The roles of epidermal growth factor receptor (EGFR) inhibitors in the management of lung cancer

Ashwaq Al Olayan [a,*,1], Hamad Al Hussaini [b,1], Abdul Rahman Jazieh [a,1]

[a] *King Abdulaziz Medical City for National Guard — King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia*
[b] *King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*

Summary   Targeting epidermal growth factor receptor (EGFR) is an important treatment option for non-small cell lung cancer (NSCLC).

These targeted therapies have been studied extensively in NSCLC in first line and subsequent lines, including maintenance in empiric fashion or in patients with tumors harboring the EGFR mutations.

In this manuscript, we will review in details the evolutions of these targeted therapy in the management of NSCLC.
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Introduction

Lung cancer, the leading cause of cancer death world wide, is classified histologically to small-cell (15%) or non-small-cell (85%). Non-small-cell lung cancer (NSCLC) is further divided into 3 subtypes based on histology: squamous-cell carcinoma, adenocarcinoma, and large-cell lung cancer.

As surgical techniques and combination treatment regimens have improved, the 1-year survival rate in lung cancer has increased slightly, from 35% in 1975—1979 to 41% in 2000—2003. Nonetheless, the 5-year survival rate for all stages of lung cancer combined remains around 15%.

The majority of patients with NSCLC are candidates for systemic treatment with chemotherapy, either as therapy for advanced disease or as adjuvant or neoadjuvant treatment with local therapy (surgery or radiation therapy) utilized in earlier stages. However, chemotherapy has only shown modest improvement in the outcome of NSCLC [1]. Chemotherapy normally yields 30% response, 4 months PFS and median survival of 8—11 months.

Therefore, new treatment approaches are needed. Targeting the epidermal growth factor receptor (EGFR) and vascular endothelial inhibitor (VGEF) has played a central role in advancing NSCLC

* Corresponding author at: Division of Adult Medical Oncology, Department of Oncology, King Abdulaziz Medical City for National Guard, Riyadh, Saudi Arabia.
Tel.: +966 01 2520088x14077/14255.
E-mail address: alolayanas@ngha.med.sa (A. Al Olayan).
[1] On behalf of the Saudi Lung Cancer Committee (see Appendix A).

research, treatment, and patient outcome over the last several years [2].

This manuscript focuses on the role of EGFR in NSCLC and current clinical data on agents targeting the EGFR pathway, and recent advances in using EGFR inhibitor in clinical practice.

EGFR role in carcinogenesis

The human genome encodes approximately 518 kinases, of which there are 90 Tyrosine kinases (TKs) and 43 tyrosine-like kinases. EGFR, — a 170-kDa (1186 amino acid) membrane-bound protein encoded by 28 exons spanning nearly 190,000 nucleotides on chromosome 7p12, is one member of the TK family, which belongs to a subfamily of four closely related receptors: HER-1/ErbB1, HER-2/*neu*/ErbB2, HER-3/ErbB3, and HER-4/ErbB4.

Structurally, EGFR receptor is composed of an extracellular ligand binding domain, a transmembrane domain, and an intracellular domain. Upon binding to ligands, such as epidermal growth factor (EGF), the receptors undergo conformational changes that facilitate intermolecular autophosphorylation which activate EGFR pathways which are important for cell survival, and the mitogen-activated protein kinase (MAPK) pathway, which induces proliferation. EGFR regulates important tumorigenic processes that include proliferation, apoptosis, angiogenesis, and invasion [3,4].

The epidermal growth factor receptor is a tyrosine kinase (TK) receptor of the ErbB family that is commonly altered in epithelial tumors. EGFR was shown to be an oncogene, capable of inducing cancer when aberrant. So using specific monoclonal antibodies against the EGFR could inhibit its activity. Since EGFR appeared to play a central role in tumorigenesis, this observation implied that targeting the receptor itself might be an effective way to treat EGFR-expressing cancers [3,4].

The first anti-EGFR drugs were developed in the 1980s. Two classes of EGFR antagonists have been successfully tested in phase 3 trials and are now in clinical use: anti-EGFR monoclonal antibodies and small-molecule EGFR tyrosine kinase inhibitors.

Cetuximab is an example of anti-EGFR monoclonal antibodies. It binds to the extracellular domain of EGFR when it is in the inactive configuration, competes for receptor binding by occluding the ligand-binding region, and thereby blocks ligand-induced EGFR tyrosine kinase activation [3,4].

Other small-molecule EGFR tyrosine kinase inhibitors, such as erlotinib and gefitinib, compete reversibly with ATP to bind to the intracellular catalytic domain of EGFR tyrosine kinase and, thus, inhibit EGFR autophosphorylation and downstream signaling [3,4].

Mutation was found in 16—39% of NSCLC. Mutation of *EGFR* mostly deletion of specific exons encoding part of the extracellular domain of the EGFR molecule, leading to constitutive receptor activation (ligand-independent), impaired receptor down regulation, activation of alternative signaling cascades, and/or abrogation of apoptotic mechanisms. Exon 19 deletion and the point mutation of L858R constitute about 90% of all EGFR mutation [5—11].

EGFR is commonly over expressed in the development and progression of lung cancer 62% of all tumors, 89% of squamous tumors, 41% of adenocarcinomas, and 80% of bronchioloalveolar tumors.

The somatic mutations are observed with increased frequency in women and in nonsmokers. As identified from previous trials 3, nonsmoker, Asian, adenocarcinoma and female gender were associated independently and collectively with improved response to EGFR TKIs [5].

HER2 kinase domain mutations (in-frame insertions in Exon 20) are also associated with female gender, nonsmoking status, and Asian background in patients with adenocarcinoma; however, these mutations are associated with resistance to EGFR TKIs (but sensitivity to HER2-targeted therapy). Conversely, HER2 amplification predicts increased sensitivity to EGFR TKIs, and increased copy number of the HER2 gene is associated with gefitinib sensitivity in EGFR-positive patients, supporting use of HER2 FISH analysis for selection of patients for TKI therapy (see Table 1).

Increased EGFR gene copy number as determined by fluorescent in situ hybridization (FISH) and EGFR protein overexpression measured by immunohistochemistry (IHC) were recently reported to correlate with improved response and survival with gefitinib and cetuximab treatment. Furthermore, significant survival benefit from erlotinib therapy was observed in patients with wild-type *KRAS* [12—15].

EGFR inhibitors use in lung cancer management

Anti-EGFR monoclonal antibodies (mAbs) bind competitively to the extracellular domain of EGFR, thereby preventing ligand binding and interrupting the signaling cascade. TKIs bind to the intracellular domain of EGFR and inhibit the downstream effects of EGFR ligand binding. TKIs are not

Table 1   Studies of EGFR targeted therapy in non-small cell lung cancer.

Medication	Line	Treatment	Patient No	Outcome	Reference
Gefitnib	First line	Gemcitabine, Carboplatin and Gefitinib versus Gemcitabine and carboplatin	80 patients	Medium over all survival 20.5 versus 14.1	Tham et al. [22]
		Carbopaltin and Paclitaxol versus Gefitnib	1217		IPASS [24]
	Second or Third line	Geftnib versus Taxtere	210 216	7.6	Interest [34]
Erlotnib	Third line	Erlotnib versus placebo	731	6.7 versus 4.7	BR 21 [36]
Cetuximab	First line	Cetuximab with vinorelbine/cisplatin versus chemotherapy alone	1125	11.3 versus 10.1	FLEX [29]

specific for EGFR, so for these agents there may be cross-reactivity between EGFR and other ErbB family members, including HER2. It appears that both categories of drugs also have antiangiogenic activity, with a negative influence on the angiogenic biochemical mediators VEGF and factor VIII [16].

First line treatment

Gefitinib

Gefitinib is the first molecularly targeted agent to be registered for advanced NSCLC. The approval was based on two large randomized phase II studies, the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL)-1 and -2 studies [17,18].

In first line treatment of lung cancer two randomized, placebo-controlled, phase 3 trials, INTACT (Iressa NSCLC Trial Assessing Combination Treatment) 1 and 2, evaluated the potential benefit of adding gefitinib to chemotherapy for first-line treatment. INTACT 1 evaluated gemcitabine/cisplatin plus placebo or gefitinib 250 mg/day or 500 mg/day in 1093 chemotherapy-naive patients with advanced NSCLC. The trial found no difference in over-all survival (OS), time to disease progression (TTP), or over-all response rate (ORR) between the 3 treatment groups, and no significant unexpected adverse events (AEs) were observed. INTACT 2 evaluated paclitaxel/carboplatin plus placebo or gefitinib 250 mg/day or 500 mg/day in 1037 chemotherapy-naive patients with advanced NSCLC and also found no difference between treatment groups in overall survival (OS), time to progression (TTP), or overall response rate (ORR). Dose-related diarrhea and skin rash were observed with gefitinib, but there were no unexpected AEs [19—21].

In another study, 80 patients with advanced non-small cell lung cancer (NSCLC) and never smokers were assigned to receive gemcitabine—carboplatin—gefitinib (GCI) as first-line therapy and compared these patients with a historical control group who received gemcitabine—carboplatin (GC) alone. The response rate for patients in the GCI group was 62.7% (95% confidence interval [CI]: 48.08—75.87), which was higher than that of the GC group, 27.6% (95% CI: 12.73—47.24).

The GCI group showed a significant improvement in progression-free survival compared with the GC group (hazard ratio of 0.19, 95% CI: 0.105—0.351, $p < 0.001$). The median overall survival for the patients on GCI was 20.5 months compared 14.1 months ($p < 0.05$) for patients on GC.

The addition of gefitinib to first-line chemotherapy improved progression-free survival and overall survival when used as a first-line therapy in the group of patients who never smokers with advanced NSCLC [22].

A phase II, open-label, parallel-group study compared gefitinib with vinorelbine in chemotherapy naïve elderly patients with advanced (NSCLC). Patients were randomly assigned to gefitinib ($n = 97$) or to vinorelbine ($n = 99$). Results showed hazard ratios (HR; gefitinib vs vinorelbine) were 1.19 (95% CI: 0.85—1.65) for PFS and 0.98 (95% CI: 0.66—1.47) for OS. Disease control rates were 43.3% for gefitinib and 53.5% for vinorelbine, ORR 3.1% for gefitinib and 5.1% for vinorelbine. Overall QOL improvement and PSI rates were 24.3% and 36.6% (for gefitinib) and 10.9% and 31.0% (for vinorelbine), respectively.

There was no statistical difference between gefitinib and vinorelbine in efficacy in chemotherapy naïve, unselected elderly patients with advanced NSCLC, but there was better tolerability with gefitinib [23].

Iressa Pan-Asia Study (IPASS) trial was conducted recently as a phase 3, randomly assigned previously untreated patients in East Asia who had advanced lung adenocarcinoma and who were nonsmokers or former light smokers to receive gefitinib (250 mg per day) (609 patients) or carboplatin plus palitaxel (608 patients). The primary end point was progression-free survival. The 12-month rates of progression-free survival were 24.9% with gefitinib and 6.7% with carboplatin—paclitaxel.

In the subgroup of 261 patients who were positive for the epidermal growth factor or receptor gene (EGFR) mutation (96% have Exon 19 deletion or Exon 21 L858R mutation), progression-free survival was significantly longer among those who received gefitinib than among those who received carboplatin—paclitaxel (hazard ratio for progression or death, 0.48; 95% CI: 0.36—0.64; $p < 0.001$), whereas in the subgroup of 176 patients who were negative for the mutation, progression-free survival was significantly longer among those who received carboplatin—paclitaxel (hazard ratio for progression or death with gefitinib, 2.85; 95% CI: 2.05—3.98; $p < 0.001$) [24].

Erlotinib

Erlotinib in combination with chemotherapy as first-line treatment of NSCLC has been evaluated in two large multicenter, randomized, placebo-controlled clinical trials.

Two platinum-based doublets (carboplatin plus paclitaxel or cisplatin plus gemcitabine) were evaluated in combination with erlotinib versus placebo in the Tarceva Responses in Conjunction with Paclitaxel and Carboplatin (TRIBUTE) and Tarceva Lung Cancer Investigation (TALENT) trials, respectively.

In the TRIBUTE study, 1000 patients with untreated advanced stage IIIB/IV NSCLC were enrolled. The median over-all survival time (OS) for patients treated with erlotinib was 10.6 months, versus 10.5 months for the placebo group, the over-all response (OR) rates were similar in the erlotinib and placebo arms (21.5% vs 19.3%, respectively) [25].

In the TALENT trial, likewise, there was no statistically significant difference in any outcome, with a median OS of 301 versus 309 days, respectively. Therefore, there was no clinical benefit in either trial, and currently concurrent use of erlotinib with chemotherapy is not recommended in the first-line treatment of NSCLC unless the tumor has EGFR mutation [26].

Optimal trial was phase III randomized trial conducted recently in China assigned previously untreated 154 patients with known EGFR mutations and measurable disease to receive erlotinib or gemcitabine plus carboplatin. Progression-free survival was significantly improved with erlotinib (13.1 vs 4.6 months, HR 0.16, 95% CI: 0.10—0.26). Similarly, treatment with erlotinib significantly improved the objective response rate (83% vs 36%) [27].

In the EURTAC trial, 174 chemonaive patients with EGFR mutation (Exon 19 deletion or L858R mutation) were randomly assigned to erlotinib or platinum-based chemotherapy. The primary-endpoint was progression-free survival which was significantly improved with erlotinib (median 9.7 vs 5.2 months, HR 0.37). The difference in overall survival was not statistically significant, but more than 80% of patients initially treated with chemotherapy subsequently received an EGFR tyrosine kinase inhibitor [28].

Cetuximab

Cetuximab is an IgG_1 monoclonal antibody directed against the extracellular domain of the EGFR, which suppresses EGFR-mediated cell signaling by blocking ligand binding to the receptor. As an IgG_1 antibody, cetuximab may also kill tumor cells via an immune mechanism: antibody-dependent cellular cytotoxicity. Accordingly, cetuximab works differently from the TKIs. Phase III clinical trials have shown that cetuximab prolongs survival in patients with metastatic colorectal cancer (mCRC) and advanced squamous cell carcinoma of the head and neck.

In lung cancer, cetuximab was evaluated in first line setting. Phase II study of patients with EGFR positive and EGFR-negative advanced NSCLC with Eastern Cooperative Oncology Group performance status 0—1, assigned to receive cetuximab 400 mg/m^2 intravenously (IV) on week 1 followed by weekly doses of cetuximab 250 mg/m^2 IV. A cycle was considered as 4 weeks of treatment and therapy was continued until disease progression or intolerable toxicities.

The response rate for all patients ($n = 66$) was 4.5% (95% CI: 0.9—12.7%) and the stable disease rate was 30.3% (95% CI: 19.6—42.9%). The response rate for patients with EGFR-positive tumors ($n = 60$) was 5% (95% CI: 1.0—13.9%). The median time to progression for all patients was 2.3 months (95% CI: 2.1—2.6 months) and median survival time was 8.9 months (95% CI: 6.2—12.6 months).

Although the response rate with single-agent cetuximab in this heavily pretreated patient population with advanced NSCLC was only 4.5%, the disease control rates and overall survival seem

comparable to that of pemetrexed, docetaxel, and erlotinib in similar groups of patients [29].

The phase 3 FLEX (first-line treatment for patients with epidermal growth factor inhibitor [EGFR]-EXpressing advanced NSCLC) trial, of cetuximab combined with vinorelbine/cisplatin, met its primary endpoint of increasing OS when compared with chemotherapy alone; this study enrolled 1125 patients with advanced NSCLC who had evidence of EGFR expression.

While median PFS was the same in both treatment groups (4.8 months), median OS was 11.3 months in the group that received cetuximab vs 10.1 months in the group that received chemotherapy alone ($p = .044$). This survival time was viewed unfavorably due to failure to cross the newly set benchmark of 12 months achieved by other targeted therapy, namely bevacizumab with chemotherapy. The 1-year survival rate was 47% in the cetuximab group versus 42% in the chemotherapy-alone group. The group receiving cetuximab also had a significantly better response rate (36% vs 29%, $p = .012$).

Number of pre specified subgroup analyses for potential survival benefit were also conducted. While the subgroup of white patients had improved OS with cetuximab (10.5 vs 9.1 months; $p = .003$). Asian patients in the cetuximab group had worse survival (17.6 vs 20.4 months), suggesting that cetuximab is not effective in this subgroup of patients (who are more likely to harbor EGFR mutations). In patients with squamous-cell tumors, OS was numerically better with cetuximab (10.2 vs 8.9 months; $p = .0567$); this was also true in patients with adenocarcinoma (12.0 vs 10.3 months; $p = .0673$). In a preplanned analysis, the development of early acne-like rash was associated with significant outcome (median OS: 15 months vs 8.8. months, HR 0.63, 95% CI: 0.52–0.77, $p < 0.0001$) [29]. Data from FLEX indicated that cetuximab does not appear to benefit patients who have K-Ras mutations. Unlike colon cancer, K-Ras testing does not help identify patients who are most likely to benefit from treatment with cetuximab [30].

Second and third line treatment

Gefitinib

In IDEAL 1 study, 210 pretreated patients were randomized to receive gefitinib at 250 or 500 mg/day. The overall RR (ORR) was 18.4% and 19% and overall survival (OS) was 7.6 months and 8.0 months for the lower dose and the higher dose groups, respectively.

In IDEAL 2 study, 216 patients who had relapsed after platinum and docetaxel regimens were randomized to receive gefitinib 250 or 500 mg/day. Efficacy results were similar between the dosing groups; the ORR was 12% and the 1-year survival rate was 25%. In both studies, grade 3–4 adverse events (AEs) such as acne form rash and diarrhea were more frequent with the higher dose [31].

Based on the results of IDEAL 2, gefitinib received accelerated FDA approval as a third-line therapy for NSCLC. However, the 500-mg gefitinib dose was more toxic as it induced more acne-like rash and diarrhea. Diarrhea was noted in 57% of patients receiving 250 mg and 75% in those receiving 500 mg. Skin toxicity (rash, acne, dry skin, pruritus) was observed in 62% and 75%, respectively. Grade 3/4 toxicities were unusual, but more frequent in the 500-mg dosing. Dose reductions as a result of toxicity were also more frequent in the higher dose [32].

The subsequent phase 3 ISEL (Iressa Survival Evaluation in Lung cancer) trial found that gefitinib did not offer a significant OS benefit compared with placebo (5.6 vs 5.1 months, respectively; $p = .087$), which led to withdrawal of its FDA approval [33].

The reasons of lack of efficacy are not clear but it can be related to the use of lower dose that are less than the maximum tolerated dose and the inclusion of primary refractory cancers. Preplanned subgroup analysis of data from ISEL did find improved OS with gefitinib versus placebo in never-smokers (median survival, 8.9 vs 6.1 months; hazard ratio [HR]: 0.67, $p = .012$) and in patients of Asian origin (median survival, 9.5 vs 5.5 months; HR: 0.66, $p = .01$). A later exploratory biomarker analysis found a numeric (but not statistically significant) RR benefit with gefitinib in patients with EGFR protein-expressing tumors as well as those with high EGFR copy numbers. Patients whose tumors expressed EGFR protein also had a numerically greater survival benefit (HR: 0.77; $p = .126$) compared with those whose tumors did not express EGFR (HR: 1.57; $p = 0.14$). The presence of somatic mutations in EGFR Exons 19 and 21 also appeared to predict response (RR, 37.5% vs 2.6%; p-value not reported) [34].

Another phase 3 trial evaluating gefitinib in lung cancer called INTEREST (Iressa Non-small-cell lung cancer Trial Evaluating REsponse and Survival against Taxotere), conducted in 1466 patients with NSCLC who had received 1 or 2 prior chemotherapy regimens, found gefitinib to be non inferior for survival (median OS of 7.6 months; 1-year survival of 32%) compared with docetaxel, and offered improved tolerability and patient quality of life. Preplanned subgroup analyses found one

significant difference between the treatment groups: patients who had received 2 prior chemotherapy regimens had better survival with docetaxel than with gefitinib ($p = .031$). Overall, among patients taking gefitinib, 2.2% had grade 3/4 hematologic AEs, whereas docetaxel-treated patients had a 58.2% incidence of grade 3/4 neutropenia and a 42.3% incidence of grade 3/4 leukopenia [35].

Erlotinib

Erlotinib has shown a significant improvement in median survival, quality of life, and related symptoms in an unselected population of advanced and metastatic NSCLC patients in the second or third-line setting and most recently in maintenance therapy.

National Cancer Institute of Canada Clinical Trials Group conducted a phase III randomized trial, named BR.21, in which erlotinib was compared with placebo in stage III/IV NSCLC patients who had failed first- or second-line chemotherapy.

A total of 731 patients were randomized in a 2:1 ratio to receive either erlotinib at 150 mg/day or placebo. Those patients had metastatic NSCLC that had previously been treated with one standard chemotherapy regimen (50% of patients) or with two chemotherapy regimens (50% of patients). Almost all patients received platinum-based chemotherapy. The OR rate was 8.9% in the erlotinib arm and 1% in the placebo group. The median durations of response were 7.9 months and 3.7 months, respectively. The median over-all survival time was 6.7 months for those in the erlotinib regimen compared with 4.7 months for those in the placebo arm.

ORs were more frequent in women (14% vs 6%), in patients with adenocarcinoma, as compared with other histotypes (14% vs 4.1%), and in patients without a smoking history (25% vs 4%) [36].

The global TRUST study of erlotinib in advanced non-small-cell lung cancer (NSCLC) phase 4 trial was conducted in over 7000 patients with advanced NSCLC to evaluate erlotinib in the second- or third-line setting. The study revealed that patients with a broad range of clinical characteristics including gender, ethnicity, smoking status, and tumor histology benefited from treatment with erlotinib in this setting. Patients had a PFS of 14.3 weeks, and while this study did not have a control arm, the PFS seen with erlotinib in the TRUST trial was almost twice that observed in the placebo arm of BR.21 (7.2 weeks). Patients in the TRUST study had an overall disease control rate of 70% at the time of analysis [37].

In the TITAN trial, 424 patients who progressed on an initial platinum-based chemotherapy were randomly assigned to erlotinib or chemotherapy with either docetaxel or pemetrexed at the investigator's discretion. There was no difference in OS (median 5.3 months with erlotinib vs 5.5 months with chemotherapy, HR 0.96) or PFS (median 6.3 weeks with erlotinib vs 8.6 weeks with chemotherapy) between both arms [38].

Maintenance therapy

Erlotinib

The SATURN (Sequential Tarceva in Unresectable Lung Cancer) phase 3 clinical trial is evaluated whether erlotinib is effective as maintenance therapy in advanced NSCLC.

In this multicenter, double-blind, randomized study, 850 patients with advanced (stage IIIB/IV) NSCLC were randomized to receive either erlotinib (150 mg/day) or placebo, after documented disease control (CR/PR/SD), after 4 cycles of standard platinum-based chemotherapy.

Treatment is continued until disease progression, unacceptable toxicity, or death. The primary endpoint of SATURN is to determine whether administration of maintenance erlotinib after standard platinum-based is beneficial. PFS was better with erlotinib versus placebo with HR 0.71, and overall survival HR was 0.81 [39]. The improvement in PFS was greater in patient with EGFR mutation (HR 0.009).

FAST-ACT: A phase II randomized double-blind trial of sequential erlotinib and chemotherapy as first-line treatment in patients with stage IIIB/IV non-small cell lung cancer (NSCLC), a placebo-control randomized phase 2 study of 150 unselected patients from Asia and Australia using gemcitabine and carboplatin on day 1 and day 8 subsequently followed by erlotinib from days 15 to 28. All patients received erlotinib or placebo as maintenance therapy. Tumor RR was 37% versus 24% in favor of the sequential erlotinib study arm. Median progression-free survival was 7.2 months with erlotinib versus 5.5 months with placebo [40]. Another international double-blind randomized trial (called ATLAS) found a benefit from combining 2 targeted maintenance therapies after initial treatment in patients with advanced non-small cell lung cancer. The trial revealed that combination therapy with erlotinib and bevacizumab is superior to bevacizumab alone for delaying disease progression.

A total of 768 patients were randomized to receive bevacizumab plus erlotinib or bevacizumab plus placebo, after initial treatment with bevacizumab. In patients treated with both drugs, investigators noted a median progression-free survival of 4.8 months, compared with 3.7 months in those receiving bevacizumab plus placebo. The progression-free survival rate at 3 months was 67.7% in the combination group versus 53.4% in the control group; at 6 months, the rates were 40.3% and 28.4%, respectively. Because of these results, which were from a planned interim analysis of the data, the ATLAS trial was stopped early [41].

Gefitinib

A randomized phase 3 trial conducted by the West Japan Thoracic Oncology Group evaluated the gefitinib maintenance therapy after platinum-doublet chemotherapy in previously untreated patients with advanced disease. Eligible patients were randomized to receive either 3 cycles of chemotherapy followed by gefitinib maintenance therapy or 6 cycles of chemotherapy. Gefitinib maintenance therapy was associated with a significant improvement in progression-free survival duration (HR, 0.68; 95% CI: 0.57−0.80; $p < .001$) but not in OS. A pre specified analysis of OS by subgroup showed a significant improvement in OS with gefitinib maintenance in patients with adenocarcinoma histology [42].

Cetuximab

Cetuximab when administered in combination with carboplatin and docetaxel, a commonly used regimen for advanced NSCLC, cetuximab has exhibited synergistic interaction in preclinical studies. Therefore, a phase 2 study was conducted to evaluate the efficacy of the combination of cetuximab, carboplatin, and docetaxel for the treatment of advanced NSCLC.

80 patients chemotherapy-naïve with stage IIIB or stage IV NSCLC received cetuximab (at a dose of 400 mg/m^2 on day 1 and 250 mg/m^2 on days 8 and 15) plus docetaxel (at a dose of 75 mg/m^2 on day 1) and carboplatin (area under the concentration vs time curve [AUC] 5−6 on day 1) every 21 days for up to 6 cycles. Thereafter, patients without evidence of disease progression were continued on single-agent cetuximab for a maximum of 1 year or until disease progression. In 5 (28%) patients, disease stabilization lasted for >6 months. The median progression-free survival was 4.6 months and 4

patients (14%) remained free of disease progression at 12 months. The median survival and 1-year survival rate were 10.3 months and 36%, respectively. The 2-year survival rate was 16% [43].

Resistance to EGFR TK inhibitors:

- Almost all patients who initially respond to an EGFR TK inhibitor subsequently develop disease progression. The two molecular mechanisms that are responsible for a majority of cases of acquired resistance are secondary mutation at EGFR (T790) or amplification of MET oncogen. There is ongoing clinical trials for agents with in vitro activity against T790M or MET for patient with NSCLC [44,45].

New tyrosine kinase inhibitor exhibits clinical activity for non-small cell lung cancer with ALK oncogene fusions

A new inhibitor of the *ALK* and c-*MET*/hepatocyte growth factor (HGF) receptor tyrosine kinases, crizotinib (PF-02341066), has produced an objective response rate (ORR) of 57%, disease control rate (DCR) of 87%, and progression-free survival (PFS) probability at 6 months of 72%, with an excellent safety profile, in patients with non-small cell lung cancer (NSCLC). 82 patients have been treated. Almost all patients had adenocarcinoma histology and were never or former smokers. Almost all patients had some tumor shrinkage. The median duration of treatment is 5.7 months. The ORR is 57% (or 63% pending five as yet unconfirmed partial responses) and the DCR is 87%. The ORR for patients with three or more previous treatments is 56%. Response duration varies from 1 to 15 months. Median PFS has not been reached. Toxicity has been observed, elevated alanine aminotransferase (ALT), lymphopenia, hypophosphatemia, neutropenia, hypoxia, dyspnea, and pulmonary embolism, totaling an overall rate of 12% [46]. Crizotinib was recently approved by the US FDA for the treatment of NSCLC with Alk fusion.

Combined irreversible inhibition of EGFR

Afatinib (BIBW2992) is a novel PanErb inhibitor. It irreversibly inhibits EGFR, HER-2 and HER-4.

In 2012 ASCO Meeting, LUX-Lung 3 study was presented revealing significant improvement in progression free survival of patients with advanced adenocarcinoma harboring EGFR mutation with Afatinib in comparison to cisplatin-pemetrexed [47].

In this phase III randomized study that included 345 patients, PFS was 11.1 months versus 6.9 months (HR: 0.47 (0.34−065), $p < 0.0001$) in favor

of Afatinib. Objective response rate was more than doubled with Afatinib (56% vs 23%; $p < 0.0001$).

These data reflect the efficacy of Afatinib in this setting but awaiting further details to incorporate this into practice including regulatory agencies decisions about the drug approval.

Side effects and management

These new agents are associated with unique side effects especially in term of skin and gastrointestinal toxicities. It is very prudent for initiate early treatment of these toxicities to avoid interruption of treatment or severe complications.

Respiratory side effects

Respiratory side effects have included reports of serious interstitial lung disease (ILD); including fatalities in the treatment of non-small cell lung cancer or other advanced solid tumors. Dyspnea (41%) and cough (33%) have also been reported. In cases of ILD, the medication should be discontinued immediately and trial of steroid or cyclophosphamide was reported but no conclusive benefit [48].

Dermatologic side effects

Dermatologic side effects are common and include rash (75%), pruritus (13%), dry skin (12%), alopecia, acneform rash and other dermatological finding .The median time to onset of rash was 8 days. Treatment should be interrupted or discontinued if the patient develops severe bullous, blistering, or exfoliating conditions. The appearance of a rash in cancer patients treated with EGFR inhibitors is strongly associated with better outcome. Patients with mild skin changes may not need any treatment. Patients who are symptomatic should be treated accordingly. Emollients can be administered for skin dryness. Moderate skin rash can be treated with topical antibiotics such as clindamycin gel or topical metronidazole, a short course of oral antibiotics such as minocycline or doxycycline may be combined with the topical therapy. Patients who fail to respond to these measures may have the dose of the EGFR inhibitor interrupted or dose reduced.

Gastrointestinal side effects

Gastrointestinal side effects including diarrhea (54%), nausea (33%), vomiting (23%), stomatitis (17%), and abdominal pain (11%) have been reported. *EGFR* is frequently overexpressed in gastrointestinal normal mucosa. There is

evidence that *EGFR* is a negative regulator of chloride secretion. *EGFR* inhibitors could, therefore, increase chloride secretion by blocking this regulation loop and thereby inducing secretory diarrhea.

Diarrhea induced by inhibitors that target the *EGFR* pathway can be managed easily by reducing the dose of the oral compound, which rapidly lowers the incidence and severity of diarrhea. Rarely does treatment have to be interrupted. Loperamide is a useful treatment that can decrease intestinal motility [49].

Other toxicities

Like ocular complication such as conjunctivitis, hepatic as increase in Liver Function Tests, renal, hematologic side effects including leukopenia (25%) and anemia (16%) have been reported in patients receiving cetuximab.

Conclusion

Remarkable developments in the systemic treatment of advanced non-small-cell lung cancer have taken place over the past few years. Targeted therapies have been largely employed in patients with far advanced disease, and some of them have demonstrated consistent activity in this setting. Epidermal growth factor receptor inhibitors cause dramatic response in patients especially with EGFR mutation. As oncology trends towards personalized therapy to reach the optimal efficacy of drug with less side effect, anti EGFR and or third line TKIs have proven to be promising effective drugs in lung cancer treatment as first, second and maintenance therapy which encouraging further trials in this field. Combined irreversible inhibition of EGFR revealed striking benefit compared to chemotherapy alone.

The development of resistance, tumor heterogeneity, and the need to rebiopsy the tumor are all challenges that requires further study to optimize the management of patients with NSCLC.

Conflict of interest

Appendix A. Committee members

Dr. Abdul Rahman Jazieh, King Saud bin Abdulaziz University for Health Sciences, Riyadh, KSA

Dr. Abdulrahman Al Hadab, King Saud bin Abdulaziz University for Health Sciences, Riyadh, KSA

Dr. Adnan Hebshi, King Faisal Specialist Hospital & Research Center, Riyadh, KSA

Dr. Ahmed Abdulwarith, King Fahad Specialist Hospital, Dammam, KSA

Dr. Ahmed Bamousa, Riyadh Military Hospital, Riyadh, KSA

Dr. Ahmed Saadeddin, Riyadh Military Hospital, Riyadh, KSA

Dr. Ashwaq Al Olayan, King Saud bin Abdulaziz University for Health Sciences, Riyadh, KSA

Dr. Turki Al Fayae, King Abdulaziz Medical City, Princess Noorah Oncology Center, Jeddah, KSA

Dr. Foad Al Dayel, King Faisal Specialist Hospital & Research Center, Riyadh, KSA

Dr. Hamed Al Husaini, King Faisal Specialist Hospital & Research Center, Riyadh, KSA

Dr. Hamdan Al Jahdali, King Saud bin Abdulaziz University for Health Sciences, Riyadh, KSA

Dr. Hana Bamefleh, King Saud bin Abdulaziz University for Health Sciences, Riyadh, KSA

Dr. Khalid Al Kattan, Al Faisal University, Riyadh, KSA

Dr. M. Hasan Rajab, Al Faisal University, Riyadh, KSA

Dr. Sara Al Ghanim, King Saud bin Abdulaziz University for Health Sciences, Riyadh, KSA

Dr. Loutfi, Shukri, King Saud bin Abdulaziz University for Health Sciences, Riyadh, KSA

Dr. Yasir Bahadur, King Faisal Specialist Hospital & Research Center, Jeddah, KSA

Dr. Azzam Khankan, King Saud bin Abdulaziz University for Health Sciences, Riyadh, KSA

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