Concurrent Metformin Use and Survival Among Finnish Non-Small Cell Lung Cancer Patients Treated With EGFR TKIs

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Abstract

Purpose

Many studies have shown correlation between metformin use and lower incidence and improved outcomes of lung cancer. We investigated the potential association between metformin use and survival among Finnish non-small cell lung cancer (NSCLC) patients treated with EGFR TKIs.

Methods

Nationwide registries were utilized to identify all the patients with use of EGFR TKIs in NSCLC between 2011–2016, and 1242 patients were included in further analyses. Data related to cancer, survival, and drug purchases were combined with personal identity codes. Concurrent use of diabetes medications was defined as their purchase +/-120 days from the first purchase of EGFR TKI. The impact of diabetes medication use was investigated separately in the whole and in the EGFR mutant type cohort (n = 481).

Results

Concurrent metformin use was found in 10 % (n = 124) and use of other diabetes medication in 5 % (n = 60) of the patients. In the whole patient cohort, metformin use did not associate with survival but in the EGFR mutant type cohort a non-significant trend for higher mortality was found (HR 1.42, 95% CI 0.99–2.02). Metformin use associated also with a shorter EGFR TKI treatment duration (HR 1.26, 95 % CI 1.04–1.52). The use of other diabetes medication than metformin did not associate with survival or EGFR TKI treatment duration.

Conclusion

Concomitant metformin use associated with a shorter EGFR TKI treatment duration, however, no statistically significant correlation with survival was found. Ethnicity, comorbidities, and metformin dosage may influence on the associations found between metformin use and EGFR TKI treatment responses.

Introduction

Epidermal growth factor receptor (EGFR) targeting with tyrosine kinase inhibitors (TKI) was initially studied in non-small cell lung cancer (NSCLC) without molecular selection (Shepherd et al. 2005; Thatcher et al. 2005). The identification of EGFR mutated NSCLC shifted the use of EGFR TKIs predominantly to EGFR mutated subtype in which they provide superior efficacy and quality of life compared to platinum doublet chemotherapy (Paez et al. 2004; Lynch et al. 2004; Greenhalgh et al. 2016). The most common side effects of EGFR TKIs include acneiform rash and diarrhea but in general

EGFR TKIs are well tolerated and treatment discontinuations due to toxicity are rare (Ding et al. 2017). A mutation-specific EGFR TKI, osimertinib, has quite recently introduced further improvements in progression free survival (PFS) compared to both first-generation EGFR TKIs and chemotherapy, with a favorable side effect profile (Mok et al. 2017; Soria et al. 2018). Even though most of the patients with EGFR mutated NSCLC respond to EGFR TKIs, eventually an acquired resistance develops, and, in addition, a small proportion of cases are primary resistant (Rotow and Bivona 2017).

Metformin is commonly used in the treatment of type 2 diabetes (T2D). Insulin resistance, hyperinsulinemia and hyperglycemia are characteristic metabolic dysfunctions in T2D, and they have also been linked to cancer progression (Shlomai et al. 2016). Metformin increases insulin sensitivity and decreases glucose and insulin levels in the blood (Shlomai et al. 2016), and may enhance immunological response against cancer (Levy and Doyen 2018). Metformin also modulates signaling pathways including the activation of adenosine monophosphate activated protein kinase (AMPK) pathway and inhibition of insulin-like growth factor-1 receptor (IGF-1R) pathway, resulting in reduced tumor cell proliferation and increased apoptosis (Levy and Doyen 2018; Deng et al. 2019). These signaling pathways are also involved in EGFR TKI resistance mechanisms which provides a rationale for combining metformin with EGFR TKIs in NSCLC (Deng et al. 2019).

Interestingly, epidemiological studies have shown a lower incidence of several cancers, including lung cancer, among T2D patients treated with metformin (Zhang, Z. et al. 2014; Tsai et al. 2014). Furthermore, the survival of lung cancer patients with T2D seems to be improved if they receive metformin (Lin et al. 2015; Tian et al. 2016). There are retrospective studies showing improved outcomes among NSCLC patients with EGFR TKI and metformin compared to patients without metformin (Chen et al. 2015; Hung et al. 2019; Han et al. 2021) but also contradicting results do exist (Su et al. 2020). In addition, two recent phase II randomized studies have investigated the role of metformin together with EGFR TKIs in advanced EGFR mutant NSCLC among non-diabetic patients (Arrieta et al. 2019; Li et al. 2019). In the study by Arrieta et al, 139 EGFR mutant NSCLC patients were randomized to receive EGFR TKI (erlotinib, gefitinib or afatinib) alone or in combination with metformin. Among the patients with metformin, both PFS and overall survival (OS) were improved (Arrieta et al. 2019). On the contrary, in another prospective study with 224 patients, addition of metformin to first line treatment with gefitinib did not improve outcome of non-diabetic EGFR mutant NSCLC patients (Li et al. 2019).

Epidemiological and preclinical studies have suggested anti-tumoral effects of metformin in lung cancer, proposing that adding metformin to lung cancer treatment might be beneficial. Retrospective studies performed in East Asian patients support the idea of metformin’s clinical benefit in EGFR mutant NSCLC, but the two randomized studies addressing this question have provided conflicting results (Arrieta et al. 2019; Li et al. 2019). In this study, we investigated the potential association between metformin use and survival in a Finnish register data of 1242 NSCLC patients treated with EGFR TKIs in Finland between years 2011–2016.

Material And Methods

Collection of patient material

Collection of the primary patient material has been described in detail previously (Alanen et al. 2020; Alanen et al. 2021). Briefly, all the patients with special reimbursement for EGFR TKIs (erlotinib, gefitinib or afatinib) between 2011–2016 were identified from the Special Reimbursement Register of Social Insurance Institution (SII) of Finland (n = 1541). In Finland, reimbursement for erlotinib in advanced NSCLC is based on the presence of activating EGFR mutation in the tumor or progression during prior chemotherapy and both are registered under the same code and cannot be separated. On the contrary, reimbursements for gefitinib and afatinib are entitled only in advanced NSCLC with activating EGFR mutations. The information on the drug purchases for EGFR TKIs, metformin, and other diabetes medications (purchase dates and the number and strength of purchased units) was collected from the Prescription database of SII, cancer related data from the Finnish Cancer Registry, and data on dates of death from Statistics Finland. The data were combined using personal identity codes and pseudonymized before analyses. The patients with at least one EGFR TKI purchase in the Prescription database and data available at the Finnish Cancer Registry were included in the study (n = 1271). The patients with afatinib as their 1st EGFR TKI were excluded from the study due to a small sample size (n = 29) resulting in a final cohort of 1242 patients, 1072 with erlotinib and 170 with gefitinib. The follow-up for drug purchases and deaths ended on December 31st, 2017. Collection of the data was performed according to the national legislation, the ethical standards of the Ethical Board of Oulu University Hospital (study no.43/2017) and under a permit from the Social Insurance Institution of Finland (study no.48/522/2017), the Finnish Institute of Health and Welfare (study no. THL/1391/5.05.00/2017), and Statistics Finland (study no.TK-53-1277-17). Informed consent was not required as this is a retrospective register-based study.

Study cohorts and endpoints

Concurrent use of metformin or other diabetes medication was defined as a purchase of diabetes medication within 120 days before or after the first purchase of EGFR TKI. A 120-day time period was selected since the number of reimbursed drugs is limited to a three-month supply per purchase and this would reflect the concurrent use of the medication. As metformin may have different effects in EGFR mutant and EGFR wild-type (wt) lung cancers, we created an EGFR mutant type cohort which included all the patients with gefitinib (based on the reimbursement criteria requiring EGFR mutant NSCLC) and patients with > 180 days of erlotinib use as patients with EGFR mutant NSCLC more often obtain long-lasting responses than patients with EGFR wt lung cancer. The impact of the concurrent metformin and other diabetes medication use was investigated separately in the whole patient cohort (n = 1242) and in the EGFR mutant type cohort (n = 481).

The purchases for medication were collected from 1st January 2010 until 31st December 2017. OS was calculated from the date of first EGFR TKI purchase to death or end of the follow-up (December 31st, 2017), and death of any cause was counted as an event. The length of EGFR TKI treatment was calculated from the first EGFR TKI purchase to the last and the number of days according to number of

tablets in the last purchase were added to the treatment length. Treatment was considered continuous based on dates of purchases and the number of tablets allowing a maximum of 10 days gap between the purchases. Discontinuation of treatment before the end of the follow-up was counted as an event. EGFR TKI dose reduction was defined as EGFR TKI purchase of lower dose compared to the first prescribed dose within 200 days from the beginning of the treatment. EGFR TKI treatment break was defined as a break of more than 30 days within the first 200 days of treatment and calculated from the EGFR TKI purchase dates and number of tablets.

Statistical analyses

Statistical analyses were performed with IBM SPSS Statistics v. 25.0.0 (IBM Corporation, Armonk, NY, USA). Chi-square test was used for analyzing the differences between the groups. Kaplan-Meier method using log-rank test was utilized for survival and EGFR TKI treatment length analyses and for plotting the curves. Univariate and multivariate (tumor histology; concomitant metformin with EGFR TKI/erlotinib/gefitinib; other diabetes medication with EGFR TKI) analyses were performed with the Cox's model. The results are presented with 95% confidence level. P-values < 0.05 were regarded as statistically significant.

Results

Patient characteristics

Of the 1242 patients, 54% (n = 670) were male and 46% (n = 572) were female, 65% (n = 812) had adenocarcinoma while the rest had other histology or defined as unknown (n = 430). The first purchased EGFR TKI was erlotinib in 86% (n = 1072) and gefitinib in 14% (n = 170) of the patients. Concurrent metformin use (-120 to + 120 days from the first EGFR TKI purchase) was found in 10% (n = 124) and the use of other diabetes medication without metformin in 5 % (n = 60) of the patients. The median follow-up time was 288 days (range 0-2606) and 1073 (86%) patients had died by the end of the follow-up. (Table 1)

Table 1
Demographics of the cases

	Whole patient cohort n = 1242	EGFR mutant type cohort n = 481
Age, years Median (range)	67 (23–92)	68 (23–90)
Sex		
Male	670 (54%)	216 (45%)
Female	572 (46%)	265 (55%)
Histology		
Adenocarcinoma	812 (65%)	367 (76%)
Other NSCLC	430 (35%)	114 (24%)
Stage		
Local	94 (8%)	76 (16%)
Advanced	888 (71%)	287 (60%)
Unknown	260 (21%)	118 (24%)
EGFR TKI		
Erlotinib	1072 (86%)	311 (65%)
Gefitinib	170 (14%)	170 (35%)
Diabetes medication		
No	1058 (85%)	419 (87%)
Metformin	124 (10%)	41 (9%)
Other than metformin	60 (5%)	21 (4%)
Death		
No	148 (12%)	112 (23%)
Yes	1073 (86%)	360 (75%)
Unknown	21 (2%)	9 (2%)

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

Erlotinib use for > 180 days was found in 25% (n = 311) of the patients. The EGFR mutant type cohort (n = 481) was formed from all the patients with gefitinib (n = 170) and the patients with erlotinib with a use of the TKI for > 180 days. Of these patients, 45% (n = 216) were male and 76% (n = 367) had adenocarcinoma. Concurrent metformin use was found in 9% (n = 41) and other diabetes medication without metformin in 4% (n = 21) of the patients. The median follow-up time was 568 days (range 1-2606) and 360 (75%) patients had died by the end of the follow-up. (Table 1)

Concurrent metformin use and survival

In the whole patient cohort (n = 1242), the concurrent metformin use with EGFR TKI did not significantly correlate with the survival of the patients (Fig. 1A, Table 2). With the gefitinib users (n = 170), there was a non-significant trend for inferior survival among those with concurrent metformin use whereas no difference was found among the patients with erlotinib (n = 1072) (Table 2). The survival of the patients with other diabetes medication than metformin was similar compared to patients without diabetes medication (Fig. 1A, Table 2). In the EGFR mutant type cohort (n = 481), the use of metformin associated with a narrowly non-significant trend for inferior survival (Fig. 1A, Table 2). The use of other diabetes medication than metformin did not correlate with survival (Fig. 1A, Table 2).

Table 2
Univariate analyses for overall survival according to metformin use in the whole patient cohort (a) and EGFR mutant type cohort (b)

a. Whole patient cohort	HR	95% CI
Concomitant metformin with EGFR TKI		
Yes vs. no	1.14	0.93–1.39
Concomitant metformin with erlotinib		
Yes vs. no	1.09	0.88–1.34
Concomitant metformin with gefitinib		
Yes vs. no	1.64	0.90-3.00
Other diabetes medication with EGFR TKI		
Yes vs. no	0.98	0.74–1.29
b. EGFR mutant type cohort	**HR**	**95% CI**
Concomitant metformin with EGFR TKI		
Yes vs. no	1.42	0.99–2.02
Other diabetes medication with EGFR TKI		
Yes vs. no	1.07	0.66–1.75

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval; vs, versus

Metformin use and EGFR TKI treatment length, dose reductions and treatment breaks

The median length of EGFR TKI treatment was 99 days (range 30-1911) for the whole patient cohort, and 92 days (30-1911) for erlotinib and 261 days (30-1771) for gefitinib. The concurrent metformin use was associated with a shorter EGFR TKI treatment period in the whole patient cohort (HR 1.26, 95% CI 1.04–1.52) (Fig. 1B, Table 3) with a median treatment length of 92 days (30–679) vs. 101 days (30-1911) among patients with and without metformin, respectively (p = 0.02). The use of metformin associated significantly also with a shorter gefitinib treatment duration (HR 1.89, 95% CI 1.08–3.32) and there was a

non-significant trend for inferior EGFR TKI treatment duration among the erlotinib users (Table 3). Concurrent metformin use remained as a significant risk factor for shorter EGFR TKI treatment duration (HR 1.23, 95% CI 1.02–1.49) in the Cox multivariate analysis including also tumor histology (Table 3). In the EGFR mutant type cohort, the median length of EGFR TKI treatment was 336 days (range 30-1911). EGFR TKI treatment duration was shorter among patients with metformin compared to the others (HR 1.59, 95% CI 1.12–2.26) (Fig. 1B, Table 3) with median treatment durations of 269 days (30–679) and 348 days (30-1911), respectively (p = 0.009). The use of other diabetes medication than metformin did not associate with EGFR TKI treatment durations in the whole patient cohort or in the EGFR mutant type cohort (Fig. 1B, Table 3).

Table 3
Univariate and multivariate analyses for the EGFR TKI treatment duration according to metformin use in the whole patient cohort (a) and EGFR mutant type cohort (b)

	Univariate		Multivariate	
a. Whole patient cohort	**HR**	**95% CI**	**HR**	**95% CI**
Adenocarcinoma				
Yes vs. no	0.74	0.65–0.83		
Concomitant metformin with EGFR TKI				
Yes vs. no	1.26	1.04–1.52	1.23	1.02–1.49
Concomitant metformin with erlotinib				
Yes vs. no	1.20	0.97–1.47		
Concomitant metformin with gefitinib				
Yes vs. no	1.89	1.08–3.32	1.87	1.02–3.40
Other diabetes medication with EGFR TKI				
Yes vs. no	0.97	0.74–1.27		
b. EGFR mutant type cohort	**HR**	**95% CI**		
Concomitant metformin with EGFR TKI				
Yes vs. no	1.59	1.12–2.26		
Other diabetes medication with EGFR TKI				
Yes vs. no	0.85	0.52–1.37		

EGFR,epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence interval; vs, versus; Factors in multivariate analysis: tumor histology; concomitant metformin with EGFR TKI/erlotinib/gefitinib; other diabetes medication with EGFR TKI

EGFR TKI dose reductions occurred in only 2.2 % (n = 27) and EGFR TKI treatment breaks of more than 30 days in 13.8 % (n = 172) of all the patients. Among patients with concurrent metformin use, EGFR TKI dose reductions were found in 4 % (5/124) compared to 2 % (22/1118) of the patients without metformin

(ns). EGFR TKI treatment breaks occurred in 10.5 % (13/124) and 14.2 % (159/1118) of the patients with and without concurrent metformin, respectively (ns). Similarly, in the EGFR mutant type cohort, there were no significant differences in EGFR TKI dose reductions or treatment breaks according to metformin use. (Table 4)

Table 4
EGFR TKI dose reductions and treatment breaks according to metformin use in the whole patient cohort (a) and EGFR mutant type cohort (b)

a. Whole patient cohort	**EGFR TKI only n = 1118**	**EGFR TKI and metformin n = 124**	**P value**
EGFR TKI dose reduction			
No	1096 (98%)	119 (96%)	
Yes	22 (2%)	5 (4%)	NS
EGFR TKI treatment break			
No	959 (86%)	111 (89.5%)	
Yes	159 (14%)	13 (10.5%)	NS
b. EGFR mutant type cohort	**EGFR TKI only** n = 440	**EGFR TKI and metformin** n = 41	**P value**
EGFR TKI dose reduction			
No	429 (98%)	40 (98%)	
Yes	11 (2%)	1 (2%)	NS
EGFR TKI treatment break			
No	326 (74%)	34 (83%)	
Yes	114 (26%)	7 (17%)	NS
EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NS, non-significant			

Discussion

To our knowledge, this is the first study investigating the role of metformin in Nordic lung cancer patient population treated with EGFR TKIs. Concurrent metformin use with EGFR TKIs showed a non-significant trend for inferior survival in the EGFR mutant type cohort. In addition, metformin use associated

significantly with a shorter EGFR TKI treatment duration. The use of other diabetes medication than metformin did not associate with survival of the patients or EGFR TKI treatment duration.

Preclinical studies have suggested that many of the anti-tumoral effects of metformin may require high doses but especially in combination with other cancer treatments metformin could provide efficacy and tolerability in conventional doses (Pollak 2014; Levy and Doyen 2018). Diarrhea is a common side effect of both metformin and EGFR TKIs, and it is possible that especially high doses of metformin may increase the side effects leading to dose reductions or interruptions of EGFR TKI treatment and subsequently impairing the efficacy of the treatment. In our study, metformin use associated with a shorter EGFR TKI treatment duration which likely reflects shorter PFS but may also indicate higher incidence of side effects leading to treatment discontinuation. Nevertheless, no significant correlations between metformin use and EGFR TKI dose reductions or treatment breaks were found but it should be noted that the number of patients in these subgroup analyses were small. In the randomized study showing survival benefit with combination of metformin and EGFR TKI (Arrieta et al. 2019), the daily dose of metformin was 1000 mg, and the combination did not result in increased toxicity. On the contrary, in the trial showing no survival benefit (Li et al. 2019), metformin dose was gradually increased up to 2000 mg daily and both diarrhea and grade 3–4 side effects occurred more commonly in the metformin group. Also, early safety results of METAL trial investigating the combination of metformin and erlotinib in the second line treatment of EGFR wt NSCLC, showed grade 3 gastrointestinal toxicity in 2/3 patients treated with 2000 mg metformin per day, whereas daily dose 1500 mg of metformin combined with erlotinib was quite well tolerated (Morgillo et al. 2017). In the present study, information of metformin dose was unavailable but based on the previous data, metformin dose may be important in the treatment combination with EGFR TKIs.

The effects of metformin in NSCLC may also be influenced by ethnicity of the patients. In a recent meta-analysis (Xiao et al. 2020), lung cancer incidence was reduced in T2D patients treated with metformin compared to those without only in studies including Asian patients, but not among European patients. Also, survival of lung cancer patients with T2D and metformin medication was better compared to those without metformin, and even though this association was found in both Asian and non-Asian populations, the possible protective effect of metformin seemed to be greater among the Asian patients (HR 0.57 and HR 0.79, respectively) (Xiao et al. 2020). The previous retrospective studies showing improved survival among NSCLC patients with metformin and EGFR TKIs are East Asian and most of these studies included only patients with EGFR mutant NSCLC (Chen et al. 2015; Han et al. 2021). On the contrary, in the present study with Nordic patients, metformin use did not statistically significantly correlate with OS and there was even a trend for shorter survival with metformin. In our study, EGFR mutation status was not known but we created an EGFR mutant type cohort based on the reimbursement criteria and erlotinib treatment duration and found that the results were similar in the whole patient cohort and in the EGFR mutant type cohort. It is well known that the incidence of activating EGFR mutations in NSCLC is much higher in East Asian patient population than in Caucasian (Zhang, Y. L. et al. 2016). In addition, the effects of metformin may vary between different ethnicities due to variation in genes involved in metformin's mechanisms of action (Zhou et al. 2015). For example, LKB1/STK11 gene, which

is important in the activation of AMPK pathway and for the functions of metformin, is mutated more frequently in NSCLC among Caucasian than Asian patients (Koivunen et al. 2008). LKB1 deficiency may alter the anti-tumoral functions of metformin although preclinical studies suggest also mechanisms independent of LKB1 (Choi and Park 2013; Fatehi Hassanabad and MacQueen 2021). In a post hoc analysis by Arrieta et al, combining metformin with EGFR TKIs seemed to improve OS only among patients expressing LKB1 (Arrieta et al. 2019).

Other factors that could explain the varying results in different populations include comorbidities and smoking status of the patients. Smoking increases the risk for developing both T2D and its complications (Zhu et al. 2017), and NSCLC with smoking associates with worse survival (Tammemagi et al. 2004). Comorbidities associated with T2D include cardiovascular diseases and diabetic nephropathy and neuropathy (Zheng et al. 2018). Comorbidities influence on all-cause mortality and therefore lung cancer specific survival endpoints might provide different results than OS. Comorbidities may also impair administration of subsequent cancer treatments, in EGFR mutant NSCLC especially platinum-based chemotherapy due to its nephrotoxicity and neurotoxicity. Nevertheless, in the present study, among patients with other diabetes medication than metformin, survival and duration of EGFR TKI treatment were similar compared to those without any diabetes medications. It is possible that T2D medication used reflects some characteristics of the patient populations, e.g., it has been suggested that metabolic dysfunction may be more difficult among T2D patients whose medication includes metformin whereas metformin monotherapy may associate with a better general health status (Fatehi Hassanabad and MacQueen 2021). It is also important to notice that the metabolic state is different among T2D patients and patients without T2D, and also the effects of metformin in cancer treatment may be different in these patient populations.

The strengths of our study include a large nationwide patient material which was collected using reliable nationwide registries and combining the data with personal identity codes. The study has also some limitations. Several possible confounding factors for which the data was unavailable, e.g., comorbidities, smoking status, and metformin doses used, may have influenced on the associations found in this study. In addition, we had no information on possible hospital treatment periods of the patients and medication received during hospitalization. Also, even though the patient material is quite large, the number of patients in some of the subgroup analyses remained rather small. Furthermore, the results cannot be extrapolated to non-diabetic patients as the effects of metformin may be different in patients without diabetes.

To conclude, in this material of Finnish NSCLC patients treated with EGFR TKIs, metformin use associated with a shorter EGFR TKI treatment duration and also a non-significant trend for inferior survival was found. Differences in the patient materials, e.g., ethnicity, differences in mutation profiles, comorbidities, smoking status and metformin doses used, may explain the variance in the results of retrospective studies investigating the role of metformin in EGFR TKI treatment responses.

Declarations

Funding

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Conflict of Interest statement

VA and MA declare no conflict of interest. ST reports personal fees or financial support for attending conferences from AstraZeneca, Boehringer-Ingelheim, BMS, MSD, Novartis, Pfizer, Roche and Takeda, all outside the submitted work. SI reports personal fees and other from MSD, grants from Roche, personal fees from BMS, grants from AstraZeneca, personal fees from Novartis, personal fees from Boehringer-Ingelheim all outside the submitted work. JPK reports grants and personal fees from Roche, grants and personal fees from AstraZeneca, grants and personal fees from Boehringer-Ingelheim, personal fees from Takeda, personal fees from BMS, personal fees from Merck all outside the submitted work.

Availability of data and material

Owing to data protection legislation in Finland, individual-level data on the study subjects cannot be released.

Code availability

Not applicable.

Author’s contributions

ST, SI, VA, MA, and JPK designed and coordinated the work. MA combined the data from different registries. MA, ST, SI, and JPK, carried out statistical analysis. All the authors participated in analysis and interpretation of the data, and drafted, read, and approved the final version of the manuscript.

Ethics approval

All data collection was carried out according to national legislation and under a permit from the Ethical Board of Oulu University Hospital (study no.43/2017), Social Insurance Institution of Finland (study no.48/522/2017), Finnish Institute of Health and Welfare (study no. THL/1391/5.05.00/2017), and Statistics Finland (study no.TK-53-1277-17). Pseudonymization was carried out before data analysis.

Consent to participate

Informed consent was not required due to the register nature of the study.

Consent for publication

All the authors' have read and approved the final version of the manuscript.

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Figures

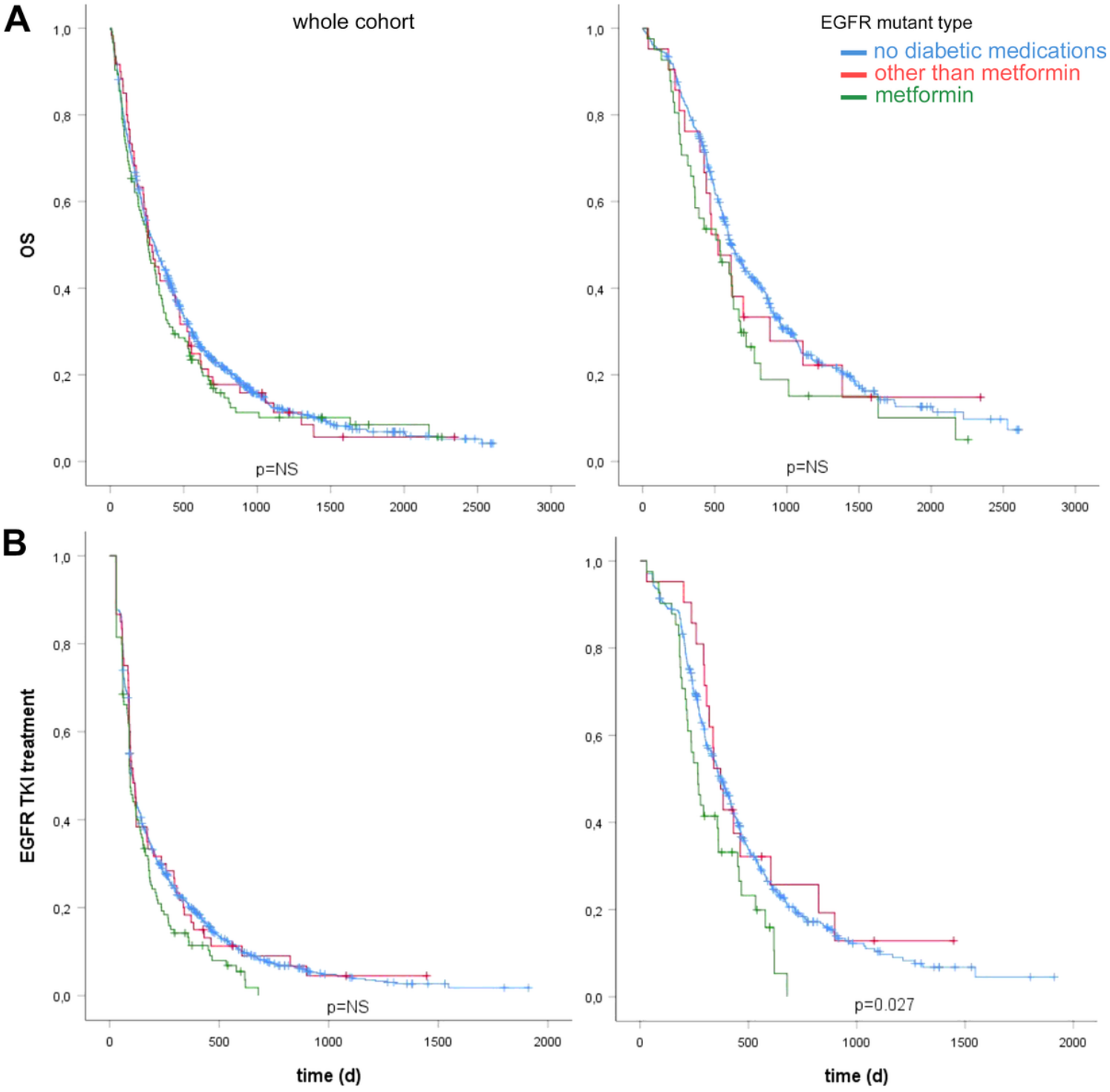

Figure 1

Kaplan-Meier analysis for overall survival and EGFR TKI treatment duration according to purchase of diabetes medication. A. Overall survival in the whole patient cohort and EGFR mutant type cohort. B. EGFR TKI treatment duration in the whole patient cohort and EGFR mutant type cohort. Blue= no diabetes medication purchases, red= other diabetes medication purchases than metformin, green= metformin purchases -120 to +120 days from the 1st EGFR TKI purchase. Crosses indicate censored events.