Background: ALK gene rearrangement occurs in 2–7% of NSCLC cases. Pts with ALK + NSCLC respond modestly to chemotherapy, and crizotinib (CRZ) is the only targeted agent currently widely approved for the treatment of ALK+ NSCLC. Ceritinib is a novel oral ALK inhibitor with 20-fold greater potency than CRZ in enzymatic assays, and sustained activity against both CRZ-resistant and CRZ-naive NSCLC in preclinical studies. In a phase I clinical study (Shaw et al NEJM 2014), the maximum tolerated dose of ceritinib was determined to be 750 mg/day and the overall response rate in 78 pts treated at this dose was 59%. In this study, substantial clinical activity was shown in both CRZ-naive and CRZ-treated pts with ALK+ NSCLC. Nausea, vomiting, diarrhea and fatigue were the most common toxicities.

Trial design: Here we describe two phase III, prospective, multicenter, randomized open-label studies designed to compare the anti-tumor activity of ceritinib with that of chemotherapy in adult pts with ALK+ advanced NSCLC who are either chemotherapy- and CRZ-naive (ASCEND-4; NCT01828099) or who have received prior chemotherapy and CRZ (ASCEND-5; NCT01828112). Pts participating in either trial must have stage IIIB or IV NSCLC and ≥1 measurable lesion, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Pts will be randomized to oral ceritinib 750 mg/day or to chemotherapy every 21 days (ASCEND-4: pemetrexed 500 mg/m² in combination with either cisplatin 75 mg/m² or carboplatin AUC 5-6; ASCEND-5: pemetrexed 500 mg/m² or docetaxel 75 mg/m²). The primary objective of both studies is to compare ceritinib with chemotherapy by analysis of progression-free survival. Secondary objectives include comparison of ceritinib with chemotherapy by evaluation of overall survival, overall response rate, duration of response, disease control rate and time to response. Enrolment is ongoing.

Disclosure: A. Shaw: Advisory board: Novartis, Pfizer, Ariad, Chugai, Genentech; L. Crinò: Advisory board and honoraria:Novartis; E. Felip: Sat on advisory boards for Novartis, Roche, BMS, BI and Lilly; T.S.K. Mok: Employee of The Chinese University of Hong Kong, Research grant: AZ; Ad board & Honoraria: AZ, Roche, Lilly, Merck Serono, Eisai, BMS, AVEO, Pfizer, Taiho, BI, Novartis, GSK, Clovis, Amgen, Jansen, BioMarin, M. Nishio: Received honoraria from Pfizer, Chugai and Novartis; L. Paz-Ares: Consultant and Speakers bureau: Lilly. Honoraria: Lilly, Roche, Pfizer, Bayer, BI; G. Scagliotti: Honoraria: Lilly, AZ, Pfizer, Roche, Clovis SB; Lilly Ad board: Lilly, Roche, AZ, Clovis; D.R. Spigel: Consultant: BMS and Novartis; J. Wolf: Employee of University Hospital of Cologne; Advisory Boards, speakers bureau and research funding: AZ, Novartis, Roche, Pfizer, BI, BMS, Clovis; Research support: Novartis, Roche, BI, Y. Wu: Speaker fees: Roche, Lilly, Sanofi, Pfizer; G. Castro: Speakers bureau and Advisory board for Novartis; F. Sen: Employee of, employee remuneration and stock options from: Novartis; C. Zheng: Cheng Zheng is an employee of Novartis; A. Joe: Employee, Employee remuneration and stock options: Novartis; J. Soria: Advisory board compensated by Novartis. All other authors have declared no conflicts of interest.