Molecular Subtyping of Extensive Stage Small Cell Lung Cancer and Relevent Clinical Significance

(**The MOSAIC study**)

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Version 1.0

Objective：

(1) Validating the predictive value of transcriptome-based molecular subtyping of extensive stage small cell lung cancer(SCLC) for the efficacy of PD-1/PD-L1 inhibitor in the first line setting.

(2) Exploring the differences of immune microenvironment between different SCLC subtypes to reveal the mechanisms of immunotherapy resistance of SCLC

Protocol:

1.1 Design

This study is a retrospective observational study without intervention in clinical treatment. In prior study, the transcriptomic data was used to classify SCLC into four subtypes, which might have different sensitivity to immunotherapy. Therefore, molecular subtyping could be used as an important biomarker for predicting efficacy of immunotherapy, which need further validation. This study will explore the predictive value of different subtypes of SCLC for immunotherapy and mechanisms of immunotherapy resistance of SCLC. Extensive stage SCLC patients receiving first-line standard treatment will be enrolled in this study. Baseline tumor tissue samples and peripheral blood samples will collected for transcriptome and immunohistochemistry analysis etc. Based on these results, patient will be classified into four subtypes and efficacy and safety of treatment will be recorded. We will compare the efficacy between different subtypes of SCLC and analyze whether molecular typing could predict the efficacy of immunotherapy; Compare the differences in immune microenvironment of different subtypes of SCLC to reveal the mechanism of immunotherapy resistance. The treatment regimen involved in this study follows guidelines for the first-line treatment of extensive stage SCLC: cisplatin+etoposide or carboplatin+etoposide with or without approved PD-(L)1 inhibitor for SCLC. Treatment options are determined by the patient's supervising physician.

1.2 Patients

Inclusion Criteria:

1) Male or female, aged 18 to 100 years
2) Patients with untreated advanced small cell lung cancer clearly diagnosed by histopathology
3) Be able to provide tumor biopsy tissue sample for molecular analysis
4) ECOG score: 0 ~2；
5) Expected survival of more than 3 months.
6) Has at least 1 measurable or evaluable tumor lesion with a longest diameter ≥ 10 mm at baseline (in case of lymph nodes, a shortest diameter ≥ 15 mm is required) according to RECIST v1.1
7) Received first-line chemotherapy or chemotherapy + PD-(L)1 inhibitor and be able to provide complete treatment information and efficacy evaluation results.
8) Voluntary signed informed consent and expected good compliance.

Exclusion Criteria:

1) Patient unable to tolerate chemotherapy.
2) Patients unable to provide tumor tissue samples for testing
3) Patients with other malignant tumors or a history of other malignant tumors
4) Patients have any other reason to be unfit to participate in this study.

1.3 Endpoint and follow up

Primary endpoint: Progression-free survival

Secondary endpoint: Overall survival; Objective response rate; molecular subtyping and tumor microenvironment biomarkers.

Follow-up plan:

1) Patients will be reviewed every 2 cycles during treatment to assess effectiveness and record vital signs and test results. 2) Patients will be reviewed periodically every 3 months after completion of treatment until disease progression. 3) After disease progression, patients will continue to be followed up every 3 months to record post treatment until die or lost follow-up.

1.4 Sample Size

Chemotherapy：80-100 cases.

Immunotherapy+chemotherapy：80-100 cases.

1.5 Statistics

All measurements will be expressed as mean ± standard deviation. COX regression analysis was used to examine the correlation between immune indicators and efficacy, and one-way ANOVA will be used to analyze the correlation between the variables and the efficacy of immunotherapy or adverse effects. The number of different cell types will be compared between patient subgroups using the Wilcoxon rank-sum and Jonckheere-Terpstra tests. Differences between the two groups will be analyzed using a two-sided t-test. Categorical variables and continuous variables will be calculated according to frequency counts and median values respectively. The statistical analysis software is GraphPad Prism and SPSS 19.0. $P < 0.05$ will be considered statistically different.

1.6 Data collection and management

1) This study has been approved by the ethics committee of Beijing Cancer hospital, and all enrolled patients will sign informed consent. Clinical treatment-related information is stored in special computer with a password to protect patient privacy. Clinical efficacy evaluation will be assessed by independent auditors.
2) Data analysis and interpretation: Bioinformatics experts and statistical experts in this project from Beijing cancer hospital will execute data interpretation and statistical

analysis.

3) Patients' personal information are replaced with uniform numbers to protect patient privacy.