Title: Results from RATIONALE 303: a global Phase 3 study of tislelizumab (TIS) vs docetaxel (TAX) as second- or third-Line therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)

Authors:

Caicun Zhou*†,[1] Dingzhi Huang,[2] Yun Fan,[3] Xinmin Yu,[3] Yunpeng Liu,[4] Yongqian Shu,[5] Zhiyong Ma,[6] Ziping Wang,[7] Ying Cheng,[8] Jie Wang,[9] Sheng Hu,[10] Zhihua Liu,[11] Elena Poddubskaya,[12] Umut Disel,[13] Andrey Akopov,[14] Mikhail Dvorkin,[15] Yiyuan Ma,[16] Yan Wang,[16] Zhenyu Pan,[16] Cunjing Yu,[16] Gareth Rivalland[17]

*Lead author

†Corresponding author

Affiliations: *[1]Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai China; [2]Department of Thoracic Medical Oncology, Lung Cancer Diagnosis and Treatment Centre, Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Centre for Cancer, Tianjin, China; [3]Department of Thoracic Medical Oncology, Cancer Hospital of University of Chinese Academy of Sciences & Zhejiang Cancer Hospital, Hangzhou, China; [4]The First Hospital of China Medical University, Shenyang, China; [5]Department of Oncology, Jiangsu Province Hospital, Nanjing, China; [6]The Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital, Zhengzhou, China; [7]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/ Beijing), Department of Thoracic Medical Oncology, Peking University Cancer Hospital and Institute, Beijing, China; [8]Department of Medical Thoracic Oncology, Jilin Cancer Hospital, Changchun, China; [9]State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Centre/National Clinical Research Centre for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [10]Hubei Cancer Hospital, Wuhan, 430079, Hubei, China; [11]Jiangxi Cancer Hospital, China; [12]Clinical Center Vitamed and Sechenov University, Moscow, Russia; [13]Acibadem Health Group- Adana Acibadem Hospital/Medical Oncology, Adana, Turkey; [14]Pavlov First State Medical University, Saint-Petersburg, Saint-Petersburg, Russian Federation; [15]BHI of Omsk Region Clinical Oncology Dispensary, Omsk, Russia; [16]BeiGene (Beijing) Co., Ltd., Beijing, China; [17]Department of Cancer and Blood, Auckland City Hospital, Auckland, New Zealand*

Objective:

Anti-programmed cell death protein-1/programmed death ligand-1 (anti-PD-[L]1) therapies have improved overall survival (OS) by 2–4 months (mo) vs docetaxel (TAX) in patients (pts) with advanced NSCLC who progressed after platinum regimens. Tislelizumab (TIS) is an anti-PD-1 antibody

engineered to minimize FcγR binding on macrophages, a mechanism of T-cell clearance and potential anti-PD-1 resistance. RATIONALE 303 (NCT03358875) compared the efficacy and safety of TIS vs TAX as second- (2L) or third-line (3L) therapy for pts with advanced NSCLC.

Methods:

Pts without an oncogenic driver mutation who failed at least 1 prior systemic therapy including a platinum regimen were randomized 2:1 to receive TIS 200 mg intravenously (IV) every three weeks (Q3W) (Arm A) or TAX 75 mg/m^2 IV Q3W (Arm B). Dual primary endpoints were OS in the intent-to-treat (ITT) analysis set and OS in the PD-L1 ≥ 25% analysis set. A prespecified interim analysis (IA) was conducted when ≈426 deaths (76% of planned events) were observed. The IA results are presented.

Results:

Overall, 805 pts were randomized (n=535, TIS; n=270, TAX) in 10 countries globally; demographics were generally balanced between arms. With a 19-mo median follow-up (441 OS events), OS_{ITT} was significantly longer in Arm A vs B (median: 17.2 vs 11.9 mo; HR=0.64 [95% CI: 0.53–0.78]; *P*<0.0001). OS benefit was also observed in the PD-L1 ≥ 25% analysis set (median: 19.1 vs 11.9 mo; HR=0.52 [95% CI: 0.38–0.71]) and across most subgroups, including histology and PD-L1 expression. In the ITT analysis set, PFS (median: 4.1 vs 2.6 mo; HR = 0.64 [95% CI: 0.53–0.76]), ORR (21.9% vs 7.0%; ORR difference: 14.9% [95% CI 10.3%–19.6%]), and DoR (median: 13.5 mo [95% CI: 8.5–21.8] vs 6.2 mo [95% CI: 2.1–7.2]) were also improved in Arm A vs B. The most common treatment-emergent adverse events (TEAEs) were anemia (28.5%), increased ALT (19.9%), and cough (19.5%) in the TIS arm and alopecia (47.3%), anemia (43.4%), and decreased neutrophil count (36.8%) in the TAX arm. The most common ≥Grade 3 TEAEs were pneumonia (TIS: 7.1%) and neutropenia (TAX: 27.9%). There were 1.5% (TIS) and 1.6% (TAX) treatment-related AEs that lead to death.

Conclusion:

RATIONALE 303 demonstrated that, as a 2L or 3L therapy in pts with advanced NSCLC, TIS was tolerable and prolonged OS by 5–7 mo with improved PFS and ORR vs TAX regardless of histology or PD-L1 expression.