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The Role of Monoclonal Antibody in Combination with First-Line Chemotherapy in Asian Patients with Advanced Non-Small Cell Lung Cancer

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The strategies of incorporating monoclonal antibodies (MoABs) have now proved efficacy in the first-line treatment of advanced non-small cell lung cancer (NSCLC). These include targeting the vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR). Bevacizumab is a MoAB targeting the vascular endothelial growth factor (VEGF), an important mediator of new blood vessel formation. Cetuximab is a MoAB directed at EGFR. Binding cetuximab to EGFR blocks signal transduction and promotes receptor internalization and degradation. In this review, we present current data of bevacizumab and cetuximab for the first line treatment of advanced NSCLC. We also refer to their potential for Asian patients with advanced NSCLC in the first-line setting.

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BEVACIZUMAB

Summary of clinical trial results: E4599 & AVAiL

In AVF0757g randomized phase II trial,[1] patients with chemotherapy-naïve, locally advanced, or metastatic non-small cell lung cancer (NSCLC) were randomized to receive six cycles of carboplatin (AUC 6) and paclitaxel (200 mg/m^2) with or without bevacizumab 7.5 mg/kg or 15 mg/kg every 3 weeks until disease progression. Patients in high-dose bevacizumab arm reported higher response rates (RR), longer time to progression (TTP), and overall survival (OS) compared with those receiving chemotherapy alone. In this study, squamous histology was identified as a risk factor for life-threatening pulmonary hemorrhage. Thus, the majority of subsequent trials of bevacizumab in NSCLC have excluded patients with predominantly squamous cell histology.

Following the phase II trial that established the safety and efficacy of bevacizumab in NSCLC, two pivotal phase III trials of carboplatin/paclitaxel with or without bevacizumab (15 mg/kg; E4599) and of cisplatin/gemcitabine with or without bevacizumab (7.5 mg/kg or 15 mg/kg; AVAiL) proved efficacy of bevacizumab in patients with previously untreated advanced non-squamous NSCLC.[2,3] Based on positive data from these trials, bevacizumab was approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMEA).

In the phase III Eastern Cooperative Oncology Group 4599 (E4599) study,[2] 878 patients were randomized to receive chemotherapy with paclitaxel/carboplatin

chemotherapy alone (PC arm) or chemotherapy plus bevacizumab 15 mg/kg (PCB arm). Patients with squamous cell tumors, brain metastases and clinically significant hemoptysis were excluded. Patients receiving bevacizumab had a significantly higher RR (35% versus 15%; $p < 0.001$), median progression-free survival (PFS) [6.2 versus 4.5 months; hazard ratio (HR), 0.66; $p < 0.001$], and also median OS (12.3 versus 10.3 months; HR, 0.79; $p = 0.003$). Although a consistent effect was observed across most subgroups, in an exploratory analysis, evidence of survival benefit was not observed in women (HR 0.98, 95% CI 0.77-1.25). The reason for this is unclear, but it may be explained by the fact that more women were receiving second-line chemotherapy in the PC arm, although there was no difference in the subsequent use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs). There might also be imbalances between the two groups with respect to known or unknown prognostic factors; there was a higher incidence of liver metastases in women receiving bevacizumab. Given that smoking history is a predictive factor for the efficacy of EGFR inhibitors,[4] the lack of this important data in this study complicated the interpretation of the potential impact of subsequent EGFR-TKIs on the clinical outcome. Additionally, because female patients with advanced NSCLC showed significantly longer survival, regardless of any treatment, they might derive little additional benefit, if any, from a bevacizumab-containing regimen.

In a second large phase III trial (AVAiL),[3] comparing cisplatin/gemcitabine (CG) alone versus CG in combination with bevacizumab (7.5 or 15 mg/kg) and PFS, the primary end point of the study was significantly longer in both bevacizumab treatment arms compared with the placebo arm. The HR for PFS was 0.75 ($p = 0.003$) for the low-dose bevacizumab arm versus placebo (median PFS, 6.7 versus 6.1 months, respectively) and 0.82 ($p = 0.03$) for the high-dose bevacizumab arm versus placebo (median PFS, 6.5 versus 6.1 months, respectively). Furthermore, the objective RR and median duration of response were significantly higher in both bevacizumab arms compared with the placebo arm (30% versus 34% versus 20% in 15 mg/kg, 7.5 mg/kg and placebo arms, respectively). Although the trial was not powered to directly compare the two bevacizumab doses, the results indicate similar efficacy in terms of PFS and RR for low- and high-dose bevacizumab arm. However, in a final OS analysis with median 12.5 months follow-up, AVAiL did not demonstrate a significant OS benefit, a secondary endpoint, in the bevacizumab arm (median OS, 13.4 versus 13.6 versus 13.1 months in 15 mg/kg, 7.5 mg/kg and placebo arms, respectively).[6]

Potential explanations for the discrepancy of OS benefit between E4599 and AVAiL may exist. Firstly, this simply indicate that second-line therapies may potentially impact study outcomes. It is critical to recognize that approximately 60% of patients in the AVAiL trial have received subsequent lines of therapy, with approximately 40% of these patients receiving EGFR-TKIs. Interestingly, in an exploratory analysis of the group who did not receive post-protocol therapies, patients receiving bevacizumab showed trend towards better OS (8.7 versus 7.3 months in placebo arm; HR, 0.84; $p = 0.20$).[6] Secondly, the remarkably long median OS in control arm (13.1 months) in AVAiL trial might necessitate larger sample size in order to demonstrate statistically significant OS benefit. Thirdly, bevacizumab may be more effective with paclitaxel/carboplatin regimen than with gemcitabine/cisplatin regimen. Nevertheless, failure to demonstrate OS benefit in AVAiL, which findings clearly contrast with those of E4599, call into question the magnitude of benefits patients will gain from the addition of bevacizumab to standard chemotherapy.

In conclusion, bevacizumab added to palliative chemotherapy has improved PFS in two phase III trials and OS in one of these trials in selected patients with advanced NSCLC. Based on these results, bevacizumab has now been approved in the first-line treatment of nonsquamous NSCLC in many countries.

Safety and toxicity results

In E4599 trial, the rate of hypertension, proteinuria, bleeding, neutropenia, febrile neutropenia, thrombocytopenia, hyponatremia, rash, and headache were significantly higher in the bevacizumab arm than in the control arm.[2] There was significantly higher incidence of treatment-related toxic deaths in bevacizumab arm compared with the control arm (4.6% versus 0.5%, $p = 0.001$). The most serious, and sometimes fatal, adverse events (AEs) in patients receiving bevacizumab were pulmonary hemorrhage, gastrointestinal (GI) hemorrhage or perforation, neutropenic sepsis, and arterial-venous thrombosis (cerebrovascular event or pulmonary embolism). The bleeding events (grade ≥ 3), mainly represented by pulmonary hemorrhage, GI bleeding, central nervous system hemorrhage and epistaxis, were 4.4% in the bevacizumab arm versus 0.7% in the control arm ($p < 0.001$). In 1.9% of patients, these events were fatal versus 0.2% in the control arm.

In the AVAiL trial, the overall incidence of ≥ grade 3 AEs were similar across all arms.[3] The incidence of serious AEs did not differ between the placebo arm and the low-dose bevacizumab arm (35% in each arm), but were higher with the high-dose bevacizumab arm (44%). The rate of ≥ grade 3 hypertension, vomiting, neutropenia, bleeding, and proteinuria were modestly higher in the bevacizumab arms than in the placebo arm. Severe pulmonary hemorrhage was increased in the bevacizumab arms (1.5% in low-dose

bevacizumab arm versus 0.9% in high-dose bevacizumab arm versus 0.6% in placebo arm) and included 7 fatal events (2.1%). There was no observed increase in the incidence of arterial or venous thrombosis or GI perforation.

Bevacizumab use in high-risk group of developing hemorrhage: is the risk real?

The risk of a pulmonary hemorrhage with bevacizumab is of concerning toxicity, and investigation of risk factors for developing this toxicity is essential. In a pooled analysis of 1,142 bevacizumab-treated patients across three bevacizumab trials (AVF0757g, E4599 and AVAiL), only 21 cases (1.8%) of severe pulmonary hemorrhages were reported.[1-3] There was no evidence for an association between any baseline clinical variables (prior radiotherapy/surgery, age, gender, ECOG performance status) and the incidence of early-onset pulmonary hemorrhages.[8] Baseline tumour cavitation may be a potential risk factor for severe pulmonary hemorrhage. Central location, tumor size, vascular involvement, and tracheobronchial involvement was not associated with a higher risk of a severe pulmonary hemorrhage. Overall, pulmonary hemorrhage associated with bevacizumab-based regimen could be considered an uncommon event in a selected patients with nonsquamous NSCLC.

In the AVF0757g study, the incidence of severe or fatal pulmonary hemorrhage was 31% in patients with squamous histology and 4% in patients with histology other than squamous cell carcinoma, suggesting that squamous cell histology may be one of the possible risk factors for the development of a severe pulmonary hemorrhage.[1] However, because squamous cell carcinoma is more likely to be centrally located and have a greater tendency to cavitate, it is not clear if histology is the central risk factor for bleeding or simply a surrogate marker for other risk factors.[8] Moreover, patients with the central nervous system (CNS) metastasis have been excluded from bevacizumab trials based on the occurrence of fatal hemorrhages in hepatoma patients with brain metastasis in the earlier phase I study.[9] However, the risk of serious CNS hemorrhage for patients with CNS metastasis has not been formally evaluated. Therefore, one may ask whether bevacizumab is safe in patients with predominantly squamous NSCLC or whether bevacizumab increases the risk of CNS bleeding in patients who have CNS metastasis or who develop CNS metastasis during the course of therapy. Additional investigation of potential risk factors and strategies to reduce the severe hemorrhage should be warranted to safely expand the eligibility for bevacizumab-based therapy in these patients with advanced NSCLC.

To this end, the AVASQ and Bridge phase II trials are focused on patients with squamous NSCLC, whereas the PASSPORT trial is enrolling patients with treated CNS metastases. Preliminary data from PASSPORT and other study suggest the safety of bevacizumab in advanced NSCLC patients with treated CNS metastasis.[10] Furthermore, a retrospective analysis of E4599 and AVAiL study showed that bevacizumab did not appear to increase the risk of CNS hemorrhages in patients with documented CNS progression.[11] Preliminary analysis in over 1,000 patients enrolled in a Safety of Avastin in Lung (SAiL) study assessing the safety of bevacizumab combined with standard chemotherapy regimens also suggests safety of bevacizumab in patients with CNS metastasis during the course of therapy.[12]

There may be some valid concern about the effect of concomitant cardiovascular or anticoagulation medication on bevacizumab-based therapy. Preliminary reports from the SAiL study suggest that bevacizumab could be safely administered in advanced NSCLC patients receiving concomitant antihypertensive or anticoagulation medication.[13] Furthermore, in the AVAiL study, nine percent of the study population received therapeutic anticoagulation after the baseline, and no pulmonary hemorrhage was observed in these patients.[3]

Role of bevacizumab maintenance

It is unclear whether maintenance treatment beyond the completion of 4 to 6 cycles of chemotherapy offers an additional survival advantage. There is indirect evidence supporting the use of bevacizumab until disease progression. In a preclinical study, Vosseler, et al.[14] showed that early withdrawal of anti-vascular endothelial growth factor (VEGF) therapy resulted in rapid vessel regrowth. In an AVF0757g study, 19 of the 32 control patients crossed over to single agent bevacizumab on disease progression and five experienced disease stabilizations for more than 6 months.[1] Furthermore, the potential beneficial effect of bevacizumab maintenance may have impacted the impressive median survival (14.9 months) of the control group in this study. Other clinical support for continued VEGF inhibition came from phase III trials of metastatic colorectal cancer, demonstrating significant increases in PFS, regardless of tumour response, through the addition of bevacizumab to chemotherapy.[15] Given that over 90% of patients eligible for bevacizumab monotherapy received maintenance bevacizumab in the AVAiL study[3] and severe adverse events were rare in 215 patients receiving bevacizumab monotherapy in the E4599 study,[2] maintenance therapy with bevacizumab could be considered feasible and safe. Because the true value of maintenance bevacizumab can be determined only in the future phase III trial, it should be used, for the present, in all eligible patients.

Bevacizumab use in elderly population

In an exploratory analysis of E4599, elderly patients (age ≥ 70 years) experienced more toxicity with PCB compared with younger patients.[16] At least one episode of grade 3 or worse toxicity was noted in 87% of the elderly patients, compared with 70% of the younger patients on the PCB arm ($p < 0.001$). Furthermore, among the 15 treatment-related deaths recorded in the PCB arm, the incidence in the elderly was 6.3% compared with 2.6% in the younger cohort. In terms of efficacy, there were trends toward superior RRs (28.7% versus 17.3 with PC; $p = 0.067$) and PFS (median PFS, 5.9 months versus 4.9 months with PC; $p = 0.063$) with PCB for elderly patients. However, there was no significant difference in OS between PCB and PC (11.3 versus 12.1 with PC; $p = 0.4$). In elderly NSCLC patients, bevacizumab-based therapy was associated with a higher degree of toxicity, but no obvious improvement in survival compared with chemotherapy alone. The increased toxicity observed in elderly may have contributed to the absence of a survival benefit in the bevacizumab arm. Subgroup analysis of the AVAiL study to evaluate the outcome for elderly could provide additional information regarding the safety of bevacizumab-based therapy in these patients.

To date, no prospective data of bevacizumab-based regimen in elderly NSCLC patients are available. Therefore, elderly-specific prospective studies are crucial to establish the therapeutic index of bevacizumab-based therapy and, more importantly, help ascertain the appropriate dose of bevacizumab in those who are most vulnerable to the toxicities of therapy.[3]

Role of bevacizumab in Asian population

Based on two pivotal trials, could bevacizumab-based therapy be considered a new standard of care for first-line treatment of advanced NSCLC in Asian populations? As a matter of fact, most patients enrolled in the E4599 study were Caucasians (only 1.9% of patients were of Asian origin), preventing any exploratory analysis in the Asian subgroup.[2] Approximately 9% of patients enrolled in the AVAiL study were East Asians, and there appeared to be no difference in the beneficial effects of bevacizumab on PFS by ethnicity in the subgroup analysis.[3] Recently, small randomized phase II study of carboplatin and paclitaxel with or without bevacizumab in chemotherapy-naïve Japanese patients with advanced nonsquamous NSCLC (JO19907) showed the addition of bevacizumab to chemotherapy significantly improved PFS and RR.[17] The HR of PFS (HR, 0.55; $p = 0.0028$) seemed at least as good as previous trials of E4599 and AVAiL.

Several points should be addressed. Because it is well known that EGFR TKIs are more effective in Asian patients,[4] the potential survival impact of second-line therapy may be an important confounding factor that influences overall survival after disease progression on bevacizumab-based first-line therapy. Additionally, because median survival of Asians with advanced NSCLC was better than that of Western population, it might be more difficult to detect small, but potentially relevant, benefits from bevacizumab in Asians. However, since the predictive role of ethnicity for antiangiogesis therapy, in contrast to EGFR inhibitors, is not yet proven, a similar degree of survival benefits might be anticipated from bevacizumab-based first-line therapy in Asian populations.

Predictive biomarker for benefit from bevacizumab combination

In a biomarker analysis of E4599 study, patients with high VEGF levels were more likely to have an increased probability of response with the addition of bevacizumab (RR, 33% on PCB arm versus 7.7% on PC arm, $p = 0.01$) than those with low VEGF levels (RR, 28.6% on PCB arm versus 29% on PC arm, p = not significant), but this was not predictive of survival.[18] On the other hand, patients with low baseline ICAM had a higher response rate (32% versus 14%; $p = 0.02$), better overall survival ($p = 0.00005$), and better 1-year survival (65% versus 25%) than those with high ICAM, respectively, regardless of treatment arm.

When comparing PFS between the high-dose bevacizumab and placebo group in biomarker analysis of AVAiL study, there was a trend towards a larger treatment effect in patients with low ICAM-1 levels compared to patients with high ICAM-1 levels.[19] Comparing OS between the low-dose bevacizumab and placebo arms, a larger treatment effect was observed in patients with high bFGF levels compared to low bFGF levels.

CETUXIMAB

Summary of clinical trial results

The potential survival advantage by adding cetuximab to standard chemotherapy was first suggested in a randomized phase II trial-the Lung Cancer Cetuximab Study (LUCAS).[20] In this trial, cisplatin/vinorelbine plus cetuximab was compared with chemotherapy alone in 86 patients with EGFR-positive NSCLC. The addition of cetuximab improved the RR (35% vs. 28%), PFS (5.0 vs. 4.6 months), and OS (8.3 vs. 7.3 months), respectively. Skin toxicity was the most common cetuximab-related adverse event (10% grade 3 or 4). In a Canadian randomized phase II trial, Butts, et al.[21] reported a trend toward improved PFS and OS for cetuximab in combination with platinum and gemcitabine compared with chemotherapy alone. On the other

hand, BMS099 phase III trial testing cetuximab in combination with taxanes (either paclitaxel or docetaxel) and carboplatin in patients (n = 676; not screened for EGFR expression in tumor) with advanced NSCLC failed to show clear-cut advantages in PFS by the Independent Radiology Review Committee, the primary endpoint of the study, compared with chemotherapy alone.[22] However, several secondary efficacy endpoints, such as RR and PFS (based on investigator's assessment), favored the cetuximab combination. Additionally, mature survival results from this trial suggest a potential benefit from the addition of cetuximab with a median survival of 9.7 months vs. 8.4 months for the control arm, although it did not reach statistical significance (HR, 0.89, 95% CI, 0.754-1.051; $p = 0.17$). Overall, three phase II and one phase III trials clearly suggested potential survival benefits with predictable and manageable toxicity profiles in cetuximab-containing regimen.

Encouraging findings from the previous studies have been confirmed prospectively in a larger phase III trial- the First-Line in Lung Cancer with Erbitux (FLEX).[23] In this trial, patients stratified according to ECOG performance status (0-1 vs. 2) and disease stage (stage IIIB vs. IV) were randomized 1 : 1 to receive either cetuximab (400 mg/m^2 initial dose then 250 mg/m^2 weekly), cisplatin 80 mg/m^2 on day 1 and vinorelbine 25 (30) mg/m^2 on days 1 and 8 of a 3-week cycle or chemotherapy alone. After up to 6 treatment cycles, patients in the cetuximab arm could continue weekly cetuximab monotherapy until disease progression or unacceptable toxicity. Contrary to the E4599 and AVAiL studies, patients with squamous carcinoma and borderline performance status (PS; e.g., PS2) could be eligible. Based on the postulated action mechanism of cetuximab, eligible patients were required to show EGFR expression in tumors detected by immunohistochemistry (IHC). The median OS, the primary endpoint, was significantly prolonged in patients treated with cetuximab in combination with chemotherapy (11.3 months) compared with chemotherapy alone (10.1 months) (HR 0.871, 95% CI 0.762-0.996; $p = 0.044$). Regarding the secondary endpoints, RR was significantly better in the cetuximab arm (36% vs. 29%, $p = 0.012$), whereas the median PFS was 4.8 months in both arms. Pre-specified subgroup analysis showed the survival benefit, regardless of histology, ECOG PS, gender, and age. This observation clearly contrasts with the results of bevacizumab, and potentially establishes cetuximab in combination with chemotherapy as a standard option in bevacizumab-ineligible patients, particularly those with squamous histology or PS2. Furthermore, given that the bevacizumab combination did not improve survival in elderly patients, the cetuximab combination might be a more reasonable option to choose in this frail population.

A recent meta-analysis of phase II/III trials based on 2,018 individual patient data demonstrated a significant benefit of adding cetuximab to first-line chemotherapy in terms of OS (HR, 0.878; $p = 0.010$), PFS (HR, 0.899; $p = 0.036$) and RR (odds ratio, 1.463; $p < 0.001$), respectively, over chemotherapy alone.[24]

Impact of FLEX in Asian population

The results of FLEX are also remarkable in highlighting a discordance in outcome between white and Asian patients.[25] Asian populations, accounting for approximately 10% of patients (n = 121) in this trial, showed a median survival nearly double that observed in white populations. However, cetuximab offered no additional benefit to Asian populations. In fact, patients receiving chemotherapy alone appeared to be slightly better, with a median survival of 20.4 months compared with 17.6 months for receiving cetuximab combination. It should be noted, however, that potential bias might explain this observation: the proportion of adenocarcinoma, which is a well-known predictor of EGFR TKI response, was significantly higher in the control arm than in the cetuximab arm (80% versus 65%). Moreover, more patients in the control arm received EGFR TKI post-study, compared with those in the cetuximab arm (73% versus 50%). These factors might obscure survival benefit from first-line cetuximab among Asian populations. Because of the potential biases and the lack of adequate power, the subset analysis cannot be inappropriately used to deny the benefit of cetuximab in Asian populations.

Among Caucasian populations (n = 946), the survival benefit from adding cetuximab appeared more prominent, with a median survival of 10.5 months compared with 9.1 months for the control arm (HR, 0.80; $p = 0.003$). Given the latest interest in histology, patients with adenocarcinoma demonstrated a 1.7 months survival benefit from cetuximab (12.0 versus 10.3 months; HR, 0.81). A significant survival benefit was also seen in patients with squamous cell carcinoma (10.2 versus 8.9 months; HR, 0.79).

Safety and toxicity results

The principal cetuximab-related adverse events in FLEX study were acne-like rash (only grade 3, 10%), diarrhea (5%), and infusion reactions (4%), respectively.[23] These toxicities typical of EGFR inhibitors were predictable and manageable. The incidence of febrile neutropenia was significantly higher in the cetuximab arm, compared with in control arm (22% vs. 15%, $p < 0.05$). However, other previous studies evaluating cetuximab in combination with platinum-based chemotherapy have shown considerably lower rates of febrile neutropenia.[21,22] Furthermore, febrile neutropenia in the cetuximab arm neither increased the incidence of sepsis or treatment-related deaths nor interfered with drug delivery. However, high incidences of

febrile neutropenia and grade 4 neutropenia in the cetuximab arm in the FLEX and LUCAS trials warrants special attention, especially when combining cetuximab with cisplatin/vinorelbine.[20,23]

Predictive biomarkers for benefits from cetuximab combination

Is a 1.2 months improvement in median OS worth it, albeit high cost? As was discussed at the American Society of Clinical Oncolgy in 2008, the median survival benefit to 2.5 months is essential for cetuximab-based therapy to be cost-effective. Therefore, selecting patients who might truly benefit from cetuximab is one of the most important research questions that needs to be addressed. The predictive value of EGFR protein expression for cetuximab-treatment still remains controversial. For example, some studies in metastatic colorectal cancer have suggested that cetuximab showed activity in patients without EGFR expression as determined by IHC.[26,27] Given that 85% of patients screened showed EGFR positivity, it may be true that there was little, if any, patient selection based on biomarkers in the FLEX study.[23] In this virtually 'unselected' population, it may be inevitable that overall clinical benefit from the addition of cetuximab is only modest. However, it is also conceivable that exclusion of EGFR-negative patients might have eliminated the pool of patients who were least likely to benefit. Therefore, until the discovery of an alternative biomarker for cetuximab, confirmation of EGFR expression by IHC may be required for the use of cetuximab in advanced NSCLC.

Then, what are the leading candidates as predictors of cetuximab efficacy? Recently, Hirsch, et al.[28] reported that EGFR gene copy numbers detected by fluorescent in situ hybridization (FISH) were associated with better outcomes in non-small-cell lung cancer (NSCLC) patients receiving chemotherapy with cetuximab in a randomized phase II trial (S0342). Among various biomarkers other than EGFR, KRAS mutation has received the most attention. Many studies have consistently shown that KRAS mutation predicts cetuximab resistance in colorectal cancer.[29,30] Development of skin rash during treatment might also be a potential predictor for significant benefit from cetuximab-based therapy, as was the case for various cancer types.[31]

In a recent biomarker analysis of FLEX study, skin rash of any grade during the first cycle, but not EGFR or KRAS mutation status, was associated with significantly better survival (median OS, 15.0 versus 8.8 months in patients who did not develop first cycle rash; HR= 0.63, $p < 0.001$).[32]

In conclusion, cetuximab is the first EGFR-targeted agent to demonstrate a survival benefit in combination with chemotherapy in the first-line treatment of advanced NSCLC regardless of histology, KRAS mutation status, and EGFR gene copy number. Results from FLEX and earlier studies strongly suggest that cetuximab in combination with platinum-based chemotherapy improves survival in patients with advanced EGFR-expressing NSCLC.

CONCLUSION

After a series of failures to demonstrate survival benefits of targeted agents plus chemotherapy in 15 randomized phase III trials with over 12,000 patients accrued, we eventually took a step forward in the first-line treatment of advanced NSCLC. Both bevacizumab and cetuximab are also likely to work in Asian patients with advanced NSCLC. Two strategies of targeting VEGF with bevacizumab or EGFR with cetuximab are complementary to improve the survival of a broad population of patients with advanced NSCLC, and hopefully open new opportunities in the treatment of those stricken with this debilitating disease in the near future. No data to support selecting patients for bevacizumab or cetuximab based-therapy on biomarker status are currently available. Given the high cost and the modest benefit with potentially serious toxicity from the addition of either of these agents to standard chemotherapy, further researches to identify biomarkers for predicting significant benefits are urgently needed.

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