Indirect comparison between real world data and clinical trial in non small cell lung cancer with bevacizumab

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BACKGROUND

- Advanced non-small-cell lung cancer (aNSCLC) is the most common type of lung cancer, accounting for 84% of all lung cancer, with 2.1 million newly diagnosed cases and 1.8 million deaths worldwide every year. [1]
- Bevacizumab is an anti-vascular endothelial growth factor (anti-VEGF) therapy.
- SAiL [2] is an international, multicenter, single-arm phase IV study that evaluated the safety and efficacy of bevacizumab combined with a range of standard first-line chemotherapy regimens in patients with non-squamous aNSCLC.
- EOLE [3] is a French non-interventional, prospective, national, that evaluated the efficacy of bevacizumab combined with a range of standard first-line chemotherapy regimens in patients with non-squamous aNSCLC.
- Indirect comparison fills a gap in Comparative Effectiveness Research methodology by leveraging available Individual Patient Data (IPD) and Aggregated Data (AgD) to provide timely and reliable comparative evidence.

OBJECTIVE

- To compare efficacy of first-line bevacizumab-bases therapy in advanced non-squamous, Non Small-Cell Lung Cancer (aNSCLC) between two unbalanced populations when we have access to individual patient data for only one study.

METHODS

- We performed an unanchored Matching-Adjusted Indirect Comparison (MAIC) by matching individual patient baseline data for EOLE were matched to published aggregated data for SAiL trial (phase IV) to adjust for key baseline characteristics including age, sex, tumor histology, ECOG score, smoking status and stage of tumor (*Figure 1*).
- Matching of outcomes, assessments schedules, dosages, statistical methods were verified: in both studies, data were collected every 3 months over 18 months, patients received bevacizumab (7.5 or 15 mg/kg on day 1 and then every 3 weeks) in combination with a standard first-line chemotherapy regimen.
- Matching weights were determined by logistic regression as described by Signorovitch and al.[4]
- SAiL's Kaplan–Meier curve was digitized using DigitizeIt software. The method developed by Guyot and al. (2012)[5] was applied to generate pseudo patient-level data.
- Patients with brain metastasis were excluded from the SAIL study, but included in the EOLE study. A sensibility analysis was conducted on this sub-population named EOLE-WBM.
- All analyses have been performed using R software V3.4.3.

RESULTS

2212 in SAiL trial and 407 patients in EOLE study were analysed. 13 Eole's patients were excluded due to missing data. Median follow up were 10.5 months for SAiL and 12.5 months for EOLE. Median treatment of bevacizumab were 4.9 months in SaiL and 4.4 in EOLE. Baseline characteristics are shown in Table 1 below.

		Primary analysis		*Sensibility analysis*	
Baseline characteristics	**SAiL**	**EOLE (before matching)**	**EOLE (after matching)**	**EOLE-WBM***	**EOLE-WBM* (after matching)**
N	2212	394**	ESS = 237	311	ESS=202
Age mean (sd), years	58.8 (10)	60.0 (9.5)	58.8 (10.3)	60.3 (10.4)	58.8 (10.3)
Sex : man, n (%)	1329 (60.1)	276 (67.8)	60.1 %	207 (66.6)	60.1 %
Disease stage, n (%)					
IIIb	436 (19.7)	34 (8.4)	19.7 %	30 (9.7)	19.7 %
IV	1775 (80.3)	369 (91.6)	80.3 %	281 (90.3)	80.3 %
ECOG PS, n (%)					
0-1	2073 (93.8)	353 (87.8)	37.2 %	128 (41.2)	37.2 %
2	138 (6.2)	49 (12.2)	6.2 %		6.2 %
Tabagic status, , n (%)					
former	670 (30.3)	51 (12.9)	30.3 %	39 (12.5)	30.3 %
older	1542 (69.7)	356 (87.1)	69.7 %	272 (87.5)	69.7 %
Histology : adenocarcinoma, n (%)	1781 (86)	364 (91.6)	86 %	284 (91.3)	86 %
Brain metastasis, n (%)	1 (<1)	84 (20.6)	20.6 %	/	/

Table 1 : Baseline characteristics for SAiL and EOLE before and after matching and after exclusion

**WBM=Without Brain Metastasis*

***missing data : disease stage n=4, ECOG PS n=5, Histology n=8*

		Primary analysis		*Sensibility analysis*
	SAiL n=2212	**EOLE (before matching) n =394**	**EOLE (after matching) ESS =237**	**EOLE-WBM (after matching) ESS =202**
Median OS (months) [IC 95%]	**14.6 [13.8-15.1]**	**12.8 [10.3-17.5]**	**14.8 [12.8-17.5]**	**13.8 [12.1-16.9]**
OS rate estimate at 6 months [IC 95%]	0.818 [0.802-0.835]	0.755 [0.713-0.799]	0.824 [0.783-0.868]	0.820 [0.773-0.869]
OS rate estimate at 12 months [IC 95%]	0.580 [0.559-0.602]	0.525 [0.476-0.579]	0.576 [0.522-0.636]	0.561 [0.501-0.629]
OS rate estimate at 18 months [IC 95%]	0.412 [0.390-0.436]	0.365 [0.317-0.420]	0.431 [0.376-0.494]	0.413 [0.353-0.483]

Table 2 : Kaplan-Meier Overall Survival (OS) estimation for SAiL and EOLE before and after matching

- Before matching, most SAiL's and EOLE's patients were current or former smokers (69.8% and 87.56% respectively), had ECOG performance status between 0-1 (93.8% vs 87.5%), had a stade IV tumor (80.3% vs 92.4%) and had an adenocarcinoma (86.0% vs 91.6%); the median of OS in EOLE's population was 12.8 months [10.3-15.1] (*Table 2*).
- After matching, all baseline characteristics were balanced across studies and the median of EOLE was 14.8 [12.8-17.5] compare to the published median of SAiL was 14.6 [13.8-15.1]. Indirect treatment comparison of OS resulted in unadjusted HR=0.84 [0.73-0.97] and adjusted HR 1.01 [0.84-1.22] (*Figure 2*).

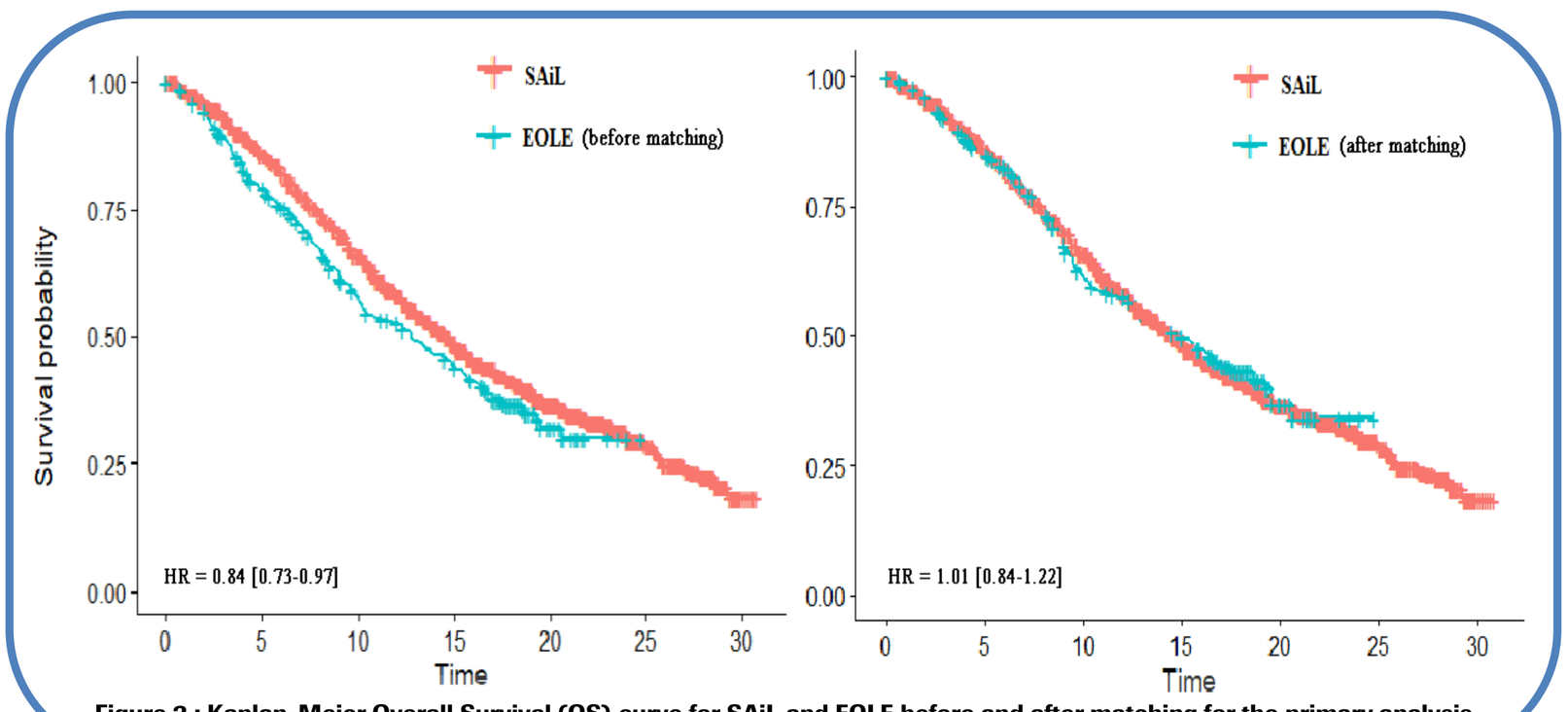


Figure 2 : Kaplan-Meier Overall Survival (OS) curve for SAiL and EOLE before and after matching for the primary analysis

Same conclusion emerged from the sensibility analysis on sub-population without brain metastasis patients (n=311). The median OS before matching was 12.3[10.1-14.9] and 13.8 [12.16.9] after matching.

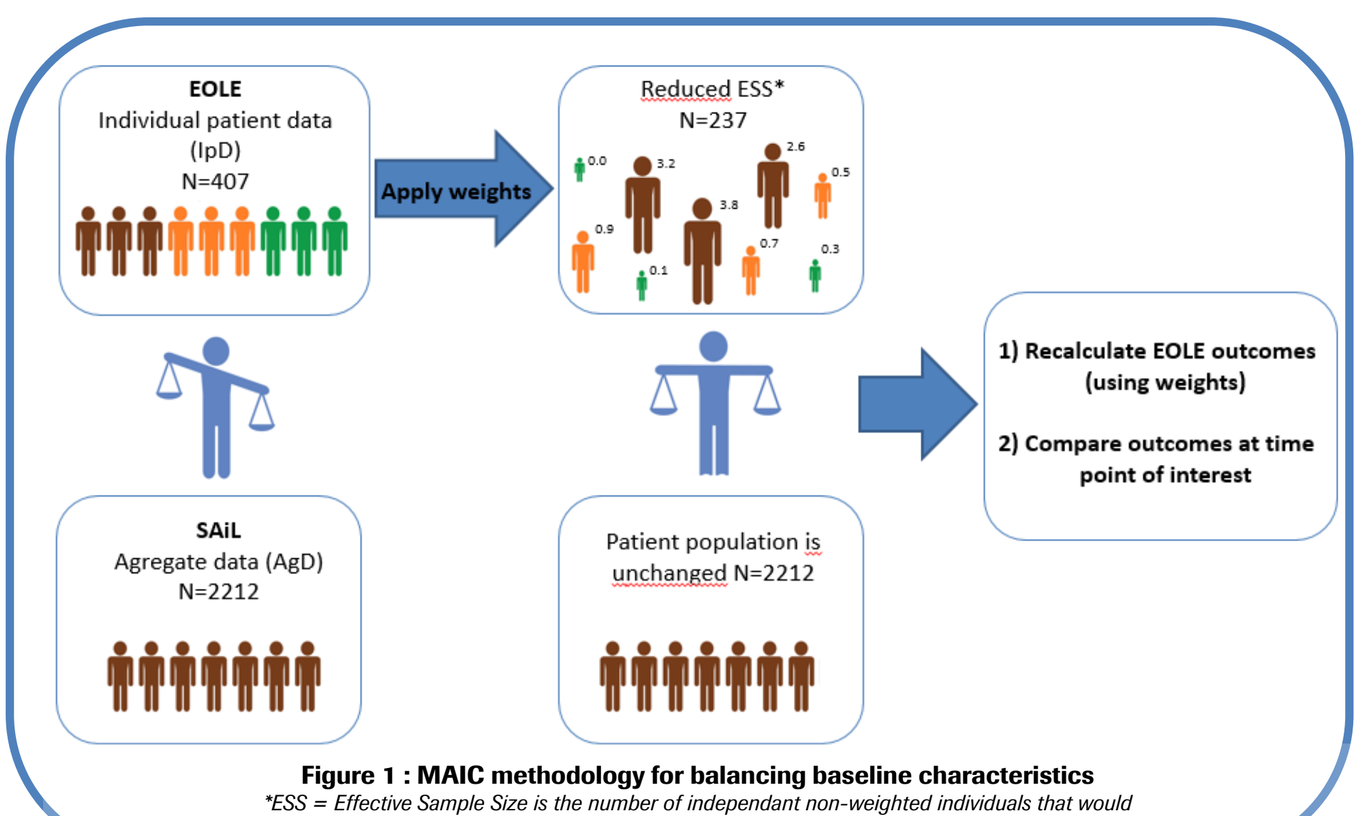


Figure 1 : MAIC methodology for balancing baseline characteristics

**ESS = Effective Sample Size is the number of independant non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate*

CONCLUSION

MAIC method allows to estimate and compare the treatment effect size by using IPD from one study and published aggregate data from another. After adjusting for difference in baseline characteristics, this indirect comparison seems to show consistent results of bevacizumab in aNSCLC patients in real world (RWD) setting with those observed in Clinical Trial (CT).

This could help decision making to explain discrepancies in treatment effect size due to non well balanced populations, between CT and RWD results or to compare two different treatments.

MAIN LIMIT

This method assumed that there were no unmeasured confounding variables. Treatment effect modifiers may not be known or information may not be in the published study. Therefore the amount of bias (systematic error) in these estimates is unknown, is likely to be substantial, and could even exceed the magnitude of treatment effects which are being estimated.

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