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TOPIC HIGHLIGHT

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Erlotinib usage after prior treatment with gefitinib in advanced non-small cell lung cancer: A clinical perspective and review of published literature

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Abstract

Erlotinib and gefitinib are among the most widely researched, used and available molecularly targeted therapies for treatment of advanced non-small cell lung cancer (NSCLC). They are both tyrosine kinase inhibitors (TKIs) of the epidermal growth factor receptor (EGFR). In the past decade, there have been reports on clinical benefit from use of erlotinib after gefitinib failure in NSCLC patients. A review of published literature on this focussed topic is provided herein. Pooled analysis of published literature shows that majority of patients were female (60.6%), non-smokers (64.5%), had adenocarcinoma histology (88.3%) and were of East Asian ethnicity (92.3%). Presence of sensitizing EGFR mutation was detected in 48.4% of subjects. Disease control rates with prior gefitinib therapy and with subsequent erlotinib treatment were 79.4% and 45.4% respectively. Based upon our review, the most important predictive factor for clinical benefit from erlotinib identified was previous response to gefitinib. The exact explanations for the potential benefit from erlotinib use in this patient population is still not known and further studies are required to determine the role of molecular mechanisms especially those related to resistance to initial EGFR TKI therapy.

Key words: Gefitinib; Erlotinib; Non-small cell lung cancer; Epidermal growth factor receptor; Tyrosine kinase inhibitor

Core tip: This manuscript is focused on the controversial yet interesting topic of whether erlotinib provides clinical benefit amongst patients who have experienced disease progression after prior therapy with gefitinib-both drugs being tyrosine kinase inhibitors of the epidermal growth factor receptor. We have reviewed available literature on this topic, carried out a pooled analysis on available data and hope readers find it useful in clearing the confusion related to this topic.

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INTRODUCTION

Lung cancer remains among the most commonly occurring cancers in the world with majority of the cases being of non-small cell lung cancer (NSCLC)[1,2]. As in other malignancies, molecularly targeted therapies are being increasingly researched and approved for clinical use in case of NSCLC especially adenocarcinoma. Among the molecularly targeted therapies available for advanced

NSCLC, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) occupy a central place and form part of the standard treatment algorithms[3]. Gefitinib, erlotinib and recently afatinib are the available, orally active agents in this group. Gefitinib was approved for use after two randomised trials-the Iressa Dose Evaluation in Advanced Lung Cancer 1 and 2 (IDEAL 1 and 2) studies-showed survival benefit as compared to placebo amongst patients with advanced NSCLC who had progressed after initial platinum based chemotherapy[4,5]. However, based on a subsequent trial, *i.e.*, the Iressa Survival Evaluation in Lung Cancer study, which did not show an improvement in overall survival (OS), the use of gefitinib was disallowed in the United States by the Federal Drugs Authority (FDA)[6]. Erlotinib was demonstrated to have efficacy in advanced NSCLC in the BR.21 trial. This was a randomised, double blind, placebo controlled trial in which the administration of erlotinib to patients with advanced NSCLC who had received prior chemotherapy led to an improvement in response rates (RR), progression free survival (PFS) and OS with an acceptable toxicity profile[7]. Subsequently, erlotinib was approved by the FDA for use in advanced NSCLC. In all of the above studies, the clinical benefit and treatment response was more evident in certain subgroups namely female gender, non-smoker status, Asian ethnicity and adenocarcinoma. Subsequently, these subgroups were proven to have a higher incidence of sensitizing EGFR mutations which till date remains the most important predictive factor for clinical benefit with EGFR TKIs[8].

Almost a decade ago, there was an initial report on the use of erlotinib after gefitinib failure in patients of non-small cell lung cancer[9]. Following this, several case reports, case series, retrospective reviews and even a few prospective trials have been published related to use of erlotinib in patients who had received prior therapy with gefitinib. This is surprising, considering that the mechanism of action of both drugs is similar. No satisfactory explanation has been found till date, though many have been postulated. In the current article, we have reviewed published literature on this focused area and carried out a pooled analysis with the data available.

MECHANISM OF ACTION OF TKIS

EGFR is a transmembrane protein which functions as the receptor for the epidermal growth factor (EGF) pathway[8]. The EGFR protein consists of three domains: an extra-cellular binding site for the EGF molecule, a transmembrane unit which spans the cell membrane and an intracellular unit which has tyrosine kinase activity. The binding of EGF causes conformational changes in the receptor which further leads to phosphorylation/dephosphorylation of the intracellular tyrosine kinase domain and subsequent downstream signalling. Mutations in the EGFR lead to a constitutive activation of the EGF pathway and subsequent activation of cell survival pathways[10].

The mutations underlying the activation of this pathway were elucidated in the earlier part of the last decade[11-13]. Based on the experience with imatinib in chronic myeloid leukaemia, inhibitors of the EGFR tyrosine kinase pathway were developed. The first of these was gefitinib, which acts by interfering with the tyrosine kinase activity of the intracellular domain of the EGFR. It was followed by erlotinib, which has a somewhat similar mechanism of action. These function as adenosine triphosphate (ATP) mimetic molecules and bind to the intracellular domain of the EGFR and block receptor phosphorylation and subsequent downstream signalling and activation of dependent pathways[14].

LITERATURE REVIEW

We carried out a PubMed search for all published literature in the English language on this topic till 2013. Multiple case reports, retrospective reviews and prospective studies were identified that have been listed in Table 1. The studies included in this review used standard treatment protocols for gefitinib and erlotinib, *i.e.,* 250 mg/d and 150 mg/d respectively. Tumour response was assessed according to the Response Evaluation Criteria in Solid Tumours[15]. The outcome measures reported in the studies included: RR, defined as combination of complete response (CR) and partial response (PR); Disease control rate (DCR), defined as the combination of CR, PR and stable disease (SD); PFS, defined as the period from the start of treatment to the date when disease progression or death was observed and OS, defined as the period from the start of treatment to the date of death (Tables 2 and 3).

Use of erlotinib after gefitinib failure was first reported in 2005[9]. Subsequently, sporadic case reports were published which demonstrated similar findings[16-18]. A prospective phase II study evaluated the use of erlotinib in patients of NSCLC who had been treated with chemotherapy followed by gefitinib and then had failure on gefitinib. A total of 21 patients were included in this study. Out of these 21 patients, who had progressed on gefitinib, 2 patients achieved PR and 4 patients SD while the remaining 15 patients had progressive disease (PD). The DCR was 28.6% (95%CI: 9.3% to 47.9%) while the median PFS and OS were 60 d (95%CI: 43 to 77 d) and 158 d (95%CI: 141 to 175 d), respectively. An interesting point noted was that the only predictor of a response to erlotinib was the presence of a prior response to gefitinib. Surprisingly, the presence of EGFR mutations was not associated with a response to erlotinib. In fact, 4 out of 6 responders to erlotinib did not have the EGFR mutation[19].

A retrospective study analysed 14 patients who had received erlotinib after failure of gefitinib over a two year period. The initial DCR for gefitinib was 64.3% (9 of 14), while it was 35.7% (5 of 14) for erlotinib. Predictors for good clinical response to erlotinib included never smoker status, adenocarcinoma subtype, good response to initial

Table 1 Baseline characteristics of subjects in studies evaluating response to erlotinib after gefitinib

Ref.	Year	Country	Type of study	No. of patients	Gender (M/F)	Smoking status (smokers/NS)	Histology (A/S/other)
Garfield[9]	2005	United States	Case report	1	1/0	1/0	0/0/1
Viswanathan *et al*[16]	2005	United States	Case report	5	1/4	2/3	NA
Walther *et al*[17]	2006	United Kingdom	Case report	1	0/1	0/1	1/0/0
Chang *et al*[18]	2007	Taiwan	Case report	1	1/0	1/0	1/0/0
Cho *et al*[19]	2007	South Korea	Prospective	21	10/11	10/11	16/3/2
Gridelli *et al*[32]	2007	Italy	Case report	3	0/3	0/3	3/0/0
Kim *et al*[33]	2007	South Korea	Case report	1	0/1	0/1	1/0/0
Costa *et al*[23]	2008	United States	Retrospective	18	7/11	7/11	16/0/2
Lee *et al*[21]	2008	South Korea	Prospective	23	4/19	0/23	22/0/1
Vasile *et al*[22]	2008	Italy	Prospective	8	4/4	1/7	6/0/2
Wong *et al*[20]	2008	Singapore	Retrospective	14	4/10	1/13	10/1/3
Wong *et al*[34]	2008	Singapore	Case report	1	0/1	0/1	1/0/0
Wu *et al*[35]	2008	Taiwan	Case report	1	0/1	0/1	1/0/0
Katayama *et al*[36]	2009	Japan	Retrospective	7	2/5	NA	7/0/0
Sim *et al*[24]	2009	South Korea	Retrospective	16	0/16	0/16	16/0/0
Zhou *et al*[25]	2009	China	Prospective	21	14/7	10/11	8/9/4
Wong *et al*[26]	2010	China	Retrospective	21	2/19	1/20	19/0/2
Asami *et al*[27]	2011	Japan	Retrospective	42	13/29	14/28	42/0/0
Hata *et al*[29]	2011	Japan	Retrospective	125	49/76	55/70	117/NA/8
Masuda *et al*[37]	2011	Japan	Case report	3	3/0	NA	3/0/0
Shoji *et al*[38]	2011	Japan	Case report	1	1/0	NA	1/0/0
Song *et al*[39]	2011	China	Retrospective	20	9/11	5/15	18/0/2
Takenaka *et al*[40]	2011	Japan	Case report	1	0/1	0/1	1/0/0
Saito *et al*[41]	2012	Japan	Retrospective	21	9/12	9/12	19/0/2
Tetsumoto *et al*[42]	2012	Japan	Case report	2	0/2	0/2	2/0/0
Koyama *et al*[43]	2013	Japan	Retrospective	104[1]	56/48	50/54	90/6/8

[1]Of the 104 patients, only 54 had prior treatment with gefitinib. A: Adenocarcinoma; S: Squamous cell carcinoma; M: Male; F: Female; NA: Not available; smokers: Includes current and ex smokers; NS: Non-smokers.

gefitinib and presence of EGFR mutations[20].

23 patients of metastatic or advanced NSCLC who had documented progression on gefitinib were studied in an open label, single institution, phase II study. All patients were never smokers and 22 out of the 23 patients were of the adenocarcinoma subtype. The initial DCR on gefitinib was 65.3% (15 out of 23). 2 patients responded to erlotinib, giving a DCR of 8.7% and a RR of 4.3%, while the rest 21 patients developed PD within 3 mo[21].

Another study included 4 males and 4 females in their study, with a mean age of 70 years. All of these patients had received chemotherapy at least twice, followed by gefitinib. 4 patients had achieved PR with gefitinib and 4 patients SD, and the median PFS was 17 mo. Two (25%) patients achieved PR and 3 (37.5%) patients SD, while 3 developed PD. The median PFS and OS were 5.9 and 14.6 mo, respectively with erlotinib. The authors observed that patients who had a longer PFS on initial gefitinib therapy had better disease control with erlotinib[22].

Another retrospective study published in 2008 included 18 patients. These patients had received primary chemotherapy and had subsequently been given gefitinib. The initial response to gefitinib included 14 patients with either CR or PR, 2 patients with SD and 2 with PD. After treatment with erlotinib, 14 out of the 18 patients developed PD, while 3 patients had SD and only 1 PR. The median PFS was 2 mo and no patient had a PFS over 6 mo[23].

The utility of established predictive factors for response to EGFR TKIs namely female sex, adenocarcinoma subtype, Asian ethnicity and never smoking status, were also assessed for their predictive value in the context of erlotinib use following progression on initial gefitinib therapy. They included 14 patients and noted a DCR of 68.8% (95%CI: 0.44-0.86) on initial gefitinib treatment and a rate of 25.0% (95%CI: 0.10-0.50) after treatment with erlotinib. The median PFS was 6.3 mo for gefitinib and 1.7 mo for erlotinib. The above mentioned factors were found to be unreliable for predicting response to erlotinib after treatment failure with gefitinib[24].

A more heterogeneous population of 10 (47.6%) smokers, 9 (42.9%) patients with squamous cell carcinoma, 8 (38.1%) with adenocarcinoma and 4 (19%) with other NSCLC subtypes, totalling 21 were included in another trial. All of them had progressed on gefitinib therapy after chemotherapy. 6 of the 21 patients responded, with 2 (9.5%) showing PR and 4 (19.0%) showing SD, giving an overall RR of 9.5% and a DCR of 28.5%. The median PFS was 55 d and the median OS was 135 d. All of these 6 patients had also had disease control with prior gefitinib therapy, either PR or SD[25].

All of the previously mentioned trials included patients who had received chemotherapy prior to initial gefitinib therapy. A retrospective review of 21 patients who had received gefitinib as first line therapy instead of chemotherapy was conducted. The patient population was selected based on clinical characteristics *i.e.*, never smokers, females, Asian ethnicity and adenocarcinoma

Table 2 Prevalence of epidermal growth factor receptor mutations and comparison of responses to gefitinib and erlotinib *n* (%)

Ref.	No. of patients	EGFR mutations no	E19 Del/E21 L858R	Response to prior gefitinib				Response to erlotinib			
				CR	PR	SD	PD	CR	PR	SD	PD
Garfield[9]	1	NA	NA				1(100)		1(100)		
Viswanathan *et al*[16]	5	NA	NA		4(80.0)		1(20.0)				5(100)
Walther *et al*[17]	1	NA	NA				1(100)		1(100)		
Chang *et al*[18]	1	1 (100)	1/0		1(100)				1(100)		
Cho *et al*[19]	21	5 (23.8)	5/0		6(28.6)	4(19.0)	11(52.4)		2(9.5)	4(19.0)	15(71.5)
Gridelli *et al*[32]	3	NA	NA			3(100)			1(33.3)	2(66.7)	
Kim *et al*[33]	1	NA	NA		1(100)				1(100)		
Costa *et al*[23]	18[1]	17 (94.4)	4/13		11(84.6)	2(15.4)			1(7.7)	2(15.4)	10(76.9)
Lee *et al*[21]	23	3 (13.0)	3/0		15(65.2)	2(8.7)	6(26.1)		1(4.3)	1(4.3)	21(91.4)
Vasile *et al*[22]	8	NA	NA		4(50.0)	4(50.0)			2(25.0)	3(37.5)	3(37.5)
Wong *et al*[20]	14	7 (50.0)	4/3		9(64.3)		5(35.7)			5(35.7)	9(64.3)
Wong *et al*[34]	1	1 (100)	1/0		1(100)					1(100)	
Wu *et al*[35]	1	1 (100)	0/1		1(100)					1(100)	
Katayama *et al*[36]	7	6 (85.7)	4/2	2(28.6)	2(28.6)	3(42.8)			3(42.9)	3(42.9)	1(14.3)
Sim *et al*[24]	16	5 (31.3)	2/3		9(56.3)	2(12.5)	5(31.2)		1(6.3)	3(18.7)	12(75.0)
Zhou *et al*[25]	21	7 (33.3)	NA/NA	2(9.5)		8(38.1)	11(52.4)		2(9.5)	4(19.1)	15(71.4)
Wong *et al*[26]	21	3 (14.3)	0/3		18(85.7)		3(14.3)		12(57.1)		9(42.9)
Asami *et al*[27]	42	28 (66.7)	14/14		22(52.4)	17(40.5)	3(7.1)		1(2.4)	24(57.1)	17(40.5)
Hata *et al*[29]	125[2]	63 (50.4)	NA/NA	3(2.5)	68(56.2)	22(18.2)	28(23.1)		11(8.8)	44(35.2)	70(56.0)
Masuda *et al*[37]	3	3 (100)	2/1		3(100)				3(100)		
Shoji *et al*[38]	1	0 (0)	0 (0)				1(100)		1(100)		
Song *et al*[39]	20	5 (25.0)	3/2		5(25.0)	9(45.0)	6(30.0)			7(35.0)	13(65.0)
Takenaka *et al*[40]	1	1 (100)	1/0			1(100)			1(100)		
Saito *et al*[41]	21	12 (57.1)	0/12		16(76.2)	5(23.8)			2(9)	6(19)	13(62)
Tetsumoto *et al*[42]	2	2 (100)	1/1		2(100)				2(100)		
Koyama *et al*[43]	54	44 (81.5)	22/22	4(7.4)	32(59.3)	13(24.0)	5(9.3)	0 (0)	4(7.4)	30(55.6)	20(37.0)

[1]Response to gefitinib and erlotinib was evaluable for 13 patients only; [2]Response to gefitinib was evaluable for 121 patients only. EGFR: Epidermal growth factor receptor; PR: Partial response; CR: Complete response; PD: Progressive disease; SD: Stable disease; E19: Exon 19; E21: Exon 21; Del: Deletion; NA: Not available.

Table 3 Response rates and survival rates with erlotinib following gefitinib therapy

Ref.	RR	DCR	PFS	OS
Cho *et al*[19]	9.50%	28.60%	60 d	158 d
Costa *et al*[23]			2 mo	
Lee *et al*[21]	4.30%	8.70%		
Vasile *et al*[22]	25%	62.50%	5.9 mo	14.6 mo
Wong *et al*[20]		35.70%	97 d	
Sim *et al*[24]		25%	1.7 mo	
Zhou *et al*[25]	9.50%	28.50%	55 d	135 d
Wong *et al*[26]		57.10%	14.9 wk	40 mo
Asami *et al*[27]	2.40%	59.50%	3.4 mo	7.1 mo
Hata *et al*[29]	9%	44%	2 mo	11.8 mo
Song *et al*[39]	0	35%	31 d	4.2 mo
Saito *et al*[41]		38.10%		369 d
Koyama *et al*[43]	7.40%	63.00%	135 d	333 d

RR: Response rate; DCR: Disease control rate; PFS: Progression free survival: OS: Overall survival.

subtype. Only 3 of these 21 patients had EGFR mutation status known. Disease control was achieved in 18 patients (85.7%) with first line gefitinib therapy and in 12 out of these 18 patients (66.7%) who received erlotinib as salvage therapy. The overall DCR for erlotinib was 57.1% (12 out of 21). All 3 patients who progressed on gefitinib did not respond to erlotinib[26].

In a retrospective review of 42 patients with lung adenocarcinoma receiving erlotinib with history of prior gefitinib treatment, PFS (4.7 mo *vs* 1.8 mo) and OS (9.2 mo *vs* 4.7 mo) were better in patients who had experienced prior response with gefitinib as compared to those who had not[27]. On multivariate analyses for prognostic factors for OS, only prior response to gefitinib was found to be significant but not presence of EGFR mutations. Interestingly in this cohort, 69% of patients had a sensitizing EGFR mutation (exon 19 deletion or L858R mutation exon 21).

A systematic review included 3 prospective studies, 3 retrospective studies and 7 case reports leading to a total of 106 patients. Out of these 9.9% patients had PR, 18.9% SD and 70.8% PD. The DCR was 37.5% in patients who had EGFR mutations and 21.7% in patients without EGFR mutations, which was not statistically different. The mean PFS varied from 1.7 to 5.9 mo. Analysis showed that the only factors which predicted response to erlotinib were the presence of SD on initial treatment with gefitinib and the presence of PFS to initial gefitinib for more than 6 mo[28].

In a large retrospective analysis of 125 patients all of whom had experienced disease progression following initial gefitinib therapy, the RR was 9%, DCR 44% and median PFS 2 mo with erlotinib treatment. Multivariate analysis showed that disease control was predicted by

Table 4 Pooled analysis of demographic profile, prevalence of epidermal growth factor receptor mutations and disease control rates with erlotinib following prior gefitinib therapy

Female gender : 60.6% (292 of 482)
Adenocarcinoma histology: 88.3% (421 of 477)
Non smokers: 64.5% (304 of 471)
East Asian ethnicity: 92.3% (445 of 482)
EGFR mutation positive status[1]: 48.4% (224 of 463)
Disease control rate with prior gefitinib treatment: 79.4% (336 of 423)
Disease control rate with subsequent erlotinib treatment: 45.4% (194 of 427)

[1]Indicates presence of sensitizing EGFR mutations (exon 19 deletion or exon 21 L858R mutation). EGFR: Epidermal growth factor receptor.

three factors: good performance status [Eastern Cooperative Oncology Group (ECOG) PS 0/1], EGFR mutation-positive status (or unknown) and benefit from prior gefitinib therapy. Longer PFS was predicted by insertion of cytotoxic chemotherapies between gefitinib and erlotinib therapies in addition to ECOG PS 0/1 and benefit from prior gefitinib therapy[29].

In another retrospective review published recently, 44 of the 54 patients had a sensitizing *EGFR* gene mutation (exon 19 deletion or L858R mutation exon 21) and all 54 patients had received gefitinib initially. DCR of 63% was observed with subsequent erlotinib treatment. The authors observed no significant differences in erlotinib efficacy between EGFR-mutated NSCLC who had developed gefitinib resistance as compared to another 50 patients of NSCLC with wild-type EGFR in whom gefitinib had not been given earlier. This study also showed that presence of skin rash was associated with better outcomes-an observation that has been reported by others also[30].

POOLED ANALYSIS

We also carried out pooled analysis of published literature involving patients who had received erlotinib treatment following prior gefitinib therapy. This has been summarized in Table 4. It was not possible to analyse objective RRs and SD separately since some of the publications included in this review had only provided DCRs which is the sum of objective responses (CR/PR) and SD. There are three important observations that are apparent from the pooled analysis. First, majority of the patients were of East Asian ethnicity, females, non-smokers and had adenocarcinoma histology all of which are clinical surrogates for presence of sensitizing EGFR mutations. Second, approximately one of every two subjects in the pooled population had a sensitizing EGFR mutation (exon 19 deletion or exon 21 L858R mutation). However, the true prevalence in this population database is likely to be higher than the figure of 48.4% that arose on pooled analysis because in several of the publications, results of EGFR mutation testing were either not mentioned or were performed in subgroup of patients included in the article. An indirect indicator that this was a highly enriched pooled population is the fact that approximately four of five patients had initial disease control with gefitinib. Third, despite progressing on gefitinib treatment, approximately 45% of patients achieved disease control with erlotinib. However, it was not possible to carry out analysis regarding the molecular mechanisms that led to gefitinib failure or resistance since these have not been provided in majority of the publications.

Table 5 Potential factors predicting response to erlotinib following prior gefitinib therapy

Previous response to gefitinib (most important)
Longer duration of response to prior gefitinib
Female gender
Adenocarcinoma histology
Non smokers
East Asian ethnicity
EGFR mutation positive status[1]
Good performance status
Chemotherapy cycles in between gefitinib and erlotinib

[1]Indicates presence of sensitizing EGFR mutations (exon 19 deletion or exon 21 L858R mutation). EGFR: Epidermal growth factor receptor.

RATIONALE

A satisfactory explanation as to cause of responsiveness to erlotinib after failure of gefitinib is yet to be given. However, several hypotheses have been put forward. One possibility is that gefitinib is usually given at a clinical dose of 250 mg, which is around one third of the maximum tolerated dose, about 750 mg. In contrast, the clinical dose of erlotinib is 150 mg, which is very close to the maximum tolerated dose. Therefore, the biological dose of these two drugs may not be equal. However, in the IDEAL 1 and 2 trials, higher doses of gefitinib were not associated with a better RR[4,5,19].

Another possibility invokes the presence of both EGFR TKI sensitive and resistant clones at the start of treatment with gefitinib. The administration of gefitinib leads to the selective dying out of the sensitive clones and subsequent development of resistance. When the TKI is stopped, the sensitive clones again propagate and are the reason for the response to the subsequent TKI[21]. This is borne out by case reports demonstrating that readministration of gefitinib to some patients after progression may sometimes lead to disease control similar to that achieved with erlotinib[31].

Patients who develop resistance to EGFR TKIs, acquire common mutations such as T790M secondary mutation or amplification of the MET oncogene. Other secondary mutations have also been reported. Some mutations, such as the L748S or E884K mutation, may result in differing sensitivities to the oral EGFR TKIs, resulting in different tumour responses[12,19,21].

An overview of the potential factors predicting clinical benefit with erlotinib is provided in Table 5. The most consistent predictive factor has been prior response to gefitinib. However the predictive role of presence of

EGFR mutations in this setting has not been as strong as it is for first line therapy. The clinical surrogates for presence of EGFR mutations namely, female gender, Asian ethnicity, adenocarcinoma histology and non-smoking status, are the other factors that remain associated with clinical benefit from erlotinib in this setting.

CONCLUSION

Oral EGFR TKIs are widely available drugs that are an important component of the therapeutic armamentarium against advanced NSCLC. The use of sequential EGFR TKIs, especially of erlotinib after prior treatment with gefitinib has remained a controversial area so far. Given the disease control rate of approximately 45% in the current pooled analysis, such an approach can be considered in carefully selected patients especially those in whom alternate treatment options are not being considered. The exact explanation of this response is still not known. Possible predictive factor for clinical benefit with erlotinib includes previous response to gefitinib. The predictive value of sensitizing EGFR mutations requires further evaluation and further studies are required to determine the underlying molecular mechanisms for observed clinical benefit with erlotinib in this setting.

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