Safety Profile of Mutant EGFR-Tyrosine Kinase Inhibitors in Advanced Non-Small Cell Lung Cancer: Meta-Analysis and Literature to Review

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Research Article

Keywords: Safety, mutant EGFR-TK inhibitors, advanced, non-small lung cancer, literature, meta-analysis

Posted Date: November 22nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1055015/v1>

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Abstract

Despite the use of platinum-based chemotherapy, lung cancer continues to be the leading cause of cancer related death in the world. To overcome the rate of lung cancer related death, scientists discovered advanced therapies including mutant Epidermal Growth Factor Receptor-tyrosine kinase (EGFR-TK) inhibitors. Included in this study are nine phase 3 randomized controlled trials designed to study the safety profile of mutant EGFR-TK inhibitors in patients with advanced non-small cell lung cancer. The study showed that mutant EGFR-TK inhibitors have an incidence of adverse effects that is far less than platinum-based chemotherapy. Adverse effects reported were tolerable and easily manageable by slowing the infusion rate, decreasing the dosage, and skipping a dosage in symptomatic patients.

Introduction

Lung cancer has been the leading cause of cancer related mortality for decades. It is also predicted to remain as the leading cause of cancer related mortality through 2030. [1]. Platinum-based chemotherapy including carboplatin and paclitaxel, introduced 3 decades ago, has revolutionized the management of advanced non-small cell lung carcinoma. A more recent advancement has been mutant EGFR tyrosine kinase inhibitors [1]. Epidermal growth factor receptor is a transmembrane protein that functions by transducing essential growth factor signaling from the extracellular milieu to the cell. As 60% of the advanced non-small cell carcinoma expresses this receptor, blocking the mutant EGFR receptor was a groundbreaking development in the management of advanced non-small cell lung carcinoma [2]. Development of mutant EGFR tyrosine kinase inhibitors has revolutionized the management of advanced non-small cell lung carcinoma. This study was conducted to determine the safety profile of mutant EGFR tyrosine kinase inhibitors in the management of advanced non-small cell lung carcinoma.

Method And Methodology

This meta-analysis was conducted according to Cochrane Collaboration guidelines and reported as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The findings are summarized in the PRISMA flow chart. Two authors (MZ and MM) performed a systematic literature search using databases such as MEDLINE (via PubMed), Embase, and Cochrane library using the medical search terms and their respective entry words with the following search strategy: "Safety, mutant EGFR tyrosine kinase inhibitors, Advanced, Non-small cell, Lung cancer, Adverse effect and Literature". Additionally, unpublished trials were identified from the clinicaltrials.gov website and references of all pertinent articles were also scrutinized to ensure the inclusion of all relevant studies. The search was completed on June 1st, 2021 and we only included studies available in English. Two authors (MM and MZ) independently screened the search results in a two-step process based on predetermined inclusion/exclusion criteria. First 890 articles were evaluated for relevance on title and abstract level, followed by full-text screening of the final list of 140 articles. Any disagreements were resolved by discussion or third-party review and a total of nine articles were included in the study. The following eligibility criteria were used: original articles reporting adverse effects of mutant EGFR tyrosine kinase inhibitors in patients with advanced non-small cell lung carcinoma as compared to control groups receiving platinum-based chemotherapy. All articles with subjective data on the adverse effects of mutant EGFR tyrosine kinase inhibitors in patients with advanced non-small cell lung carcinoma as compared to control groups receiving platinum-based chemotherapy were included in the analysis. Only nine articles qualified the aforementioned selection criteria for eligibility. All qualifying studies were nationwide inpatient or pooled clinical trials data. The reasons for exclusion of other 71 articles were: irrelevant (n = 31), duplicate (n = 13), reviews (n = 14) and poor data reporting (n = 12). Out of the nine included studies, nine studies showed correlation of adverse effects including rash, diarrhea, nausea, and fatigue. Seven studies showed correlation of adverse effects including neutropenia, anorexia, and vomiting. Six studies showed correlation of anemia, cough, and stomatitis. Five studies showed correlation of elevated aspartate aminotransferase, alanine aminotransferase and leucopenia. Four studies showed correlation of fever in between mutant EGFR tyrosine kinase inhibitors and platinum-based chemotherapy.

The primary endpoint was adverse effects including rash, diarrhea, elevated alanine aminotransferase, elevated aspartate aminotransferase, stomatitis, nausea, leucopenia, fatigue, neutropenia, anorexia, anemia, cough, vomiting and fever respectively. Data on baseline characteristics and clinical outcomes were then extracted and summary tables were created. Summary estimates of the clinical endpoints were then calculated with risk ratio (RR) and 95% confidence intervals using the random-effects model. Heterogeneity between studies was examined with the Cochran's Q based I² statistic which can be defined as low (25% to 50%), moderate (50% to 75%), or high (>75%). Statistical analysis was performed using Comprehensive Meta-analysis software (CMA version 3.0, Biostat Inc).

Results

A total of 9 studies including 3415 patients (1775 in EGFR inhibitor-treatment group while 1640 patients in platinum-based chemotherapy-control group) were included in the study. All nine studies included were phase III randomized control clinical trials conducted to compare the safety profile of mutant EGFR tyrosine kinase inhibitors in patients with advanced non-small cell lung carcinoma. Mean age was 61 years in both treatment and control groups. Further details on study and participant characteristics and safety profile including adverse effects are summarized in Tables 1, 2A and 2B respectively. No evidence of publication bias was found (Prisma flow chart).

45.8% of patients in treatment group receiving mutant EGFR tyrosine kinase inhibitors developed rash as compared to only 5.6% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 7.38 with the confidence interval of 95% was noted which was statistically

significant confirming higher rash event rates in patients receiving EGFR inhibitors for their advanced non-small cell lung carcinoma (Table 2A, Figure -1).

33.6% of patients in mutant EGFR tyrosine kinase inhibitors treatment group developed diarrhea as compared to 13.5% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 2.63 with the confidence interval of 95% was noted which was statistically significant confirming higher diarrheal rates in patients receiving EGFR inhibitors for their advanced non-small cell lung carcinoma (Table 2A, Figure 2).

27.9% of patients in treatment group receiving mutant EGFR tyrosine kinase inhibitors developed elevated alanine aminotransferase as compared to 15.1% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 1.37 with the confidence interval of 95% was noted which was statistically significant confirming higher alanine aminotransferase levels in patients receiving EGFR inhibitors for their advanced non-small cell lung carcinoma (Table 2A, Figure 3).

40.7% of patients in mutant EGFR tyrosine kinase inhibitors treatment group developed elevated aspartate aminotransferase as compared to 12.8% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 1.77 with the confidence interval of 95% was noted which was statistically significant confirming elevated aspartate aminotransferase levels in patients receiving EGFR inhibitors for their advanced non-small cell lung carcinoma (Table 2A, Figure 4).

17.2% of patients in treatment group receiving mutant EGFR tyrosine kinase inhibitors developed stomatitis as compared to 7.9% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 1.53 with the confidence interval of 95% was noted which was statistically significant confirming higher stomatitis event rates in patients receiving EGFR inhibitors for their advanced non-small cell lung carcinoma (Table 2A, Figure 5).

16.5% of patients in mutant EGFR tyrosine kinase inhibitors group developed nausea as compared to 42.5% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 0.37 with the confidence interval of 95% was noted which was statistically significant confirming higher nausea rates in patients receiving platinum-based chemotherapy as compared to treatment group for their advanced non-small cell lung carcinoma (Table 2A, Figure 6).

9.7% of patients in mutant EGFR tyrosine kinase inhibitors group developed leucopenia as compared to 51.3% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 0.18 with the confidence interval of 95% was noted which was statistically significant confirming higher leucopenia incidence in patients receiving platinum-based chemotherapy as compared to treatment group for their advanced non-small cell lung carcinoma (Table 2A, Figure 7).

17% of patients in mutant EGFR tyrosine kinase inhibitors group developed fatigue as compared to 29.5% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 0.59 with the confidence interval of 95% was noted which was statistically significant confirming higher fatigue rates in patients receiving platinum-based chemotherapy as compared to treatment group for their advanced non-small cell lung carcinoma (Table 2B, Figure 8).

6.1% of patients in mutant EGFR tyrosine kinase inhibitors group developed neutropenia as compared to 48.2% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 0.11 with the confidence interval of 95% was noted which was statistically significant confirming higher neutropenia rates in patients receiving platinum-based chemotherapy as compared to treatment group for their advanced non-small cell lung carcinoma (Table 2B, Figure 9).

21.3% of patients in mutant EGFR tyrosine kinase inhibitors group developed anorexia as compared to 31.4% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 0.44 with the confidence interval of 95% was noted which was statistically significant confirming higher anorexia rates in patients receiving platinum-based chemotherapy as compared to treatment group for their advanced non-small cell lung carcinoma (Table 2B, Figure 10).

8.7% of patients in mutant EGFR tyrosine kinase inhibitors group developed anemia as compared to 32.1% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 0.24 with the confidence interval of 95% was noted which was statistically significant confirming higher anemia rates in patients receiving platinum-based chemotherapy as compared to treatment group for their advanced non-small cell lung carcinoma (Table 2B, Figure 11).

17.8% of patients in mutant EGFR tyrosine kinase inhibitors group developed cough as compared to 18.9% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 0.99 with the confidence interval of 95% was noted which was statistically significant confirming slightly higher cough rates in patients receiving platinum-based chemotherapy as compared to treatment group for their advanced non-small cell lung carcinoma (Table 2B, Figure 12).

11% of patients in mutant EGFR tyrosine kinase inhibitors group developed vomiting as compared to 30.1% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 0.35 with the confidence interval of 95% was noted which was statistically significant confirming higher vomiting rates in patients receiving platinum-based chemotherapy as compared to treatment group for their advanced non-small cell lung carcinoma (Table 2B, Figure 13).

5.6% of patients in mutant EGFR tyrosine kinase inhibitors group developed fever as compared to 30.1% of patients in control group receiving platinum-based chemotherapy. Overall risk ratio of 0.41 with the confidence interval of 95% was noted which was statistically significant confirming higher fever rates in patients receiving platinum-based chemotherapy as compared to treatment group for their advanced non-small cell lung carcinoma (Table 2B, Figure 14).

Discussion

Despite the advancement in the treatment of metastatic non-small cell lung cancer. Lung cancer stays as most common cause of cancer related death in North America and European Countries, as patients usually have an advanced disease at the time of diagnosis [3]. In the past, platinum-based chemotherapy remained the standard of care for most patients affected with advanced non-small cell lung cancer (NSCLC) but the higher recurrence rate and increase in frequency and intensity of adverse effects with platinum-based chemotherapy led to the development of targeted therapy for NSCLC, one of which includes mutant EGFR tyrosine kinase inhibitors including Erlotinib, gefitinib, dacomitinib, lapatinib and Osimertinib respectively [4].

Smoking is the most common reversible risk factor associated with lung cancer. EURTAC trial was the first perspective study in this regard which compared safety and efficacy of mutant EGFR tyrosine kinase inhibitors with platinum-based chemotherapy. Results analyzed in this study were in the favor of mutant EGFR tyrosine kinase inhibitors except in the group of former smokers [5]. In contrary, OPTIMAL trial showed results in the favor of mutant EGFR tyrosine kinase inhibitors both in active and former smokers, OPTIMAL trial confirmed the efficacy of mutant EGFR tyrosine kinase inhibitors in European and Asian populations confirming the rationale for routine testing of EGFR mutation in all patients being diagnosed with advanced non-small cell lung carcinoma [6]. Similarly, Osimertinib is one of the most recent mutant EGFR tyrosine kinase inhibitors developed for the treatment of advanced non-small cell lung cancer in patients with EGFR positive receptors. According to FLAURA trial, patients receiving Osimertinib showed significantly longer progression-free survival as compared to platinum-based chemotherapy and ancient mutant EGFR tyrosine kinase inhibitors. Median progression free survival was noted to be 18.9 months which showed 54% lower risk of disease progression in the treatment group receiving Osimertinib [7]. ARCHER study emphasized on significant improvement in overall survival as well as on progression free survival among patient population receiving Dacomitinib as compared to platinum-based chemotherapy [8,9].

Being a potent-targeted-therapy, mutant EGFR tyrosine kinase inhibitors does come with some adverse effects including diarrhea which was seen in 33.6% of the patients receiving mutant EGFR tyrosine kinase inhibitors in our study as compared to 53% in chemotherapy group as was observed in the study conducted by Pless et al [10]. Similarly, only 16.5% of patients receiving mutant EGFR tyrosine kinase inhibitors developed nausea as compared to 66% being observed in patients receiving chemotherapy, likewise only a small fraction of patients up to 9.7% receiving mutant EGFR tyrosine kinase inhibitors developed leucopenia which was ten times less reported in mutant EGFR tyrosine kinase inhibitors as compared to patients receiving chemotherapy having a percentage of 100%. Similar trend was reported for neutropenia and anemia in mutant EGFR tyrosine kinase inhibitors with an incidence of 6.1% and 8.7% as compared to platinum-based chemotherapy group having incidence of 80% and 100%. It was concluded that platinum-based chemotherapy had played a vital role in the treatment of advanced non-small cell lung cancer but at an expense of serious and severe adverse effects which had led to discontinuation or withdrawal of treatment, ultimately leading to relapse and recurrence of lung cancer [10,11].

Zhong et al conducted a phase II randomized clinical trial comparing mutant EGFR tyrosine kinase inhibitors with platinum-based chemotherapy. They concluded that in patients receiving platinum-based chemotherapy incidence of rash, vomiting, anorexia, neutropenia, and nausea were 29.4%, 47%, 41.2%, 55.8% and 32.4% as compared to 45.8%, 11%, 21.3%, 6.1%, and 16.5% reported in patients receiving mutant EGFR tyrosine kinase inhibitors for their advanced non-small cell lung cancer [12].

Another study was conducted in 2019 by Noronha et al to determine the impact of platinum-based chemotherapy when combined with gefitinib on patients with advanced non-small cell lung cancer. They concluded that 70% of patients receiving the combination treatment developed rash which was significantly higher as compared to 45.8% patient receiving mutant EGFR tyrosine kinase inhibitors alone in our study. Also, 56% of patient receiving combination therapy developed diarrhea as compared to 33.6% of patients receiving mutant EGFR tyrosine kinase inhibitors as was observed in our study. Similarly, 96% of patient in combination therapy group develop some degree of anemia as compared to only 8.7% patients in mutant EGFR tyrosine kinase inhibitors included in our study. Likewise, neutropenia was observed in 55% of patients receiving combination therapy as compared to 6.1% in patient receiving mutant EGFR tyrosine kinase inhibitors included in our study. They concluded that mutant EGFR tyrosine kinase inhibitors when combined with platinum-based chemotherapy increase the incidence of adverse effects of chemotherapy by many folds [13,14].

Kato and colleagues conducted a study to determine the impact on adverse effects when erlotinib was combined with anti-VEGF inhibitors like bevacizumab, they stated that 98.7% of patient in combination therapy developed rash, incidence of which was 45.8% in patient receiving mutant EGFR tyrosine kinase inhibitors as was observed in our study, Similar kind of trend was noticed with other adverse effects including diarrhea, fatigue, nausea, and elevated liver enzymes respectively [15].

With the latest advancements in the management of advanced non-small cell lung cancer, Nivolumab a programmed death 1 (PD-L1) inhibitors were developed which was either used as monotherapy in patients with PD-L1 expression or was combined with platinum-based chemotherapy regardless

of PDL-1 expression [16,17]. Patient expressing lower level of PD-L1 levels weren't omitted from receiving nivolumab as no significant difference was noted in progression free span and overall survival in patients receiving nivolumab irrespective of PD-L1 levels [15]. 17% of the patients developed rash after receiving nivolumab as compared to 45.8% patients being observed in our study, Similar trend was observed with diarrhea as only 17% of the population receiving nivolumab developed diarrhea as compared to 33.6% of population receiving mutant EGFR tyrosine kinase inhibitors in our study. Likewise, only 9.9% of the patient receiving nivolumab developed nausea as an adverse effect as compared 16.5% being observed in mutant EGFR tyrosine kinase inhibitors in our study. Also, fatigue was observed in 14.4% of population receiving nivolumab as compared to 17% observed in patients receiving mutant EGFR tyrosine kinase inhibitors as was noticed in our study [7,8]. Rizvi et al conducted a study on role of nivolumab when combined with platinum-based chemotherapy in patient with advanced non-small cell lung cancer and reported that 40% of patients included in the study developed rash as compared to 45.8% reported in mutant EGFR tyrosine kinase inhibitors being studied in our study. Similarly, only 13% of patient in nivolumab group developed diarrhea as compared to 33.6% cases reported in mutant EGFR tyrosine kinase inhibitors group included in our study. Also, 7% of patient in nivolumab group developed elevated alanine aminotransferase as compared to 27.9% of patients receiving mutant EGFR tyrosine kinase inhibitors included in our study concluding that addition of immune-check point inhibitors like nivolumab to platinum-based chemotherapy doesn't increase the frequency of adverse effects [18].

Conclusion

Our study focused on the safety profile of mutant EGFR tyrosine kinase inhibitors as compared to platinum-based chemotherapy in the treatment of advanced non-small cell lung cancer. mutant EGFR tyrosine kinase inhibitors are safer as compared to platinum-based chemotherapy when compared for nausea, leucopenia, fatigue, neutropenia, anorexia, anemia, cough, vomiting and fever. On the other end, mutant EGFR tyrosine kinase inhibitors causes slightly higher adverse effects including rash, diarrhea, elevated aspartate aminotransferase, elevated alanine aminotransferase and stomatitis but considering that, development of mutant EGFR tyrosine kinase inhibitors laid a foundation of targeted therapy, we recommend continuing using mutant EGFR tyrosine kinase inhibitors in patient with advanced non-small cell lung cancer especially in patient having mutant EGFR tyrosine kinase inhibitors. Adverse effects caused by mutant EGFR tyrosine kinase inhibitors are significant but are usually tolerable and can be avoided by reducing the dosage of it with each cycle or by skipping or delaying the dose till patient is symptomatic.

Declarations

Conflict of Interest:

There were no financial or non-financial conflicts noticed or witnessed among all the authors of the manuscript part of the submitted project.

Disclosure and Declaration Statement:

There were no human and animal subjects included in the study

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Tables

Table 1: Study characteristics including in our meta-analysis.

Study	Trial Name	Publication year	Design	Country	Treatment group	Control group
Zhong et al	ADJUVANT/CTONG1104 trial	2018	Phase 3 Randomized control trial	China	EGFR inhibitors	Platinum based chemotherapy
Wu et al	LUX LUNG 6 trial	2018	Phase 3 randomized control trial	China	EGFR inhibitors	Platinum based chemotherapy
Shi et al	CONVINCE trial	2017	Phase 3 randomized control trial	USA China Middle East	EGFR inhibitors	Platinum based chemotherapy
Soria et al	Impress trial	2015	Phase 3 randomized control trial	Europe and the Asia-Pacific region	EGFR inhibitors	Platinum based chemotherapy
Goss et al	NCIC CTG BR19 trial	2013	Phase 3 randomized control trial	USA Asia pacific Europe	EGFR inhibitors	Platinum based chemotherapy
Mu Sun et al	KCSG-LU08-01 trial	2012	Phase 3 randomized control trial	USA Asia pacific Europe	EGFR inhibitors	Platinum based chemotherapy
Mitsudomi et al	WJTOG3405 trial	2011	Phase 3 randomized control trial	Japan	EGFR inhibitors	Platinum based chemotherapy
Lee et al	Istana trial	2010	Phase 3 randomized control trial	USA Middle East Australia	EGFR inhibitors	Platinum based chemotherapy
Kim et al	Interest trial	2008	Phase 3 randomized control trial	Japan	EGFR inhibitors	Platinum based chemotherapy

TABLE 2A: Adverse effects included in our meta-analysis:

Study/Trial name	Treatment/ Control group	Rash	Diarrhea	Elevated ALT	Elevated AST	Stomatitis	Nausea	Leucopenia
Zhong et al/ ADJUVANT/CTONG1104 trial	Treatment group	43(40.6%)	28(26.4%)	29(27.4%)	12(11.3%)	8(7.5%)	3(2.8%)	4(3.7%)
	Control group	0(0%)	4(4.6%)	3(3.5%)	1(1.2%)	5(5.7%)	38(43.7%)	41(47%)
Wu et al/ LUX LUNG 6 trial	Treatment group	144(82.3%)	153(87.4%)	39(22.3%)	32(18.3%)	88(50.3%)	11(6.3%)	5(2.8%)
	Control group	9(9.5%)	10(10.5%)	16(17%)	10(10.5%)	5(5.3%)	72(75.8%)	53(55.8%)
Shi et al/CONVINCE trial	Treatment group	22(15%)	11(7.4%)	10(6.7%)	12(81%)	-	4(2.7%)	11(7.4%)
	Control group	2(1.5%)	6(4.3%)	19(13.9%)	15(11%)	-	63(46%)	60(43.8%)
Soria et al/ Impress trial	Treatment group	14(11%)	44(33.3%)	17(12.9%)	30(22.7%)	14(10.6%)	85(64.4%)	27(20.5%)
	Control group	11(8%)	19(14.9%)	23(17%)	29(22%)	5(3.7%)	81(61.4%)	22(16.7%)
Goss et al/ NCIC CTG BR19 trial	Treatment group	21(8.5%)	18(7.2%)	-	-	-	6(2.4%)	-
	Control group	1(0.5%)	5(2%)	-	-	-	1(0.4%)	-
Mu Sen et al/ KCSG-LU08-01 trial	Treatment group	31(46%)	18(26%)	-	-	-	11(16.2%)	-
	Control group	3(4.5%)	3(4.4%)	-	-	-	11(16.4%)	-
Mitsudomi et al/ WJTOG3405 trial	Treatment group	74(85%)	47(54%)	61(70%)	61(70%)	19(21.8%)	15(17.2%)	13(14.9%)
	Control group	7(8%)	35(40%)	35(40%)	17(19.3%)	13(14.7%)	83(94%)	82(93.2%)
Lee et al/Istana trial	Treatment group	61(75%)	21(26%)	-	-	3(3.7%)	13(16%)	-
	Control group	6(8%)	12(15.7%)	-	-	9(1.8%)	14(18.4%)	-
Kim et al/Interest trial	Treatment group	360(49%)	255(35%)	-	-	67(9.2%)	148(20.3%)	-
	Control group	73(10.3%)	177(24.7%)	-	-	93(13%)	187(26.2%)	-

TABLE 2B: Adverse effects included in our meta-analysis:

Figures

Study/Trial name	Treatment/ Control group	Fatigue	Neutropenia	Anorexia	Anemia	Cough	Vomiting	Fever
Zhong et al/ ADJUVANT/CTONG1104 trial	Treatment group	4(3.7%)	3(2.9%)	2(1.8%)	2(1.8%)	11(10.4%)	5(4.7%)	1(0.9%)
	Control group	4(4.6%)	46(52.9%)	20(23%)	44(50.6%)	15(17.2%)	36(41.4%)	9(10.3%)
Wu et al/ LUX LUNG 6 trial	Treatment group	14(8%)	3(1.7%)	11(6.3%)	9(5.2%)	-	14(8%)	-
	Control group	37(39%)	53(55.8%)	39(41%)	26(27.4%)	-	75(78.9%)	-
Shi et al/CONVINCE trial	Treatment group	5(3.4%)	5(3.4%)	3(2%)	4(2.7%)	2(1.4%)	2(1.4%)	0(0%)
	Control group	20(14.6%)	58(42.3%)	32(23.4%)	17(12.4%)	3(2.2%)	40(29.2%)	4(2.9%)
Soria et al/ Impress trial	Treatment group	28(21.2%)	29(22%)	65(49.2%)	0(0%)	18(13.6%)	55(41.6%)	22(16.7%)
	Control group	23(17.4%)	28(21.2%)	45(34.1%)	1(0.7%)	15(11.4%)	44(33.3%)	14(10.6%)
Goss et al/ NCIC CTG BR19 trial	Treatment group	15(6%)	-	-	-	-	3(1.2%)	-
	Control group	6(2.5%)	-	-	-	-	0(0%)	-
Mu Sen et al/ KCSG-LU08-01 trial	Treatment group	15(22.1%)	0(0%)	22(32.4%)	-	25(36.7%)	-	-
	Control group	14(21%)	1(1.5%)	20(29.8%)	-	24(35.8%)	-	-
Mitsudomi et al/ WJTOG3405 trial	Treatment group	34(39.1%)	7(8.1%)	-	33(37.9%)	-	-	-
	Control group	73(82.9%)	81(92%)	-	79(89.7%)	-	-	-
Lee et al/Istana trial	Treatment group	20(24.7%)	-	29(35.8%)	-	25(30.8%)	4(4.9%)	4(4.9%)
	Control group	28(36.9%)	-	36(47.4%)	-	25(32.9%)	8(10.5%)	8(10.5%)
Kim et al/Interest trial	Treatment group	182(25%)	35(4.8%)	159(21.8%)	34(4.7%)	108(14.8%)	109(15%)	-
	Control group	334(46.7%)	514(72%)	151(21.2%)	84(11.7%)	102(14.3%)	123(17.2%)	-

Figure 1

The risk ratio above 1 indicates higher rash event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 2

The risk ratio above 1 indicates higher Diarrhea event rates in the EGFR inhibitor group compared to the Chemotherapy group

Figure 3

The risk ratio above 1 indicates higher elevated ALT event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 4

The risk ratio above 1 indicates higher elevated AST event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 5

The risk ratio above 1 indicates higher stomatitis event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 6

The risk ratio above 1 indicates higher nausea event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 7

The risk ratio above 1 indicates higher leucopenia event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 8

The risk ratio above 1 indicates higher fatigue event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 9

The risk ratio above 1 indicates higher neutropenia event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 10

The risk ratio above 1 indicates higher anorexia event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 11

The risk ratio above 1 indicates higher anemia event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 12

The risk ratio above 1 indicates higher cough event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 13

The risk ratio above 1 indicates higher vomiting event rates in the EGFR inhibitor group compared to the Chemotherapy group.

Figure 14

The risk ratio above 1 indicates higher fever event rates in the EGFR inhibitor group compared to the Chemotherapy group.