Reply to: Pharmacotherapy for lung cancer with comorbid interstitial pneumonia: limited evidence requires appropriate evaluation

Received: 12 Sept 2022
Accepted: 16 Sept 2022

From the authors:

We appreciate the interest raised by our recent article [1] and take the opportunity to address the points raised by Y. Ishida and colleagues.

Y. Ishida and colleagues questioned our suggestions for second-line lung cancer therapy in fibrotic interstitial lung disease (ILD) with vinorelbine (squamous cell carcinoma) and pemetrexed (adenocarcinoma). They suggest docetaxel rather than vinorelbine and pemetrexed, but there are opposing arguments. They refer to acute exacerbation rates from one retrospective nationwide surveillance of 396 patients with idiopathic interstitial pneumonia and lung cancer in Japan [2]. However, this study does not reflect experience in other populations and regions. Drug-induced lung toxicities vary greatly between studies and ethnicities. For example, the incidence of adverse events associated with pemetrexed has been as low as 12.5% and 13.3% in idiopathic pulmonary fibrosis (IPF) and ILD, respectively [3]. Drug chemotherapeutic toxicities are reportedly higher in Asians than in Caucasians [4].

Furthermore, docetaxel causes acute exacerbation in 18.4% and 20.8% of patients with ILD and IPF, respectively [3]. In a limited number of patients, the incidence of docetaxel-associated ILD exacerbation was reported to be as high as 50%, with none associated with pemetrexed and vinorelbine [5]. Kenmotsu *et al.* [6] reported the incidence of acute exacerbation of ILD with use of second-line chemotherapy in non-small cell lung cancer (NSCLC) to be 26% with docetaxel, 25% with pemetrexed and 20% with vinorelbine. Watanabe *et al.* [7] found that docetaxel monotherapy has a poor activity and substantial risks when used for the treatment of platinum-resistant NSCLC with interstitial pneumonia. Tamiya *et al.* [8] explicitly recommended against the use of docetaxel in pre-existing ILD patients with NSCLC due to a high incidence of chemotherapy-associated radiological ILD changes. Finally, in the very recently published results of the J-Sonic Phase III trial using nab-paclitaxel plus carboplatin±nintedanib in the first-line setting for lung cancer associated with fibrosing ILD, Japanese patients received, in the second line, most frequently, S-1 and, less frequently but in similar proportions, docetaxel, vinorelbine or pemetrexed [9].

Hayashi and Mitsudomi [10] summarise why docetaxel represents an inferior choice and elaborate reasons for regional differences in S-1 use. S-1 is an effective anticancer drug in patients with ILD in Japan [11] but is not used in Europe. Firstly, the higher incidence of side-effects in Caucasians compared to Asian populations argues against S-1 [12, 13]. Secondly and most importantly, S-1 is authorised for use in advanced gastric cancer and metastatic colorectal cancer [10] but has not been approved in lung cancer patients by the European Medicines Agency.

Thus, the divergence in views on lung cancer treatments in patients with fibrosing ILD is likely to reflect differences in chemotherapy approval and usage, based in part on the variable incidence of side-effects in different countries and among ethnicities.

Lung cancer and fibrosing ILD are both heterogeneous conditions, and treatment plans for both conditions depend on case-by-case considerations and regional variability. The onset of lung cancer in pre-existing

Shareable abstract (@ERSpublications)
The divergent views on lung cancer treatments in fibrosing lung patients reflect differences due to variable side-effect incidences in different countries and among ethnicities. International efforts are needed to better define treatment approaches. https://bit.ly/3DX40fq

Cite this article as: Funke-Chambour M, Kewalramani N, Machahua C, *et al.* Reply to: Pharmacotherapy for lung cancer with comorbid interstitial pneumonia: limited evidence requires appropriate evaluation. *ERJ Open Res* 2022; 8: 00469-2022 [DOI: 10.1183/23120541.00469-2022].

fibrosing ILDs greatly complicates management, which must be individualised according to patient tolerance, ethnicity and local resources. This gives rise to considerable variability in reports on anticancer chemotherapy in ILD.

Y. Ishida and colleagues aptly summarise the challenge faced with immune checkpoint inhibitor (ICI) trial data. We have pointed out that alarming data concerning the use of ICIs were mostly retrospective and have described the only two phase II trials published at the time of our review submission. Owing to editorial constraints, we did not cite the pilot study of six patients treated with nivolumab by Fujimoto *et al.* [14].

We are surprised that Y. Ishida and colleagues argue for the supposed superior efficacy of immunotherapy, compared to chemotherapy, in lung cancer associated with fibrosing ILD based on the recent article by Ikeda *et al.* [15]. That study was halted due to drug-related toxicity.

We acknowledge that we misleadingly formulated the trial design of the J-Sonic trial as a study result. Unfortunately, the publication became available only after submission of our paper [9]. The primary end-point of reduced acute exacerbation rate was not met. A correction to our publication has now been published [1].

In conclusion, the complexity of lung cancer associated with fibrosing ILD requires international efforts to better define treatment approaches. However, regional data must be generated as ethnicity influences the phenotype, as well as drug efficacy and toxicities.

Manuela Funke-Chambour[1,2], Namrata Kewalramani[1], Carlos Machahua[1,2], Venerino Poletti[3], Athol U. Wells[4,5] and Jacques Cadranel[6]

[1]Department for BioMedical Research DBMR, Department of Pulmonary Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. [2]Department of Pulmonary Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. [3]Department of Thoracic Diseases, "G.B. Morgagni" Hospita, Forlì, Dipartimento di Medicina Specialistica Diagnostica e Sperimentale (DIMES) University of Bologna, Bologna, Italy. [4]Royal Brompton and Harefield NHS Foundation Trust, London, UK. [5]National Heart and Lung Institute, Imperial College London, London, UK. [6]Department of Pulmonary Medicine and Thoracic Oncology, Constitutive Reference Center of Rare Pulmonary Diseases, AP-HP, Hôpital Tenon and GRC04 Theranoscan, Sorbonne Université, Paris, France.

Corresponding author: Manuela Funke-Chambour (manuela.funke-chambour@insel.ch)

Provenance: Invited article, peer reviewed.

Conflict of interest: M. Funke-Chambour reports grants from Boehringer Ingelheim and Roche, and other support from MSD, outside the submitted work. N. Kewalramani reports grants and nonfinancial support from CSL Behring outside the submitted work. C. Machahua has nothing to disclose. V. Poletti reports personal fees from Boehringer Ingelheim, Roche, AMBU and ERBE, outside the submitted work. A.U. Wells reports personal fees and nonfinancial support from Boehringer Ingelheim, Bayer and Roche Pharmaceuticals, and personal fees from Blade, outside the submitted work. J. Cadranel reports fees for participation to boards of experts for the development of cancer drugs from AbbVie, AZ, BI, BMS, Jansen, MSD, Novartis, Pfizer, Roche and Takeda.

References

1 Kewalramani N, Machahua C, Poletti V, *et al.* Lung cancer in patients with fibrosing interstitial lung diseases: an overview of current knowledge and challenges. *ERJ Open Res* 2022; 8: 00115-02022.
2 Minegishi Y, Gemma A, Homma S, *et al.* Acute exacerbation of idiopathic interstitial pneumonias related to chemotherapy for lung cancer: nationwide surveillance in Japan. *ERJ Open Res* 2020; 6: 00184-02019.
3 Kanaji N, Tadokoro A, Kita N, *et al.* Impact of idiopathic pulmonary fibrosis on advanced non-small cell lung cancer survival. *J Cancer Res Clin Oncol* 2016; 142: 1855–1865.
4 Li LJ, Chong Q, Wang L, *et al.* Different treatment efficacies and side effects of cytotoxic chemotherapy. *J Thorac Dis* 2020; 12: 3785–3795.
5 Sekine A, Satoh H, Baba T, *et al.* Safety and efficacy of S-1 in combination with carboplatin in non-small cell lung cancer patients with interstitial lung disease: a pilot study. *Cancer Chemother Pharmacol* 2016; 77: 1245–1252.

6 Kenmotsu H, Naito T, Mori K, *et al.* Effect of platinum-based chemotherapy for non-small cell lung cancer patients with interstitial lung disease. *Cancer Chemother Pharmacol* 2015; 75: 521–526.

7 Watanabe N, Niho S, Kirita K, *et al.* Second-line docetaxel for patients with platinum-refractory advanced non-small cell lung cancer and interstitial pneumonia. *Cancer Chemother Pharmacol* 2015; 76: 69–74.

8 Tamiya A, Naito T, Miura S, *et al.* Interstitial lung disease associated with docetaxel in patients with advanced non-small cell lung cancer. *Anticancer Res* 2012; 32: 1103–1106.

9 Otsubo K, Kishimoto J, Ando M, *et al.* Nintedanib plus chemotherapy for non-small cell lung cancer with IPF: a randomized phase 3 trial. *Eur Respir J* 2022; in press [https://doi.org/10.1183/13993003.00380-2022].

10 Hayashi H, Mitsudomi T. S-1 as an option for second-line treatment of NSCLC. Is the “East Side Story” applicable in the West? *Ann Oncol* 2017; 28: 2627–2629.

11 Kakiuchi S, Hanibuchi M, Tezuka T, *et al.* Analysis of acute exacerbation of interstitial lung disease associated with chemotherapy in patients with lung cancer: a feasibility of S-1. *Respir Investig* 2017; 55: 145–152.

12 Chuah B, Goh BC, Lee SC, *et al.* Comparison of the pharmacokinetics and pharmacodynamics of S-1 between Caucasian and East Asian patients. *Cancer Sci* 2011; 102: 478–483.

13 Chhetri P, Giri A, Shakya S, *et al.* Current development of anti-cancer drug S-1. *J Clin Diagn Res* 2016; 10: XE01–XE05.

14 Fujimoto D, Morimoto T, Ito J, *et al.* A pilot trial of nivolumab treatment for advanced non-small cell lung cancer patients with mild idiopathic interstitial pneumonia. *Lung Cancer* 2017; 111: 1–5.

15 Ikeda S, Kato T, Kenmotsu H, *et al.* Atezolizumab for pretreated non-small cell lung cancer with idiopathic interstitial pneumonia: final analysis of phase II AMBITIOUS study. *Oncologist* 2022; 27: 720–e702.