Reproduction of Control Groups in Two Global RCTs of Anti-cancer Drugs Using Health Insurance Claims Data in Japan

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Background

- A randomized controlled trial (RCT) is the gold standard for clinical trials and has internal validity. However an RCT often has ethical issues.
- A control group for a clinical trial using real-world data (RWD) is desirable and ethically sound, however it is unknown to produce the internal validity.

Objective

- As the first step to verify the internal validity, we tried to reproduce the control groups in the two completed RCTs using RWD and evaluate the difference of the outcomes between them on each of the two RCTs.

Method

- We selected the KEYNOTE-426 phase III trial of pembrolizumab for renal cell carcinoma and VIALE-A phase III trials of venetoclax for acute myelogenous leukemia (AML). Overall survival (OS) was one of the endpoints of both trials. We reproduced the control groups using health insurance claims data, one of RWD, provided by DeSC Healthcare Inc.
- Kaplan–Meier OS curves reproduced by RWD and the control group of original RCTs were compared. The survival times in the KEYNOTE-426 trial were examined at the point of 60%.

What is KEYNOTE-426?

A KEYNOTE-426 study is randomised, open-label, phase 3 trial of advanced renal cell carcinoma therapy for patients with it who were treatment naïve to receive pembrolizumab plus axitinib or sunitinib monotherapy[1].

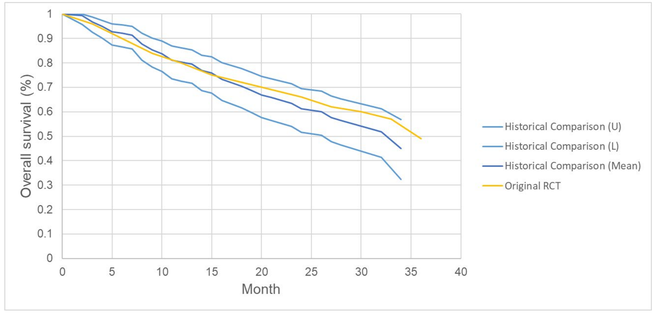
	Original control	Reproduced control
Main criteria※	Key inclusion criteria: ・Adult patients aged 18 years or older with newly diagnosed stage IV or recurrent renal cell carcinoma with clear cell histology who received no previous systemic treatment for advanced disease. ・All patients had measurable disease according to RECIST version 1.111 and a Karnofsky performance status score of 70 or higher at baseline. Key exclusion criteria: ・A history of or current symptomatic CNS metastases, active autoimmune disease, poorly controlled hypertension (systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg), an ischaemic cardiovascular event or New York Heart Association class III or IV congestive heart failure within 1 year before screening, or if the patient was receiving systemic immunosuppressive treatment.	・18 years of age or older ・Having a diagnosis of C64, renal cell carcinoma. ・Without any record of renal cell carcinoma treatment drugs. ・Patients with renal cell carcinoma treated only with sunitinib.

※Not full criteria

Result and Discussion

- We selected the KEYNOTE-426 phase III trial of pembrolizumab for renal cell carcinoma and VIALE-A phase 3 trials of venetoclax for AML. Overall survival (OS) was one of the endpoints for both trials. We reproduced the control groups using health insurance claims data, one of RWD, provided by DeSC Healthcare Inc.
- Kaplan–Meier OS curves reproduced by RWD and the control group of original RCTs were compared. The survival times in the KEYNOTE-426 trial were examined at the point of 60%.

KEYNOTE-426 trial



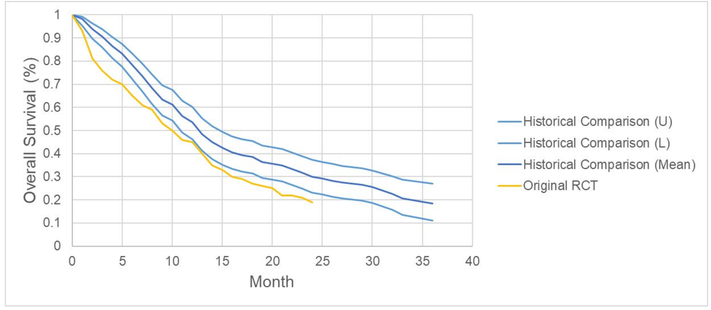
What is VIALE-A?

A VIALE-A study is phase 3 trial of AML therapy for patients with AML who have coexisting conditions or are 75 years of age or older, or both to azacitidine plus either venetoclax or placebo[2].

	Original control	Reproduced control
Main criteria※	Key eligibility criteria ・Patient must have confirmation of AML by WHO criteria, previously untreated, and be ineligible for treatment with a standard cytarabine and anthracycline induction regimen due age or comorbidities. ・Patient must be ≥18 years of age. ・Patient must have a projected life expectancy of at least 12 weeks. ・Patients were considered to be ineligible for standard induction therapy if they were 75 years of age or older or if they had at least one of the following coexisting conditions precluding intensive chemotherapy: a history of congestive heart failure for which treatment was warranted or an ejection fraction of 50% or less or chronic stable angina, a diffusing capacity of the lung for carbon monoxide of 65% or less or a forced expiratory volume in 1 second of 65% or less, and an Eastern Cooperative Oncology Group performance-status score of 2 or 3 (on a 5-point scale, with higher numbers indicating greater disability).	・65 years of age or older ・Having a diagnosis of C92.0, Acute myeloblastic leukemia. ・Without any record of AML treatment drugs. ・Patients with AML who were treated only azacitidine are included.

※Not full criteria

VIALE-A trial



- One of the reasons why the control group of the VIALE-A trial could not be reproduced may be the difference in selection criteria between original and reproduced (i.e. the age, patients having coexisting conditions)

Conclusion

- Though a significant difference was found between original OS curves and those produced by RWD in the VIALE-A trial, the RWD cohort did approximate the clinical trials results found in the KEYNOTE-426 trial.
- Furthers studies are needed to judge the credibility of the control group using RWD.

Reference

1. Powles T, Plimack ER, Soulières D, Waddell T, Stus V, Gafanov R, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. Lancet Oncol. 2020;21(12):1563-73.
2. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383(7):617-29.