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Randomized phase 2 study of tivantinib plus erlotinib versus single-agent chemotherapy in previously treated *KRAS* mutant advanced non-small cell lung cancer

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ABSTRACT

Background: *KRAS* mutations are identified in approximately 25% of non-small cell lung cancer (NSCLC) cases and are associated with resistance to currently available targeted therapies. The MET oncogene may be implicated in malignant progression of *KRAS*-mutant tumors. In a pre-specified subset analysis of *KRAS* mutant cancers in an earlier phase 2 study of erlotinib plus the oral MET inhibitor tivantinib, combination therapy was associated with substantial clinical benefit compared to erlotinib alone (progression-free survival [PFS] HR 0.18; $P < 0.01$). The current study was conducted to evaluate this combination further in *KRAS* mutant non-small cell lung cancer (NSCLC).

Materials and methods: Previously treated patients with advanced *KRAS* mutant NSCLC were randomized to receive either oral tivantinib (360 mg twice daily) plus erlotinib (150 mg daily) (ET) or single-agent chemotherapy (investigator's choice of pemetrexed, docetaxel, or gemcitabine) (C). The primary endpoint was PFS. At progression, crossover from C to ET was permitted.

Results: Ninety-six patients were randomly assigned to ET (n = 51) or to C (n = 45). Median PFS was 1.7 months (mos) for ET and 4.3 mos for C (HR 1.19; 95% CI, 0.71-1.97; $P = 0.50$). There was no difference in overall survival (HR 1.20; 95% CI, 0.76-1.88; $P = 0.44$). There were 4 partial responses in the C arm, and none in the ET arm. Overall, adverse events occurred more frequently in the C arm, with more cytopenias, nausea, fatigue, and alopecia. Dermatologic toxicities were more common in the ET arm.

Conclusion: In previously treated patients with advanced *KRAS* mutant NSCLC, the combination of the MET inhibitor tivantinib and erlotinib is not superior to conventional single-agent chemotherapy.

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1. Introduction

The identification of druggable molecular alterations has broadened treatment options and improved outcomes for a subset of patients with advanced non-small cell lung cancer (NSCLC). Unfortunately, while the number of identified driver mutations is growing, the individual frequency of most of these subtypes remains low. Among them, *KRAS* mutations are the most common, occurring in about 25 percent of adenocarcinoma cases [1]. In contrast to epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) alterations, *KRAS* mutations are associated with smoking [2]. Also unlike other identified molecular subtypes, including *EGFR, ALK, BRAF, HER2, RET, ROS1,* and *MET* alterations, specific therapy for *KRAS* mutant NSCLC remains a major unmet clinical need in thoracic oncology.

High affinity binding of KRAS to its GTP substrate has hindered the development of targeted therapeutic agents that directly inhibit KRAS. In recent years, initial reports of inhibitors that bind directly and specifically to the mutant KRAS protein have been published [3,4]. However, such drugs are likely years away from clinical use. Other treatment strategies that have been investigated clinically against *KRAS* mutant cancers include inhibition of post-translational modification, inhibition of downstream effector pathways, and synthetic lethality [5–7].

The c-MET (MET) receptor tyrosine kinase plays central roles in cancer cell migration, invasion, proliferation, and metastasis [8,9]. In NSCLC, *MET* amplification is recognized as a key mechanism of primary and secondary resistance to EGFR inhibitors [10–12]. High-level *MET* amplification has also been linked to higher recurrence rates after surgical resection and poor prognosis [13,14]. *MET* also plays central roles in KRAS-driven cancers. In animal models of colorectal cancer, *MET* overexpression cooperates with oncogenic *KRAS* mutations to enhance tumorigenicity [15]. Additionally, MET function may relate to putative autocrine feedback loops through which transmembrane receptors such as EGFR act as downstream effectors of KRAS signaling [16,17]. In contrast to *EGFR* and other oncogenic driver mutations, where co-occurrence in the same tumor is rare [18], *MET* amplification frequently co-occurs in the setting of *KRAS* mutant backgrounds.

Tivantinib (ARQ 197; ArQule, Burlington, MA; Daiichi Sankyo, Tokyo, Japan) is a non-adenosine triphosphate-competitive small molecule inhibitor of MET that stabilizes the inactive conformation of MET and attenuates downstream intracellular signaling [19]. In multiple cancer models, tivantinib inhibits proliferation [20]. Tivantinib was studied in phase 1–3 trials in various malignancies, in particular NSCLC and hepatocellular carcinoma [21–24]. To date, the drug has exhibited relatively mild toxicity, with principal toxicities of low-grade myelosuppression and nausea/vomiting [21]. In a phase 1 trial of erlotinib plus tivantinib, the recommended phase 2 dose was tivantinib 360 mg orally twice daily, combined with standard dose erlotinib 150 mg orally daily [22].

In an earlier phase 2 trial of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated advanced NSCLC, a pre-planned subset analysis of patients with *KRAS* mutant cancers demonstrated particular benefit from combination therapy (PFS HR 0.18; 95% CI, 0.05–0.70; $P < 0.01$) [25]. We therefore compared erlotinib (which at the time of study initiation was a standard-of-care second-line therapy for advanced NSCLC) plus tivantinib to single-agent cytotoxic chemotherapy in an open-label, randomized phase 2 trial in *KRAS* mutant NSCLC.

2. Materials and methods

2.1. Patients

This trial (NCT01395758) was approved by the institutional review boards of all participating institutions. Eligible patients were recruited at 11 U.S. medical centers and had inoperable locally advanced or metastatic (stage III–IV, AJCC 7th edition) NSCLC (all histologies) harboring a documented *KRAS* mutation, had received at least one prior line of chemotherapy, had measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines [26], and had no prior treatment with a MET or EGFR inhibitor. Adequate bone marrow, cardiovascular, liver and renal function, and performance status (ECOG 0–2) were required. Radiographically and clinically stable brain metastases were allowed without requirement for prior radiation or surgical resection. Patients with known activating *EGFR* mutations were excluded. Submission of archival and/or fresh tumor tissue biopsy samples (10 unstained paraffin-embedded slides or tissue block) for molecular analysis was optional.

2.2. Study design and treatment

Patients were randomly assigned to receive either erlotinib (150 mg orally daily at least 1 h prior to and at least 2 h after ingestion of food) in combination with tivantinib (360 mg orally twice daily with meals) or investigator's choice chemotherapy (gemcitabine 1250 mg/m^2 days 1 and 8 every 21 days, docetaxel 75 mg/m^2 day 1 every 21 days, or pemetrexed 500 mg/m^2 day 1 every 21 days). Tivantinib was supplied as 120 mg tablets. Patients assigned to erlotinib-tivantinib were counseled to avoid the use of CYP3A4 inhibitors, CYP3A4 inducers, and CYP2C19 substrates or inhibitors. Partway through study enrollment, the protocol was modified such that erlotinib was provided by the study Sponsor.

For patients assigned to chemotherapy, premedication and supportive care were administered according to approved labeling or in accordance with institutional standard of care. Use of hematopoietic growth factors and erythropoietin stimulating agents was permitted. The selected chemotherapy could not have been previously administered to the patient.

Randomization was stratified by number of prior lines of therapy (1 vs ≥2), sex, and smoking history (never [using the Centers for Disease Control and Prevention definition of < 100 cigarettes in lifetime [27] vs ever) using a dynamic allocation procedure to balance the treatment groups. Patients were treated continuously in 21 day cycles until disease progression or unacceptable toxicity. Radiographic assessment of response was performed every two cycles. On Day 1 Cycle 1, blood was collected for analysis of polymorphisms of CYP2C19, the CYP450 enzyme principally responsible for tivantinib metabolism. Following radiographically confirmed progression, patients randomly assigned to receive chemotherapy had the option to cross over to erlotinib-tivantinib.

Up to three dose reductions were permitted for tivantinib (240 mg twice daily; 120 mg twice daily; 120 mg once daily). Up to two dose reductions were permitted for erlotinib (100 mg daily; 50 mg daily). Up to two dose reductions were allowed for chemotherapy agents. Dose re-escalation was not allowed, with the exception of erlotinib-associated rash or diarrhea that subsequently improved with supportive care. Patients who discontinued erlotinib due to the drug-related toxicity could continue to remain in the study and receive tivantinib. Conversely, patients who discontinued tivantinib due to the drug-related toxicity could remain in the study and receive erlotinib.

2.3. Endpoints and statistical considerations

The primary endpoint of this study was progression-free survival (PFS). PFS was measured from the first day of study treatment until radiographic disease progression per RECIST 1.1 criteria, or death of any cause in the intent to treat (ITT) population. Secondary endpoints included overall survival (OS) in the ITT population, overall response rate (ORR) in the ITT population, ORR among subjects who crossed over from chemotherapy to erlotinib-tivantinib, and safety. Adverse events were classified based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and were