PACIFIC-更新.pdf.txt

# 研究患者

Methods PACIFIC is an ongoing, international, multicentre, double-blind, randomised, controlled, phase 3 trial. Eligible patients were aged at least 18 years, had a WHO performance status of 0 or 1, with histologically or cytologically documented stage III, unresectable non-small-cell lung cancer, for which they had received at least two cycles of platinum-based chemoradiotherapy, with no disease progression after this treatment.

# 样本量

Findings Between May 9, 2014, and April 22, 2016, 476 patients were assigned to receive durvalumab, and 237 patients were assigned to receive placebo.

# 基线特征

Between May 7, 2014, and April 22, 2016, we screened 983 patients for the trial, of whom 270 (27%) patients were excluded because they did not meet eligibility criteria (n=225), did not consent to be included (n=35), died (n=6), or for other reasons (n=4; figure 1). Between May 9, 2014, and April 22, 2016, we randomly assigned 713 (73%) patients to groups. 476 (67%) patients were assigned to receive durvalumab, of whom 473 (99%) patients received the drug, and 237 (33%) patients were assigned to receive placebo, of whom 236 (>99%) patients received placebo. Three patients in the durvalumab group (two who withdrew consent and one who developed neutropenia) and one patient in the placebo group (who reported worsening chronic obstructive pulmonary disease) did not receive their assigned treatment. As of the data cut- off date, March 22, 2018, the median follow-up was 25·2 months (IQR 14·1–29·5). Patient characteristics, including use of and response to previous chemo- radiotherapy treatment, were well balanced between treatment groups.

# 试验设计

Contributors DV, AR, and SJA conceived of and designed the study. RH, MÖ, AV, DD, DV, SM, AC, KHL, MdW, BCC, JEG, and SJA provided study materials or recruited patients. RH, MÖ, DD, TY, KHL, MdW, BCC, LV, LP, and SJA collected and assembled data. RH, MÖ, AC, MdW, BCC, JEG, AR, LV, LP, YZ, and PAD analysed and interpreted data. All authors were involved in writing the manuscript and approved the final version. SJA provided administrative support. Declaration of interests RH reports serving on advisory boards for AstraZeneca, MSD, Novartis, Roche, Bristol-Myers Squibb, and Eli Lilly and reports honoraria from AstraZeneca, MSD, Novartis, Roche, Bristol-Myers Squibb, and Eli Lilly. MÖ reports serving on an advisory board for Janssen Pharmaceutica. AV reports honoraria from AstraZeneca, Gilead Sciences, and Seattle Genetics. DD reports research funding to his institution from ER Squibb and Sons, AstraZeneca, Boehringer Ingelheim, Genentech, Eli Lilly, Novartis, Pfizer, Celgene, and Roche. AC reports speaker’s fees from Genentech, Merck & Co, Takeda, Novartis, Boehringer-Ingelheim, and Celgene and research funding from Novartis and Bristol-Myers Squibb. MdW reports speaker’s fees from AstraZeneca. JEG reports serving on an advisory board for AstraZeneca and reports research funding from AstraZeneca, Merck & Co, Bristol-Myers Squibb, and Genentech. AR, LP, YZ, and PAD are employed by and own stock in AstraZeneca. All other authors declare no competing interests. Data sharing Data underlying the findings of this study can be obtained in accordance with AstraZeneca’s data sharing policy described online. Acknowledgments This study was funded by AstraZeneca. We thank the patients, their families and caregivers, and all investigators involved in this study. Medical writing support, which was in accordance with Good Publication Practice guidelines, was provided by Elizabeth Andrew and Lauren Donaldson of Cirrus Communications (Macclesfield, UK), an Ashfield company, and was funded by AstraZeneca. References 1 Yoon SM, Shaikh T, Hallman M. Therapeutic management options for stage III non-small cell lung cancer. World J Clin Oncol 2017; 8: 1–20. 2 GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1459–544. 3 Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010; 28: 2181–90. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28 (suppl 4): 1–21. 5 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: 2660–66. Yoon SM, Shaikh T, Hallman M.

# 研究背景

Background In the ongoing, phase 3 PACIFIC trial, durvalumab improved the primary endpoints of progression-free survival and overall survival compared with that for placebo, with similar safety, in patients with unresectable, stage III non-small-cell lung cancer. In this analysis, we aimed to evaluate one of the secondary endpoints, patient-reported outcomes (PROs).

# 研究结果

results to studies of anti-PD-1 and anti-PD-L1 therapies. Evidence regarding the effect of immunotherapy on PROs in patients with advanced or metastatic non-small-cell lung cancer is emerging.

# 研究结论

Findings Between May 9, 2014, and April 22, 2016, 476 patients were assigned to receive durvalumab, and 237 patients were assigned to receive placebo. As of March 22, 2018, the median follow-up was 25·2 months (IQR 14·1–29·5). More than 79% of patients given durvalumab and more than 82% of patients given placebo completed questionnaires up to week 48. Between baseline and 12 months, the prespecified longitudinal PROs of interest, cough (MMRM- adjusted mean change 1·8 [95% CI 0·06 to 3·54] in the durvalumab group vs 0·7 [–1·91 to 3·30] in the placebo group), dyspnoea (3·1 [1·75 to 4·36] vs 1·4 [–0·51 to 3·34]), chest pain (–3·1 [–4·57 to –1·60] vs –3·5 [–5·68 to –1·29]), fatigue (–3·0 [–4·53 to –1·50] vs –5·2 [–7·45 to –2·98]), appetite loss (–5·8 [–7·28 to –4·36] vs –7·0 [–9·17 to –4·87]), physical functioning (0·1 [–1·10 to 1·28] vs 2·0 [0·22 to 3·73]), and global health status or quality of life (2·6 [1·21 to 3·94] vs 1·8 [–0·25 to 3·81]) remained stable with both treatments, with no clinically relevant changes from baseline. The between-group differences in changes from baseline to 12 months in cough (difference in adjusted mean changes 1·1, 95% CI –1·89 to 4·11), dyspnoea (1·6, –0·58 to 3·87), chest pain (0·4, –2·13 to 2·93), fatigue (2·2, –0·38 to 4·78), appetite loss (1·2, –1·27 to 3·67), physical functioning (–1·9, –3·91 to 0·15), or global health status or quality of life (0·8, –1·55 to 3·14) were not clinically relevant. Generally, there were no clinically important between- group differences in time to deterioration of prespecified key PRO endpoints.  
Interpretation Our findings suggest that a clinical benefit with durvalumab can be attained without compromising PROs.

# 表格相关

Findings Between May 9, 2014, and April 22, 2016, 476 patients were assigned to receive durvalumab, and 237 patients were assigned to receive placebo. As of March 22, 2018, the median follow-up was 25·2 months (IQR 14·1–29·5). More than 79% of patients given durvalumab and more than 82% of patients given placebo completed questionnaires up to week 48. Between baseline and 12 months, the prespecified longitudinal PROs of interest, cough (MMRM- adjusted mean change 1·8 [95% CI 0·06 to 3·54] in the durvalumab group vs 0·7 [–1·91 to 3·30] in the placebo group), dyspnoea (3·1 [1·75 to 4·36] vs 1·4 [–0·51 to 3·34]), chest pain (–3·1 [–4·57 to –1·60] vs –3·5 [–5·68 to –1·29]), fatigue (–3·0 [–4·53 to –1·50] vs –5·2 [–7·45 to –2·98]), appetite loss (–5·8 [–7·28 to –4·36] vs –7·0 [–9·17 to –4·87]), physical functioning (0·1 [–1·10 to 1·28] vs 2·0 [0·22 to 3·73]), and global health status or quality of life (2·6 [1·21 to 3·94] vs 1·8 [–0·25 to 3·81]) remained stable with both treatments, with no clinically relevant changes from baseline. The between-group differences in changes from baseline to 12 months in cough (difference in adjusted mean changes 1·1, 95% CI –1·89 to 4·11)

>>>>>>>>>>>>>>>>>>

(the primary endpoints) compared with placebo in patients with stage III, locally advanced, unresectable non-small-cell lung cancer who had not progressed after two or more cycles of platinum-based concurrent chemoradiotherapy. The addition of up to 12 months of durvalumab treatment did not compromise patients’ symptoms, functioning, or global health status or quality of life compared with placebo during the study period, complementing previous efficacy and safety findings and further establishing the PACIFIC regimen (durvalumab after concurrent chemoradiotherapy)

>>>>>>>>>>>>>>>>>>

PACIFIC is an ongoing, international, multicentre, double-blind, randomised, controlled, phase 3 trial. The primary and secondary endpoints of this phase 3 trial have been reported previously.12,13 This was a global trial, conducted at 235 cancer treatment centres across 26 countries in Asia, Australia, Europe, north and south America, and south Africa. A full list of the study sites is provided in the appendix (pp 12–21). Patients were eligible if they had histologically or cytologically documented stage III, unresectable non- small-cell lung cancer, as per the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology (version 7)

>>>>>>>>>>>>>>>>>>

Patients provided archived tumour tissue samples for PD-L1 testing if available; however, enrolment was not restricted to any PD-L1 expression thresholds. Patients received 10 mg/kg intravenous durvalumab (AstraZeneca; Wilmington, DE, USA) or matching placebo, every 2 weeks for up to 12 months. Dose reductions were not permitted. Dose delays, inter- ruptions, or discontinuation were allowed for manage- ment of toxicity, as defined in the protocol (appendix pp 210–31). Patients who had a dose interruption because of toxicity at any time during the first 12 months of treatment could resume treatment, but the treatment period could not exceed 12 months (including the interruption time). Study drug could be discontinued because of confirmed progression, initiation of an alternative anticancer therapy, unacceptable toxicity, or withdrawal of consent. Patients could be treated with their study drug during progression if they fulfilled predefined criteria, and treatment could resume if disease control was achieved at the end of 12 months and the disease progressed during follow-up. PROs were assessed with paper-based questionnaires at the time of random allocation to groups, week 4, week 8, every 8 weeks until week 48, then every 12 weeks until disease progression. The last assessment for patients who discontinued treatment because of pro gression was day 30 after the final dose. Patients who continued treatment after progression because of clinical benefit, at the investigator’s discretion, continued completing question naires for as long as they received treatment. Patients who discontinued treatment for reasons other than confirmed progression continued completing the question naires until confirmed progression. We evaluated patient-reported symptoms, functioning, and global health status or quality of life with two questionnaires that were developed by the European Organisation for Research and Treatment of Cancer (EORTC)

>>>>>>>>>>>>>>>>>>

and placebo (figure 2). Physical functioning (0·1 [–1·10 to 1·28] vs 2·0 [0·22 to 3·73]) and global health status or quality of life (2·6 [1·21 to 3·94] vs 1·8 [–0·25 to 3·81]; both QLQ-C30) also remained stable with both treatments throughout the study. We found no difference between durvalumab and placebo on the reported between-group differences in changes from baseline to 12 months in cough (difference in adjusted mean changes 1·1, 95% CI –1·89 to 4·11)

>>>>>>>>>>>>>>>>>>

The proportion of patients whose scores improved for symptoms, functioning, and global health status or quality of life were similar between treatment groups, except for emotional functioning, which favoured durvalumab. This finding might be associated with the improved efficacy observed with durvalumab. These PRO data complement previously reported data on the safety profile of durvalumab use after concurrent chemoradiotherapy.13 Grade 3 or 4 adverse events were comparable between durvalumab (30·5%) and placebo (26·1%).13 Therefore, although the incidence of some adverse events was greater with durvalumab versus placebo (eg, cough, pneumonitis, or radiation pneu- monitis), these were low-grade events with no clinically meaningful impairment to PROs (for instance, there were no between-group differences in times to deter- ioration or the proportion of patients whose score improved for dyspnoea in the QLQ-LC13).9 Overall, analysis of investigator-assessed adverse events in PACIFIC suggested a manageable safety profile.13 Patients with advanced non-small-cell lung cancer who were treated with immune checkpoint inhibitors have shown stable or improved quality of life and a manageable safety profile in other trials.21–24 The PRO data we report are consistent with these observations. Improvement in quality of life is likely to be observed with first-line and second-line anti-PD-1 drugs in stage IV non-small-cell lung cancer; however, such improvement in stage III non-small-cell lung cancer after chemoradio- therapy was not expected because of a lower symptom burden and better baseline functioning. Furthermore, patients with stage III non-small-cell lung cancer who receive frequent surveillance imaging in the study protocol would usually have a low symptom burden at the time of radiological disease progression (although other determinants of deterioration of quality of life besides progression might contribute)

>>>>>>>>>>>>>>>>>>