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Clinical Trial

Maintenance pazopanib versus placebo in Non-Small Cell Lung Cancer patients non-progressive after first line chemotherapy: A double blind randomised phase III study of the lung cancer group, EORTC 08092 (EudraCT: 2010-018566-23, NCT01208064) ☆

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Abstract ***Background:*** Switch maintenance is an effective strategy in the treatment of advanced Non-Small Cell Lung Cancer (NSCLC). Pazopanib is an oral, multi-targeted tyrosine kinase inhibitor (TKI). EORTC 08092 evaluated pazopanib given as maintenance treatment following standard first line platinum-based chemotherapy in patients with advanced NSCLC.
Methods: Patients with non-progressive disease after 4–6 cycles of chemotherapy were randomised to receive either pazopanib 800 mg/day or matched placebo until progression or unacceptable toxicity. The primary end-point was overall survival and secondary end-points were progression-free survival (PFS) and safety.
Results: A total of 600 patients were planned to be randomised. The trial was prematurely stopped following an early interim analysis, after 102 patients were randomised to pazopanib ($n = 50$) or placebo ($n = 52$). Median age was 64 years in both arms. Median overall survival was 17.4 months for pazopanib and 12.3 months for placebo (adjusted hazard ratio (HR) 0.72 [95% confidence interval (CI) 0.40–1.28]; $p = 0.257$). Median PFS was 4.3 months versus 3.2 months (HR 0.67, [95% CI 0.43–1.03], $p = 0.068$). PFS rates at 4 months were 56% and 45% respectively. The majority of treatment-related adverse events (AEs) were grade 1–2. Grade 3–4 AEs (pazopanib versus placebo) were hypertension (38% versus 8%), neutropenia (8% versus 0%), and elevated SGPT (6% versus 0%). Of the patients randomised to pazopanib, 22% withdrew due to a treatment-related AE.
Conclusions: Switch maintenance with pazopanib following platinum-based chemotherapy in advanced NSCLC patients had limited side-effects. This study was stopped due to lack of efficacy by stringent criteria for PFS at a futility interim analysis.

1. Introduction

Of the 410,000 cases of lung cancer diagnosed in Europe each year, 70% will have died by the end of the first year. Worldwide, lung cancer accounts for an annual 1.82 million cases and 1.6 million deaths [1].

Changes in treatment have occurred during the last 10 years due largely to discoveries in cancer biology, which have resulted in targeted treatment options for around 20% of advanced Non-Small Cell Lung Cancer (NSCLC) patients at some point during their disease. The way we develop drugs and conduct clinical trials has also changed. Trials for molecularly unselected patients need a timely interim analysis with stringent stopping rules to reduce the exposure of patients to ineffective agents.

1.1. Maintenance chemotherapy

The standard approach for chemotherapy in advanced NSCLC has been to administer up to six cycles of a platinum-based doublet and then stop [2]. Recent studies, however, have demonstrated that maintenance therapy with docetaxel, pemetrexed, erlotinib or gefitinib can prolong remission (progression-free survival (PFS)), but with little Overall Survival (OS) benefit.

Anti-angiogenic agents do have activity in NSCLC, specifically antibodies to vascular endothelial growth factor (VEGF). Bevacuzimab and ramicurimab have both shown benefit in combination with chemotherapy [3,4].

Pazopanib is an oral multi targeted tyrosine kinase inhibitor (TKI), targeting VEGF receptors -1, -2, and -3, platelet-derived growth factor (PDGF) receptors-α and -β, stem cell factor receptor (CD-117 or c-Kit ligand) and fibroblast growth factor (FGR) receptors -1 and -3. Pazopanib monotherapy is active in early stage NSCLC as pre-surgical treatment. Thirty patients (86%) achieved a reduction in tumour volume after a short course of pazopanib treatment [5]. However a randomised trial with compliance to the treatment regimen as primary outcome tested the use of pazopanib 800 mg per day or placebo in patients with stage I resected NSCLC. The study closed prematurely because of toxicity and slow recruitment [6].

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