MATCHING-ADJUSTED INDIRECT COMPARISON (MAIC) OF CRIZOTINIB WITH STANDARD OF CARE IN PROGRESSED NSCLC ALK+ PATIENTS BASED ON REAL-WORLD EVIDENCE (RWE) AND CLINICAL TRIAL DATA IN THE CZECH REPUBLIC

Authors: Pásztor B.[1], Losenický L.[2], Mazan P. [2], Duba J.[1], Kolek M.[1]

1) OAKS Consulting s.r.o. Czech Republic
2) PFIZER spol. s.r.o. Czech Republic

OBJECTIVES

Non-small-cell-lung-carcinoma (NSCLC) markedly shortens and deteriorates life of patients. The aim of this analysis was to compare the relative effectiveness of crizotinib in progressed NSCLC ALK+ patients to Czech standard of care based on RWE and clinical trial data while adjusting for patients' characteristic differences.

METHODS

Patient characteristics and outcomes data were taken from RWE NSCLC Registry TULUNG [1] and Registry of Highly Innovative Drug VILP [2] in the Czech Republic and the PROFILE 1007 clinical trial [3]. Patient-level data were available for crizotinib RWE only. As there were major differences between the treatment arms of interest, naïve comparison would result in misleading outcomes and potentiate a wrong decision on relative efficacy of crizotinib. Differences in patients' characteristics in the crizotinib and pemetrexed arms were thus adjusted by MAIC approach as developed and published by Signorowitch [4]. After matching, median overall survival (OS) and progression free survival (PFS) were estimated.

Patients characteristics included in MAIC

Age, sex, ECOG, smoking status, stage and histology types were included in the matching analysis. The main differences before matching were evident in age, ECOG status, smoking status and Stage. The characteristics before weighting are present in Figure 1. It was not possible to compare the outcomes.

Figure 1 • **Patients' characteristics before MAIC (crizotinib vs pemetrexed)**

Patients' characteristics	VILP Registry [2]	TULUNG Registry [1]	PROFILE 1007 [3]
	crizotinib	pemetrexed	pemetrexed
Number of patients	50	1124	99
Sex			
Male	50 %	57 %	46 %
Age (initiation of treatment)			
Mean	58	63	NR
Median	60	64	50
ECOG status			
0	24 %	15 %	34 %
1	60 %	78 %	58 %
2	16 %	7 %	8 %
3	0 %	0 %	0 %
Number of previous treatments			
1	68 %	100 %	100 %
2	22 %	0 %	0 %
3	4 %	0 %	0 %
4	4 %	0 %	0 %
Histology tumour type			
Adenocarcinoma	86 %	80 %	95 %
Non-adenocarcinoma	12 %	19 %	3 %
Smoking status			
Non-smoker	36 %	23 %	60 %
Ex-smoker	40 %	37 %	33 %
Smoker	24 %	40 %	7 %
Length of treatment			
Median (months)	3	3	NR
Stage			
III B	10 %	21 %	11 %
IV	88 %	59 %	89 %

Adjustment method

The matching was performed on patient-level-data which were available for crizotinib arm in VILP registry. The aim was to match these data to the aggregate values for pemetrexed data from TULNG Registry and PROFILE 1007 study. The values of weighting were calculated by gradient method using Solver in MS Excel as described in [4].

Matched patients' characteristics

After matching the patients' characteristics were comparable. This has brought more reliable outcomes for assessment of relative effectiveness. The characteristics after matching are captured in Figure 2 (crizotinib vs pemetrexed TULUNG) and Figure 3 (crizotinib vs pemetrexed PROFILE 1007).

Figure 2 • **Patients' characteristics after MAIC (crizotinib vs pemetrexed TULUNG Registry)**

Patients' characteristics	Crizotinib (before MAIC) [2]	Crizotinib (after MAIC)	Pemetrexed TULUNG Registry [1]
Sex			
Male	50.0 %	57.2 %	57.0 %
Age (treatment initiation)			
Mean	58	59	62
Median	59.5	62	64
% of patients <65 years old	66.0 %	64.8 %	50.0 %
ECOG			
0	24.0 %	15.4 %	15.0 %
1	60.0 %	74.8 %	78.0 %
2	16.0 %	10.6 %	7.0 %
Smoking status			
Non-smoker	36.0 %	28.7 %	23.0 %
Ex-smoker	40.0 %	33.1 %	37.0 %
Smoker	24.0 %	38.1 %	40.0 %
Stage			
III	10.0 %	13.6 %	12.9 %
IV	88.0 %	84.4 %	85.9 %
Histology type			
Adenocarcinoma	86.0 %	88.3 %	79.7 %

Figure 3 • **Patients' characteristics after MAIC (crizotinib vs pemetrexed PROFILE 1007)**

Patients' characteristics	Crizotinib (before MAIC) [2]	Crizotinib (after MAIC)	Pemetrexed PROFILE 1007 [3]
Sex			
Male	50.0 %	44.5 %	46.5 %
Age (treatment initiation)			
Mean	58	53	NR
Median	59.5	54	50
% of patients <65 years old	66.0 %	74.2 %	83.0 %
ECOG			
0	24.0 %	30.8 %	34.3 %
1	60.0 %	55.6 %	57.6 %
2	16.0 %	13.6 %	8.1 %
Smoking status			
Non-smoker	36.0 %	58.7 %	59.6 %
Ex-smoker	40.0 %	29.3 %	33.3 %
Smoker	24.0 %	12.0 %	7.1 %
Stage			
III	10.0 %	9.1 %	11.1 %
IV	88.0 %	90.0 %	88.9 %
Histology type			
Adenocarcinoma	86.0 %	84.4 %	94.9 %

From the tables it is evident that the populations are significantly closer than before matching and the estimation of outcomes on these adjusted populations would give more reliable results.

RESULTS

There were 51 crizotinib patients in the Czech RWE arm receiving 2nd or later line of crizotinib. Median follow-up of crizotinib RWE patients was 11.5 months. The PFS and OS outcomes were estimated using Kaplan-Meier (K-M) survival analysis.

Naïve comparison of PFS and OS resulted in medians 5.8 and 15.3 months for crizotinib from RWE [2], 3.1 and 9.5 months for pemetrexed from RWE [1] and 4.2 and 22.8 for pemetrexed from PROFILE 1007 [3].

After matching, the median PFS and OS of crizotinib from RWE changed to 4.8 and 14.2 months when adjusted to pemetrexed RWE and 6.2 and 27.2 months when adjusted to pemetrexed PROFILE 1007 data.

The K-M curves are depicted in the figures below. It clearly shows that the PFS and OS estimates changed considerably.

Progression-free-survival (PFS)

Figure 4 • **Crizotinib PFS (before and after MAIC) - comparison to pemetrexed TULUNG Registry**

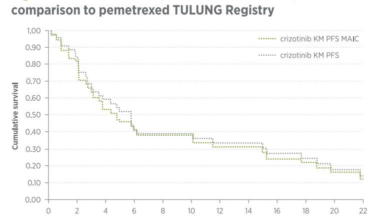
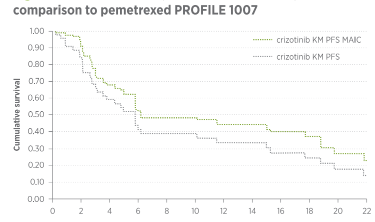


Figure 5 • **Crizotinib PFS (before and after MAIC) - comparison to pemetrexed PROFILE 1007**



Overall survival (OS)

Figure 6 • **Crizotinib OS (before and after MAIC) - comparison to pemetrexed TULUNG Registry**

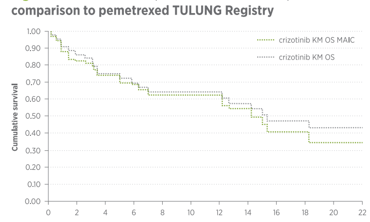
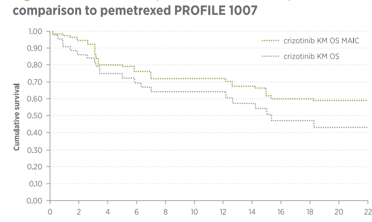


Figure 7 • **Crizotinib OS (before and after MAIC) - comparison to pemetrexed PROFILE 1007**



After estimation of the matched PFS and OS outcomes it was calculated that crizotinib increased median PFS by 54% and 47% and median OS by 49% and 19% when compared to pemetrexed RWE and pemetrexed PROFILE 1007 data, respectively in previously treated ALK positive NSCLC patients.

CONCLUSIONS AND DISCUSSION

Treatment of progressed ALK+ NSCLC with crizotinib is associated with major prolongation of PFS and OS compared to pemetrexed in the Czech real-world settings after adjusting for the patients' characteristic differences. The final results from PROFILE 1007 study showed median PFS on crizotinib 7.7 months [3] and median OS 21.7 months [5] which are comparable with results of this analysis in which PFS and OS of crizotinib was estimated at 6.2 and 27.2 months.

The limitation of MAIC is that the adjustment can be done only on differences which are monitored and captured in the respective data sources. Also, the patients on crizotinib in VILP Registry were treated in 2nd or later lines whereas pemetrexed patients were treated in 2nd line only. This is rather a conservative approach when assessing crizotinib effectiveness. Last, but not least is the fact that overall survival is influenced by the following treatments which is not adjusted for in this analysis.

During the PROFILE 1007 study, 89 % patients in the chemotherapy arm received crizotinib after progression on the chemotherapy treatment. This influenced the OS outcomes of pemetrexed arm significantly [5]. As this MAIC analysis did not consider the re-calculated estimates for OS of pemetrexed after adjusting for crossover, the gain of overall survival of crizotinib compared to pemetrexed data from PROFILE 1007 study would be even higher.

References: **[1]** TULUNG. TULUNG Registry – pemetrexed. [Online] 2016. http://tulung.registry.cz/index.php?pg=vysledky--tulung-alimta-29-9-2014. **[2]** VILP. VILP Registry – crizotinib. 2016. **[3]** Shaw, A., Dong-Wan, K., Nakagawa, K. & Seto, T. Crizotinib versus Chemotherapy in Advanced ALK-Positive Lung Cancer. N Engl J Med. 368, 2013, stránky 2385-94. **[4]** Signorovitch, J. a et, al. Comparative Effectiveness Without Head-to-Head Trials A Method for Matching-Adjusted Indirect Comparisons Applied to Psoriasis Treatment with Adalimumab or Etanercept (Supplemental Digital Content). PharmacoEconomics. 28, 2010. **[5]** Alice T Shaw, 1 Pasi A Jänne,2 Benjamin Besse,3 Benjamin J Solomon,4 Fiona Blackhall,5 D Ross Camidge,6 Tony Mok,7 Vera Hirsh,8 Judith R Scranton,9 Anna Polli,10 Yiyun Tang,11 Keith D Wilner,11 Dong-Wan Kim12. Crizotinib vs Chemotherapy in ALK+ Advanced Non-Small Cell Lung Cancer (NSCLC): Final Survival Results From PROFILE 1007. ASCO Conference. 2016, Abstract 9066.