Matching-adjusted indirect comparison (MAIC) of entrectinib versus crizotinib in patients with NSCLC with ROS1 rearrangement:

INTRODUCTION

• Co-cancer 1 (ROS1) fusion positive advanced NSCLC: accounts for approximately 1.2% of non-squamous NSCLC.1

Targeted therapies are the standard of care for ROS1 positive NSCLC.2

Entrectinib was approved by the US Food and Drug Administration (FDA) in August 2018 and by the European Commission (EMA) in July 2020 for the treatment of adults with ROS1 fusion-positive, metastatic NSCLC.

The aim of the current study is to perform an Indirect Treatment Comparison (ITC) to estimate relative treatment effects of entrectinib compared with crizotinib in patients with ROS1 fusion-positive NSCLC.

This is an update of a previously published systematic literature review (SLR) and MAIC analyses which used earlier data cut-off for both entrectinib and crizotinib. The previous analysis suggested improved ORR compared with crizotinib in patients treated with entrectinib versus crizotinib.

METHODS

Systematic literature review

• To inform the ITC, a SLR was required to identify all trials for entrectinib and crizotinib in ROS1 fusion-positive advanced or metastatic NSCLC.

• The electronic searches were performed using defined keywords in the database Medline, Medscape Quick Ahead of Print (in Process & Other Non-Indexed Citations). Embase, and EMB Reviews on 31st March 2020. Additional searches of congress proceedings from the past 3 years, reference lists of included publications, Health Technology Assessment (HTA) reports, and clinical trial registries were conducted to identify relevant inclusion. Exclusion criteria are presented in Table 1.

• A study was performed assessing the feasibility of performing an ITC comparing entrectinib and crizotinib in patients with ROS1 fusion-positive NSCLC, and considered both clinical and methodological heterogeneity.

Indirect Treatment Comparison

• Unstratified matching adjusted indirect treatment comparison (MAIC) was used to perform the indirect treatment comparison, as data came from single clinical trials.

• Matching was based on known prognostic and predictive factors: age, sex, smoking status, line of treatment, ECOG performance status.

• Consistently with the previously published analysis, results from the updated MAIC analysis suggest a trend towards improved ORR and PFS with entrectinib compared with crizotinib in patients with ROS1 fusion-positive NSCLC, and considered both clinical and methodological heterogeneity.

RESULTS

Systematic literature review

• The screening process resulted in a final evidence base for the SLR of 54 publications related to 41 unique studies (Figure 1).

• Following meta-analysis feasibility assessment, data available for evidence synthesis included pooled data from three entrectinib studies (ASCEND-3, ASCEND-4, and ASCEND-6) and a single study investigating crizotinib (PROFILE 1001).

• These studies reported overlapping patient population characteristics and comparable endpoints, permitting a MAIC for entrectinib with crizotinib (PROFILE 1001). The previously published MAIC was based on PROFILE 1001 data with shorter follow-up at the time of the initial analysis.

Indirect Treatment Comparison

• The feasibility study was performed on an entrectinib patient population that is equivalent to the PROFILE 1001 population based on the matching characteristics, as seen in Table 2.

Table 2. Baseline Characteristics included in estimation of MAIC weights

Table 3. Summary of the results of entrectinib versus crizotinib in ROS1 NSCLC patients

Scenario | Endpoint | Effect Size
---|---|---
1 | 1.10 % (0.75, 1.48) Crizotinib vs Entrectinib | 0.70 (0.30, 1.30) OS
2 | 1.26 % (0.89, 1.74) Crizotinib vs Entrectinib | 0.70 (0.30, 1.30) AA
3 | 0.80 % (0.50, 1.27) Crizotinib vs Entrectinib | 0.70 (0.30, 1.30) AD
4 | 1.23 % (0.87, 1.68) Crizotinib vs Entrectinib | 0.70 (0.30, 1.30) AE

• This is an update of a previously published systematic literature review (SLR) and MAIC analyses which used earlier data cut-off for both entrectinib and crizotinib. The previous analysis suggested improved ORR compared with crizotinib in patients treated with entrectinib versus crizotinib.

DISCUSSION

• Effective treatments are needed for patients with ROS1 fusion-positive tumors with both systemic and CNS activity. CNS metastasis is a common scenario with ROS1 fusion-positive NSCLC.

• Entrectinib has been designed to effectively penetrate and remain in the CNS as opposed to crizotinib. Preclinical and clinic outcome data support a CNS activity for entrectinib.

• While these results support the value of entrectinib as an efficacious new treatment for ROS1 fusion-positive patients, further evidence comparing entrectinib directly with crizotinib will help to better understand the value of entrectinib in clinical practice. A head-to-head randomized clinical trial of entrectinib versus crizotinib will be initiated in mid-2021 to provide direct comparative evidence.

CONCLUSIONS

• Consistently with the previously published analysis, results from the updated MAIC analysis suggest a trend towards improved ORR and PFS with entrectinib versus crizotinib in ROS1 NSCLC patients.

• Comparing different trials without patient level data requires assumptions to be made around characteristics and weighting; this therefore limits the inference that can be drawn from the results. Additionally, given the granularity of the data, the small sample size and the uncertainty around the impact of CNS metastases in PROFILE 1001, results should be interpreted with care.

• While these results support the value of entrectinib as an efficacious new treatment for ROS1 fusion-positive patients, further evidence comparing entrectinib directly with crizotinib will help to better understand the value of entrectinib in clinical practice. A head-to-head randomized clinical trial of entrectinib versus crizotinib will be initiated in mid-2021 to provide direct comparative evidence.

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6. National Institute for Health and Care Excellence (NICE). TA 529: Crizotinib for treating ROS1 fusion-positive non-small cell lung cancer in adults with advanced non-small cell lung cancer at baseline with no brain metastases. March 2020. Additional searches of congress proceedings from the past 3 years, reference lists of included publications, Health Technology Assessment (HTA) reports, and clinical trial registries were conducted to identify relevant inclusion. Exclusion criteria are presented in Table 1.

Figure 1. Kaplan-Meier plots for Scenario 1

Figure 2. PRISMA diagram for SLR and MAIC analyses by RWD team

Figure 3. Comparison of Adjusted indirect comparison: entrectinib versus crizotinib in PROFILE 1001 and entrectinib versus crizotinib in PROFILE 1001 in PROFILE 1001....