Afatinib Superior to Gefitinib as First-Line Treatment for EGFR Mutation–Positive NSCLC

**BACKGROUND:** The epidermal growth factor receptor (EGFR)-targeting tyrosine kinase inhibitors (TKIs) gefitinib (Iressa), erlotinib (Tarceva), and afatinib (Gilotrif) are approved by the US Food and Drug Administration for the first-line treatment of EGFR mutation–positive non–small-cell lung cancer (NSCLC).

Data show that all 3 drugs are superior to standard chemotherapy in terms of progression-free survival (PFS), objective responses, and safety profiles. However, head-to-head clinical trials comparing the safety and efficacy of approved TKIs are needed to help clinicians select the most appropriate first-line treatment in this patient population.

**METHODS:** A prospective, multicenter, international, open-label, exploratory, randomized controlled phase 2b study (LUX Lung 7) was conducted to compare the efficacy and safety of afatinib, a first-generation, irreversible ErbB family blocker, versus gefitinib, a second-generation, reversible EGFR TKI, in treatment-naive patients with EGFR mutation–positive NSCLC.

A total of 319 patients with stage 3B or 4 EGFR mutation–positive NSCLC were randomly assigned to receive afatinib 40 mg (n = 160) or gefitinib 250 mg (n = 159) until disease progression or beyond, if deemed beneficial. The primary end points included PFS, time to treatment failure, and overall survival (OS).

**RESULTS:** Patients receiving afatinib had a median PFS of 11 months versus 10.9 months in patients receiving gefitinib (*P* = .017). The objective response rate was 70% among patients taking afatinib versus 56% among patients taking gefitinib.

Furthermore, the time to treatment failure was 13.7 months with afatinib versus 11.5 months with gefitinib (*P* = .0073). OS data were not mature at the time of this analysis.

Serious treatment-related adverse events occurred in 11% of patients taking afatinib and 4% of patients taking gefitinib. In addition, fatal events occurred in 9% of patients taking afatinib versus 6% of patients taking gefitinib; all deaths but 1 were considered unrelated to treatment.

Afatinib’s superior efficacy over gefitinib may be explained by its mechanism of action, and has an important clinical implication: irreversible ErbB blockade with afatinib could be more effective than reversible EGFR inhibition in the treatment of EGFR mutation–positive NSCLC. “The results suggest that first-generation and second-generation tyrosine kinase inhibitors are not interchangeable and imply that the broader and irreversible mechanism of action of afatinib compared with gefitinib could have led to better tumor control,” the investigators concluded.

Combination Chemotherapy plus Radiation Prolongs Survival in Low-Grade Glioma

BACKGROUND: Low-grade gliomas account for 5% to 10% of all primary brain tumors and are associated with premature death.

Initial data from a phase 3 clinical trial published in 2012 indicated that treating grade 2 gliomas with combination chemotherapy comprising procarbazine, lomustine (also called CCNU), and vincristine plus radiation therapy resulted in longer PFS than radiation therapy alone. However, combination chemotherapy plus radiation did not result in improved OS compared with radiation therapy alone. The long-term follow-up of this clinical trial investigated whether combination chemotherapy plus radiation therapy resulted in better PFS and OS than radiation therapy alone in patients with grade 2 glioma.

METHODS: A total of 251 patients with grade 2 astrocytoma, oligoastrocytoma, or oligodendroglioma aged <40 years who had undergone subtotal resection or biopsy, or who were aged ≥40 years and had undergone biopsy or resection of any part of the tumor, were randomized to receive combination chemotherapy plus radiation or radiation therapy alone, with a median follow-up of 11.9 years.

RESULTS: OS among patients who received combination chemotherapy plus radiation was 13.3 years versus 7.8 years with radiation therapy alone (P = .003). The estimated PFS at 10 years was 51% with combination chemotherapy plus radiation versus 21% with radiation therapy alone. In addition, the estimated OS at 10 years was 60% with combination chemotherapy plus radiation versus 40% with radiation therapy alone.

Patients who received radiation plus combination chemotherapy experienced more adverse events than those who received radiation therapy alone; the majority of adverse events were grade 1 or 2; grade 3 or 4 adverse events were rare.

Patients with IDH1 R132H mutations derived the most benefit from combination chemotherapy plus radiation. This finding is consistent with results from 2 phase 3 studies that showed patients with newly diagnosed anaplastic oligodendroglioma with 1p/19q codeletion, IDH mutations, or both, had longer PFS and OS with radiation therapy plus chemotherapy than with radiation therapy alone.

Because IDH mutations are associated with the CpG island methylator phenotype, “it is plausible that DNA-repair enzymes that repair alkylator damage, such as O6-methylguanine DNA methyltransferase, are silenced by promoter methylation, which results in greater sensitivity to alkylating agents,” the investigators noted.

The use of combination chemotherapy with radiation therapy in patients with low-grade gliomas is a promising treatment option but is associated with more frequent adverse events than radiation therapy alone. “Patients and their physicians will have to weigh whether the longer survival justifies the more toxic therapeutic approach,” the researchers advised.


COMMENTARY BY ROBERT J. IGNOFFO

Over the past several years, temozolomide has generally been preferred over the vincristine regimen based on its ease of administration, better patient tolerance, and more consistent availability in some regions. The results of this long-term study will change the treatment paradigm in this setting.

The Radiation Therapy Oncology Group study justifies that combination chemotherapy plus radiation therapy is the preferred treatment for low-grade gliomas. Except for astrocytoma, all other gliomas had significantly longer survival with combination treatment versus radiation therapy alone at 12 years. Although the combination group had improved OS and PFS, the difference in survival compared with radiation alone was not seen until 4 years after randomization.

Combination treatment produced frequent side effects involving the hematologic and gastrointestinal systems. Grade 3 and 4 toxicities, including neutropenia, were seen in 35% and 9% of patients receiving combination treatment and radiation therapy alone, respectively; nausea and vomiting were also more common with the combination treatment. The authors conclude that “patients and their physicians will have to weigh whether the longer survival justifies the more toxic therapeutic approach.” However, I would think that with more than 50% survival rate at 12 years, and improvement in hazard ratios for death of 0.56 and 0.43 in patients with oligoastrocytoma or oligodendroglioma, respectively, the decision would strongly favor combination treatment.

In select patients, combination chemotherapy plus radiation therapy is the only treatment that significantly prolongs survival, and is better than temozolomide in the setting of low-grade glioma.
Acalabrutinib Demonstrates Efficacy and Safety in Relapsed CLL

BACKGROUND: Although the introduction of reversible Bruton’s tyrosine kinase (BTK) inhibitors, such as first-generation ibrutinib (Imbruvica), represents a major advancement in the treatment of chronic lymphocytic leukemia (CLL), ibrutinib also irreversibly inhibits other kinase agents that may compromise its therapeutic index; side effects are the most common reason that patients discontinue ibrutinib therapy. This finding led researchers to evaluate the safety and efficacy of acalabrutinib. It is a second-generation, more selective, irreversible BTK inhibitor with improved pharmacologic features that was specifically designed to improve on the safety and efficacy of first-generation BTK inhibitors.

METHODS: The uncontrolled, multicenter, phase 1/2 clinical trial was designed to determine the recommended dose, safety, efficacy, pharmacokinetics, and pharmacodynamics of acalabrutinib in 61 patients with relapsed CLL.

RESULTS: The median age of the patients was 62 years, and the patients had received a median of 3 previous therapies for CLL. In the phase 1 dose-escalation portion of the trial, patients received 100 mg to 400 mg of acalabrutinib once daily, followed by 100 mg twice daily in the phase 2 expansion of the trial. At a median follow-up of 14.3 months, the overall response rate was 95%, including 85% with a partial response and 10% with a partial response with lymphocytosis; the remaining 5% of patients had stable disease. In patients (31%) with 17p13.1 deletion, the overall response rate was 100%. The researchers noted that no patients had Richter’s transformation, and only 1 patient had progression of CLL. Acalabrutinib demonstrated robust clinical activity, with 98% of patients achieving a reduction in lymphadenopathy. The safety profile of acalabrutinib was also favorable. Most adverse events were grade 1 or 2 and resolved over time. The most common grade 1 or 2 adverse events were headache (43%), diarrhea (39%), increased weight (26%), and upper respiratory infection (23%). Severe diarrhea, rash, arthralgia or myalgia, bruising, and bleeding events each occurred in ≤2% of patients. No cases of major hemorrhage or atrial fibrillation were reported.


FROM THE LITERATURE

According to the National Comprehensive Cancer Network (NCCN) guidelines, ibrutinib and idelalisib in combination with rituximab are the standard of care for patients with refractory CLL. The results from this study are very impressive and may soon lead to US Food and Drug Administration approval of acalabrutinib for refractory CLL. Acalabrutinib is not only more effective but also safer than the first-generation BTK inhibitor, ibrutinib. Almost all the patients in the study responded to acalabrutinib with very few grade 3 or 4 toxicities, and no patients had major bleeding events or atrial fibrillation, which have been reported with ibrutinib use. The most common adverse events were headache, hypertension, and diarrhea.

The National Cancer Institute is currently supporting a phase 3 comparative trial of acalabrutinib versus ibrutinib in high-risk patients with relapsed CLL, and may answer the question of which BTK inhibitor is preferred.

Acalabrutinib is an alternative BTK inhibitor that has more selective pharmacodynamic features, and may improve on the efficacy and safety observed with ibrutinib.