Targeted Therapies in Non-Small Cell Lung Cancer: Review

Küçük Hücreli Dışı Akciğer Kanserinde Hedef Tedaviler

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ABSTRACT Lung cancer is a crucial problem in Turkey and worldwide. The primary risk factor for lung cancer is smoking. Reduction of lung cancer mortality will require effective puplich health policies to prevent initiation of smoking. Oncologists should encourage smoking cessation, especially in patient with cancer. In Turkey the incidence of lung cancer is 30.13 per 100.000. Lung cancer is the first common cancer of all cancers in males and the fourth common cancer in females. About 80-90% of all lung cancers is non-small cell lung cancer (NSCLC). Therapy for NSCLC is surgery, neoadjuvant or adjuvant chemotherapy, palliative chemotherapy or radiotherapy, concomitant radiochemotherapy, targeted therapy alone or with chemotherapy due to stage. 40-50% of these apply to the hospital at locally advanced and metastatic stage. In advanced stage of lung cancer the average survival rate is 8-10 months and the standart treatment is chemotherapy in this stage. Even though their high costs, targeted therapies are getting popular in recent years for their effects. Targeted therapies for non small cell lung cancer are anti epidermal growth factor receptor(EGFR), anti EGF and tyrosine kinase inhibitörs (TKI). Epidermal growth factor receptor (EGFR) plays an essential role in normal cell growth and diffentiation, and is involved in tumor proliferation and survival. EGFR is detected in aproximately 80-85% of patients with NSCLC. EGFR overexpression is associated with poor clinical prognosis. EGFR overexpression and mutations, gene amplifications are clinical predictors of EGFR tyrosine kinase inhibitors responsiveness. Two oral EGFR inhibitors, gefitinib and erlotinib, are small-molecule agent that selectively inhibit the intracellular tyrosine kinase activity of the EGFR. On the other hand K-ras mutations are associated with TKI resistance and cigarette smoking. These drugs should be used in selected patients. We discussed targeted therapies (bevacizumab, cetuximab, gefitinib, erlotinib, vandetanib) in non small cell lung cancer.

Key Words: Carcinoma, Non-Small-Cell Lung; therapy; erlotinib; gefitinib; cetuximab; N-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine

ÖZET Akciğer kanseri tüm dünyada ve Türkiye de önemli bir sorundur. Akciğer kanserinin birincil risk faktörü sigara içimidir. Akciğer kanserinden ölümü azaltmak sigaraya başlamayı önlemek için etkili sağlık politikalarına ihtiyaç olacaktır. Onkologlar özellikle kanserli hastalarda sigara bırakmayı teşvik etmelidirler. Türkiye de akciğer kanseri insidansı (100.000'de) 30.13'dür. Tüm kanserler içinde erkeklerde 1. kadınlarda ise 4.sıradadır. Akciğer kanserlerinin yaklaşık %80-90'ı küçük hücreli dışıdır (Non Small Cell Lung Cancer=NSCLC). Küçük hücreli dışı akciğer kanserinde tedavi evrelere göre cerrahi; ameliyat öncesi ve sonrası veya palyatif amaçlı kemoterapi; radyoterapi; kemoradyoterapi; tek başına veya kemoterapilerle birlikte hedef tedavilerdir. Bu hastaların %40-50'si lokal ileri ve metastatik evrede başvurmaktadır. İleri evre akciğer kanserinde ortalama yaşam süresi 8-10 ay olup bu evrelerde standart tedavi kemoterapidir. Maliyetleri yüksek olmasına rağmen etkinlikleri göz önüne alınarak hedef tedaviler son senelerde çok gündeme gelmiştir. Küçük hücreli dışı akciğer kanserlerinde hedef tedaviler epidermal büyüme faktörü reseptörüne karşı, epidermal büyüme faktörüne karşı ve trozin kinazı engelleyenlerdir. Epidermal büyüme faktör reseptörü (EGFR) normal hücrelerde büyüme ve diferansiasyonunda esas rol oynamaktadır. Tümör çoğalması ve devamı ile ilgilidir. EGFR overekspresyonu kötü klinik prognozla ile ilgilidir. EGFR overekspresyonu ve gen amplifikasyonu ve EGFR mutasyonu trozin kinaz inhibitörü ilaçlarına cevabın bir ön göstergesidir. Gefitinib ve erlotinib EGFR'nin hücre içi trozin kinase aktivasyonunu engelleyen 2 tane ağızdan alınan küçük moleküllü ajanlardır. Diğer taraftan K-ras mutasyonu trozin kinase engelleyen ilaçlara direnç ve sigara içimiyle birliktedir. Seçilmiş hastalarda bu ilaçlar kullanılmalıdır. Küçük hücreli dışı akciğer kanserinde hedef tedavileri (bevacizumab, cetuximab, gefitinib, erlotinib, vandetanib) tartıştık.

Anahtar Kelimeler: Karsinom, küçük hücreli olmayan; Tedavi; erlotinip; gefitinip; setuksimap; N-(4-bromo-2-florofenil)-6-metoksi-7-((1-metilpiperidin-4-yl)metoksi)kinazolin-4-amin

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Lung cancer is a crucial problem in Turkey and worldwide. According to the year 2005 datas of Presidency of Health Ministry Cancer Care the incidence of lung cancer is 30.13 per 100.000. Lung cancer is the first common cancer of all cancers accounts for 52.73 in males. In females the incidence is 7.20, the fourth common cancer. According to the Ankara oncology hospital datas lung cancer is the second common cancer of all cancers.[1] About 80-90 % of all lung cancers is non-small cell lung cancer (NSCLC).[2,3] 40-50% of these apply to the hospital at locally advanced and metastatic stage. In advanced stage of lung cancer the average survival rate is 8-10 months and the standart treatment is chemotherapy in this stage. Advanced in our understanding of cancer biology have led to the discovery of a number of potential molecular targets and the development of novel agents. Most advanced in clinical research for NSCLC targeted therapy are EGFR and Vascular Endothelial Growth Factor (VEGF).

TARGETED THERAPIES

1) Anti-vascular endothelial growth factor(anti-VEGF)

2) Anti-epidermal growth factor (anti-EGF)

3) Tyrosine kinase inhibitors

In targeted therapies the Erb (human epidermal receptor=HER) family presents importance. This family includes four variety of HER 1, 2, 3, 4. HER1 (EGFR: epidermal growth factor receptor) is a transmembrane receptor. It has extracellular and intracellular domains. Various ligands form dimers binding to receptors (homodimer: EGFR-EGFR or heterodimer: EGFR or one of another members of HER).

As a result of dimerisation intracellular tyrosine kinase domains become active and affect nucleus via various pathways account for proliferation, cell cycle and transcription (Figure 1 and 2).

EGFR is expressed in 40-80% of lung cancers.[6] The most common EGFR mutations are exon 19 deletion and exon 21 mutation. Both two mutations result with activation of tyrosine kinase domain Although the prognostic effect of EGFR mutation is not clear, the predictive effect is known

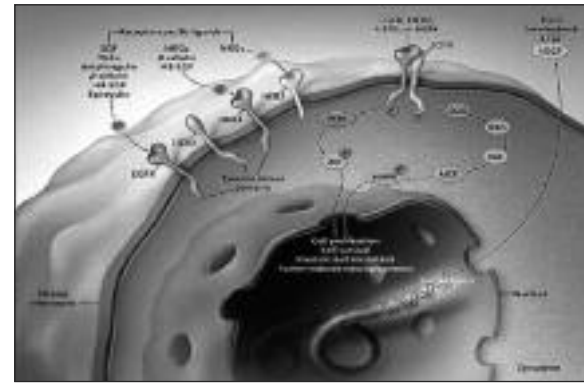

FIGURE 1: Signal transmission pathways controlled via EGFR activation.[4]

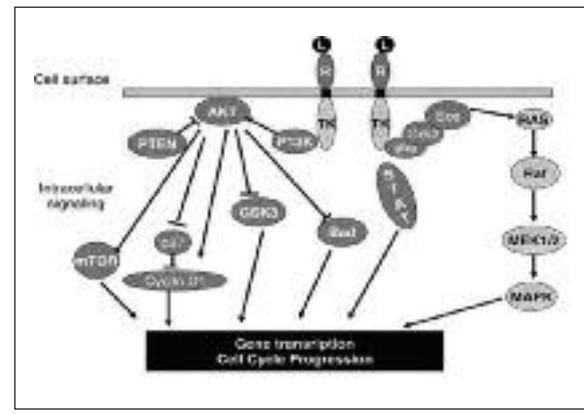

FIGURE 2: Ligand, receptor, tyrosine kinase and transmission pathways.[5]

well. Patients who have these mutations are more responsive to tyrosine kinase inhibitors.

Kirsten-raus sarcoma (K-ras): A GTP bindirng proteine. Mutation of this proteine is an indicator of resistance to tyrosine kinase inhibitors. Patients with k-ras mutations have shorter survival than patients with wild type k-ras. Status of k-ras mutation has predictive value for effectiveness of EGFR-TKI treatment. TRIBUTE(Tarceva Responses In Conjunction with Paclitaxel and Carboplatin) study has shown the importance of this.[7,8] Chemotherapy+erlotinibe arm versus chemotherapy arm. Response rate to erlotinibe in patients with K-ras mutation is 8%, in chemotherapy arm 23%, but in patients without K-ras mutation the response rate was found 26% in both arm. Time to progression (TTP) and overall survival (OS) were found shorter. And this also is an indicator of resistance to tyrosine kinase inhibitors.

ANTI VEGF TREATMENT (BEVACIZUMAB)

Bevacizumab is a recombinant monoclonal antibody that blocks VEGF receptor. In 2006 FDA permitted using bevacizumab in metastatic, recurrent, locally advanced or irresectable non-squamous NSCLC. There are two important study.

ECOG 4599 Study:[9] Including 842 patients treated with Paklitaksel+Carboplatin in one arm and in the another arm bevacizumab was added to Paklitaksel+Carboplatin. Response rate in the bevasizumab arm was 27%, 10% in only chemotherapy arm, p< 0.0001. Median survival was 12.5 month and 10.2 month respectively, p=0.0075, progression free survival was 6.4 month and 4.5 month respectively, 0<0.0001. One year survival was 1.9% versus 43.7, two-years survival was 22.1% versus 16.9%. In same study toxicities were evaluated and grade 4 neutropenia in bevasizumab arm was 24%, in chemotherapy only arm was 16.4 %; grade 3-4 haemorragia was 4.5% and 0.7%; haemoptisia 1.9% and 0.2%, hipertension 6% versus 0.7% and treatment related deaths were 9 versus 2 respectively.

BO17704 (AVAIL) Study:[10] A phase II-I study. 1043 patients with advanced or recurrent non-squamous cell lung cancer were administered as first line cisplatin+gemsitabine (CG) with low dose (7.5 mg/kg, n =345) and high dose (15 mg/kg, n=351) bevasizumab. Primary end point as progression free survival (PFS), secondary end point as overall survival(OS), response rate, response time and safety were detected. Results: Median PFS was 6.7 month in low dose bevasizumab versus 6.1 month in plasebo arm, hazard ratio (HR): 0.75, p=0.003. In high dose bevasizumab arm median PFS was 6.5 month versus 6.1 month, HR: 0.82, p=0.03. Response rates were 34.1% in low dose arm versus 30.4% in high dose arm, 20.1% in placebo arm. Time of follow up wasn't enough for overall survival.

CETUXIMAB

A monoclonal antibody targeting EGFR. In previous studies in patients with NSCLC treated with monotherapy response rate was 4.5% and in 30% of patients were stabilized.

FLEX study:[11,12] 1125 patients with advanced (stage 3B and 4, most of them were stage 4) NSCLC were admistered as first line sisplatin+vinorelbine with or without cetuximab. Response rate in chemotherapy+cetuximab (CT+cet) arm was 36%, in chemotherapy(CT) arm was 29%, p=0.012; PFS: no difference; OS: in CT+cet arm 11.3 month, in CT arm 10.1 month, p=0.04. Toxicities: grade 3-4 neutropenia were 22% and 15% respectively, P<0.05.

A phase 2 study of cetuximab:[13] 80 patients, no prior chemotherapy, with stage 3B or metastatic disease were administered carboplatin+docetaxel plus cetuximab. Objective response rate: 15.2%, median PFS:4.6 month, median OS:10.3 month, grade 3-4 neutropenia 30%.

BMS099 Study, retrospective analysis:[14] Addition of cetuximab to taxan+carboplatin chemotherapy, in patients with wild type K-ras median PFS in CT-cet arm was 5.1 month, in CT arm 5.3 month; median OS was 9.7 month versus 9.9 month. In K-ras mutant patients median PFS was 5.6 month versus 2.8 month and median OS was 16.8month versus 10.8 month, p=not significant. No association could has found between any molecular marker and response to cetuximab.

STUDIES WITH ERLOTINIB

Erlotinib is an EGFR tyrosine kinase inhibitor. In 2004 FDA and in 2005 EMEA (European Medicinal Evaluation Agency) gave permission to use erlotinib in patients with locally advanced and metastatic NSCLC whom were prior administered at least one time chemotherapy. The most important study is the study of Canada Cancer Institute.

National Cancer Institute of Canada Clinical Trial Group (**BR.21 NCIC CTG**).[15] In this study 731 patients that were administered first or second line chemotherapy were randomised at a percent of 2/1 to erlotinib or placebo arm. Response rate (RR) in erlotinib arm was 8.9%, in placebo arm less than 1%, p<0.001. OS was 6.7 month and 4.7 month respectively, p<0.001; PFS was 2.2 month versus 1.8 month; median response time was 7.9 month versus 3.7 month.

With this study erlotinib was being used in second or third line treatment. It was recommended to follow-up liver function tests closely. Rash, diarrhea, pulmonary toxicity (interstitial lung disease) were the important adverse events. In subgroup analysis response to erlotinib was considered to be better in female gender, adenocarcinoma, Asian race and non-smokers. Response rate in females in erlotinib group was 14%, in placebo group 6%, p=0.0065, in adenocarcinomas 14% versus 4.1%, p<0.0001; in non-smokers 25% versus 4%, p<0.0001; in Asian group 19% versus 7%.

There are some different phase 3 studies. Carboplatin+paklitaxel+erlotinib (**TRIBUTE**=Tarceva responses in conjunction with paklitaxel and carboplatin)[8] at first line with 1059 patients and cisplatine+gemsitabine+erlotinib **(TALENT) (**Tarceva Lung Cancer Investigation**)**[16] with 1172 patients. The addition of erlotinib to chemotherapy was observed not beneficial in RR, PFS and OS. So that it has not been offered using erlotinib at first line. In TRIBUTE study the effect of smoking was investigated. Although it wasn't beneficial in all patient population, compared with non-smokers the average survival in smokers was found 10 months versus 22.5 months in non-smokers, p=0.01.

In **SATURN** study[17] patients with advanced NSCLC treated with platine based chemotherapy and achieved response (complete response, partial response and stable disease) were randomised to erlotinib or placebo arm after four cycles.

The primary end point in all patients was progression free survival. 889 patients were randomised. In all patients groups the erlotinib arm was shown to be superior to placebo arm in PFS. HR: 0.71, p<0.0001, in EGFR İHC+ patients HR:0.69, p<0.0001. Response rates in erlotinib arm was 12%, in placebo arm 5%, disease control rates (complete response+partial response+stable disease over 12 weeks) was 40.8% versus 27.4%. Datas have not been reached to evaluate overall survival. Erlotinib has been well tolerated in most of patients.

The another study is **TORCH**[18] (Tarceva or chemotherapy) study. The results of thisstudy is expected to be explained in 2010.

There are some studies together with bevacizumab and erlotinib. In **ATLAS**[19] study patients with stage 3B-4 NSCLC after treated for four cycle chemotherapy together with bevacizumab that evident toxicites were not seen and not progressed were randomised either bevacizumab(B)+erlotinib€ or bevacizumab(B)+placebo(P). 768 patients were randomised. Median PFS in B+E arm was 4.8 month versus 3.7 month in B+P arm. HR=0.722, p=0.0012. Consequently, in locally advanced, recurrent or metastatic NSCLC after chemotherapy+bevacizumab addition of erlotinib to bevacizumab treatment improves PFS significantly.

The another study is **BETA**[20] study. Patients with advanced NSCLC who were progressed after first line chemotherapy or chemoradiotherapy were participated into study. This was a phase 3 study that 636 patients were randomized to either Bevacizumab(B)(Avastin)+Tarceva (Erlotinib)(E) or Tarceva+Placebo (P). The primary end point was overall survival (OS). Secondary end points were PFS and objective response rate (ORR). Median OS was 9.3 month in B+E arm, 9.2 month in E+P arm, p=0.75. Median PFS was 3.4 month versus 1.7 month, p<0.0001. ORR was 12.6% versus 6.2%, p=0.006. In BETA study addition of bevacizumab to erlotinib was not improved in OS.

GEFITINIB STUDIES

IDEAL 1[21] and **IDEAL 2**[22] Study (Iressa Dose Evaluation In Lung Cancer): As a result of these studies FDA gave permission to use gefitinib at third line in 2003.

Two phase 3 trials: Addition of gefitinib to cisplatin+gemcitabine (**INTACT 1**= Iressa NSCLC Trial Assessing Combination Therapy)[23] and addition of gefitinib to carboplatin+paclitaxel (**INTACT 2**)[24] showed not benefit to add gefitinib to chemotherapy.

ISEL (Iressa Survival Evaluation In Lung Cancer) Trial:[25-27] 1692 patients, a phase 3 study, Iressa was compared with supportive care. Advantage for overall survival was not shown. Then FDA was withdrew approval in 2005.

Comparison of Gefitinib and Docetaxel: 489 patients with NSCLC treated previously with 1 or 2 chemotherapy regimen and not benefit from chemotherapy were participated in a phase 3 Japanese study (**V-15-32**).[28] No difference in OS. ORR with gefitinibe: 22.5%, with Taxotere: 12.8%, p=0.009. PFS, disease control and improvement of symptoms were found similarly in both arms. Grade 3-4 adverse effect in gefitinib arm was 40.6% and 81.6% in Taxotere arm. It was commented that gefitinib was effective treatment option in Japanese patients treated previously.

INTEREST:[29] A phase 3 study of comparison of gefitinib with docetaxel in NSCLC patients treated with first or second line chemotherapy. No difference between two groups neither at survival (1 year survival was 32% versus 34%, median survival 7.6 month versus 8 month) nor at TTP. But gefitinib was favourable for less toxicity and better quality of life.

IPASS(Iressa Pan Assia Study):[30] At first line gefitinibe (G) versus carboplatin+paclitaxel (C/P): 1217 patients, no chemotherapy previously, nonsmokers, adenocarcinoma histology, stage IIIB/IV NSCLC. Results: Rates of PFS in gefitinib 24.9%, 6.7% in C/P, beter in gefitinib arm (HR:0.74, p<0.0001). PFS was longer in patients with positive EGFR mutations in gefitinib arm. In EGFR negative subgroup in gefitinib arm PFS was shorter than the others. ORR: In all population in G arm was beter than C/P arm (43.0% vs 32.2%, p=0.0001). This rate in mutation positive subgroup was 71.2% versus 47.3%. OS was similar. Quality of life was beter in gefitinib arm (Functional Assessment of Cancer Treatment –Lung= FACT-L 48% vs 41%, p=0.0148; TOI 46% vs 33%, p< 0.0001); improvement of symptoms was similar in both arm.

MULTITARGETED TYROSINE KINASE INHIBITORS

Sunitinib (Sutent), sorafenib (Nexavar), vandetanib (Zactima) studies has got importance. Vandetanib is an EGFR, VEGF and RET signal inhibitor drug, taken orally once a day. In ASCO 2009 three important studies were presented. One of them is **ZODIAC**,[31] a phase 3 study. Patients previously received one chemotherapy were administered at second line vandetanib+docetaxel or docetaxel + placebo. 1391 patients were participated into study. Primary end point was PFS. ORR in arm included vandetanib was 17%, in the other arm was 10%, HR:NR and p<0.001. Median PFS was 4 month versus 3.2 month. No difference for adverse events in both arms. The another study is **ZEAL**[32] study. 534 stage IIIB-IV patients previously treated for one chemotherapy were participated into study. Both at PFS (HR:0.86, p=0.108) and at OS (HR:0.86, p=0.219) an advantage was found in one's favour of vandetanib+pemetrexed arm. There is also an evident advantage statistically at overall response rate (19.1% vs 7.9%, p<0.001). Although vandetanib+pemetrexed was well tolerated, there was no evident improvement in PFS. The third study was **ZEST**.[33] Stage 3B-4 patients previously received at least one chemotherapy were randomized either vandetanib ar mor erlotinib arm. 1240 patients were participated into study. Median follow time was 14 months, 88% of patients were progressed and 67% were died. Primary end point was PFS and no difference between two arms. Also no difference at OS. Diarrhea (50% vs 38%) and hipertension (16% vs 2%) were more frequent seen in vandetanib arm.

Consequently, EGFR TKIs must be given to selected patients and they must be participated into clinical studies. EGFR protein overexpression, gene amplification and EGFR mutation are predictive of response to these agents.

REFERENCES

1. Alkis N, Utkan G, Durnalı AG, Arslan UY, Çelenkoglu G,Tokluoglu S, et al. Epidemiologic properties of patients who had admitted to Ankara Oncology hospital department of medical oncology. Ann Oncol 2006:17(suppl 9) abst:830.
2. Yaren A, Öztop İ. Adjuvant chemotherapy for early stage non small cell lung cancer. Turkiye Klinikleri J Med Sci 2006; 26:649-54.
3. Onn A, Vaporciyan AA, Chang CY, Komaki R, Roth JA, Herbst RS. Cancer of the lung. In: Kufe DW, Bast RC, Haıt WN, Hong WK, Pollock RE, Weıchselbaum RR, Holland JF, Freı E, eds. Cancer Medicine 7th ed. London, AACR; 2006. p.1179-24.
4. Fortunato C, Giampaolo T. EGFR antagonists in cancer treatment. NEJM 2008;358(11): 1160-74.
5. Murer B. Targeted therapy in non small cell lung cancer: A commentary. Arch Pathol Lab Med 2008; 132:1573-1575
6. Schrump DS, Giaccone G, Kelsey CR, Marks LB. Non small cell lung cancer, In De Vita VT, Lawrence TS, Rosenberg SA, eds. Cancer Principles and Practice of Oncology, 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2008. p.896-946.
7. Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, et al. TRİBUTE: a phase lll trial of erlotinib hydrochloride combined with carboplatin and paclitaxel chemotherapy in advanced non small cell lung cancer. JCO 2005;23(25):5892-9.
8. Eberhard DA, Johnson BE, Amler LC, Goddard AD, Heldens SL, Herbst RS, et al. Mutations in the Epidermal Growth Factor Receptor and in KRAS Are Predictive and Prognostic Indicators in Patients With Non-Small-Cell Lung Cancer Treated With Chemotherapy Alone and in Combination With Erlotinib JCO 2005;23(25):5900-9.
9. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. NEJM 2006;355(24): 2542-50.
10. Martin R, Joachim VP, Petr Z, Rodryg R, Vera G, Vera H, et al. Phase lll trial of cisplatin plus gemcitabine with either placebo or bevacizumab as firs line therapy for nonsquamous non small cell lung cancer: AVAİL JCO 2009; 27(8):1227-34.
11. Pirker R, Szczesna A, Pawel JV, Krzakowski M, Ramlau R, Pak K, et al. FLEX: A randomized, multicenter, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC). JCO 2008;26(suppl 20):6s.
12. Eberhardt W, Pawel JV, Vynnychenko I, Zatloukal P, De Marinis F, O'Byrne K, et al. FLEX: cetuximab in combination with platinum based chemotherapy(CT) vs CT alone improves survival in 1st line treatment of patients with advanced non small cell lung cancer(NSCLC). Ann Oncol 2008;19(suplI 8), viii45 (730).
13. Belani CP, Schreeder MT, Steis RG, Guidice RA, Marsland TA, Butler EH, et al. Cetuximab in combination with carboplatin and dosetaxel for patients with metastatic or advanced stage non small cell lung cancer. A Multicenter phase 2 study Cancer 2008; 113(9)2512-7.
14. Khambata FS, Harbison C, Woytowitz D, Awad M, Horak C, Xu LA, et al. K-ras mutation, EGFR-related, and exploratory markers as response predictors of cetuximab in first line advanced NSCLC: Retrospective analyses of the BMS099 trial. JCO 2009;27(15S suppl): 412s.
15. Frances AS, Jose RP, Tudor C, Eng HT, Vera H, Sumitra T, et al. Erlotinib in previously treated non small cell lung cancer. NEJM 2005;353(2):123-32.
16. Gatzemeıer U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, Rosa FD, et al. Phase lll study of erlotinib in combination with cisplatin and gemcitabine in advanced non small cell lung cancer(NSCLC):The Tarceva lung cancer investigation trial. JCO 2007; 25(12):1545-52.
17. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczesna A, Juhazs E, et al. SATURN: A double blind, randomized, phaselll study of maintenance erlotinib versus placebo following nonprogression with first line platinum based chemotherapy in patients with advanced NSCLC. JCO 2009;27 (15S)(suppl): 407s.
18. Gridelli C, Butts C, Ciardiello F, Feld R, Gallo C, Perrone F. An international multicenter, randomized phase lll study of first line erlotinib followed by second line cisplatin/gemcitabine versus first line cisplatin/gemcitabine followed by second line erlotinib in advanced non small cell lung cancer: treatment rationale and protocol dynamic of the TORCH trial, Clinical Lung Cancer 2008;9(4):235-8.
19. Miller VA, O'Connor P, Soh C, Kabbinavar F. A randomized, double-blind, placebo-controlled, phase IIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). ASCO Annual Meeting Proceedings JCO 2009; 27(18S).
20. Hainsworth J, Herbest R. A phase lll, multicenter, placebo-controlled, doubled- blınd, randomized clınical trial to evaluate the efficacy of Bevacizumab (Avastin) in combination with erlotinib (Tarceva) compared with erlotinib alone for treatment of advanced non small cell lung cancer after failure of standart first line chemotherapy (BETA). J Thoracic Oncol 2008; 3(11)suppl4:S302.
21. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, et al. İDEAL 1 Multi-Institutional Randomized Phase II Trial of Gefitinib for Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer. JCO 2003;21(12):2237-46.
22. Kris MG, Natale RB, Herbst RS, Lynch TJ, Prager D, Belani CP, et al. IDEAL-2: Efficacy of Gefitinib, an Inhibitor of the Epidermal Growth Factor Receptor Tyrosine Kinase, in Symptomatic Patients With Non-Small Cell Lung Cancer. A Randomized Trial JAMA 2003;290(16):2149-58.
23. Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, et al. Gefitinib in Combination With Gemcitabine and Cisplatin in Advanced Non-Small-Cell Lung Cancer: A Phase III Trial-INTACT 1 JCO 2004;22(5):777-84.
24. Roy SH, Giuseppe G, Joan HS, Ronald BN, Vincent M, Christian M, et al. Gefitinib in Combination With Paclitaxel and Carboplatin in Advanced Non-Small-Cell Lung Cancer: A Phase III Trial-INTACT 2. JCO 2004;22(5):785-94.
25. Thatcher N, Chang A, Parikh P, Rodrigues PJ, Ciuleanu T, Pawel JV, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: Results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366 (9496):1527-37.
26. Hirsch FR, Garcia MV, Bunn PA, Franklin WA, Dziadziuszko R, Thatcher N, et al. Molecular Predictors of Outcome With Gefitinib in a Phase III Placebo-Controlled Study in Advanced Non-Small-Cell Lung Cancer JCO 2006;24 (31):5034-42.
27. Alex C, Parikh P, Thongprasert S, Tan EH, Perng RP, Ganzon D, et al. Gefitinib (IRESSA) in Patients of Asian Origin with Refractory Advanced Non-small Cell Lung Cancer: Subset Analysis from the ISEL Study. J Thorac Oncol 2006;1(8):847-55.
28. Riichiroh M, Yutaka N, Tomohide T, Nobuyuki Y, Masahiro T, Kazuhiko N, et al. Phase III Study, V-15-32, of Gefitinib Versus Docetaxel in Previously Treated Japanese Patients With Non-Small-Cell Lung Cancer JCO 2008;26 (26):4244-52.
29. Edward SK, Vera H, Tony M, Mark AM, Radj G, Yi-Long W, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial Lancet 2008; 372(9652):1809-18.
30. Tony SM, Yi-Long W, Sumitra T, Chih-Hsin Y, Da-Tong C, Nagahiro S, et al. Gefitinib or Carboplatin-Paclitaxel in Pulmonary adenocarcinoma NEJM 2009;361(10):947-57.
31. Herbest RS, Sun Y, Korfee S, Germonpre P, Saijo N, Zhou C, et al. Vandetanib plus dosetaxel versus dosetaxel as second-line treatment for patients with advanced non small cell lung cancer(NSCLC): A randomized, double-blind phase lll trial(ZODIAC). JCO 2009; 27(suppl):407s.
32. De Boer R, Arrieta O, Gottfried M, Blackhall FH, Raats J, Yang CH, et al. Vandetanib plus pemetrexed versus pemetrexed as second line therapy in patients with advanced non small cell lung cancer (NSCLC): A randomized, double-blind phase lll trial (ZEAL). JCO 2009;27(suppl):409s.
33. Natale RB, Thongprasert S, Greco FA, Thomas M, Tsai CM, Sunpaweravong P, et al. Vandetanib versus erlotinib in patients with advanced non small cell lung cancer (NSCLC) after failure of at least one prior cytotoxic chemotherapy: A randomized, double-blind phase lll trial (ZEST). JCO 2009;27(suppl): 409s.