Indirect Comparison and Survival estimates of Seven PD-1/PD-L1 Inhibitors in Treatment of Patients with Advanced Squamous Non-small Cell Lung Cancer

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Background and Objectives

- After Gemstone-302 was published in Lancet in January 2022, seven PD-(L)1 inhibitors launched or about to be launched in China, but there are no head-to-head RCTs reporting the comparative efficacy for squamous non-small cell lung cancer (sq-NSCLC)[1].
- Our study aimed to indirectly compare the efficacy of these treatments to provide evidence for clinical decision and Chinese national reimbursement drug listing.

Competitive Landscape of Immune Target Inhibitors

- Market: Internationally, nivolumab (second-line treatment of NSCLC), pembrolizumab (squamous + non-squamous), atezolizumab (non-squamous), durvalumab (Phase III NSCLC) has been approved in China; domestically, camrelizumab (non-squamous carcinoma), sintilimab (squamous + non-squamous), tislelizumab (squamous + non-squamous) and sugelimumab (squamous + non-squamous) have also been approved. Toripalimab has now completed Phase 3 clinical trials and will be launched soon.
- Medical insurance: Non-squamous of camrelizumab (2020), squamous and non-squamous of sintilimab and tislelizumab (2021) have approved in medical insurance.

Methods

- We collected phase III clinical trials targeted on stage IIIB–IV patients for first-line immunotherapy of sq-NSCLC by systematically searching databases and conference abstracts. Chemotherapy was limited to paclitaxel/gemcitabine plus platinum. Relative effects of competing treatments were assessed by Bayesian network meta-analysis. Hazard ratios (HR), serious adverse events (SAEs), progression-free survival years (PFS) and overall survival years (OS) were the outcomes. We performed sensitivity analysis using the range of parameters distribution as well as different comparison methods to test the robustness of the results.

Fit of Survival data

- The best fitting model was selected among **standard distribution, FP** (Fractional polynomial)**, RCS** (Restricted cubic spline) **and RP** (Royston-Parmar) **model** by comparing AIC as well as visual inspection.

Indirect comparison model

- Non-proportional hazard (PH) FP model was adopted under the Bayesian framework; PH model was used when lack of related curves and to test the robustness of the results. FP model can be expressed as follows:

$$\text{1-order FP: } y = \beta_0 + \beta_1 \times t^p$$

$$\text{2-order FP: } y = \beta_0 + \beta_1 \times t^{p_1} + \beta_2 \times t^{p_2}$$

$$(t^0 = log(t), p = -2, -1, -0.5, 0, 0.5, 1, 2, 3)$$

Results

- A total of 7 clinical trials with 2640 patients were included. Proportional hazard models and non-proportional hazard models showed consistent efficiency ranks. Sensitivity analysis results show that the basic analysis conclusions were reliable.
- PH model: For PFS, the efficacy ranks from high to low were sugemalimab (HR, 0.33; 95%CI, 0.24-0.45), camrelizumab (HR, 0.37; 95%CI, 0.30-0.46), tislelizumab (HR, 0.53; 95%CI, 0.36-0.79), sintilimab (HR, 0.54; 95%CI, 0.42-0.69), toripalimab (HR, 0.56; 95%CI, 0.38-0.83), pembrolizumab (HR, 0.57; 95%CI, 0.47-0.70) and atezolizumab (HR, 0.71; 95%CI, 0.59-0.85). Forest plots of relative effect are shown in **Figure 1A and Figure 1B**.
- PH model: For both PFS and OS, sugemalimab had the highest probability to rank first (38% and 42%).
- Sugemalimab achieved the most 10-years' OS life-years gained with 3.597 LYs; followed by Camrelizumb (3.110 LYs), Sintilimab (2.994 LYs), Pembrolizumb (2.495 LYs), Atezolizumab (2.031 LYs).
- Safety: PD-(L)1 drugs increased the incidence of SAEs when combined with chemotherapy, sugemalimab were the safest drugs. (As shown in **Figure 1C**)

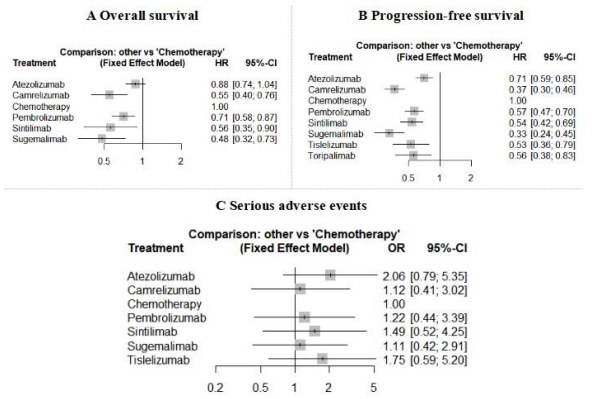

Figure 1 Forest Plots of Relative Effect

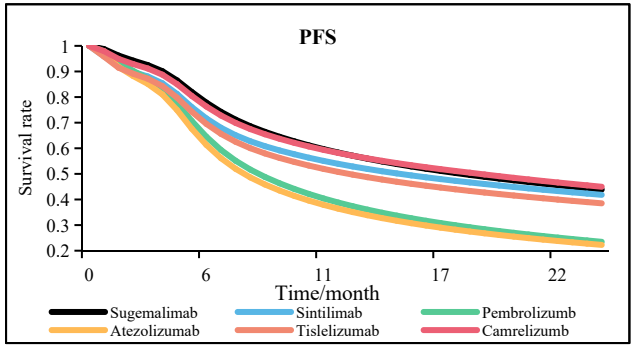

Figure 2 PFS Survival Rates over time for Different Regimens Added to Chemotherapy

- Non-PH model: Sugemalimab achieved the highest PFS benefit in 2 years (1.323 LYs), with camrelizumab (1.320 LYs), sintilimab (1.243 LYs), tislelizumab (1.189 LYs), pembrolizumab (0.990 LYs) and atezolizumab (0.947 LYs) ranking in order. (**Figure 2**) Sugemalimab was the optimal option over time.(**Figure 3**)
- PH model: For OS, the efficacy ranks from high to low were sugemalimab (HR, 0.48; 95%CI, 0.32-0.73), camrelizumab (HR, 0.55; 95%CI, 0.40-0.76), sintilimab (HR, 0.56; 95%CI, 0.35-0.90), pembrolizumab (HR, 0.71; 95%CI, 0.58-0.87) and atezolizumab (HR, 0.88; 95%CI, 0.73-1.05).

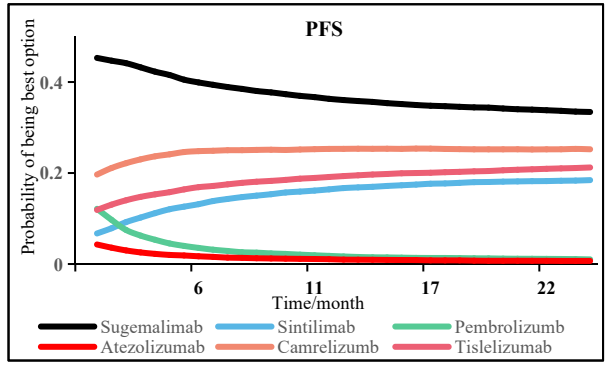

Figure 3 Probabilities of Optimal Effectiveness over Time for PFS for Different Regimens Added to Chemotherapy

Conclusions

- In this indirect comparison, Sugemalimab is superior both in PFS and OS benefits for advanced sq-NSCLC patients
- Based on the comprehensive results of this study, sugemalimab is recommended for the first-line treatment of advanced sq-NSCLC in China in terms of PFS and OS benefit. Although the conclusions of this study are conservative, these findings provide relevant evidence for clinical decision-making and health insurance.
- Future clinical trials with more comparable baseline information or even direct head-to-head comparison are anticipated, which can fill the lack of evidence on the efficacy of PD-1/PD-L1 in the treatment of sq-NSCLC in China.

Reference

[1] Zhou C, Wang Z, Sun Y, et al. Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer (GEMSTONE-302). Lancet Oncol.

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Declaration of interests

The authors have no conflicts of interest to declare.