Maintenance Pazopanib versus Placebo in Non Small Cell Lung Cancer Patients Non Progressive after First Line Chemotherapy: A double blind randomized phase III study of the Lung Cancer Group, EORTC 08092.

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Abstract:
TITLE: Maintenance pazopanib versus placebo in Non Small Cell Lung Cancer patients non progressive after first line chemotherapy: A double blind randomized phase III study of Lung Cancer Group, EORTC 08092.

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 randomized to receive either pazopanib 800 mg/day or matched placebo until progression or unacceptable toxicity. The primary endpoint was overall survival and secondary endpoints were progression-free survival (PFS) and safety.

Results: A total of 600 patients were planned to be randomized. 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. Overall survival was not significantly different, median 17.4 months for pazopanib vs. 12.3 months for Placebo (adjusted HR 0.72 [95% CI 0.40-1.28]; p=0.257). Median PFS was 4.3 months vs. 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. Reported grade 3 - 4 AEs (% pazopanib vs. placebo) were neutropenia (8% vs. 0%), hypertension (38% vs. 8%) and elevated SGPT (6% vs. 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.

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Comment [BHA1]: The planned IA would have been much later (approx. 200 pts)

Comment [U2]: Cancer Research UK?

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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 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.

Maintenance Chemotherapy

The standard approach for chemotherapy in advanced NSCLC has been to administer up to 6 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 (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, 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 800mg per day or placebo in patients with

stage I resected NSCLC. The study closed prematurely because of toxicity and slow recruitment [6].

The present study was designed to evaluate pazopanib as switch maintenance therapy after standard first-line chemotherapy for advanced NSCLC. Stringent criteria for an interim analysis were applied as only a large benefit was considered to be clinically useful.

Patients and Methods

This was a randomized double blind phase III study of maintenance oral pazopanib versus placebo in patients who had received at least 4 cycles of first line platinum-based chemotherapy for advanced NSCLC [Figure 1].

The main eligibility criteria included patients: 18 years or older with a life expectancy of 12 weeks or more; WHO PS 0-2, with no more than 15% of patients of PS 2, and less than 15% of patients > 70 years and PS 0-1. Patients had to have newly diagnosed stage IIIB- IV (TNM version VII) or recurrent NSCLC (after surgery or radical radiotherapy), pathologically confirmed. All histological subtypes were eligible. In case of adjuvant chemotherapy after previous surgery, time interval from start of previous treatment to induction chemotherapy for metastatic disease was 6 months. If previous palliative radiotherapy was administered, this had to be completed at least 2 weeks before study enrolment. Previous radical radiotherapy was permitted if there was an interval of at least 6 months from the start of the radiotherapy to the start of induction chemotherapy for metastatic disease. EGFR wild type or unknown were eligible (known EGFR mutations were not eligible). Non measurable disease was allowed in this maintenance study.

No prior TKI or prior bevacizumab/cetuximab was allowed with the induction chemotherapy. The most commonly used platinum based chemotherapy regimens were allowed and patients were allowed to continue up to 6 cycles as per local policy.

Patients must have not progressed during induction chemotherapy: for patients without measurable disease, no symptomatic/clinical progression was allowed.

Patients were stratified according to histology – squamous versus nonsquamous, performance status – 0-1 versus 2 and response to induction chemotherapy – partial response versus stable disease.

Patients had to start study treatment within 6 weeks of completing chemotherapy. The starting dose was 600mg orally per day increasing after 2 weeks to 800mg if tolerated. A list of prohibited medication was included in the protocol in view of the potential drug interaction with CYP3A4 substrates and pazopanib.

Statistics

The primary endpoint was overall survival. Secondary endpoints included PFS and toxicity.

In the control arm, a median OS of 9.7 months was assumed [7]. To detect an hazard ratio (HR) = 0.764 with 85% power using a one-sided 0.025 alpha level test and taking into account an interim analysis (IA) for futility based on PFS [8,9], a total of 498 deaths was required. With an accrual rate of 12.5 patients randomized per month, and taking into account patients who were lost to follow up, it was planned to accrue 600 patients in total.

The trial was activated in July 2011 and at the beginning of 2013 the manufacturer of pazopanib informed the EORTC of their concerns about the safety and efficacy of pazopanib in lung cancer patients and noted the poor compliance in the adjuvant study and awaited results of their randomized study of the value of pazopanib when added to erlotinib in the secondline unselected setting [6, 10]. In light of the newly emerging information, the EORTC LCG was concerned about exposing patients to an inefficacious treatment. In consultation with the IDMC, it was agreed to undertake an early interim analysis for futility after 63 PFS events were observed with a one-sided futility alpha = 0.01 to detect a HR = 0.35. The interim analysis was powered at 84% and the overall power for the study was 71.4% and Carroll's approach [11] was used to take into account the loss of power due to discreteness of the time windows used in the evaluation.

In October 2013 the EORTC IDMC thus concluded that the trial might be stopped and upon updating the analysis, results could be published.

In this article, unless stated otherwise, reported confidence intervals (CIs) were 2-sided 95% CIs. The log-rank tests for the OS and PFS were adjusted by the stratification factors (histology and response to induction chemotherapy) used in the randomization. PS status (0/1 vs. 2) was not used due to homogeneity, only 2 patients were recorded to be PS = 2 (Table 1).

Toxicity and treatment information were reported on 100 patients who started treatment (per protocol population), including patients subsequently found ineligible. Efficacy was reported on all 102 randomized patients based on intent to treatment (ITT population). Details can be found in the general outline and CONSORT diagram (Fig. 1)

Results

Patient characteristics

Between July 2011 and October 2013, 102 patients were randomized in 18 centres in 6 countries. Their characteristics are shown in Table 1.

A median of 4 (range 4-6) cycles of induction chemotherapy were given. The median time from the start of chemotherapy to randomization was 15.8 (11.4-30.1) weeks in the placebo arm and 15.1 (11.4-30.1) weeks in the pazopanib arm (Table 2). All analyses on the primary and secondary endpoints were done from the date of randomisation.

The number of patients with medically controlled hypertension at baseline was similar in the two groups. One patient in the placebo arm gave a history of deep venous thrombosis within the previous 6 months. Only 4 patients had brain metastases at presentation, 2 patients had documented endobronchial lesions, not in major bronchi and 3 patients had tumour close to vessels.

Overall and progression-free survival

The median follow-up time with respect to the OS was similar in both arms (12.9 months in the placebo and 13.4 months in the pazopanib). A total of 47 deaths had been observed, primarily caused by disease progression (85% in placebo and 80% in pazopanib arm). The median OS was 17.4 (CI: 8.9, NR [not reached]) months in pazopanib and 12.3 (CI: 10.3, 16.6) months in placebo arm. The adjusted p-value based on the Wald test to test the difference in OS between the two arms was 0.257. The hazard ratio for the OS in pazopanib relative to the placebo arm was 0.72 (CI: 0.40-1.28) in favour of pazopanib. These p-value and HR estimates were confirmed by another

sensitivity method, namely logrank test without adjustment where p-value = 0.252 and a HR of 0.71 (CI: 0.40-1.27) were observed. Kaplan Meier curves for OS were shown in Figure 2.

Of 102 randomized patients, there were 85 observed events (PD or death). The median PFS was 4.3 (CI: 3.0-7.4) months in pazopanib and 3.2 (CI: 2.1-5.1) months in placebo arm. The adjusted p-value based on Wald test to test the difference in PFS between the two arms was 0.068. The hazard ratio for the PFS in pazopanib relative to the placebo arm was 0.67 (CI: 0.43-1.03) in favour of pazopanib. Again these p-value and HR estimates were confirmed by the logrank test without adjustment where p-value = 0.066 and a HR of 0.67 (CI: 0.44-1.03) were observed. Kaplan Meier curves for PFS were shown in Figure 3.

Sub-group analyses according to stratification and other important factors show similar results as the in overall population. Median OS in male patients was not reached on pazopanib and was 12.3 months in placebo with a HR ~~and p-value~~ of 0.41 (CI: 0.15-1.11) and p-value of 0.071 in favour of pazopanib.

Duration of treatment and toxicity

Of the 102 randomized patients, 100 started study treatment (at least one dose of the study drug(s)). Two patients did not start study treatment because they had been unable to discontinue drugs with potential CYP3A4 substrate interaction. Ninety-five patients had stopped study treatment at the time of this analysis while 5 were still taking it.

The median duration of treatment was 14 (CI: 6.43-14.86) weeks in the placebo arm and 14 (CI: 8.86-25) weeks in the pazopanib arm (Figure 2). All patients received the

planned daily dose of 600 mg for the first 2 weeks. ~~but~~ Only 50% of patients in the pazopanib arm received a full dose of 800 mg/day after week 2 compared to~~weeks as opposed to~~ 88% on placebo. The lower received dose in the pazopanib arm was due to either no dose escalation to 800 mg/day or treatment interruptions mainly attributed to non-hematological toxicity. The most common toxicity was hypertension, which differed between placebo and pazopanib in the frequency of grade 3 hypertension. Other toxicities associated with pazopanib were diarrhoea and anorexia. Nausea, vomiting and fatigue were prevalent in both groups.

The main adverse events noted with pazopanib were grade 3-4 haematological toxicity- neutropenia (8% in the pazopanib arm versus 0% in the placebo arm), grade 3-4 hypertension (38% versus 8%) and laboratory abnormalities - grade 3-4 elevated SGPT (6% versus 0%), see Table 4. Most patients went on to receive further antitumor therapy after stopping study therapy, over 66% of patients in both arms (Table 5).

Discussion

Here we report the results of a double blind randomized phase III maintenance study of pazopanib versus placebo in patients with advanced NSCLC after achieving disease control following 4-6 cycles of induction chemotherapy. One hundred and two patients ~~with NSCLC~~ were randomized. This study was closed prematurely because of~~due to~~ lack of ~~a strong signal of~~ meaningful clinical activity.

In this population of advanced NSCLC, most patients had adenocarcinoma histology, were of good performance status and had received ~~mostly~~ 4 ~~courses~~ cycles of induction chemotherapy. Pemetrexed with carboplatin or cisplatin were the most frequently used induction combination chemotherapies.

Comment [U3]: What resons were given for this?

Comment [M4R3]: Protocol said if tolerated…

Comment [U5]: Please include fatigue – even if not G3-4

Comment [U6]: Put the commonest first - hypertension

There was no difference in outcome for OS or PFS in the whole population of patients as well as in the subgroups according to gender, smoking status, histology, response to induction chemotherapy. We confirmed that stable disease (SD) after chemotherapy was as meaningful as a PR for overall outcome, as has been shown in other maintenance studies [12,13,14]. No analysis can be made on a comparison between 4 and 6 ~~courses~~ cycles of induction chemotherapy, as most patients received only 4 ~~courses~~cycles. The results with pazopanib in squamous histology compared to non-squamous (median PFS=3.29 versus 4.83 months) are in line with the nintedanib data [15] with a greater effect from in the non-squamous group.

The commonest toxicity with this class of drugs was hypertension, which only differed between placebo and pazopanib in the frequency of grade 3 hypertension. Overall pazopanib patients did have more toxicity but most of it would have been acceptable if increased activity had been seen. On the other hand, the discontinuation rate due to adverse events was higher in the pazopanib arm and fewer patients reccieved the planned dose escalation~~dose density was lower~~ in the pazopanib compared to the placebo arm. These factors might contribute to the lack of efficacy observed in this trial.

Stopping a trial early is a difficult decision. If there was to be a pazopanib effect, it would be small and probably not of clinical relevance. However, there is still an important question of clinical relevance of a small but statistically significant benefits observed in prospective clinical trials enrolling hundreds of patients with advanced cancer.

Comment [U7]: I didn't see any discussion of G1-2 toxicity – did fatigue, nausea, etc impact on the patient experience?

Comment [U8]: I don't have the tables – what were the reasons for treatment discontinuation?

In summary, pazopanib as a maintenance therapy in patients with advanced NSCLC will not be explored further without biomarker subgroup selection. An interim analysis is essential in the design of trials in large unselected patient populations.

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