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BACKGROUND

Osimertinib has been the standard first line therapy for metastatic non-small cell lung carcinoma (NSCLC) harboring EGFR exon 19 deletion or L858R mutation, based on the phase III clinical trial that compared it with erlotinib or gefitinib (1). Recently, a new phase III trial has found that adding chemotherapy to osimertinib improves progression-free survival (PFS) and duration of response, with increased toxicity (2). A randomized phase II trial suggests that using gefitinib as first line and osimertinib when molecular or radiologic progression may achieve the same overall survival (OS) that using first line osimertinib (3). There are scarce real world data (RWD) studies concerning use of osimertinib as first line therapy in EGFR-mutated NSCLC. A single-institution retrospective RWD study showed results of 56 patients (4). The FLOURISH study is a multicenter analysis of RWD of China hospitals, with 441 patients enrolled in the last update (5). No comparative RWD studies have been published so far. Here we present descriptive and comparative RWD results of osimertinib versus first/second generation TKIs (erlotinib, gefitinib, afatinib, dacomitinib) first line therapy for EGFR-mutated NSCLC using TrinetX. TrinetX is the global federated health research network providing access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) across large healthcare organizations (HCOs). This study was run on the set of HCOs grouped into a network called Global Collaborative Network, including 117 HCOs.

METHODS AND STATISTICS

TrinetX network was used to search and analyze clinical anonymized information. The analysis process included two main steps:

- 1) Defining the cohorts through query criteria: metastatic/advanced NSCLC, no prior systemic therapy, survival information available; visit at least 6 months before; osimertinib or 1st/2nd generation TKI as first line therapy.
- 2) Setting up and running the analysis. Research was done in a time window of 3 years. Index event was defined as the diagnosis of metastasis.

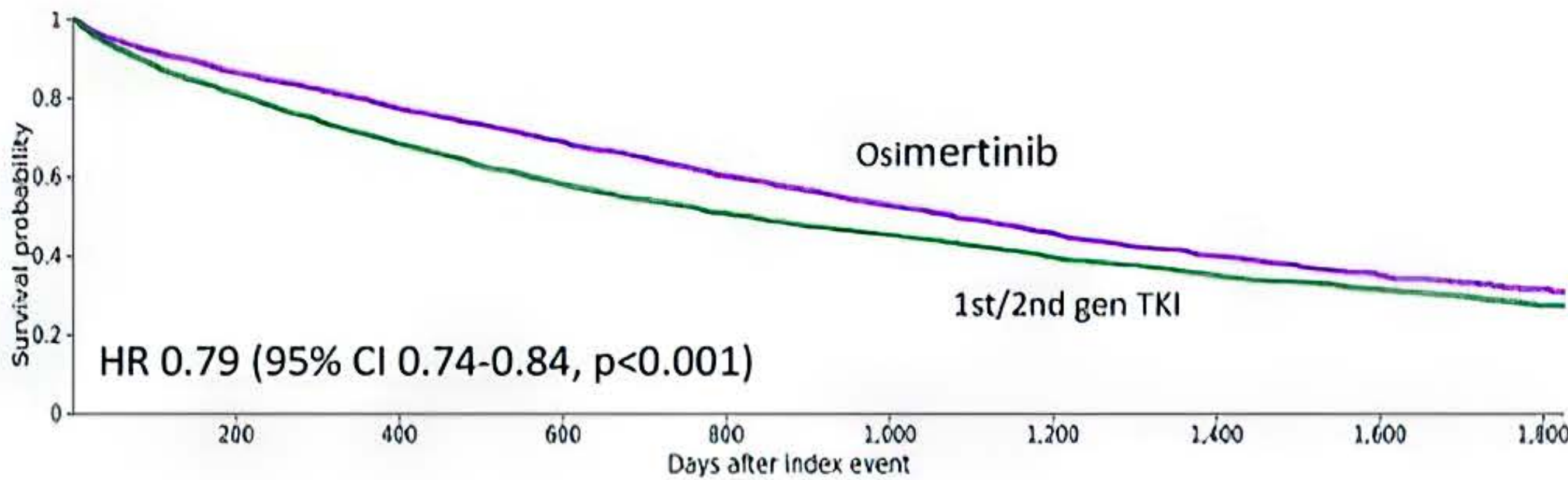
Kaplan Meier, log-rank, and hazard ratio analysis was used to estimate survivals and comparison between cohorts.

RESULTS

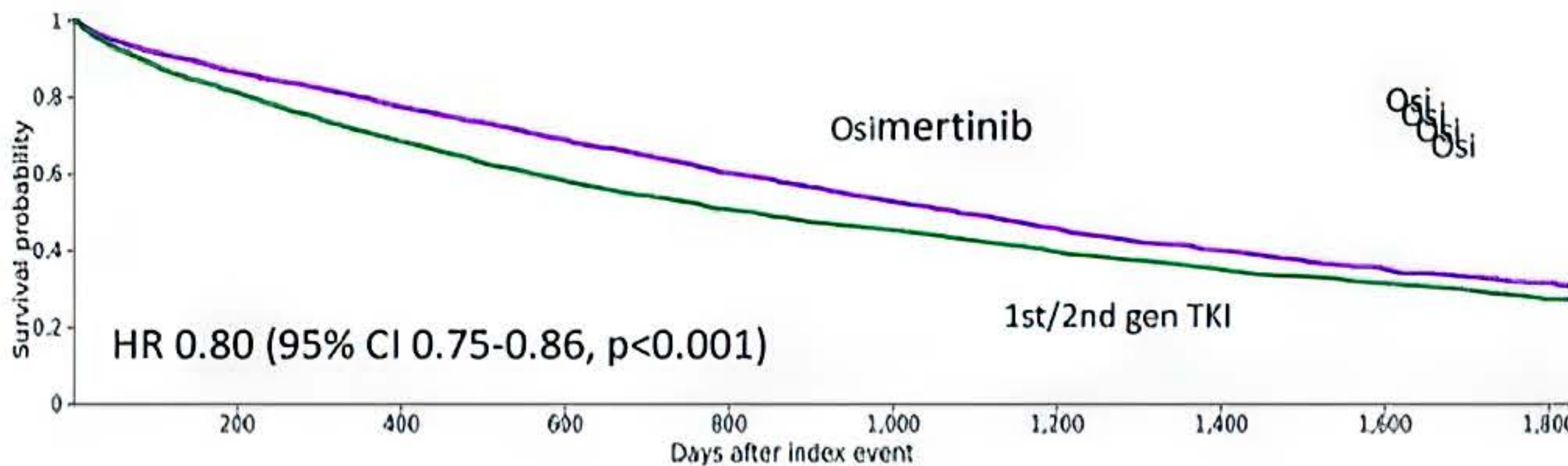
TABLE 1: DEMOGRAPHICS AND CLINICAL INFORMATION

	OSIMERTINIB	1st/2nd gen TKI	p
N	3176	4467	-
Age (mean+/-SD)	66.4 +/- 11.4	65.8 +/- 11.3	0.013
Sex: Females	2,047 (65.8%)	2641 (60.8%)	<0.001
Asian population	557 (17.9%)	919 (21.1%)	0.082

Kaplan Meier survival curves are in **Graphic 1 (not matched) and 2 (matched)**. Overall survival was significantly better for Osi (median OS 1095 days) versus oTKI (median OS 826 days), with HR 0.79 (95% CI 0.74-0.84, p<0.001). After matching cohorts by age, sex, and race, OS benefit was maintained for Osi with HR 0.80 (95% CI 0.75-0.86, p<0.001).



Graphic 1: OS raw data



Graphic 2: OS matched by sex, age, and race

We found overall survival information of 7643 patients: 3176 (41.5%) treated with Osi and 4467 (58.5%) treated with other TKI, that included erlotinib, gefitinib, afatinib, and dacomitinib. Demographic information of both cohorts is described in **Table 1**. Mean age was 66 and 65 years (p=0.058), female proportion was 65.8 vs 60.8% (p<0.001), and Asian population proportion was 17.9 vs 21.1% (p=0.001) for Osi and oTKI group, respectively.

Subsequent therapies were as follow: In the Osi group, 24% received pemetrexed plus platin, and 8.8% anti-PD1/PDL1 as second line. In the 1st/2nd generation TKI group, 32% received pemetrexed plus platin, 10.6% anti-PD1/PDL1, and 27.2% osimertinib as second line.

CONCLUSIONS

This is the biggest retrospective real world data study of Western world patients with EGFR-mutated advanced/metastatic NSCLC. Upfront osimertinib as first line improves overall survival compared to first/second generation TKIs, independently of subsequent therapies and even after matching cohorts by age, sex, and race. The strength of this study is the big size of both cohorts of Western population. Main weakness is that it is a retrospective study with lack of relevant clinical information, as type of EGFR-mutation, response rate, and progression-free survival. Many subsequent therapies are missing too. Nevertheless, this study suggests that best first line option in these patients is still osimertinib versus other TKIs. Combination with chemotherapy has become the new standard for many patients, and amivantab as second line therapy will be approved; so future update of results is warranted.

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