**e20608** **Publication Only**

# Striking effect of low-dose radiotherapy combined with PD-1 blockade on small cell lung cancer in mice and refractory patients (Achilles Study).

*Hui Wang, Min Yu, Feifei Na, Limei Yin, Lin Zhou, Zhuoran Yao, Xiangyu Pan, Xuanwei Zhang, Lin Chen, Yanying Li, Bingwen Zou, Youling Gong, Jiang Zhu, Yongmei Liu, Linglu Yi, Ruizhan Tong, Jianxin Xue, Meijuan Huang, Chong Chen, You Lu; Department of Thoracic Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; Laboratory of Clinical Cell Therapy, West China Hospital, Sichuan University, Chengdu, China; State Key Laboratory of Biotherapy and Collaborative Innovation Center for Biotherapy, West China Hospital, Sichuan University, Chengdu, China; Department of Radiation Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; Department of Thoracic Oncology, Cancer Centre, Sichuan University West China Hospital, Chengdu, China; State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China*

**Background:** Immune checkpoint inhibitors (ICIs) provide a durable and long-term benefit but still unsatisfactory clinical efficacy for extensive-stage small cell lung cancer (ES-SCLC). An optimized dose and schedule of radiotherapy for ES-SCLC remain to be studied. We hypothesized that the addition of low-dose radiotherapy (LDRT) to ICI could improve the efficacy of ES-SCLC. **Methods:** In SCLC bearing mice, the tumor was irradiated with LDRT in dose-escalation starting at 3Gy×1 fractions (f) up to 3Gy×7f, and combined with PD-1 antibody injection (0.2mg/mouse, i.p, every 3 days). Mice were followed for tumor growth and survival. The tumor microenvironment was dynamically analyzed every 3 days till day 18 by flow cytometry and immunofluorescence. 15 patients (pts) with relapsed ES-SCLC who received the treatment with LDRT and PD-1 blockade were retrospectively reviewed. **Results:** LDRT with 3Gy×5f delivered over 5 days ($LDRT_{15Gy/5f}$) was determined to be the optimized dose when combined with PD-1 blockade. Combined group exhibited obvious growth retardation and prolonged survival compared to either monotherapy.The most robust infiltration of T cells in combined group was observed on day 9 after start of treatment. Bulk and single-cell RNA-seq showed significant immune cells infiltration, predominately $CD8^+$ T cells and M1 macrophage. The activation and degranulation of $CD8^+$ T cells in combination group were enhanced. Intra-tumoral $CD8^+$ T cells were mainly assigned to effector memory (Tem) cells, then exhausted precursor (Texp) cells and exhausted (Tex) cells. Pseudotime analysis supported a state evolution model that $CD8^+$ Tem cells differentiate into intra-tumoral $CD8^+$ Tex cells through an intermediate $CD8^+$ Texp state. Tumor cells were divided into clusters 0, 1, and 2. Cluster 0 nearly disappeared while the proportion of cluster 1 increased in combination therapy. Cluster 1 enriched inflammatory response pathways and higher expression of MHC class I versus clusters 0 and 2. Additionally, the density of intra-tumoral microvessel was decreased, while vascular perfusion and the number of pericyte-covered vessels increased in combined group. Correspondingly, 15 recurrent ES-SCLC pts who treated with up-front $LDRT_{15Gy/5f}$ plus PD-1 blockade showed an ORR of 80%. Median PFS and OS were 4.3 months and 10.9 months. PFS rates at 6, 12 and 24 months were 40%, 20% and 6.7%, and OS rates were 60%, 40% and 24%, respectively. No patient experienced above grade 4 radiation- and immunotherapy-related toxicity. **Conclusions:** Our study is the first report of the synergistic effect of $LDRT_{15Gy/5f}$ and PD-1 blockade in SCLC mice model and recurrent ES-SCLC pts. The $LDRT_{15Gy/5f}$ demonstrates both immunologic adjuvant and cytotoxic effect on SCLC, and is safe and feasible in clinical pts. Further translational research, Match trial (NCT04622228), is ongoing. Research Sponsor: 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University, The National Natural Science Foundation of China.