

APRICOXIB, A NEW POTENT COX-2 INHIBITOR IN COMBINATION WITH ERLOTINIB IN METASTATIC OR RECURRENT NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS: A Phase I Study

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ABSTRACT:

Objectives: Apricoxib is a once-daily oral, potent and selective inhibitor of COX-2. The COX-2 pathway plays a key role in tumor growth, angiogenesis and resistance to therapy. Preclinical studies of apricoxib show in vitro and in vivo activity in human lung cancer xenograft models. COX-2 signaling activates the Erk/MAPK pathway, thus combinations of COX-2 and EGFR inhibitors are of interest, particularly in NSCLC. The purpose of this study was to determine the safety and feasibility of combining apricoxib with erlotinib in NSCLC patients and to determine the recommended Phase II dose (RP2D) based on either the MTD or the optimum biologic dose (OBD). OBD was based on decreases in PGE-M, a urinary metabolite of PGE2. **Methods:** Pts with recurrent or metastatic NSCLC were treated with erlotinib (150 mg PO daily) and escalating doses of apricoxib (100-1200mg PO daily). Prior treatment with an EGFR TKI was allowed. PK for apricoxib and erlotinib were evaluated. PGE-M a urinary metabolite of PGE2, was collected at baseline and Day 15 of C1 and Day 1 of C2. The RP2D was to be based on > 75% inhibition of PGE-M and/or the MTD. DLT was defined as drug related G3 and G4 events. **Results:** 19 patients have been enrolled (3 at apricoxib 100mg; 3 at apricoxib 200mg, 12 at apricoxib 400mg). **Characteristics:** Sex: M/F: 7/12; Age range 54-81; The majority were ECOG PS 0 or 1. Number of prior therapies: 1-5. There were no DLTs; most common adverse events include G1 and G2 nausea, diarrhea and rash. 2 serious adverse events (gastric ulcer, SOB) and 2 deaths due to disease progression occurred. The RP2D selected was 400mg based on decline in urinary PGE-M and PK. Of 14 evaluable patients: 1 PR, 8 SD, and 5 PD as best response. SD was seen in pts having failed prior EGFR TKI therapy. Apricoxib pharmacokinetics revealed a median T_{max} of 2 hours (range 1.5-4), mean (SD) T_{1/2} of 11.8 (5.3) hours, C_{max} of 313.0 (99.6) ng/ml and AUC (0-t) of 2816 (1204) ng.h/ml. **Conclusions:** 1) Apricoxib and erlotinib have been safely administered in this Phase I study. 2) The RP2D of the combination is apricoxib 400mg and erlotinib 150mg. 3) The activity observed warrants further evaluation in a randomized Phase II study. That study is ongoing.

BACKGROUND RATIONALE

Apricoxib is an oral, potent and selective inhibitor of COX-2. The COX-2 pathway plays a key role in tumor dependent angiogenesis and growth. Preclinical studies of apricoxib show in vitro and in vivo activity in xenograft models. COX-2 signaling activates the Erk/MAPK pathway thus combinations of COX-2 and EGFR inhibitors are of interest in advanced NSCLC.

STUDY OBJECTIVES-PRIMARY

The primary objective of the study was to determine the recommended Phase II dose (RP2D) of the combination of apricoxib and erlotinib defined as the optimal biological dose (OBD) or the maximum tolerated dose (MTD).

The OBD is defined as the dose level at which the average percent decrease of three patients' urinary PGE-M is > 75.0%. The 3 patients that will be used to determine the group average will be the first 3 patients who decrease in urinary PGE-M and who complete day 28 of the given cohort. In addition, there must be 1 DLT in 3 or 6 patients.

STUDY OBJECTIVES-SECONDARY

- Determine the safety and tolerability of the combination of apricoxib and erlotinib
- Measure pharmacokinetics of apricoxib and erlotinib
- Determine the utility of PGE-M for the selection of patients for treatment with apricoxib
- Assess preliminary evidence of antitumor activity of the combination of apricoxib and erlotinib by RECIST
- Investigate exploratory biomarkers for the combination including pathway inhibition and gene polymorphisms involved in apricoxib metabolism

KEY ELIGIBILITY CRITERIA

- Recurrent or relapsed Stage IIIB or IV NSCLC
- Must have failed at least one prior chemotherapy regimen or refused chemotherapy
- May be currently receiving erlotinib at a dose of 150 mg but may have been failing erlotinib
- ECOG PS 0, 1, 2
- Adequate organ function
- Treated and stable CNS metastases allowed
- No history of MI, CVS or peptic ulcer disease
- Concurrent NSAID and aspirin not allowed

TREATMENT SCHEDULE

TG01-100 Tablet Dose Escalation Scheme		
TG01-100 Tablet Dose		
Cohort 1	100 mg p.o. daily	
Cohort 2	200 mg p.o. daily	
	Arm A: If PK results of Cohorts 1 and 2 are $\geq 2X$ the C _{max} and AUC using unmilled drug substance	Arm B: If PK results of Cohorts 1 and 2 are $< 2X$ the C _{max} and AUC using unmilled drug substance
Cohort 3	300 mg p.o. daily	400 mg p.o. daily
Cohort 4	400 mg p.o. daily	600 mg p.o. daily
Cohort 5	500 mg p.o. daily	800 mg p.o. daily
Cohort 6	600 mg p.o. daily	1200 mg p.o. daily

All patients received erlotinib 150 mg po daily

PATIENT DEMOGRAPHICS

Total enrolled	20
100 mg Cohort	3
200 mg Cohort	3
400 mg Cohort	14
Males/females	7/13
Median age (range)	67 yrs (42-85 yrs)
White/Asian	15/5
ECOG 0, 1, 2	9/11/0

DISEASE CHARACTERISTICS

Stage IIIB/IV	2/18
Histology	
Adenocarcinoma	8 (40%)
Squamous cell	6 (30%)
Large cell	1 (5%)
Adenocarcinoma with squamous elements	2 (10%)
Adenocarcinoma with BAC	2(10%)
Other	1 (5%)

PREVIOUS THERAPY

Surgery	6 (30%)
Radiation Therapy (Lung/Chest)	7 (35%)
Chemotherapy (Metastatic disease)	16 (80%)
Number of regimens	
0	4* (20%)
1-2	12 (60%)
>3	4 (20%)
TKI Kinase therapy	8 (40%)

* 3 patients received chemotherapy as radiation sensitization or as adjuvant treatment
1 patient received erlotinib alone

PHARMACOKINETICS

Summary of Pharmacokinetic Parameters of Apricoxib for Cohorts 1-3 (Study TP-2001-101)

Cohort/AP Dose	Patients (N) Gender	Mean \pm Standard Deviation Values				
		C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (ng·h/mL)	AUC _{0-inf} (ng·h/mL)	
Cohort 1 100mg (1 x 100mg)	N=3 3 F	334.6 \pm 55.8 331.7 (16.7%) ^a	2.0 (2.0 - 4.0) ^b	3273.1 \pm 1605.7 3004.4 (49.1%) ^a	4439.5 \pm 2280.8 3928.0 (51.4%) ^a	11.3 \pm 6.6
Cohort 2 200mg (2 x 100mg)	N=3 2 M 1 F	291.4 \pm 142.4 271.0 (48.9%) ^a	1.5 (1.5 - 2.0) ^b	2359.2 \pm 647.6 2303.0 (27.5%) ^a	3061.1 \pm 789.3 2996.7 (25.8%) ^a	12.3 \pm 4.9
Cohort 3 400mg (4 x 100mg)	N=4 4 F	693.5 \pm 204.0 669.5 (29.4%) ^a	2.25 (1.0 - 3.0) ^b	6527.5 \pm 4794.6 5369.4 (73.5%) ^a	8479.3 \pm 3990.3 7752.3 (47.1%) ^a	16.5 \pm 8.1

^a Geometric means (%CV) are presented beneath arithmetic means for C_{max}, AUC_{0-t}, and AUC_{0-inf}.
^b Median (range) is given for T_{max}.
AP, apricoxib; F, female; M, male.

PHARMACOKINETICS-SUMMARY

- AUC and C_{max} increased in a more than dose proportional manner in first 3 cohorts
 - Small sample size must be considered
 - Data presented from first 10 patients
 - No differences between groups (gender)
- Half-life 15-18 hrs
 - Supports once daily dosing

SAFETY-1

Organ System	100 mg	200 mg	400 mg	All
Pts. With TSEAE	3	3	14	20
100%	100%	100%	100%	100%
Skin	100%	33%	100%	90%
GI Tract	67%	100%	86%	85%
General Dis.	100%	67%	57%	85%
Metabolism	100%	33%	50%	50%
Hematological	33%	0	43%	45%

SAFETY-2

Respiratory	33%	0	87%	38%
Infections	67%	33%	21%	30%
CNS	67%	33%	21%	30%
Musculoskeletal	33%	33%	21%	25%
Renal	33%	0	14%	15%
Vascular	0	33%	14%	15%
Hepatobiliary	0	0	14%	15%
Cardiac	33%	0	0	5%

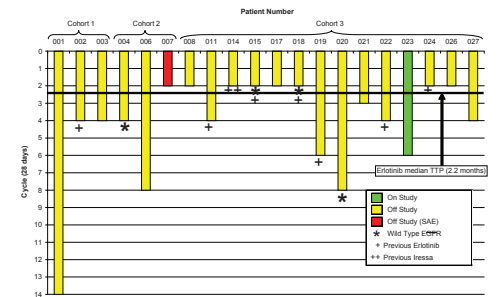
SAFETY SUMMARY

- Most common AE are skin and GI
 - Skin rash-responds to antibiotics and steroid creams
 - Diarrhea-controlled with Lomotil
- Most AE are mild to moderate and do not require changes in dose
 - 8 (40%) patients had treatment emergent events Grade 3
- 2 SAE reported
 - Perforated gastric ulcer-related
 - Hospitalization for pleural effusion drainage-not related
- 2 deaths on study
 - Failure to thrive-not related
 - Disease progression-not related

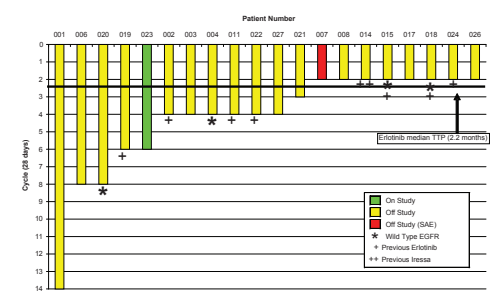
ACTIVITY

- One PR-ongoing for 14 cycles (5%)
- Eleven SD as best response(55%)
- Overall tumor control rate of 12/20 (60%)
- Anecdotal comments from sites indicate reduction of cancer-related pain

TIME TO TUMOR PROGRESSION BY COHORT



TIME TO TUMOR PROGRESSION – WATERFALL PLOT



CONCLUSION:

- The combination of apricoxib and erlotinib can be given safely and was well tolerated
 - No new serious adverse events detected with the combination
- The RP2D for apricoxib is 400mg daily
- Tumor control rate encouraging for this population
- Combination currently being tested in a randomized Phase II study