8516 Rapid Oral Abstract Session

Randomized trial of relevance of time-of-day of immunochemotherapy for progression-free and overall survival in patients with non-small cell lung cancer.

Yongchang Zhang, Zhe Huang, Liang Zeng, Zhaohui Ruan, Qun Zeng, Huan Yan, Wenjuan Jiang, Jiacheng Dai, Nachuan Zou, Shidong Xu, Jun Deng, Xue Chen, Jing Wang, Hua Xiang, Xiaomei Li, Boris Duchemann, Guoqiang Chen, Christoph Scheiermann, Nong Yang, Francis Albert Lévi; Hunan Cancer Hospital/The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; Hunan Cancer Hospital, Changsha, China; University of Geneva, Geneva, Switzerland; Early Clinical Trial Center, Hunan Cancer Hospital, Central South University, Changsha, Hunan, China; Department of Gynecologic Oncology, Hunan Cancer Hospital, Changsha, China; Faculty of Medicine, Paris-Saclay University, Villejuif, France; Department of Thoracic and Medical Oncology, Avicenne AP-HP, Université Sorbonne Paris Nord, Bobigny, France; School of Basic Medicine and Life Science, Hainan Academy of Medical Sciences, Haikou, China; UPR Chronotherapie, Cancers et Transplantation, Université Paris Saclay, Hôpital Paul Brousse ID Isco 13918, Villejuif, France

Background: Recent retrospective studies across 10 cancer types suggest increased efficacy of Early rather than Late Time-of-Day (ToD) infusions of immune checkpoint inhibitors (ICIs). This first randomized controlled phase III trial aimed to determine the relevance of ToD of immunochemotherapy for efficacy in patients (pts) with non-small cell lung cancer (NSCLC). **Methods:** Eligible pts received ICI pembrolizumab or sintilimab combined with chemotherapy, as 1st line treatment for stage IIIC-IV NSCLC without driver mutation. Pts were randomly assigned in a 1:1 ratio to receive the initial four immunochemotherapy cycles either before 15:00 in the Early ToD group, or after 15:01 in the Late ToD group. We hypothesized an increase in median progression-free survival (PFS) from 6 months in the Late ToD group up to 10 months in the Early ToD group. A total of 210 pts was required to validate PFS differences, using a two-sided significance level (α, 0.05; β, 0.80). Secondary endpoints were overall survival (OS) and objective response rate (ORR). **Results:** From 09/2022 to 05/2024, 210 pts (median age, 61 y.o.; male sex, 90.5%; Stage IV, 80.5%) were randomized. The pts in each group had similar characteristics. After a median follow-up of 18.9 months (mo.), median PFS was 13.2 mo. [95% CI, 10.1-16.3] in the early ToD group and 6.5 mo. [5.9-7.1] in the late ToD group, with a hazard ratio (HR) of an earlier progression of 0.43 [0.31-0.60] ($P < 0.0001$). Median OS was not reached in the early ToD group, whereas it was 17.8 mo. [14.2-21.5] in the late ToD group (HR of an earlier death, 0.43 [0.27-0.69]; $P = 0.0003$). ORR was 75.2% [66.8%-83.6%] for early ToD and 56.2% [46.5%-56.8%] for Late ToD ($P = 0.007$). PFS, OS, and ORR were consistently improved in the early ToD group regardless of age, sex, performance status, tumor stage, histology, PD-L1 status, and ICI agent. **Conclusions:** In this randomized trial, all three efficacy endpoints of immunochemotherapy were significantly improved through Early vs Late ToD dosing in pts with previously untreated stage IIIC-IV NSCLC. The near doubling in PFS and OS in our trial support the need for further randomized trials to determine the relevance of ToD for ICI efficacy and their underlying circadian mechanisms in pts with various cancer types. Clinical trial information: NCT05549037. Research Sponsor: National Natural Science Foundation of China.