ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Molecular Marker Analyses From the SATURN Trial

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H&O Can you discuss the SATURN trial?

WB The SATURN (Sequential Tarceva in Unresectable Non–Small-Cell Lung Cancer) trial was a maintenance trial in patients with advanced, inoperable, metastatic non-small cell lung cancer (NSCLC). Patients were first treated with first-line chemotherapy with a platinum doublet. The chemotherapy was investigator's choice, with either cisplatin and gemcitabine or carboplatin and paclitaxel. After 4 cycles, the patients who were stable or who had partial (PR) or complete remission (CR) were randomized to receive either placebo or erlotinib (Tarceva, Genentech/OSI Pharmaceuticals) as maintenance at the conventional dose of 150 mg/day until disease progression. Of note was that all patients were required to provide tumor tissue prior to any therapy. The co-primary endpoints were progression-free survival (PFS) in all patients, as well as in the subset of patients who were epidermal growth factor receptor (EGFR)-positive by immunohistochemistry (IHC). All histologies of NSCLC were included in the study. The findings showed that all patients had some kind of benefit from erlotinib treatment regardless of EGFR mutation status, EGFR protein expression level, EGFR gene copy number, or *KRAS* mutation status. The biomarker analyses were performed to determine which patients had the greatest magnitude of benefit. There were 2 important publications discussing the SATURN findings. In the *Lancet Oncology,* Cappuzzo and colleagues described the total study population and the clinical results. They concluded that first-line maintenance with erlotinib could be considered in patients who do not progress after 4 cycles of chemotherapy. A paper published in the *Annals of Oncology* by Coudert and coworkers stated that patients with stable disease, but not PR or CR, had an overall survival (OS) benefit from erlotinib maintenance treatment.

H&O Why was this trial of importance?

WB The SATURN trial is significant because it was the first prospective clinical phase III study that mandated tumor tissue collection in every single patient. Prior biomarker studies in NSCLC, like BR.21 (OSI-774 [Tarceva] in Treating Patients With Stage III or Stage IV Non-Small Cell Lung Cancer) and ISEL (Iressa Survival Evaluation in Lung Cancer), did not require tissue collection, and any biomarker analyses were performed as post-hoc nonplanned and not prespecified analyses; only patients who donated tumor samples were analyzed.

H&O Can you discuss the prospective analysis of the biomarkers in the SATURN trial?

WB The PFS benefit was seen in all patients who received erlotinib compared to placebo (hazard ratio [HR], 0.71); this was statistically significant but not very clinically relevant. As previously mentioned, all subgroups—regardless of EGFR mutation status, EGFR protein expression level, EGFR gene copy number, or *KRAS* mutation status—showed some kind of benefit. However, the greatest benefit was observed in the EGFR mutation-positive group (HR, 0.10), with a 90% reduction in the risk of

disease progression with erlotinib compared to placebo. Although this was highly statistically significant and predictive of PFS, only 11% of patients had an activating EGFR mutation. The results also showed that there was no predictive value of EGFR-IHC, fluorescence in situ hybridization analyses, or receptor polymorphism.

H&O The study demonstrated feasibility in prospective biomarker collection. What are the implications of this finding?

WB I think it is necessary to collect tumor samples prospectively. Erlotinib is approved as a treatment in the second- and third-line settings, and in these situations, testing the tumor for an EGFR mutation is not required. However, if we are considering treating NSCLC patients with erlotinib or other TKIs in the first-line setting, it is necessary to show that they indeed have an activating EGFR mutation. Based on the biomarker study published by my colleagues and I in the *Journal of Clinical Oncology*, it is evident that only those patients who have an EGFR mutation have the greatest magnitude of benefit.

Outside of a clinical trial, it is questionable whether erlotinib should be given as maintenance treatment because the clinical benefit is quite small. Treatment should be discussed with patients on an individual basis. In patients who do not have any symptoms, it is not quite clear whether the use of erlotinib improves OS, even in patients with stable disease. If a patient has an activating EGFR mutation, it is clear that he/she is a candidate for erlotinib maintenance if he/she has not received it as first-line therapy.

H&O Why is the idea of incorporating EGFR markers into clinical decision-making controversial?

WB I think it is a contended topic because, as previously mentioned, in the second- and third-line settings, it is not required to test the tumor for EGFR mutation status prior to administering erlotinib. Only if the patient is being treated upfront with an EGFR tyrosine kinase inhibitor (TKI) like erlotinib or gefitinib (Iressa, AstraZeneca), must we prove that the patient does indeed have an activating EGFR mutation. The cost of testing also contributes to this debate; I think biomarker testing will become more widespread, but we hope that it will be less costly in the near future.

In Germany and several other European countries, many patients are not tested for an EGFR mutation because even if they have a mutation, they will still receive erlotinib in the second- or third-line setting. It is also known that even if a patient has received EGFR TKI inhibition as maintenance and this patient has a mutation, the OS does not improve with treatment, since the vast majority of patients will receive erlotinib later in the course of their disease (ie, in the second- or third-line setting). The main discrepancy in terms of testing is that the crossover of placebo patients to erlotinib dilutes the effect of OS benefit.

H&O Where should research efforts focus?

WB It is increasingly more important to get molecular markers determined upfront so that we are better able to choose the right treatment for every patient with NSCLC. If the goal is to provide more personalized treatment, we need to find the right target and attack it with the appropriate treatment.

In addition, we know that even if patients respond very well to EGFR TKI inhibition at one point in time—that is, approximately 1 year after starting treatment—they will develop secondary resistance. The main focus of research is therefore to overcome this resistance by either adding a novel TKI which also works in patients with secondary resistance mutations, or by discovering novel targets.

Suggested Readings

Brugger W, Triller N, Blasinska-Morawiec M, et al. Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non-small-cell lung cancer. *J Clin Oncol*. 2011;29:4113-4120.

Brugger W, Triller N, Blasinska-Morawiec M, et al. Biomarker analyses from the phase III placebo-controlled SATURN study of maintenance erlotinib following first-line chemotherapy for advanced NSCLC. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27:15s. Abstract 8020.

Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol*. 2010;11:521-529.

Coudert B, Ciuleanu T, Park K, et al. Survival benefit with erlotinib maintenance therapy in patients with advanced non-small-cell lung cancer (NSCLC) according to response to first-line chemotherapy. *Ann Oncol*. 2011; Epub ahead of print.