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Lung Cancer

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Randomized phase 2 study of the cyclin-dependent kinase inhibitor dinaciclib (MK-7965) versus erlotinib in patients with non-small cell lung cancer[☆]

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ARTICLE INFO

Article history:

Received 2 July 2013

Received in revised form

15 November 2013

Accepted 24 November 2013

Keywords:

CDK inhibitor

Dinaciclib

NSCLC

Phase 2

Erlotinib

Monotherapy

ABSTRACT

Objectives: Dinaciclib (MK-7965, formerly SCH 727965), a novel, small-molecule inhibitor of cyclin-dependent kinases, has been shown to induce apoptosis in preclinical studies of human tumor cell lines, including non-small cell lung cancer (NSCLC) cells. Erlotinib, an epidermal growth factor receptor inhibitor, is approved for the treatment of advanced NSCLC as second- or third-line therapy. This phase 2, randomized, multicenter, open-label study compared dinaciclib with erlotinib in patients with previously treated NSCLC.

Materials and methods: The study was comprised of 2 parts: in part 1, patients were randomized to either intravenous (IV) dinaciclib (50 mg/m²) or oral erlotinib (150 mg) using an adaptive Bayesian design that adjusted the randomization ratio in favor of the more active arm, and in part 2, patients who had progressed on erlotinib were permitted to cross over to receive dinaciclib at the same dosage as in part 1. Patients were followed until disease progression or death, initiation of nonstudy cancer treatment, discontinuation, or withdrawal of consent. The primary efficacy end point was time-to-progression (TTP) in part 1 and objective response rate (ORR) in part 2.

Results: Based on Kaplan–Meier estimates, the median TTP was 1.49 months (95% confidence interval [CI]: 1.31, 2.63) following initial treatment with dinaciclib, compared with 1.58 months (95% CI: 1.38, 2.83) with erlotinib. No objective responses were observed following initial treatment with dinaciclib. Common severe (grade 3 or 4) drug-related adverse effects included neutropenia, leukopenia, vomiting, and diarrhea.

Conclusions: Dinaciclib, administered IV, was well tolerated at the 50 mg/m² dose, but does not have activity as monotherapy in previously treated NSCLC. Evaluation of dinaciclib in combination with other agents for other indications including breast cancer and multiple myeloma is in progress.

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1. Introduction

Dinaciclib (MK-7965, formerly SCH 727965) is a novel, potent, small-molecule inhibitor of cyclin-dependent kinase (CDK) 1, CDK2, CDK5, and CDK9 [1]. Preclinically, dinaciclib has been shown to be a potent inducer of apoptosis both in vitro in a panel of human tumor cell lines that included non-small cell lung cancer (NSCLC) and in murine xenograft models of human cancers that included human lung adenocarcinoma [1–4]. Phase 1 dose-escalation studies have assessed the safety, tolerability, and pharmacokinetics (PK)/pharmacodynamics (PD) of intravenous (IV) dinaciclib in patients with advanced malignancies [5,6]. In one trial, dinaciclib

[☆] Trial registration: ClinicalTrials.gov, NCT00732810.

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was given as a 2-h infusion once every 21 days; the recommended phase 2 dose (RP2D) was determined to be 50 mg/m² [5]. Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, is approved for the treatment of advanced NSCLC as second- or third-line therapy [7]. In the pivotal phase 3 trial, treatment with erlotinib following first- or second-line therapy resulted in a significant increase in the response rate (8.9% vs <1%) and prolonged overall survival (6.7 months vs 4.7 months) compared with placebo, in stage IIIB or IV NSCLC patients [8]. The current study was designed to assess the efficacy (objective response rate [ORR] and time-to-disease progression [TTP]) and safety of dinaciclib 50 mg/m² in patients with NSCLC, compared with standard doses of erlotinib.

2. Methods

2.1. Patients and study design

This phase 2, randomized, multicenter, open-label study compared dinaciclib with erlotinib in patients with previously treated NSCLC. Patients aged 18 years or older with measurable disease; Eastern Cooperative Oncology Group performance status ≤ 1 ; and adequate renal, hepatic, and bone marrow function were enrolled. Eligible patients must have received at least one, but no more than 2, prior chemotherapeutic regimens for advanced disease. Patients could not have received erlotinib either as monotherapy or as part of a previous regimen. Patients with known brain metastases were included, provided they had received definitive local therapy, had stopped receiving corticosteroid treatment, and were asymptomatic for at least 4 weeks prior to randomization. Patients were excluded if they had received chemotherapy or investigational drugs within 4 weeks, cytochrome P450 3A4 (CYP3A4) inhibitors or inducers within 1 week, or radiation therapy within 2 weeks of starting treatment.

Dinaciclib (50 mg/m²) was administered as a 2-h IV infusion on day 1 of a 21-day cycle, and erlotinib (150 mg) was self-administered orally once daily at least 1 h before or 2 h after ingestion of food. The study was composed of 2 parts: in part 1, patients were randomized to either dinaciclib or erlotinib using an adaptive Bayesian design that adjusted the randomization ratio in favor of the more active arm with respect to TTP, and in part 2, patients who had progressed on erlotinib were permitted to cross over to receive dinaciclib at the same dosage as in part 1. A Simon 2-stage design was used for part 2: if no responses were observed in the first 15 patients who crossed over to dinaciclib, the crossover portion would be terminated. Otherwise, the trial would continue until an additional 20 patients crossed over. If ≥ 5

responses were observed among the 35 patients who crossed over to dinaciclib, then dinaciclib would be considered to have activity for those subjects who progressed on erlotinib. Of note, this trial was conducted before the widespread availability of EGFR mutational testing; therefore, EGFR mutational status was not available. The study was conducted in accordance with the Declaration of Helsinki; the trial protocol was reviewed and approved by the institutional review board and ethics committee of each participating institution prior to the enrollment of the first patient. All patients gave written informed consent before enrollment in the trial. The trial was registered with clinicaltrials.gov as NCT00732810; <http://clinicaltrials.gov/ct2/show/NCT00732810>; Protocol P04716.

2.2. Efficacy and pharmacokinetic assessments

Patients were followed until disease progression or death, initiation of nonstudy cancer treatment, discontinuation due to toxicity, or withdrawal of consent. Assessments were performed every 6 weeks for the first 30 weeks (every 9 weeks thereafter), and responses were determined using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. The primary efficacy end point was TTP in part 1 and ORR (partial response [PR] + complete response [CR]), in part 2. Sparse PK samples were collected and drug exposure was estimated using population PK modeling.

2.3. Statistical analyses

A Bayesian adaptive design and its associated analyses were used to compare TTP between the 2 treatment arms in part 1 [9]. Kaplan–Meier curves were also used to estimate corresponding TTP distributions for dinaciclib and erlotinib, and the median TTP was estimated for each treatment group. The intent-to-treat population was used for the primary efficacy assessments in part 1 of the study, as well as for baseline patient characteristics. For ORR, efficacy was evaluated using the 95% confidence limit of the difference in the response rate between the 2 arms. All patients who received at least one dose of study medication (dinaciclib or erlotinib) were analyzed for safety.

3. Results

Patients were enrolled in the trial between October 2008 and May 2011. Baseline patient demographics and disease characteristics are shown in Table 1. A total of 67 patients were enrolled (17 to dinaciclib and 50 to erlotinib, based on the adaptive randomization): 64 patients were treated (15 with dinaciclib, 49 with

Table 1
Summary of demographic and baseline data for all randomized patients (N = 67).

Baseline characteristic ^a	Dinaciclib (N = 17)	Erlotinib (N = 33)	Erlotinib crossover to dinaciclib (N = 17)
Gender, n (%)			
Female	7(41)	12(36)	5(29)
Male	10(59)	21(64)	12(71)
Age, years			
Mean (SD)	63.2 (10.8)	63.3 (10.2)	64.8 (12.3)
Range	48–82	44–88	46–82
ECOG performance status			
Median (range)	1(0–2)	1(0–2)	1(0–2)
Prior chemotherapy regimens			
Median (range)	1(1–2)	2(1–4)	1(1–4)
Histology, n (%)			
Adenocarcinoma	10(59)	18(55)	5(29)
Squamous cell	4(24)	9(27)	3(18)
Large cell	0(0)	0(0)	1(6)
Not specified	3(18)	6(18)	8(47)

SD = standard deviation; ECOG = Eastern Cooperative Oncology Group.

^a Note: smoking history was not collected for patients enrolled in this study.

Table 2
Mean plasma concentration of dinaciclib on day 1 of cycles 1, 2, and 3 after 2-h intravenous infusion of a 50-mg/m² dose.

Time, ^a h	Patients, n	Cycle 1		Cycle 2		Cycle 3	
		Mean, ng/mL	CV%	Mean, ng/mL	CV%	Mean, ng/mL	CV%
2	16	1640	54	1650 ^b	50 ^b	1530 ^c	53 ^c
2.25	18	932	91	NA ^d	NA ^d	NA ^d	NA ^d
3	10	624	150	NA ^d	NA ^d	NA ^d	NA ^d
5	6	219	170	NA ^d	NA ^d	NA ^d	NA ^d

CV = coefficient of variation; NA = not available.

^a Time after the initiation of the dinaciclib infusion.

^b n = 13.

^c n = 9.

^d Sample was not collected.

erlotinib) in part 1 of the study, and 3 patients discontinued before receiving study drug for reasons unrelated to assigned treatment. A total of 32 patients received dinaciclib during the course of the study (including 17 patients who crossed over). In part 1, a median of 2 (range 1–7) cycles of dinaciclib and a median of 3 (range 1–30) cycles of erlotinib were administered. In part 2, a median of 2.5 (range 1–30) cycles of dinaciclib (after progression on erlotinib) were administered. Mean plasma concentrations of dinaciclib versus time data from cycles 1, 2, and 3 for all patients receiving 50 mg/m² dinaciclib are summarized in Table 2. The model-predicted plasma concentrations generally correlated with the observed values in the current study (Fig. 1) [5,10].

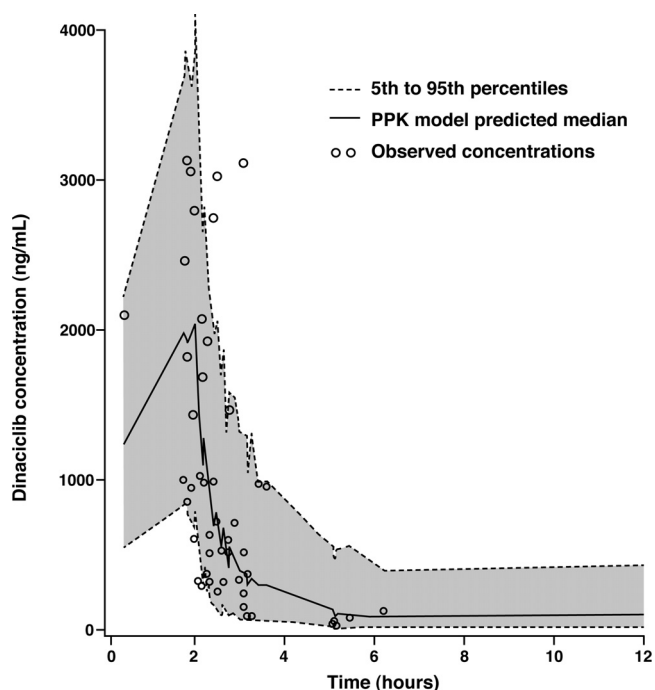


Fig. 1. Visual predicted check of PK population model prediction versus observed data on cycle 1, day 1. Simulation was performed using Perl-Speaks-NONMEM (n = 500), and model fits were conducted using the NONMEM V, level 1.1 software (GloboMax LLC, Hanover, MD). Because of the sparse PK sampling used in this study, a PPK approach was applied to estimate the systemic exposure and predict the plasma-concentration versus time profile of dinaciclib. A 2-compartment PPK model was developed using data from previous phase 1 studies [5,10]. Data from another part of the study that examined dinaciclib in breast cancer patients was included in the PPK model. The visual predictive check showed that observed data were within the PPK model-predicted 5th to 95th percentiles. This comparison indicates that a PPK model-based approach can be used to estimate systemic exposure and define the PK of dinaciclib in this study. The model-predicted mean exposure (AUC_[0-12]) at dinaciclib doses of 50 mg/m² was 5780 h ng/mL (CV% = 81). PK = pharmacokinetic; PPK = population pharmacokinetic; AUC_[0-12] = area under the concentration-time curve; CV% = coefficient of variation.

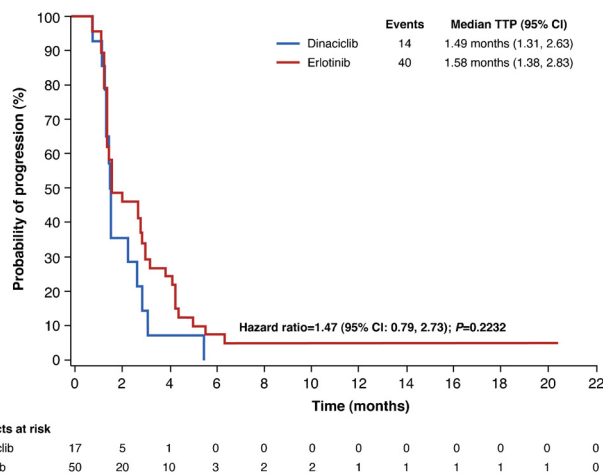


Fig. 2. Kaplan-Meier curve of TTP from randomization for the ITT population (N = 67). TTP = time to progression; ITT = intent to treat; CI = confidence interval.

Based on Kaplan-Meier estimates, the median TTP was 1.49 months (95% confidence interval [CI]: 1.31, 2.63) following initial treatment with dinaciclib, compared with 1.58 months (95% CI: 1.38, 2.83) with erlotinib (Fig. 2). The Bayesian estimate (hazard rate/month) of the median TTP was 0.48 and 0.31 for dinaciclib and erlotinib, respectively. Based on TTP data in part 1, the posterior probability that erlotinib is a better treatment than dinaciclib (i.e., has a longer mean TTP) is 0.916. No responses were observed following initial treatment with dinaciclib. With erlotinib, 2 patients achieved PR, resulting in an estimated 4% ORR (95% CI: -2%, 10%) (Table 3). In part 2 of the study, no responses were observed among the 17 patients who crossed over to dinaciclib after progression on erlotinib. The median TTP for the 17 patients after crossover to dinaciclib was 2.03 months (95% CI: 1.08, 5.31). Those 17 patients had a median TTP of 2.00 months (95% CI: 1.21, 3.02) on erlotinib.

TTP after crossover was defined as the time from the date of crossover to the first date of documented disease progression or death due to progressive disease. Note that a direct comparison of the TTP prior to crossover and after crossover should not be made, because TTP was measured from date of randomization to disease progression in part 1 and TTP was measured from date of first dose after crossover due to progression on erlotinib to disease progression on dinaciclib in part 2. The trial was stopped in January 2010, based on the low Bayesian estimate for success from part 1 of the study and the protocol-specified rule that required one or more responses in the first 15 evaluable patients who crossed over to dinaciclib after progression on erlotinib. As a result of early termination of the trial, exploratory studies on quality of life were not conducted.

Most patients enrolled in the trial experienced drug-related adverse events (AEs): the most common AEs occurring in ≥50% of

Table 3
Response rate for all treated and eligible patients before crossover.

Treatment	Evaluable patients, <i>n</i>	Objective responses, <i>n</i>	Response rate		Difference ^a		<i>P</i> value ^b
			Estimate	95% CI	Estimate	95% CI	
Dinaciclib	14	0	0.00	–	–0.044	–0.150, 0.176	0.426
Erlotinib	45	2	0.04	–0.02, 0.10			

CI = confidence interval.

^a Difference (dinaciclib–erlotinib) is based on Mietinnen and Nurminen.^b *P* value is based on Mietinnen and Nurminen.**Table 4**
Drug-related adverse events occurring in ≥20% of patients and all grade 3 or 4 adverse experiences following treatment within either dinaciclib or erlotinib.

Adverse event, <i>n</i> (%)	Dinaciclib (<i>n</i> = 32) ^a		Erlotinib (<i>n</i> = 49)	
	All grades	Grade 3–4	All grades	Grade 3–4
Patients reporting any AE	29 (91)	25 (78)	41 (84)	14 (29)
Diarrhea	22 (69)	4 (13)	21 (43)	0 (0)
Neutropenia	20 (63)	16 (50)	0 (0)	0 (0)
Vomiting	17 (53)	5 (16)	6 (12)	0 (0)
Nausea	16 (50)	3 (9)	12 (24)	0 (0)
Fatigue	11 (34)	3 (9)	10 (20)	0 (0)
Leukopenia	11 (34)	8 (25)	0 (0)	0 (0)
Decreased appetite	5 (16)	0 (0)	13 (27)	0 (0)
Dermatitis acneiform	1 (3)	0 (0)	14 (29)	3 (6)
Rash	0 (0)	0 (0)	19 (39)	4 (8)
Febrile neutropenia	2 (6)	2 (6)	0 (0)	0 (0)
Electrolyte imbalance	2 (6)	2 (6)	0 (0)	0 (0)
Hyperuricemia	3 (9)	2 (6)	0 (0)	0 (0)

AE = adverse event.

^a Includes all patients who had the adverse event while on dinaciclib, per randomized treatment assignment or after crossover from erlotinib.

patients treated with dinaciclib were diarrhea (69%), neutropenia (63%), vomiting (53%), and nausea (50%) (Table 4). Severe grade 3 or 4 drug-related AEs (observed in ≥10% of patients treated with dinaciclib) were neutropenia (50%), leukopenia (25%), vomiting (16%), and diarrhea (13%). Serious AEs (SAEs) associated with dinaciclib treatment and observed in >one patient were pneumonia (9%) and febrile neutropenia (6%). The primary erlotinib toxicities, rash (39%) and diarrhea (43%), are typical of this agent. There were no unexpected erlotinib toxicities. The primary reason for treatment discontinuation was disease progression (*n* = 45; 70% of all treated patients). One patient (7%) in the dinaciclib arm, 2 patients (6%) initially treated with erlotinib, and 2 patients (12%) who crossed over to dinaciclib discontinued due to AEs; for the 3 patients treated with dinaciclib who discontinued due to AEs, all were considered probably related to the drug.

Eighteen patients died during this trial: 3 patients (18%) randomized to dinaciclib, 11 patients (33%) randomized to erlotinib, and 4 patients (24%) treated with dinaciclib after progression on erlotinib. Thirteen (72%) of these deaths were due to disease progression and 5 (18%) were due to AEs. Of the 5 deaths due to AEs, 4 occurred during dinaciclib treatment. One (pneumonia) was considered unrelated to dinaciclib treatment during part 1; in the crossover arm, 2 deaths (respiratory distress related to the SAE empyema in 1 patient and acute renal failure with hyperkalemia and multiple electrolyte imbalances in the other patient) were considered probably related to dinaciclib and 1 (hypoxia) was probably unrelated to dinaciclib. One patient who developed pneumonitis possibly related to erlotinib 20 days after initiating therapy died 23 days later due to respiratory failure that was considered probably related to erlotinib.

4. Discussion

Monotherapy with dinaciclib failed to induce significant anti-tumor activity in unselected patients with advanced NSCLC. Dinaciclib has been shown to sensitize leukemia cells to chemotherapy by inhibiting the expression of MCL-1, a BCL-2

antiapoptotic family member [11]. Recent results have shown that high BCL-2 expression predicts favorable outcome in NSCLC patients [12], and that high expression of MCL-1 mRNA, is a predictive biomarker for dinaciclib antitumor response in solid tumors [13]. These results suggest that MCL-1 could potentially be explored as a biomarker for response to dinaciclib in patients with NSCLC. Trials currently in progress are evaluating dinaciclib in combination with both classic cytotoxic agents as well as “targeted agents” in both hematologic malignancies and solid tumors.

5. Conclusion

Dinaciclib administered at 50 mg/m² as a 2-h IV infusion had manageable adverse events consisting primarily of myelosuppression and gastrointestinal toxicities in patients with advanced NSCLC. However, antitumor activity was not observed and further studies of dinaciclib as a single agent will not be pursued. Studies evaluating dinaciclib as part of combination strategies with other agents or in select patient populations are in progress.

Conflict of interest statement

Y-MJ owns stock in Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ (hereafter referred to as Merck). DZ, YZ, and HZ are employees of Merck. PS, S-LY, and KS are employees of and own stock in Merck. RB was employed by and owned stock in Merck at the time of the study, and is listed on patent applications for dinaciclib that were submitted when he was a Merck employee (he did not receive compensation for the patents). MJE received consulting fees/honorarium and support for travel from Merck. JJS, JN, AAJ, and JCM have no conflicts of interest to disclose.

Role of the funding source

This study was funded by Merck & Co., Inc., Whitehouse Station, NJ.

Acknowledgments

We thank Dr Benoit Samson at Charles LeMoyne Hospital (Greenfield Park, QC, Canada) for his clinical contributions to the study. Medical writing and editorial assistance was provided by Joseph J. Abrajano, PhD, and Kakuri M. Omari, PhD, of Integrus Scientific, a division of Medicus International New York (New York, NY). This assistance was funded by Merck & Co., Inc. (Whitehouse Station, NJ). The authors are fully responsible for all content and editorial decisions and received no financial support or other compensation related to the development of the manuscript.

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