

# ACTIVITY OF TG01, A SELECTIVE COX-2 INHIBITOR, ALONE AND IN COMBINATION WITH DOCETAXEL IN HUMAN NON-SMALL CELL LUNG CARCINOMA XENOGRAFTS (Abstract # 5663)

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## ABSTRACT

TG01 is an oral, potent and selective inhibitor of COX-2 which is in Phase I development for the treatment of solid tumors in combination with standard agents. The COX-2 pathway has been demonstrated to impact several pathways involved in signaling in cancer including the erbB family of receptors. Among the indications to be explored clinically is relapsed NSCLC. To support studies in this indication, we evaluated TG01 in a number of human NSCLC xenograft models. The compound was administered orally on a continuous daily regimen in female athymic nude mice bearing established sc-implanted xenografts. The models evaluated included MV522, A549 and H460 NSCLC. In each tumor model, TG01 was compared over a broad dosage range with celecoxib. In addition to monotherapy, combinations of the COX-2 inhibitors with docetaxel were evaluated in the H460 model, which was chosen for its moderate sensitivity to taxanes. The experiments used a tumor growth delay (TGD) endpoint based on median time to endpoint, i.e., tumor volume of 1000-2000 cu mm, and treatments were compared to untreated controls using the Logrank test for statistical significance. In the slow-growing MV522 model, TG01 at its MTD of 30 mg/kg produced a significant 32.1-day TGD (96%, p = .030). There was also a significant TGD of 19.1 days at 10 mg/kg of TG01 (57%, p = .0002). In contrast, celecoxib did not produce dose-dependent TGD in MV522 NSCLC. TG01 also had significant activity in the slow-growing A549 NSCLC with a 24.3-day TGD (62%, p = .030) at its MTD. In this model, celecoxib also showed a significant but smaller TGD of 15.4 days (39%, p = .035) at 100 mg/kg. In the fast-growing H460 NSCLC, both TG01 and celecoxib produced a minimal, albeit statistically significant, TGD of 4.0 days (30%, p = .0042) and 3.0 days (22%, p = .0080), respectively. Docetaxel was active with a TGD of 10.8 days (80%, p < .0001) at 25 mg/kg (iv weekly x 3). Combinations of docetaxel with TG01 or celecoxib were not significantly different from docetaxel alone with TGD values of 12.4 (92%, p = .99) and 12.3 (91%, p = .85) days, respectively. TG01 had statistically significant activity in all 3 tumor models evaluated, although the activity in the fast-growing H460 NSCLC was minimal. TG01 had greater activity than celecoxib in MV522 and A549 NSCLC and the data would support the planned clinical evaluation of TG01 in NSCLC.

## BACKGROUND-COX-2 and LUNG CANCER

The cyclooxygenase (COX) pathway has been implicated in carcinogenesis since the 1970s when increased concentrations of prostaglandins were detected in neoplastic tissues, especially colon cancer. Epidemiological studies have documented a decreased incidence of colorectal and breast cancer in patients taking non-specific COX inhibitors such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). COX occurs in 2 isoforms: COX-1 is expressed constitutively in most tissues and is thought to serve a function in maintaining the integrity of the gastrointestinal (GI) tract and the renal medulla. COX-2 is in general not detectable in normal tissues and is upregulated in the presence of inflammation and neoplasia. COX-2 is consistently over expressed in a large percentage and variety of human tumors. The presence of elevated COX-2 in tumor tissue represents a poor prognostic factor in a number of tumors including breast cancer.

There are considerable preclinical and clinical data showing that COX-2 is important in the pathogenesis of NSCLC (Csiki and Johnson 2006). COX-2 is over expressed in 70% to 80% of patients with NSCLC. Selective COX-2 inhibitors have been shown to inhibit the growth of lung cancer cell lines and, in xenograft models, to enhance the effectiveness of selected chemotherapy against NSCLC cell lines (Csiki and Johnson 2006). In early-stage NSCLC, treatment with celecoxib can modulate the increased expression of prostaglandin E2 (PGE2) in tumor tissue after neoadjuvant treatment (Altorki et al. 2005).

Evidence that epidermal growth factor receptor (EGFR) and COX-2 have related signaling pathways that can interact to regulate cellular proliferation, migration, and invasion has triggered an interest in evaluating the combination of COX-2 inhibition and EGFR inhibition in NSCLC. A recent phase 1 study looked at the combination of celecoxib and erlotinib in second- and third-line NSCLC treatment (Reckamp et al. 2006). The study design used endpoints of optimal biologic dose selected by the decrease in the urinary prostaglandin E metabolite (PGE-M) as well as a traditionally determined maximum tolerated dose (MTD). The RR in these pretreated patients was 33% and the recommended phase 2 dose (RP2D) for celecoxib was 600mg twice daily (BID)—an increase of 30% over the doses that have previously been reported in clinical studies using celecoxib. The combination was well-tolerated.

## BACKGROUND-APRICOXIB

Apricoxib (TG01) is a novel oral nonsteroidal anti-inflammatory drug, selective for the cyclooxygenase-2 (COX-2) isoform of cyclooxygenase.

Apricoxib has an *in vitro* IC<sub>50</sub> for COX-2 of 36nM and a COX-2:COX-1 selectivity ratio that ensures that at clinically relevant doses COX-1 inhibition is minimal. Initial data with apricoxib show potent anti-inflammatory and analgesic effects in standard animal models used for NSAIDs. *In vivo* data using human tumor xenografts implanted in mice demonstrate tumor growth inhibition superior to celecoxib used in the same experiments.

In initial clinical studies in normal volunteers apricoxib was well tolerated. Pharmacokinetics demonstrate dose proportional increases in exposure, a T<sub>max</sub> of 1-2 hours and a T<sub>1/2</sub> of 15-17 supporting once daily dosing.

## METHODOLOGY

- Female athymic mice
- Cells for implantation harvested during log phase growth and injected at 1 x 10<sup>7</sup> cells in 0.2 mL
- Monitored tumors until reached 100 – 200 mm<sup>3</sup> before dosing began
- Apricoxib and celecoxib given once daily by gavage
- Paclitaxel and docetaxel given ip

## Protocol Designs

- A549
  - Group 1: no treatment
  - Groups 2-6: apricoxib at 0.3, 1, 3, 10 and 30 mg/kg, po, qdx85
  - Groups 7-11: celecoxib at 1, 3, 10, 30 and 100 mg/kg, po, qdx85
  - Group 12: paclitaxel at 30 mg/kg, iv, qdx5
- MV522
  - Group 1: no treatment
  - Groups 2-6: apricoxib at 0.3, 1, 3, 10 and 30 mg/kg, po, qdx77
  - Groups 7-11: celecoxib at 1, 3, 10, 30 and 100 mg/kg, po, qdx77
  - Group 12: paclitaxel at 30 mg/kg, iv, qdx5
- H460
  - Group 1: no treatment
  - Groups 2-3: docetaxel at 25 and 35 mg/kg, iv, qwk x 2
  - Groups 4-7: apricoxib at 3, 10, 30 and 100 mg/kg, po, qdx59
  - Groups 8-11: celecoxib at 10, 30, 100 and 300 mg/kg, po, qdx59
  - Groups 12-14: apricoxib at 3, 10, and 30 mg/kg, po, qdx59 and docetaxel at 25 mg/kg, iv, qwk x 2
  - Groups 15-17: celecoxib at 10, 30 and 100 mg/kg, po, qdx59 and docetaxel at 25 mg/kg, iv, qwk x 2

## Endpoints

- Tumors were assessed biweekly and animals euthanized when tumors reached the protocol defined size
- The time-to-endpoint (TTE) for each mouse was calculated from the following equation:

$$TTE(\text{days}) = \frac{\log^{10}(\text{endpoint vol. mm}^3) - b}{m}$$

b = intercept and m = slope of the line obtained by linear regression of a log-transformed tumor growth data set

- Treatment outcome was determined from tumor growth delay (TGD), defined as the increase in the median TTE in a treatment group compared to a control group:

$$TGD = T - C,$$

expressed in days, or as a percentage of the median TTE of the control group:

$$\%TGD = \frac{T - C}{C} \times 100$$

where:

T = median TTE for a treatment group,

C = median TTE for the control group (Group 1).

## RESULTS

### A549

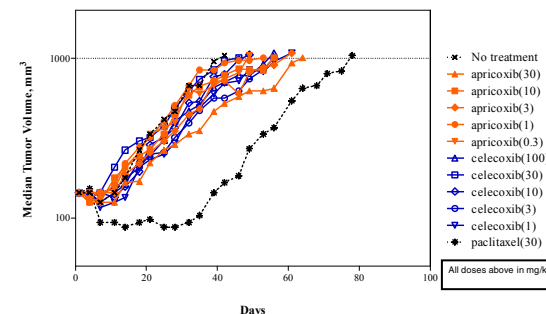
- Response to apricoxib showed dose dependent tumor growth delay
- Apricoxib at 0.3, 1, 3, 10, and 30 mg/kg produced respective tumor growth delay of 62%, 42%, 48%, 17% and 25%
- Response to celecoxib showed no dose dependent tumor growth delay
- Celecoxib at 1, 3, 10, 30, and 100 mg/kg produced respective tumor growth delay of 39%, 13%, 19%, 42% and 45%
- The groups receiving apricoxib 30 mg/kg and celecoxib 100 mg/kg had statistically significant tumor growth delay over no treatment
- Apricoxib and celecoxib were well-tolerated

### Response Summary for A549 NSCLC

n	Treatment Regimen				Median TTE	T-C	%TGD	Statistical Significance	MTV (n)	Regressions		
	Agent	mg/kg	Route	Schedule						Day 85	PR	CR
10	No treatment	-	-	-	39.0	---	---	---	847 (1)	0	0	0
10	apricoxib	0.3	po	qdx85	63.3	24.3	62	*	478 (2)	0	0	0
10	apricoxib	1	po	qdx85	55.5	16.5	42	ns	416 (3)	0	0	0
10	apricoxib	3	po	qdx85	57.9	18.9	48	ns	388 (2)	0	0	0
10	apricoxib	10	po	qdx85	45.7	6.7	17	ns	446 (1)	0	0	0
10	apricoxib	30	po	qdx85	48.8	9.8	25	ns	288 (1)	1	0	0
10	celecoxib	100	po	qdx85	54.4	15.4	39	*	446 (4)	0	0	0
10	celecoxib	30	po	qdx85	43.9	4.9	13	ns	---	0	0	0
10	celecoxib	10	po	qdx85	46.5	7.5	19	ns	---	0	0	0
10	celecoxib	3	po	qdx85	55.5	16.5	42	ns	---	0	0	0
10	celecoxib	1	po	qdx85	56.5	17.5	45	ns	---	0	0	0
10	paclitaxel	30	iv	qod x 5	76.4	37.4	96	**	600 (3)	4	0	0

Statistical Significance = Logrank test: ns = not evaluable, ns = non-significant, \* = 0.01 < P < 0.05, \*\* = 0.001 < P < 0.01, \*\*\* = P < 0.001 when compared to group indicated

### Tumor Growth Delay in A549 NSCLC



### MV522

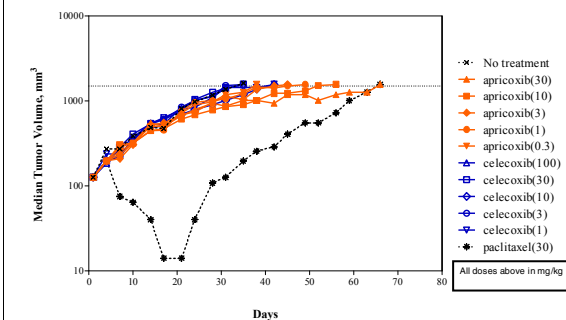
- Response to apricoxib showed dose dependent tumor growth delay and median tumor growth
- Apricoxib at 0.3, 1, 3, 10, and 30 mg/kg produced respective tumor growth delay of 13%, 28%, 26%, 57%, and 96%
- The groups receiving apricoxib at 1, 3, 10, and 30 mg/kg had statistically significant tumor growth delay over no treatment and, at 1 and 3 mg/kg, had one and two regressions, respectively
- Celecoxib at all doses produced no tumor growth delay and included no regressions
- Apricoxib and celecoxib were well-tolerated

### Response Summary for MV-522 NSCLC

n	Treatment Regimen				Median TTE	T-C	%TGD	Statistical Significance	MTV (n)	Regressions		
	Agent	mg/kg	Route	Schedule						Day 77	PR	CR
10	No treatment	-	-	-	33.3	---	---	---	---	0	0	0
9	apricoxib	30	po	qdx77	65.4	32.1	96	**	787 (4)	0	0	0
10	apricoxib	10	po	qdx77	52.4	19.1	57	***	288 (4)	0	0	0
10	apricoxib	3	po	qdx77	42.1	8.8	26	**	0 (2)	2	0	0
10	apricoxib	1	po	qdx77	42.7	9.4	28	**	405 (3)	0	1	0
10	apricoxib	0.3	po	qdx77	37.7	4.4	13	ns	---	0	0	0
10	celecoxib	100	po	qdx77	33.9	0.6	2	ns	256 (1)	0	0	0
10	celecoxib	30	po	qdx77	33.0	-0.3	-1	ns	726 (1)	0	0	0
10	celecoxib	10	po	qdx77	40.5	7.2	22	*	---	0	0	0
10	celecoxib	3	po	qdx77	31.3	-2.0	-6	ns	550 (1)	0	0	0
10	celecoxib	1	po	qdx77	35.8	2.5	8	ns	726 (1)	0	0	0
9	paclitaxel	30	iv	qod x 5	65.2	31.9	96	***	0 (4)	5	3	2

Statistical Significance = Logrank test: ns = not evaluable, ns = non-significant, \* = 0.01 < P < 0.05, \*\* = 0.001 < P < 0.01, \*\*\* = P < 0.001 when compared to group indicated

### Tumor Growth Delay in MV-522 NSCLC



### H460

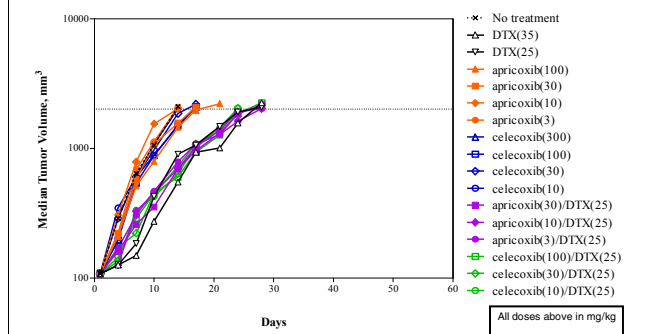
- Response to apricoxib showed dose dependent tumor growth delay
- Apricoxib at 3, 10, 30 and 100 mg/kg produced respective tumor growth delay of -2%, -6%, 19%, and 30%
- Celecoxib at 10, 30, 100 and 300 mg/kg produced respective tumor growth delay of 2%, 13%, 20%, and 22%
- Apricoxib at 3, 10 and 30 mg/kg in combination with docetaxel (25 mg/kg) produced tumor growth delay of 102%, 84%, and 92% that were statistically significant compared to no treatment
- Celecoxib at 10, 30 and 100 mg/kg in combination with docetaxel (25 mg/kg) produced tumor growth delay of 74%, 78%, and 91% that were statistically significant compared to no treatment
- Apricoxib and celecoxib were well-tolerated

### Response Summary for H460 Docetaxel Combination

n	Treatment Regimen 1				Treatment Regimen 2				Median TTE	T-C	%TGD	Statistical Significance	MTV (n)	Regressions		
	Agent	mg/kg	Route	Schedule	Agent	mg/kg	Route	Schedule						Day 99	PR	CR
10	No treatment	-	-	-	-	-	-	-	13.3	---	---	---	---	0	0	0
10	docetaxel	35	iv	qwk x 2	-	-	-	-	27.0	13.5	100	***	---	0	0	0
10	docetaxel	25	iv	qwk x 2	-	-	-	-	24.3	11.0	80	***	---	0	0	0
10	apricoxib	100	po	qdx59	-	-	-	-	17.5	4.0	30	***	---	0	0	0
10	apricoxib	30	po	qdx59	-	-	-	-	16.1	2.6	19	**	---	0	0	0
10	apricoxib	10	po	qdx59	-	-	-	-	12.7	-0.8	-4	ns	---	0	0	0
10	apricoxib	3	po	qdx59	-	-	-	-	13.2	-0.3	-2	ns	---	0	0	0
10	celecoxib	300	po	qdx59	-	-	-	-	16.3	3.0	22	**	---	0	0	0
10	celecoxib	100	po	qdx59	-	-	-	-	16.2	2.7	20	**	---	0	0	0
10	celecoxib	30	po	qdx59	-	-	-	-	13.1	1.8	13	ns	---	0	0	0
10	celecoxib	10	po	qdx59	-	-	-	-	11.8	0.5	2	ns	---	0	0	0
10	apricoxib	30	po	qdx59	docetaxel	25	iv	qwk x 2	24.4	11.3	84	***	9(1)	0	1	1
10	apricoxib	10	po	qdx59	docetaxel	25	iv	qwk x 2	27.1	13.8	100	***	---	0	0	0
10	celecoxib	100	po	qdx59	docetaxel	25	iv	qwk x 2	25.8	12.3	91	***	8(1)	0	1	1
10	celecoxib	30	po	qdx59	docetaxel	25	iv	qwk x 2	24.0	10.5	78	***	---	0	0	0
10	celecoxib	10	po	qdx59	docetaxel	25	iv	qwk x 2	23.2	9.9	74	***	---	0	0	0

Statistical Significance = Logrank test: ns = not evaluable, ns = non-significant, \* = 0.01 < P < 0.05, \*\* = 0.001 < P < 0.01, \*\*\* = P < 0.001 when compared to group indicated

### H460 Docetaxel (DTX) Combination Tumor Growth Delay



## CONCLUSIONS

- Apricoxib produced significant tumor growth delay in the NSCLC models, MV522 and A549, and was superior to celecoxib
- In monotherapy, apricoxib produced a numerical increase in TGD in the NSCLC model, H460, but was not significantly different from celecoxib
- Apricoxib combined with docetaxel demonstrated a numerical increase in TGD compared to the single agents
- Celecoxib demonstrated a lesser effect in combination with docetaxel
- Kaplan-Meier curves demonstrate prolonged survival in apricoxib-treated animals compared to celecoxib-treated animals (data not shown)
- Apricoxib was well tolerated as a single agent and in combination with paclitaxel and docetaxel
- These results are currently being investigated in a Phase II clinical trial

## REFERENCES

- Csiki I, Johnson DH. Did targeted therapy fail cyclooxygenase too? *J Clin Oncol.* 2006 Oct 20;24(30):4798-4800.
- Altorki NK, Port JL, Zhang F, et al. Chemotherapy induces the expression of cyclooxygenase-2 in non-small cell lung cancer. *Clin Cancer Res.* 2005 Jun 1;11(11):4191-4199.
- Reckamp KL, Krysan K, Morrow JD, et al. A phase I trial to determine the optimal biological dose of celecoxib when combined with erlotinib in advanced non-small cell lung cancer. *Clin Cancer Res.* 2006 Jun 1;12(12 Pt 1):3381-3388.