

INFORM; C-TONG 0805: a multicenter, double blind randomized phase III trial of maintenance gefitinib compared to placebo in advanced non-small cell lung cancer

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The standard first-line therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) is platinum-based chemotherapy (1). With standard first line platinum-based therapy approximately 75% of patients will obtain disease control, the median progression-free survival (PFS) is 4-6 months, and median overall survival (OS) is 10-13 months (2-5). Phase III trials that investigated a longer duration compared to a shorter duration of platinum-based therapy failed to reveal an improvement in OS with the longer duration of therapy (6-9). This led to phase III trials of maintenance therapy with single agent chemotherapy or epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) to extend the duration of therapy (10,11). The goal of maintenance therapy is to delay disease progression and consequently improve OS and maintain health-related quality of life (HRQOL). In order to achieve these goals the therapy must have a low rate of grade 3 or 4 toxicity and limited cumulative toxicity so that patients can tolerate the extended duration of therapy. A phase III trial of gefitinib compared to docetaxel revealed the non-inferiority of gefitinib in an unselected patient population, and a lower rate of grade 3 or 4 neutropenia febrile neutropenia and of all grades of asthenia (12). Thus, gefitinib is an attractive maintenance agent.

The INFORM; C-TONG 0804 trial randomized patients who had completed four cycles of platinum-based therapy without disease progression or unacceptable toxicity to gefitinib or placebo; the primary end-point was PFS (13). Patients assigned to the gefitinib arm (n=148) compared to the placebo (n=148) had a significantly longer

PFS (hazard ratio (HR) of 0.42, 95% confidence interval of 0.33 to 0.55; $P<0.0001$); the OS did not differ between the treatment groups (HR of 0.84, 95% CI, 0.62 to 1.14; $P=0.26$). The temptation is to compare the results of this trial to the Sequential Tarceva in Unresectable NSCLC (SATURN) trial which investigated maintenance erlotinib compared to placebo after four cycles of platinum-based therapy (n=889) (11). The SATURN trial revealed that maintenance erlotinib compared placebo improved PFS (HR of 0.71, 95% CI, 0.62 to 0.82; $P<0.0001$) and OS (HR of 0.81, 95% CI, 0.70 to 0.95; $P=0.0088$). However, the clinical characteristics of the patients enrolled in the two trials differed vastly, and most likely the prevalence of EGFR tyrosine kinase (TK) mutations probably differed substantially. In the SATURN trial the majority of patients were current or former smokers (>80%), were Caucasian (84%), and only a minority of patient's tumor were adenocarcinoma histology (45%). In contrast, in the INFORM trial all the patients were Asian, the majority of patients had adenocarcinoma (71%), and the majority of patients were never smokers (54%). The numerical difference in the HR for PFS between the two trials is most likely due to a difference in the prevalence of EGFR TK mutations. The lack of OS benefit observed in the INFORM trial could be due to the smaller size of the trial and/or a high rate of EGFR TKI therapy in the placebo arm at the time of disease progression.

In both trials analyses based on EGFR TK mutation status were performed, but only a small subset of patients had confirmed EGFR TK mutant tumors. In the INFORM trial, among patients with a known EGFR TK mutation,

patients in the gefitinib arm (n=15) compared to the placebo arm (n=15) experienced a significantly longer PFS (HR of 0.17, 95% CI, 0.07 to 0.42). This is similar for to the HR for PFS observed for patients with EGFR TK mutant tumors in the SATURN trial (HR of 0.10, 95% CI, 0.04 to 0.25; P<0.0001) (11). The authors should be commended for not performing an exploratory OS analysis in the EGFR TK mutant since the small sample size, the confounding factor on subsequent EGFR TKI therapy, and the limited number of events would have made such an analysis fundamentally flawed. Patients with EGFR TK wild-type tumors in the gefitinib (n=25) compared to the placebo arm (n=24) did not experience a statistically significant improvement in PFS (HR of 0.86, 95% CI, 0.48 to 1.51); OS analysis was not performed.

Patients' HRQOL was assessed, and 81% of patients had assessable HRQOL data; mean compliance with the FACT-L questionnaire completion in the gefitinib and placebo arms was 47% and 33%, respectively. Patients in the gefitinib arm compared to the placebo arm experienced a significant and clinically relevant improvement in lung cancer symptoms and median time to worsening in lung cancer symptoms. The improvement in symptoms observed in the gefitinib compared to the placebo arm is probably related to the higher overall response rate observed in the gefitinib arm (24% vs. 1%, P=0.0001), and the delay in time to worsening of lung cancer symptoms is probably related to the higher disease control rate (72% vs. 51%, P=0.0001). The toxicities observed were consistent with previous trials of gefitinib; three treatment-related deaths were observed in the gefitinib arm.

The results of the INFORM trial provide evidence of clinical benefit of maintenance gefitinib. However, since the trial was designed and initiated there have been significant changes in the treatment of advanced NSCLC. The majority of patients with advanced NSCLC are undergoing EGFR TK mutational testing at the time of diagnosis, and patients with EGFR TK mutant tumors are receiving EGFR TKI therapy as first-line therapy. Thus, the role of EGFR TKI maintenance therapy in patients with known EGFR TK mutant tumors is limited. In the increasingly rare situation in which patients have completed chemotherapy and are subsequently found to have an EGFR TK mutation I initiate maintenance EGFR TKI therapy based on the significant improvement in PFS observed in this patient population. Thus, the more frequent clinical question is the role of EGFR TKI therapy in patients with EGFR wild-type tumors. Maintenance erlotinib compared

to placebo did demonstrate a statistically significant improvement PFS and OS among patients with EGFR wild-type tumors (n=388) in the SATURN trial. The lack of a statistically significant benefit among EGFR wild-type patients in the INFORM trial is most likely related to the smaller size of the EGFR wild-type cohort. For the patients who are candidates for maintenance therapy with confirmed EGFR wild-type tumor and non-squamous histology, I have generally used pemetrexed maintenance therapy based on the larger improvement in PFS and OS observed in the maintenance pemetrexed trials (10,14). In patients with EGFR wild-type tumors who are not candidates for maintenance pemetrexed I discuss with the patient the potential risks and benefits of maintenance EGFR TKI and observation.

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