Research Review
SPEAKER SERIES

Advances in the treatment of non-small cell lung cancer

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Dr Roman Perez-Soler M.D.

Chairman, Department of Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York.

Dr Roman Perez-Soler received his M.D. from the Universidad Autonoma, Barcelona, Spain in 1977 and completed his fellowship in Medical Oncology at the MD Anderson Cancer Center in Houston, Texas in 1982.

His research interests and accomplishments are in the area of drug delivery of antitumour agents and new therapies for lung cancer, encompassing drug discovery, preclinical studies and early clinical studies.

His laboratory has been funded by the NIH since 1989 for the development of new tumour targeted therapies using a variety of drug delivery systems. He was a leading investigator for early Phase II studies of topotecan and erlotinib in small cell lung cancer and non-small cell lung cancer, respectively, which led to the pivotal studies.

He is currently a member of the editorial boards of Clinical Cancer Research and the Journal of Clinical Oncology. He has authored 170 publications and is an inventor on 16 patents for new antitumour agents and ways to treat drug-related toxicities.

This publication is a summary of a presentation by Dr Roman Perez-Soler, Gutman Professor of Medicine, Chairman of the Department of Oncology at Montefiore Medical Center, Chief of the Division of Medical Oncology, and Associate Director for Clinical Research at the Albert Einstein College of Medicine, Bronx, New York. He spoke throughout New Zealand in August 2011 about advances in the treatment of non-small cell lung cancer (NSCLC).

Lung cancer is a disease caused by cumulative carcinogen-induced genetic damage to the bronchial epithelium. In smokers, tobacco is the carcinogen that after 20-40 years may lead to hyperplasia, dysplasia, carcinoma and eventually invasive carcinoma. There is now an understanding of the molecular mechanisms involved in the development of this disease. Namely, cellular proliferation through independent growth signalling, cellular acquisition of an insensitivity to antigrowth signals and promotion of survival signals resulting in a limitless potential for replication.

Recent advances in the treatment of non-small cell lung cancer (NSCLC) have significantly improved patient outcomes. Such advances include the use of adjuvant chemotherapy for patients with stage IB-IIIA disease (this has increased the chance of cure by 5-10%), the use of erlotinib [Tarceva] as second-line therapy in wild-type (wt) epidermal growth factor receptor (*EGFR*) tumours, angiogenesis blockade with bevacizumab [Avastin] in front-line chemotherapy, the switching of maintenance therapy in patients who benefit from front-line therapy, the development of genetically-driven therapies targeting *EGFR* mutations and anaplastic lymphoma kinase (ALK) mutations, and the use of spiral computed tomography screening for the early detection of disease.

Major genetic abnormalities in lung cancer

Molecular profiling can explain the heterogeneity of lung cancer and direct therapy. It is now possible to categorise an individual's type of lung cancer on more than just a histological basis. A number of genetic abnormalities in patients with lung cancer have been known for years. Unfortunately, some of the most common known mutations, such as the *p53* mutation which is present in 50-75% of lung cancer patients, have not been targeted therapeutically. The optimal goal with the *p53* mutation would be to replace the non-functional *p53* with *p53* wt, thus restoring function. Another mutation known for many years, the *KRAS* mutation which occurs in 10-30% of patients with the adenocarcinoma type of NSCLC, has not yet been successfully targeted with a *KRAS* mutant inhibitor. However, one of the more recently discovered mutations, the *EGFR* kinase mutation has been successfully targeted. This mutation is present in 10-40% of patients with the adenocarcinoma subtype of NSCLC, but is very rare in patients with the squamous cell carcinoma subtype of NSCLC, or in patients with SCLC. Other mutations identified in some patients with lung cancer include the MET, ALK, HER2 and PIK3CA mutations.

EGFR mutations

The *EGFR* tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib [Iressa] have been available since the mid 1990s, and it became evident early on in their use in lung cancer that some patients did particularly well on these agents. It has subsequently been discovered that such patients are those exhibiting *EGFR* mutations.[1] Gazdar et al have shown that most mutations occur in the TK domain of the *EGFR* gene and while exon 19-21 mutations account for 85% of *EGFR* mutations, mutations also occur on other regions of the gene.[1] Furthermore, a secondary mutation, the T790M mutation has been associated with resistance to TKIs.[1]

In early studies of TKIs in NSCLC, certain patient subgroups appeared to have higher response rates, namely non-smokers, females, Japanese and those with adenocarcinoma.[2] Not surprisingly, *EGFR* mutations are predominantly found in these types of patients.[2] However, a small percentage of smokers do exhibit *EGFR* mutations. This factor has raised the controversial issue of whether or not all patients with lung cancer should be screened for such mutations. Dr Perez-Soler says that in the US, the tendency is to test all patients with non-squamous histology.

ALK rearrangement

One of the newest molecular targets in NSCLC is the EML4-ALK fusion oncogene.[3] EML4-ALK possesses potent oncogenic activity and can be effectively blocked by small-molecule inhibitors that target ALK. An agent targeting this rearrangement is currently being developed.

Importance of identifying NSCLC subtype

Dr Perez-Soler emphasises the importance of identifying which subtype (squamous or non-squamous) of NSCLC a patient exhibits. This is an important issue as it impacts significantly on a patient's response to therapy. One out of five NSCLC patients will have squamous carcinoma, while four out of five patients will have the non-squamous form (either adenocarcinoma or large cell carcinoma). He points out that pemetrexed [Alimta] and bevacizumab [Avastin] are not effective in patients with squamous histology and emphasises that adequate amounts of tissue need to be obtained at the time of biopsy in order to perform both histological and molecular analysis. He believes that the gains of taking a larger amount of tissue outweigh the risks in most cases.

Randomised trials of chemotherapy +/- targeted therapies

By the end of the 1990s, several new agents had been developed for the treatment of lung cancer, and combination chemotherapy gave a median survival of approximately 10 months. At the beginning of the new millennium, the aim in treatment was to find new front-line therapies exhibiting higher efficacy with reduced toxicity. The strategy was to add new molecular-targeted agents to existing chemotherapy regimens (gemcitabine/cisplatin or paclitaxel/carboplatin). While a number of randomised trials aimed at a variety of molecular targets in treatment-naïve patients with NSCLC were undertaken, only a few showed benefit. These were the Roche E4599 and Avastin in Lung (AVAiL) studies looking at the addition of bevacizumab to first-line chemotherapy, and the Merck FLEX (First-line in Lung Cancer with Erbitux) study which investigated the addition of cetuximab (Erbitux).[4-6]

Bevacizumab

The exact mechanism of action of the monoclonal antibody bevacizumab on tumour cells is not fully understood, but it appears that the agent blocks vascular endothelial growth factor [*VEGF*] -induced tumour angiogenesis by binding and thereby neutralising *VEGF*. It is postulated that the agent works on three particular mechanisms; inhibition of new tumour vasculature, regression of existing tumour microvasculature and normalisation of remaining tumour vasculature.[7-11] Normalisation of tumour vasculature increases the rate at which antineoplastic agents can enter to the tumour. These mechanisms constitute the current explanation for the increased response rate seen by adding bevacizumab to chemotherapy.

Phase III trials of bevacizumab

The phase III E4599 trial, which commenced in 2001, was designed to investigate if the addition of bevacizumab to paclitaxel/carboplatin improves survival in patients with stage IIIB/IV non-squamous-cell NSCLC.[4] A total of 878 patients were randomised to paclitaxel/carboplatin alone (n = 444) or paclitaxel/carboplatin + bevacizumab 15 mg/kg every three weeks (n = 434). Chemotherapy was repeated every 21 days for a total of six cycles unless there was evidence of disease progression or drug intolerance. The median overall survival (OS) and progression-free survival (PFS) were 12.3 months and 6.2 months in the paclitaxel/carboplatin + bevacizumab group compared with 10.3 months and 4.5 months in the paclitaxel/carboplatin group: hazard ratio [HR] for death 0.79 (95% CI 0.67-0.92); HR for disease progression 0.66 (0.57-0.77). Furthermore, a pre-planned retrospective subgroup analysis of the E4599 study revealed that patients with adenocarcinoma exhibited the greatest benefit of bevacizumab therapy, with an increase in OS of 3.9 months (OS 14.2 months vs 10.3 months for controls; HR 0.69 [95% CI 0.58-0.83]).[12]

Dr Perez-Soler says that the best data available supporting the use of bevacizumab in lung cancer comes from the E4599 trial and, therefore, in the US bevacizumab is used with paclitaxel/carboplatin and not with cisplatin/gemcitabine.

The safety profile of bevacizumab

Despite reports of fatal lung haemorrhage (particularly in patients with squamous-cell carcinoma) and bleeding in the brain of patients receiving bevacizumab, the agent has a well-established safety profile from experience with more than 5000 NSCLC patients across clinical trials.[4,5,13-15]

With regard to ≥ grade 3 adverse events of special interest, bleeding (all types) has occurred at a rate of 3.6%-4.4%, pulmonary haemorrhage/haemoptysis at a rate of 0.7%-1.9%, hypertension at a rate of <5%-8.5% and proteinuria at a rate of <1%-3%.[4,5,13-15] Findings from the Avastin Regimens: Investigation of Treatment Effects and Safety (ARIES) and the Safety of Avastin in Lung (SAiL) studies indicate that there is no increased risk of ≥ grade 3 pulmonary haemorrhage/haemoptysis with bevacizumab in patients receiving concomitant anticoagulation therapy.[15,16]

However, Dr Perez-Soler emphasises that it is important to carefully select patients for treatment with bevacizumab. He points out that 8/10 patients can safely receive bevacizumab, but that the agent should not be used in patients with large tumours invading major blood vessels or in patients with a history of gross haemoptysis or significant cardiovascular dysfunction.

Pemetrexed/cisplatin vs gemcitabine/cisplatin

In second-line therapy, pemetrexed has exhibited equivalent efficacy to other standard chemotherapy agents and has a good tolerability profile.[17,18] Further progress in the treatment of advanced NSCLC has come from the findings of a phase III study sponsored by Eli Lilly comparing the efficacy of pemetrexed/cisplatin with that of the standard and widely used regimen gemcitabine/cisplatin in first-line therapy.[19] In this non-inferiority trial, referred to as JMDB, patients received either cisplatin 75 mg/m^2 on day 1 plus IV pemetrexed [Alimta] 500 mg/m^2 every 21 days (n = 862) or cisplatin 75 mg/m^2 on day 1 plus gemcitabine [Gemzar] 1250 mg/m^2 on days 1 and 8 (n = 863) for up to six cycles.

The study findings confirmed that pemetrexed/cisplatin was non-inferior to gemcitabine/cisplatin with no difference in median survival between the two regimens (10.3 months each).[19] However, a pre-planned analysis revealed that median OS was significantly longer for pemetrexed/cisplatin versus gemcitabine/cisplatin in patients with adenocarcinoma (12.6 months vs 10.9 months; adjusted HR 0.84 [95% CI 0.71-0.99]; n = 847) and large-cell carcinoma (10.4 months vs 6.7 months; adjusted HR 0.67 [0.48-0.96]; n = 153). In contrast to this finding, patients with squamous-cell carcinoma exhibited a shorter median OS on pemetrexed/cisplatin than they did on gemcitabine/cisplatin (9.4 months vs 10.8 months; adjusted HR 1.23 [95% CI 1.00-1.51]; n = 473). The study also revealed that the pemetrexed/cisplatin regimen was associated with fewer treatment-related grade 3/4 haematologic toxicities than the gemcitabine/cisplatin regimen.[19]

Dr Perez-Soler says that these findings indicate that pemetrexed is a suitable agent for first-line use in patients with non-squamous NSCLC, but should not be used in patients with squamous-cell carcinoma.

First-line regimens in adenocarcinoma

A comparison of findings from subgroup analysis on adenocarcinoma patients in the phase III JMDB, FLEX and E4599 studies reveals that the greatest benefit in OS is with bevacizumab-based therapy, with an observed increase in median OS of approximately 4 months in this group of patients (see **Figure 1**).[6,12,19]

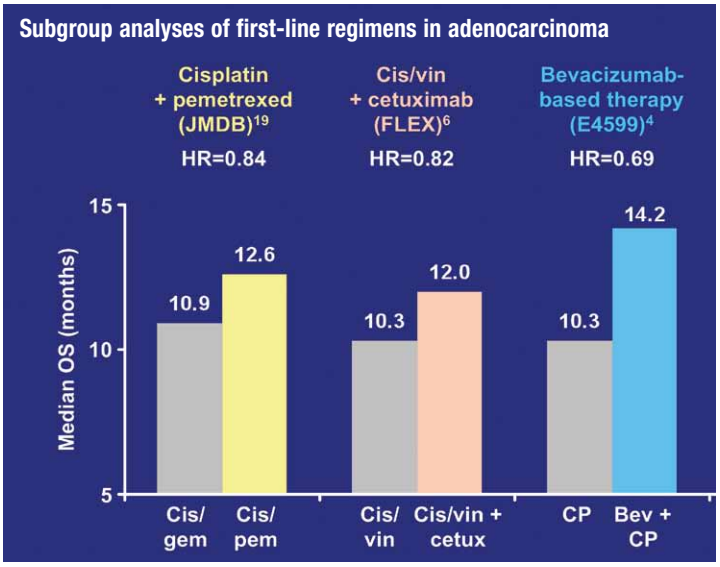

Figure 1: Median overall survival (OS) reported in subgroups analyses from four studies investigating first-line regimens in adenocarcinoma.[6,12,19]

Bev = bevacizumab; cetux = cetuximab; Cis = cisplatin; CP = carboplatin/paclitaxel; gem = gemcitabine; HR = hazard ratio; OS = overall survival; pem = pemetrexed; vin = vinorelbine

Ongoing issues with bevacizumab

Dr Perez-Soler says that despite earlier concerns, he does not believe toxicity to be an issue with bevacizumab. One of the issues with the agent is that even though all tumours use *VEGF* to perfuse vessels, and patients do well initially with bevacizumab, when the agent is given as maintenance therapy some tumours continue to grow. A focus of future research with bevacizumab will be to further determine mechanisms of resistance and to develop predictive biomarkers to identify which patients will do well on the agent.

Maintenance therapy: a new treatment approach in advanced NSCLC

In the 1990s, treatment guidelines for patients with a diagnosis of NSCLC recommended giving 4-6 cycles of platinum-based doublet chemotherapy and then to watch and wait for disease progression before administering second- and third-line regimens. With the development of less toxic chemotherapeutic agent such as pemetrexed and erlotinib, the idea arose of giving patients first-line chemotherapy and then immediately starting pemetrexed or erlotinib as maintenance therapy.

Amongst several phase III studies investigating a variety of agents including docetaxel, erlotinib, pemetrexed, gefitinib and gemcitabine, the two chemotherapeutic agents showing the greatest survival benefits were pemetrexed in the JMEN study and erlotinib in the Sequential Tarceva in Unresectable NSCLC (SATURN) study.[20,21]

The randomised double-blind JMEN study involved 663 patients with stage IIIB or IV NSCLC who had not progressed on 4 cycles of platinum-based chemotherapy and were given either pemetrexed 500 mg/m^2 on day 1 plus best supportive care (n = 441) or placebo plus best supportive care (n = 222) every 21 days until disease progression.[20] PFS was significantly increased in the pemetrexed group compared with placebo group (median 4.3 months vs 2.6 months; HR 0.50 [95% CI 0.42-0.61]), as was OS (median 13.4 months vs 10.6 months; HR 0.79 [0.65-0.95]). Furthermore, subgroup analysis of PFS and OS for patients with adenocarcinoma revealed HRs of 0.51 and 0.73, respectively, in favour of pemetrexed therapy.

Similar findings were seen in the randomised SATURN study in which 889 patients with advanced NSCLC whose disease had not progressed following first-line platinum-based doublet therapy received erlotinib 150 mg/day (n = 438) or placebo (n = 451) until disease progression or unacceptable toxicity.[21] In this study, median PFS was increased with erlotinib compared with placebo (12.3 weeks vs 11.1 weeks; HR 0.71 [95% CI 0.62-0.82]), as was median OS (HR 0.81). Subgroup analysis of PFS and OS for patients with adenocarcinoma revealed HRs of 0.60 (95% CI 0.48-0.75; n = 401) and 0.77 (0.61-0.97; n = 403), respectively, in favour of erlotinib therapy.

Erlotinib: efficacy in squamous-cell carcinoma

The efficacy of erlotinib has been demonstrated in patients with squamous-cell carcinoma of the lung in two large randomised, placebo-controlled studies, the SATURN study[21] and the BR.21 trial by Roche.[22] In the SATURN study, subgroup analysis of patients with squamous-cell carcinoma (n = 360) demonstrated a HR for PFS of 0.76 (95% CI 0.60-0.95) and a HR for OS of 0.86 (0.68-1.10), in favour of treatment with erlotinib.[21]

The BR.21 trial was designed to test the efficacy of erlotinib in patients with stage IIIB or IV NSCLC whose disease had progressed following first- or second-line chemotherapy. Subgroup analysis of patients with squamous-cell carcinoma (n = 222) demonstrated a HR for PFS of 0.53 (95% CI 0.39-0.70) and a HR for OS of 0.67 (0.50-0.90), in favour of treatment with erlotinib.[22] In this study, both PFS and OS with erlotinib were slightly better for patients with squamous-cell carcinoma than for those with adenocarcinoma.

Response to erlotinib and pemetrexed is dependent on induction response

Pre-planned sub-analysis of data from the SATURN study revealed that while erlotinib maintenance therapy significantly prolonged PFS in patients with stable disease (SD) and complete or partial remission (CR/PR) following first-line platinum-based doublet chemotherapy, OS was significantly prolonged in the SD group only (HR = 0.72; 95% CI 0.59-0.89).[22] The erlotinib-related OS benefit in the SD group remained significant irrespective of tumour histology and/or *EGFR* mutation status.

This phenomenon was also seen in data from the JMEN study (using pemetrexed for maintenance therapy) in which patients with non-squamous NSCLC who demonstrated a response to initial therapy (CR/PR) had a HR for OS of 0.81 (p = 0.198) compared with those who remained stable (HR 0.61; p < 0.005).[20]

Dr Perez-Soler says that patients with SD may well be a mixed bag, with many having early progressive disease who, therefore, respond well to what is essentially early second-line therapy in the form of maintenance therapy.

Second-line therapy

In the early 1990s, most patients with NSCLC were not receiving second-line therapy. One of the first studies investigating agents for second-line therapy in this setting was by Shepherd et al investigating docetaxel.[23] Their study showed superiority of docetaxel over best supportive care and this agent became the agent of choice for second-line therapy.

During the new millennium, two new agents have been used in second-line therapy, erlotinib and pemetrexed and these agents have shown similar efficacy to each other and to docetaxel.[17,22-25] Docetaxel, however, appears to be the most toxic of the three agents.[17]

Dr Perez-Soler says that while erlotinib, pemetrexed and docetaxel are similarly efficacious as second-line therapy for NSCLC, his tendency is to choose the least toxic agent for his patients. His personal choice in this setting is to give either erlotinib or pemetrexed. He adds that in choosing which of these agents to use, one must consider which agent the patient has received for first-line therapy and to consider if the patient may have an *EGFR* mutation (in which case erlotinib would be the agent of choice).

While pemetrexed has been shown to be non-efficacious for patients with squamous-cell tumours[19], erlotinib has been shown to be effective in both squamous and non-squamous NSCLC.[21,22] Furthermore, it appears that while TKIs are efficacious in first-line therapy only in patients with *EGFR* mutant tumours,[1] in second-line therapy, erlotinib, is also efficacious in patients with wt tumours.[26] Recent findings from the ISEL study by AstraZeneca investigating gefitinib in second-line therapy have shown that the agent is not efficacious in patients with *EGFR* wt tumours.

Pharmacokinetics of erlotinib in smokers

It appears that the pharmacokinetic profile for erlotinib is very different in smokers than in non-smokers. Studies by Hamilton et al have shown that following a single dose of erlotinib 150mg, the geometric mean erlotinib $AUC_{0-\infty}$ in smokers was 2.8-fold lower than in non-smokers, the C_{max} in smokers was two-thirds of that in nonsmokers and C_{24hr} was 8.3-fold lower for smokers.[27] The likely explanation for this phenomenon is that cigarette smoke induces CYP enzymes responsible for the metabolism of erlotinib.

Dr Perez-Soler says that one option for smokers would be to give a higher dose of erlotinib, but that this is an expensive option. He believes that smokers should be told that they should quit before receiving the agent. He adds that some active smokers have been seen to develop a rash with erlotinib after quitting smoking.

Treatment algorithms

In summary, Dr Perez-Soler presented three treatment algorithms (see **Figures 2-4**) outlining the way that the majority of oncologists in the US, himself included, treat patients with NSCLC dependent on their *EGFR* status and the type of histology they exhibit (squamous or non-squamous).

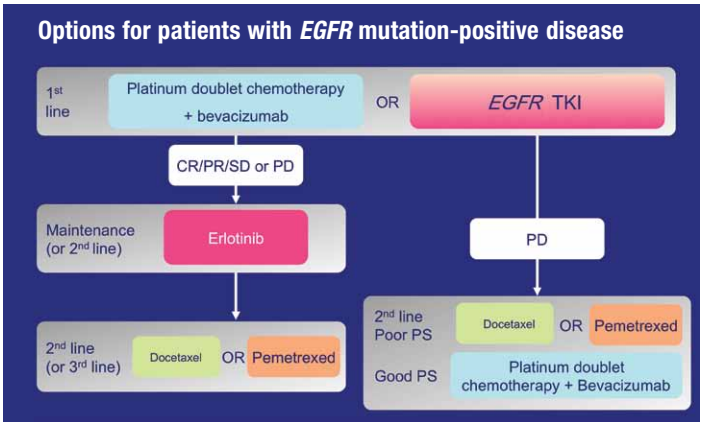

Figure 2: Treatment algorithm for patients with non-small cell lung cancer (NSCLC) exhibiting epidermal growth factor receptor (*EGFR*) mutation-positive disease.

EGFR = epidermal growth factor receptor; CR/PR/SD = complete response/partial response/stable disease; PD = progressive disease; PS = performance status

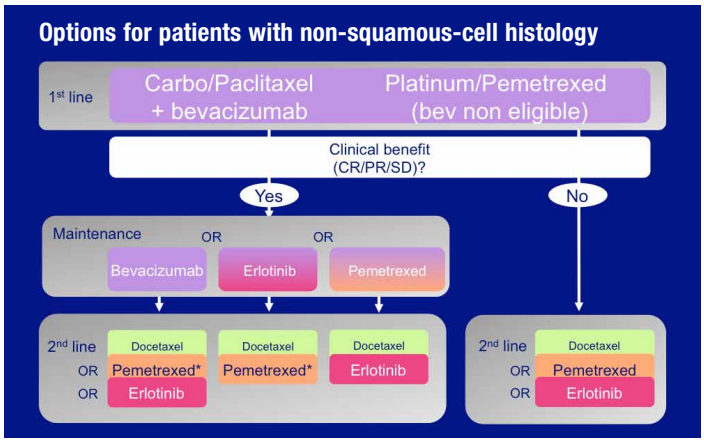

Figure 3: Treatment algorithm for patients with non-small cell lung cancer (NSCLC) with non-squamous-cell histology.

bev = bevacizumab; Carbo = carboplatin; CR/PR/SD = complete response/partial response/stable disease

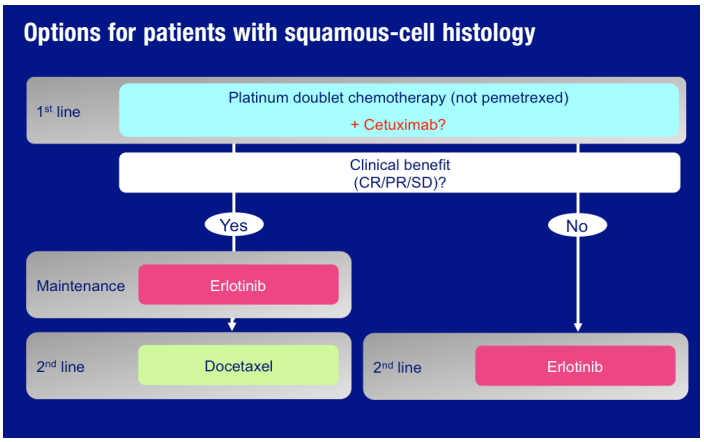

Figure 4: Treatment algorithm for patients with non-small cell lung cancer (NSCLC) with squamous-cell histology.

CR/PR/SD = complete response/partial response/stable disease

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