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A randomized, phase 2 evaluation of the CHK1 inhibitor, LY2603618, administered in combination with pemetrexed and cisplatin in patients with advanced nonsquamous non-small cell lung cancer

Thomas Wehler[a,b,1], Michael Thomas[c,1], Christian Schumann[d,e], Joaquim Bosch-Barrera[f], Nuria Viñolas Segarra[g], Nicolas J. Dickgreber[h], Klaus Dalhoff[i], Martin Sebastian[j], Jesus Corral Jaime[k], Miriam Alonso[k], Scott M. Hynes[l], Ji Lin[l], Karla Hurt[l], Aimee Bence Lin[l], Emiliano Calvo[m], Luis Paz-Ares[n,o,p,q,*]

[a] III. Medical Department, University Hospital Mainz, Mainz, Germany
[b] 5th Medical Department, University Hospital Saarland, Homburg, Germany
[c] Department of Thoracic Oncology, Thoraxklinik, Thoraxklinik im Universitätsklinikum Heidelberg, Translational Lung Research Center, Heidelberg, Germany
[d] Department of Internal Medicine II, University Clinic Ulm, Ulm, Germany
[e] Klinik für Pneumologie, Thoraxonkologie, Schlaf-und Beatmungsmedizin, Klinikverbund Kempten-Oberallgäu, Kempten and Immenstadt, Germany
[f] Department of Medical Oncology, Catalan Institute of Oncology, Doctor Josep Trueta University Hospital, Girona, Spain
[g] Clinico Y Provincial Barcelona, Barcelona, Spain
[h] Department of Respiratory Medicine and Thoracic Oncology, Mathias-Spital Rheine, Rheine, Germany
[i] Department of Pulmonology, University Medical Center Schleswig-Holstein, Lübeck, Germany
[j] Department of Hematology/Oncology, Rheumatology, HIV, J.W. Goethe University, Frankfurt, Germany
[k] University Hospital Virgen del Rocío, Seville, Spain
[l] Eli Lilly and Company, Indianapolis, IN, USA
[m] START Madrid, Clara Campal Comprehensive Cancer Center, Medical Oncology Division, Madrid Norte Sanchinarro University Hospital, Madrid, Spain
[n] Hospital Universitario 12 de Octubre, Madrid, Spain
[o] CNIO, Madrid, Spain
[p] Universidad Complutense, Madrid, Spain
[q] CIBEROnc, Madrid, Spain

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ABSTRACT

This phase 2 portion of a phase 1/2 study examined the efficacy and safety of LY2603618, a selective checkpoint kinase 1 inhibitor, combined with pemetrexed and cisplatin (LY + Pem + Cis) in patients with advanced nonsquamous non-small cell lung cancer (NSCLC). This multicenter, randomized, controlled, open-label study (NCT01139775) enrolled patients with stage IV nonsquamous NSCLC and an Eastern Cooperative Oncology Group performance status ≤1. Patients were randomized (2:1) to LY + Pem + Cis or pemetrexed and cisplatin (Pem + Cis). Induction therapy comprised four 21-day cycles of 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin on Day 1 (both arms) and 275 mg LY2603618 on Day 2 (LY + Pem + Cis arm). Maintenance therapy comprised 500 mg/m^2 pemetrexed on Day 1 (both arms) and 275 mg LY2603618 on Day 2 (LY + Pem + Cis arm) until disease progression. The primary endpoint was progression-free survival (PFS). Enrollment was permanently halted before target enrollment was met due to a greater number of thromboembolic events in the LY + Pem + Cis arm. Sixty-two patients were enrolled (LY + Pem + Cis, n = 39; Pem + Cis, n = 23). Bayesian and frequentist analysis demonstrated superior PFS in the LY + Pem + Cis arm vs the Pem + Cis arm (median [90% confidence interval]: LY + Pem + Cis, 4.7 months [4.–7.1]; Pem + Cis, 1.5 months [1.3–2.9]; $P = 0.022$). Seven patients in the LY + Pem + Cis arm (vs 0 in the Pem + Cis arm) experienced serious thromboembolic events: pulmonary embolism (n = 5),

Abbreviations: CHK1, selective inhibitor of checkpoint kinase 1; LY + Pem + Cis, LY2603618 + pemetrexed + cisplatin; Pem + Cis, pemetrexed + cisplatin.

* Corresponding author at: Medical Oncology, Hospital Universitario 12 de Octubre, Av de Cordoba SN, 28041 Madrid, Spain.
E-mail address: lpazaresr@seom.org (L. Paz-Ares).

[1] Equal first authors.

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ischemic stroke (n = 1), and cerebrovascular accident (n = 1). Although the primary endpoint was met, the combination of LY2603618 + Pem + Cis will not be further developed for treating advanced nonsquamous NSCLC due to the potential increased risk of thromboembolic events with this combination. ClinicalTrials.gov Identifier: NCT01139775.

1. Introduction

LY2603618 is a small molecule selective inhibitor of checkpoint kinase 1 (CHK1) [1] that has been investigated as a chemopotentiator. In phase 1 and 2 studies, LY2603618 combined with pemetrexed had acceptable safety and pharmacokinetics [2,3]. Recently, the phase 1 results of this phase 1/2 study showed that LY2603618 combined with standard doses of pemetrexed and cisplatin had acceptable safety in patients with advanced/metastatic tumors, with 2 patients achieving partial responses and 8 stable disease [4]. The recommended phase 2 dose was found to be 275 mg every 3 weeks [4].

The primary objective of the phase 2 portion of this phase 1/2 study was to determine if progression-free survival (PFS) is improved in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) when LY2603618 is added to standard first-line therapy with pemetrexed and cisplatin, and to maintenance therapy with pemetrexed.

2. Materials and methods

2.1. Study design/patients

This phase 2, multicenter, randomized, controlled, open-label study (ClinicalTrials.gov Identifier: NCT01139775) ran from March 2012 to November 2013. Patients with histologically diagnosed stage IV, nonsquamous NSCLC were randomized (2:1) to LY2603618 combined with pemetrexed and cisplatin (LY + Pem + Cis) or pemetrexed and cisplatin (Pem + Cis). Key eligibility criteria were as previously described [4].

The protocol was approved by the Ethics Review Board at each center and was implemented per the Declaration of Helsinki, Good Clinical Practice, and applicable laws and regulations. Patients provided written informed consent.

2.2. Protocol

Patients received four 21-day cycles of induction therapy. Day 1 (all patients): 500 mg/m^2 pemetrexed intravenous (iv) over 10 min and 75 mg/m^2 cisplatin iv (30 min after pemetrexed) over 60 min. Day 2 (LY + Pem + Cis arm): 275 mg LY2603618 (Eli Lilly and Company, Indianapolis, IN) iv over 60 min. All patients received standard pemetrexed premedication with folic acid, vitamin B_{12}, and dexamethasone.

After induction, patients received maintenance therapy until treatment discontinuation due to progressive disease or clinical progression, unacceptable toxicity, or investigator/patient decision. Day 1 (all patients): pemetrexed as per induction. Day 2 (LY + Pem + Cis arm): LY2603618 as per induction. Dose adjustments were made based on toxicities.

In October 2012, a routine review of serious adverse event (SAE) data revealed an imbalanced rate of thromboembolic events in patients who received LY2603618; enrollment was permanently halted on 25 October 2012. Thereafter, patients in the LY + Pem + Cis arm received pemetrexed and cisplatin only in the induction phase. Patients in the LY + Pem + Cis arm could continue with the LY2603618/pemetrexed in the maintenance phase.

2.3. Study endpoints

The primary endpoint was PFS. Secondary endpoints were overall survival, duration of response, duration of disease control, clinical benefit rate, objective response rate, change in tumor size, and the proportion of patients who received maintenance therapy. Safety outcomes included adverse events (AEs), laboratory evaluations, and vital signs. Pharmacokinetic analyses were carried out as previously described [4].

2.4. Statistical analysis

The primary analysis for comparison of PFS was a Bayesian hierarchical exponential-likelihood model incorporating historical data from a reference study [5] to augment prospective control data. Superiority of LY + Pem + Cis was indicated if the posterior probability of superiority of LY + Pem + Cis to Pem + Cis exceeded 85%. Standard frequentist analysis was performed for PFS using the Kaplan-Meier method [6]; arms were compared by log-rank test. The efficacy analysis population comprised the intent-to-treat population.

Secondary efficacy outcomes were summarized by descriptive characteristics and were compared by log-rank test, two sample *t*-test, or chi-square test.

3. Results

3.1. Patient disposition/characteristics

Sixty-two patients were enrolled in the study (Supplemental Fig. 1); demographic parameters and baseline characteristics were balanced between arms (Supplemental Table 1).

Note: several patients who consented prior to enrollment had not entered the study when enrollment was halted. These patients were permitted to enroll, but were not permitted to receive LY2603618 and were included in the control arm; therefore, the final distribution of patients was not 2:1.

3.2. Treatment

Patients in the LY + Pem + Cis arm received a median of 5 (range: 1–24) treatment cycles. Patients in the Pem + Cis arm received a median of 2 (range: 0–14) treatment cycles.

Of the patients in the LY + Pem + Cis arm, 26/39 (66.7%), 28/39 (71.8%), and 24/39 (61.5%) had LY2603618, pemetrexed, and cisplatin dose adjustments, respectively. Of the patients in the Pem + Cis arm, 9/23 (39.1%) and 10/23 (43.5%) had pemetrexed and cisplatin dose adjustments, respectively.

3.3. Efficacy

Bayesian analysis demonstrated that the probability of a PFS hazard ratio <1 for LY + Pem + Cis vs Pem + Cis was 96%. Therefore,