disease that is curable by the radiation protocol; 6) PD-L1 $\geq$ 1% (SP263 antibody); and 7) adequate organ function, including hematologic, lung, hepatic and renal function.

Study Assessments

Objective tumour assessments are performed by independent central review and investigators in accordance with RECIST v1.1. The assessments are conducted at baseline and every 8 weeks until PD. Safety variables include symptoms, vital signs, physical examinations, evaluation of changes to concomitant medications, clinical laboratory parameters (hematology, serum chemistry), and the incidence, timing and severity of AE. AEs will be graded using the Common Terminology

Criteria for Adverse Events (CTCAE), version 5.0. An independent external data safety monitoring committee will review progress of study treatment, the radiation treatment delivered, and safety data throughout the study. All data will be collected by an electronic data capture (EDC) system.

Early analysis was conducted to examine whether the study could be continued when 20 patients had completed the combination therapy of radiotherapy and durvalumab.

If patients with PD assessed by the investigator were found in 6 cases (30%) or more, the study was discontinued early.

Statistical Analysis

The 12-month PFS rate in the PACIFIC trial was 35.3% (95% confidence interval (CI), 29.0 to 41.7) in the placebo group and 55.9% (95% CI, 51.0 to 60.4) in the durvalumab group.⁴ We assumed the threshold of the 12-month PFS rate to be 28% and the expected rate to be 50%. The number of patients needed to provide 80% power for a one-sided 0.05 level of type I error was calculated to be 32. Considering ineligible patients after enrolment, the sample size was set at 35. PFS and OS will be analysed using the Kaplan-Meier method to estimate the median points with 95% CIs.

Ethical Considerations

This study is being conducted in accordance with the principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. Written informed consent will be obtained from all patients before study enrolment. Moreover, it has been approved by the institutional review

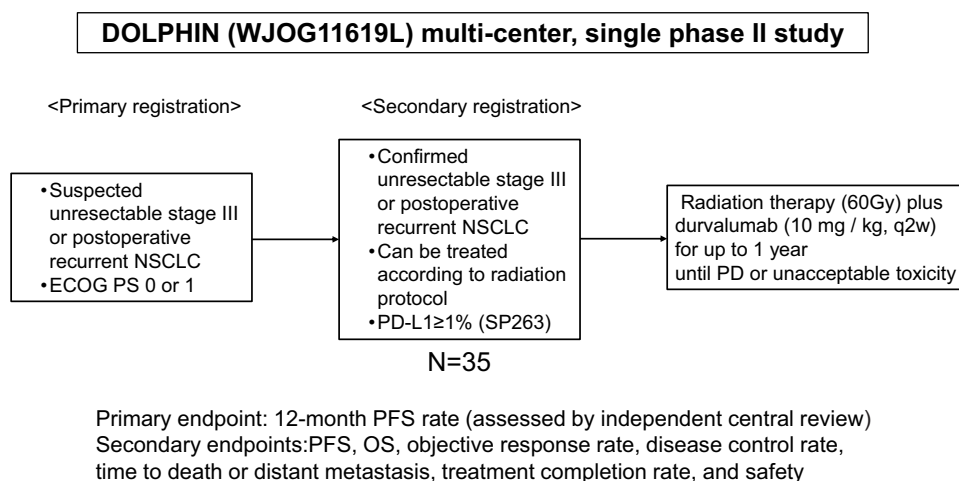


Figure 1 Design of the DOLPHIN study.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PFS, progression free survival; OS, overall survival.

Table 2 Inclusion and Key Exclusion Criteria

Inclusion Criteria
<The primary inclusion criteria> Written informed consent Age ≥20 years old Histologic evidence of NSCLC Suspected locally advanced NSCLC (stage IIIA, B, C) or postoperative recurrence ECOG performance status of 0 or 1 With measurable lesions Availability of tumor tissue for IHC Adequate organ and bone marrow function SpO ₂ ≥93% No past history of thoracic radiation therapy and chemotherapy 24 weeks have passed since adjuvant chemotherapy Life expectancy of ≥12 weeks Body weight ≥30kg <The secondary inclusion criteria> Confirmed unresectable locally advanced NSCLC is curable by the radiation protocol PD-L1 positive of tumor cells (SP263) Irradiation is possible (60 Gy in 30 fractions prescribed to D95% of PTV to involved fields)
Key Exclusion criteria
Active double cancer Active infection, including tuberculosis, hepatitis B and C Interstitial lung disease detected by chest-CT Complication of active autoimmune disease Prescription of more than 10mg PSL continuously

Abbreviations: NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; IHC, Immunohistochemistry; SpO₂, arterial oxygen saturation of pulse oximetry; PD-L1, programmed cell death ligand-1; CT, computed tomography; PSL, prednisolone.

board of all 12 participating institutions (Kobe University Graduate School of Medicine, Hyogo Cancer Center, Kindai University, Kobe City Medical Center General Hospital, Kansai Medical University Hospital, Sendai Kousei Hospital, Kyushu University, Wakayama Medical University, Kurume University School of Medicine, Osaka City General Hospital, National Hospital Organization Kyushu Cancer Center, and Aichi Cancer Center

Hospital). The study protocol has been registered in the JapicCTI database: JapicCTI-194840.

Discussion

New treatment options are required for patients with unresectable LA-NSCLC. The DOLPHIN study was designed to evaluate the efficacy and safety of durvalumab plus concurrent radiation therapy for unresectable LA-NSCLC without chemotherapy.

Combined ICI and cCRT are possible new treatment strategy, but the efficacy and safety concerns remain unclear. In the NICOLAS study, which is a single-arm phase II trial of cCRT along with the PD-1 antibody nivolumab, grade 3 or higher pneumonitis occurred in 11.7% (grade 5; 1) of cases, which was three times higher than that of the PACIFIC trial.⁹ It may be due to cCRT combined with immunotherapy. Notably, the treatment success rate of the protocol was 39.2%, and 43.5% of treatment cases were terminated due to adverse events (AEs). Moreover, the 1-year PFS (53.7%) and the median PFS (12.7 months) were lower than expected based on the results from the PACIFIC study.⁴ The other phase I–II studies also showed the similar results.^{10,11} Now, the Phase III study to evaluate the efficacy and safety of cCRT plus concurrent durvalumab compared with conventional cCRT is now ongoing (PACIFIC II). Even if PACIFIC II regimen results in better, we cannot know whether cCRT plus concurrent ICI or cCRT followed by ICI is better.

Although the best choices and timing of immunotherapy, radiotherapy, and systematic chemotherapy remain unclear, the essential key drug type used in combination with radiotherapy seems to be ICIs. Currently, there are limited trials of combined immunotherapy and radiation therapy without chemotherapy (Table 3). Our trial is the first prospective study for only unresectable LA-NSCLC, and which will not be confirmed by the PACIFIC and ongoing PACIFIC II. We believe we can present the new

Table 3 Ongoing Studies of Combination Immune Checkpoint Inhibitors with Radiation

Trial	Trial Number	Phase	n	Stage	Eligibility Biomarker	Type of Radiation	Systemic Treatment
ARCHON-I	NCT03801902	I	24	II–III	PD-L1 ≥50%	AHF or conventional radiotherapy	Durvalumab
SPRINT	NCT03523702	I	63	II–III	PD-L1 status	Conventional	Pembrolizumab or chemotherapy
This trial	JapicCTI-194840	II	35	III	PD-L1 ≥1%	Conventional, IMRT	Durvalumab

Abbreviation: AHF, accelerated hyperfractionated.

significance of combination therapy with concurrent ICI and radiotherapy by investigating the safety and efficacy of durvalumab plus concurrent radiotherapy in this study. If this clinical trial has promising results, the therapeutic protocol may be a candidate for a new treatment strategy with low toxicity and high therapeutic effect for patients with unresectable LA-NSCLC. Recruitment began in September 2019, all 35 patients were registered in November 2020, and treatments are now ongoing.

Conclusion

The phase II study will be able to evaluate the efficacy and safety of durvalumab plus concurrent curative radiation therapy for PD-L1-positive unresectable LA-NSCLC without chemotherapy.

Acknowledgments

We thank the patients, their families, and all of the investigators participating in the study. We are grateful to Yasumasa Nishimura (Kindai University), Yasutaka Noda (Wakayama Medical University), Masaki Kokubo (Kobe City Medical Center General Hospital), Yoshiyuki Shioyama (Kyushu University), Junichi Shimizu (Aichi Cancer Center Hospital), Naonobu Kunitake (National Hospital Organization Kyushu Cancer Center), Etsuyo Ogo (Kurume University School of Medicine), Satoaki Nakamura (Kansai Medical University Hospital), Hiroko Ikeda (Osaka City General Hospital), Misako Miwa (Sendai Kousei Hospital), Koji Takeda (the data manager of WJOG), Kazuhiko Sawa (the staff of WJOG), Tomomi Moritani (clinical research coordinator of Kobe University Hospital), and Shinji Tsudou (medical physicist of Hyogo Cancer Center). This study is funded by AstraZeneca K.K., Japan.

Disclosure

Dr. Tachihara reports grants and personal fees from AstraZeneca K.K., personal fees from Eli Lilly Japan K.K., Taiho Pharmaceutical Co., Ltd., MSD K.K., Nippon Boehringer Ingelheim Co., Ltd., Chugai Pharmaceutical Co., Ltd., and Ono Pharmaceutical Co., Ltd. Dr. Tsujino reports personal fees from AstraZeneca K.K. Dr. Hayashi reports grants and personal fees from AstraZeneca K.K., Boehringer Ingelheim Japan Inc., Chugai Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., personal fees or grants from Astellas Pharma Inc., Symbio Pharmaceuticals Limited, AbbVie Inc, inVentiv Health Japan, ICON Japan K.K., GRITSONE

ONCOLOGY.INC, PAREXEL International Corp., Kissei Pharmaceutical Co., Ltd., EPS Corporation., Syneos Health., Pfizer R&D Japan G.K., A2 Healthcare Corp., Quintiles Inc./ IQVIA Services JAPAN K.K., EP-CRSU CO., LTD., Linical Co., Ltd., Eisai Co., Ltd., CMIC Shift Zero K.K., Kyowa Hakko Kirin Co., Ltd, Bayer Yakuhin, Ltd, EPS International Co., Ltd., Otsuka Pharmaceutical Co., Ltd, Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., Kyorin pharmaceutical co. ltd, Merck Biopharma Co., Ltd., MSD K. K., Novartis pharmaceuticals K.K., Shanghai Haihe Biopharm, Taiho Pharmaceutical Co. Ltd, and Takeda Pharmaceutical Co., Ltd., Pfizer Japan Inc., Shanghai Haihe Biopharm, Merck Biopharma Co., Ltd. Dr. Sato reports honoraria from Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., MSD K.K., Novartis, Taiho Pharmaceutical Co., Ltd., AstraZeneca K.K., Novartis, and Nippon Kayaku. Dr. Kurata reports grants and personal fees from AstraZeneca K.K., Bristol-Myers Squibb, MSD K.K., grants from Novartis, Takeda Pharmaceutical Co., Ltd., and personal fees from Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Boehringer Ingelheim Co., Ltd. Dr. Sugawara reports personal fees from AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., Boehringer Ingelheim Co., Ltd., Taiho Pharmaceutical Co., Ltd., Pfizer, Eli Lilly Japan K. K., Novartis, Bristol-Myers Squibb, Ono Pharmaceutical Co., Ltd., MSD Oncology, Yakult Honsha, Kyowa Hakko Kirin Co., Ltd. Dr. Okamoto reports grants from AbbVie, Novartis, Astellas Pharma, grants and personal fees from AstraZeneca K.K., Taiho Pharmaceutical Co., Ltd., Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd., MSD Oncology, Eli Lilly Japan K.K., Chugai Pharmaceutical Co., Ltd., Bristol-Myers Squibb, and personal fees from Pfizer. Dr. Teraoka reports personal fees from Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., Taiho Pharmaceutical Co., Ltd., Novartis, Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd. Dr. Azuma reports personal fees from AstraZeneca K.K., Ono Pharmaceutical Co., Ltd., MSD K.K., Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd. Dr. Daga reports personal fees from Chugai Pharmaceutical Co., Ltd., MSD K.K. Dr. Kodaira reports personal fees from Merck Serono. Co., Hitachi Co., Bristol-Myers Squibb, Elekta Co., Ono Pharmaceutical Co., Ltd., AstraZeneca K.K., Taiho Pharmaceutical Co., Ltd., Canon Co., Ltd. Dr. Satouchi reports grants and personal fees from AstraZeneca K.K., Boehringer Ingelheim Japan Inc., Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., Pfizer Japan Inc., MSD K.K., Novartis

pharmaceuticals K.K., Bristol-Myers Squibb Co. Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo, EPS International, Janssen Pharmaceutical K.K., personal fees from Ono Pharmaceutical Co. Ltd., Merck Biopharma Co., Ltd., Taiho Pharmaceutical Co. Ltd., Eisai, Bayer, Nippon Kayaku, and grants from AbbVie Inc, Amgen. Dr. Yamamoto reports grants and personal fees from Chugai Pharmaceutical Co., Ltd., Boehringer-Ingelheim Co., Ltd., personal fees from AstraZeneca K.K., MSD K.K., Ono Pharmaceutical Co., Ltd., TAIHO Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Novartis, Bristol-Myers Squibb, Nippon Kayaku, Life Technologies Japan Ltd., Thermo Fisher Scientific, Daiichi Sankyo, GlaxoSmithKline K.K., Sanofi K.K., Hisamitsu Pharmaceutical Co. Inc., Merck biopharma, Amgen Inc., Guardant Health Japan, Janssen Pharmaceutical K.K., and grants from Tosoh Life Science Research Laboratory. Dr. Nakagawa reports grants and personal fees from AstraZeneca K.K., Astellas Pharma Inc., MSD K.K., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K., Bristol Myers Squibb Company, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Merck Serono Co., Ltd./Merck Biopharma Co., Ltd., grants, personal fees and consulting fees from Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., Eli Lilly Japan K.K., during the conduct of the study; personal fees from Clinical Trial Co., Ltd., MEDICUS SHUPPAN, Publishers Co., Ltd., Care Net, Inc, Reno. Medical K.K., Medical Review Co., Ltd., Roche Diagnostics K.K., Bayer Yakuhin, Ltd, Medical Mobile Communications co., Ltd, 3H Clinical Trial Inc., Nichi-Iko Pharmaceutical Co., Ltd., Hisamitsu Pharmaceutical Co., NANZANDO Co., Ltd., YODOSHA CO., LTD., Nikkei Business Publications, Inc, Thermo Fisher Scientific K.K., YOMIURI TELECASTING CORPORATION., Nippon Kayaku Co., Ltd., personal fees and consulting fees from KYORIN Pharmaceutical Co., Ltd., grants, personal fees and consulting fees from Takeda Pharmaceutical Co., Ltd., grants and personal fees from Taiho Pharmaceutical Co., Ltd., SymBio Pharmaceuticals Limited., AbbVie Inc, grants from inVentiv Health Japan, ICON Japan K.K., GRITSONE ONCOLOGY, INC, PAREXEL International Corp., Kissei Pharmaceutical Co., Ltd., EPS Corporation., Syneos Health., Pfizer R&D Japan G.K., A2 Healthcare Corp., Quintiles Inc./IQVIA Services JAPAN K.K., EP-CRSU CO., LTD., Linical Co., Ltd., Eisai Co., Ltd., CMIC Shift Zero K.K., Kyowa Hakko Kirin Co., Ltd, Bayer Yakuhin, Ltd, EPS International Co., Ltd., Otsuka Pharmaceutical Co., Ltd, PRA Health Sciences, Covance

Japan Inc., Medical Research Support, Sanofi K.K., PPD-SNBL K.K., Japan Clinical Research Operations, Sysmex Corporation Mochida Pharmaceutical Co., Ltd. GlaxoSmithKline K.K. Dr. Ishihara, Dr. Yamaguchi, and Dr. Shimokawa report no conflicts of interest.

References

- Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:39–51. doi:10.1016/j.jtho.2015.09.009
- Ahn JS, Ahn YC, Kim JH, et al. Multinational randomized phase III trial with or without consolidation chemotherapy using docetaxel and cisplatin after concurrent chemoradiation in inoperable stage III non-small-cell lung cancer: KCSG-LU05-04. *J Clin Oncol*. 2015;33:2660–2666. doi:10.1200/JCO.2014.60.0130
- Zenke Y, Tsuboi M, Chiba Y, et al. Effect of second-generation vs third-generation chemotherapy regimens with thoracic radiotherapy on unresectable stage III non-small-cell lung cancer: 10-year follow-up of a WJTOG0105 Phase 3 randomized clinical trial. *JAMA Oncol*. 2021;18:e210113.
- Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919–1929. doi:10.1056/NEJMoa1709937
- Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol*. 2010;28:3739–3745. doi:10.1200/JCO.2009.24.5050
- Senan S, Brade A, Wang LH, et al. PROCLAIM: randomized Phase III Trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol*. 2016;34:953–962. doi:10.1200/JCO.2015.64.8824
- Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest*. 2014;124:687–695. doi:10.1172/JCI67313
- Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res*. 2014;74:5458–5468. doi:10.1158/0008-5472.CAN-14-1258
- Peters S, Felip E, Dafni U, et al. Progression-free and overall survival for concurrent nivolumab with standard concurrent chemoradiotherapy in locally advanced stage IIIA-B NSCLC: results from the European Thoracic Oncology platform NICOLAS Phase II trial. *J Thorac Oncol*. 2021;16:78–88. doi:10.1016/j.jtho.2020.10.129
- Lin SH, Lin Y, Yao L, et al. Phase II trial of concurrent atezolizumab with chemoradiation for unresectable NSCLC. *J Thorac Oncol*. 2020;15:248–257. doi:10.1016/j.jtho.2019.10.024
- Jabbour SK, Berman AT, Decker RH, et al. Phase 1 trial of pembrolizumab administered concurrently with chemoradiotherapy for locally advanced non-small cell lung cancer, a nonrandomized controlled trial. *JAMA Oncol*. 2020;6:848–855. doi:10.1001/jamaoncol.2019.6731
- Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393:1819–1830. doi:10.1016/S0140-6736(18)32409-7

Cancer Management and Research

Dovepress

Publish your work in this journal

Cancer Management and Research is an international, peer-reviewed open access journal focusing on cancer research and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient.

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/cancer-management-and-research-journal>