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MONOGRAPH

APRICOXIB

Rec INN; USAN

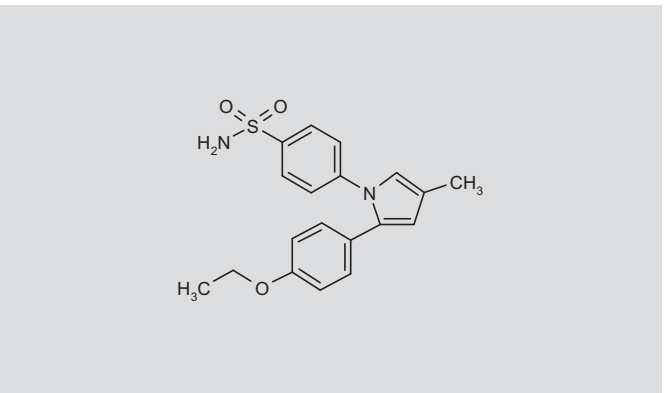
Cyclooxygenase-2 (COX-2) Inhibitor
Oncolytic

CS-706
R-109339
TG-01
TP-1001
TP-2001

Capoxigem®

4-[2-(4-Ethoxyphenyl)-4-methyl-1*H*-pyrrol-1-yl]benzenesulfonamide

InChI: 1S/C19H20N2O3S/c1-3-24-17-8-4-15(5-9-17)19-12-14(2)13-21(19)16-6-10-18(11-7-16)25(20,22)23/h4-13H,3H2,1-2H3,(H2,20,22,23)



$C_{19}H_{20}N_2O_3S$

Mol wt: 356.439

CAS: 197904-84-0

EN: 280412

SUMMARY

Overexpression of cyclooxygenase-2 (COX-2) has been implicated as a tumor-initiating and -promoting event for a number of common solid tumors, including lung, breast and colon cancer. Considerable epidemiological evidence supports COX-2 inhibition as a method of chemoprevention. Inhibition of COX-2 in laboratory models has been demonstrated to be antineoplastic both by itself and in combination with cytotoxic and targeted agents. Apricoxib is a novel, potent and selective inhibitor of COX-2 currently under development as an anti-cancer agent, as well as an analgesic. This review discusses the pharmacology, preclinical and clinical results with apricoxib, focusing on its potential use in oncology.

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*Synthesis prepared by R. Pandian, C. Estivill, N. Díaz. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

SYNTHESIS*

Apricoxib can be prepared by two strategies:

In one strategy, bromination of 4-ethoxyacetophenone (I) with Br_2 yields 2-bromo-1-(4-ethoxyphenyl)ethanone (II) along with the byproduct 2-bromo-1-(3-bromo-4-ethoxyphenyl)ethanone, which are separated using HPLC. Alkylation of propionaldehyde *N,N*-diisobutylenamine (III) with bromo ketone (II) and subsequent ketalization with neopentyl glycol (IV) using *p*-TsOH·H_2O and, optionally, H_2SO_4 in MeCN gives monoprotected ketoaldehyde (V) (1). Finally, cyclization of ketoaldehyde derivative (V) with 4-aminobenzenesulfonamide (VI) in the presence of AcOH in PrOH/H_2O at 90-100 °C furnishes apricoxib (1, 2).

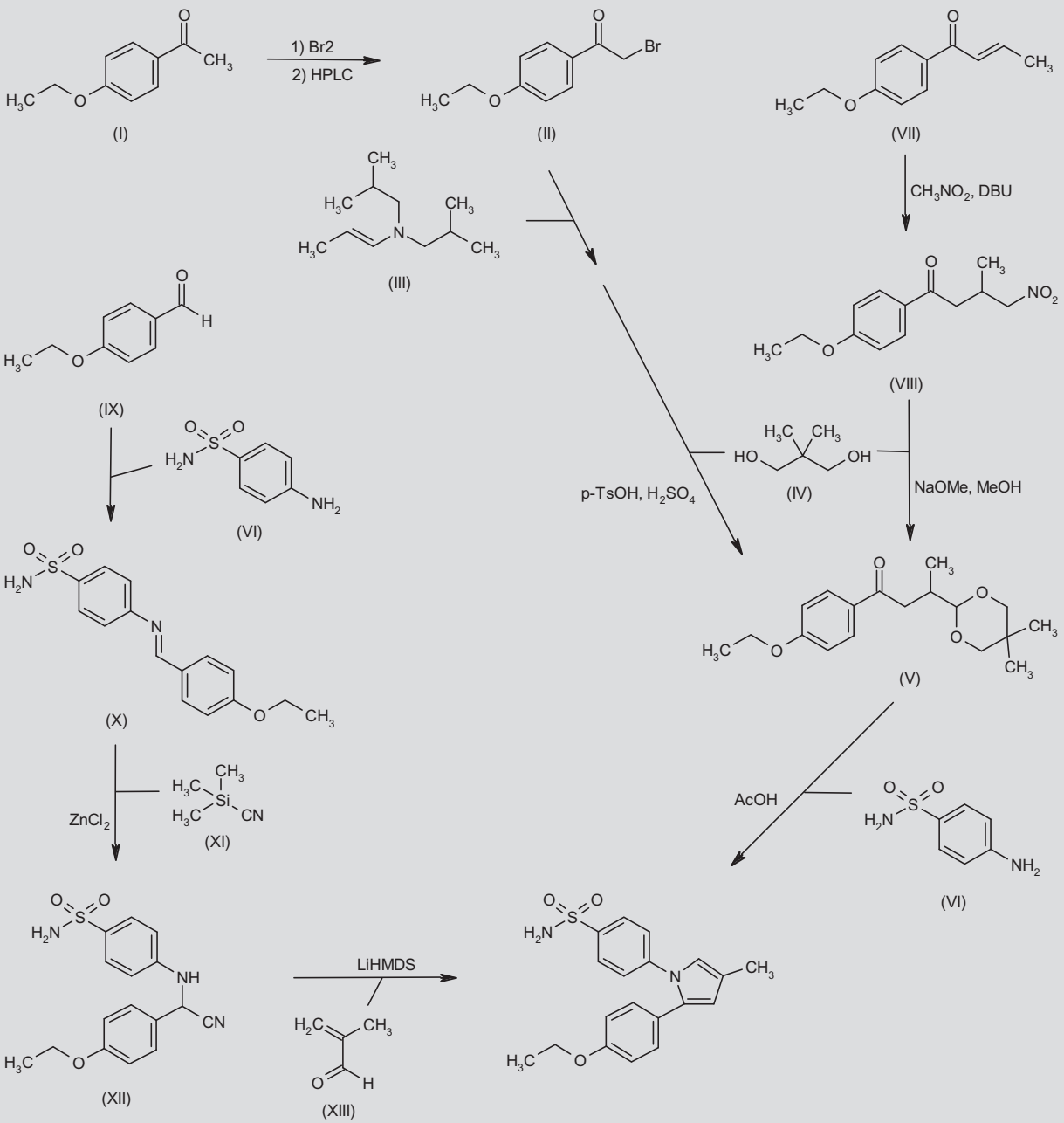
Intermediate (V) can also be prepared by reaction of 1-(4-ethoxyphenyl)-2-buten-1-one (VII) with CH_3NO_2 in the presence of DBU in THF to produce nitro ketone (VIII). Subsequent treatment of nitro derivative (VIII) with neopentyl glycol (IV) and NaOMe and MeOH gives acetal (V) (2).

In an alternative strategy, condensation of 4-ethoxyacetaldehyde (IX) with 4-sulfamoylaniline (VI) in refluxing EtOH furnishes *N*-(4-ethoxybenzylidene)-4-sulfamoylaniline (X), which then condenses with trimethylsilyl cyanide (XI) in the presence of $ZnCl_2$ in THF yielding α-amino nitrile (XII). Cyclization of this compound with methacrolein (XIII) using LiHMDS in THF affords apricoxib (3). Scheme 1.

BACKGROUND

Cyclooxygenase (COX) enzymes are part of the prostaglandin pathway and play a critical role in homeostasis, as well as in inflammation and cancer. COX occurs in two isoforms: COX-1 is

Scheme 1. Synthesis of Apricoxib



expressed constitutively in most tissues and is thought to function in maintaining the integrity of the gastrointestinal (GI) tract and the renal medulla. COX-2 is, in general, not detectable in normal tissue and is upregulated in the presence of inflammation and neoplasia. COX-2 is consistently overexpressed in a large percentage and variety of human tumors (4).

The COX pathway has been implicated in carcinogenesis since the 1970s, when increased concentrations of prostaglandins were detected in neoplastic tissues, especially colon cancer cells. Epidemiological studies have documented a decreased incidence of colorectal and breast cancer in patients taking nonspecific COX inhibitors, such as aspirin and nonsteroidal antiinflammatory drugs

(NSAIDs). The presence of elevated COX-2 in tumor tissue represents a poor prognostic factor in a number of cancers, including colorectal cancer, breast cancer and non-small cell lung cancer (NSCLC) (5).

Multiple lines of evidence using genetic manipulation that either increased or decreased COX-2 expression in cell lines and xenograft models have confirmed the growth or inhibition of tumors in the presence of up- or downregulated COX-2, respectively. COX-2 inhibitors have been shown to inhibit proliferation, induce apoptosis, stimulate the immune system and downregulate angiogenesis (6-8). There are considerable preclinical and clinical data showing that COX-2 is important in the pathogenesis of NSCLC. COX-2 is overexpressed in 70-80% 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. In early-stage NSCLC, treatment with celecoxib can modulate the increased expression of prostaglandin E_2 (PGE_2) in tumor tissue after neoadjuvant treatment (9).

Inhibition of COX-2 in addition to chemotherapy has been evaluated in a number of malignancies, including lung, breast and colon cancer (10). To date, no randomized, controlled trial has demonstrated an advantage for this approach (11, 12). These failures, coupled with increased concern regarding the safety of this approach that emerged during the evaluation of rofecoxib as a chemopreventive agent, sharply reduced enthusiasm for COX-2 inhibitors in cancer. A possible reason for the failure of the phase III experience has emerged from a trial performed by the Cancer & Leukemia Group B (CALGB) of eicosanoid modulation in advanced NSCLC (13). CALGB 30203 tested the concept of eicosanoid inhibition in advanced lung cancer. The hypothesis was that eicosanoid inhibition in addition to standard chemotherapy would potentially increase progression-free survival (PFS). Furthermore, the concept of single versus double pathway inhibition was tested with inhibitors of COX-2 and 5-lipoxygenase (5-LO) as both single agents and in combination. The study did not achieve its objective of demonstrating improved disease-free survival for any of the groups studied. However, the study required the submission of tissue specimens. The study protocol hypothesized that immunohistochemistry for COX-2 and/or 5-LO expression might identify a population of patients who would be particularly benefited by this strategy. This analysis demonstrated that patients with overexpression of COX-2 had a worse overall survival than those who did not have overexpression (hazard ratio [HR] for moderate overexpression = 2.68; $P = 0.018$). For those with high levels of expression, the result was even more dramatic, with an HR of 4.16 ($P = 0.009$). Patients receiving celecoxib (with or without zileuton) who had overexpression of COX-2 had a superior outcome compared with patients with COX-2 overexpression who did not receive celecoxib. The higher the degree of COX-2 overexpression, the greater the degree of benefit from celecoxib. Those with moderate to high expression (i.e., ≥ 4) had an HR of 0.420 ($P = 0.039$), while those with high levels of expression (i.e., > 9) had an HR of 0.194 ($P = 0.006$). Patients who did not demonstrate overexpression of COX-2 and received celecoxib appeared to have an inferior outcome (HR = 1.84; $P = 0.178$). Multivariate analysis considering potentially confounding factors of stage (IIIb vs. IV), sex and performance status, confirmed the independent predictive value of COX-2 expression and response to celecoxib (HR = 0.17 [0.06-0.49]; $P = 0.0011$). These findings clearly indicated that the potential benefits of COX-2 inhibition in addition to chemotherapy were restricted to patients with tumors expressing moderate to high levels of COX-2, as determined by immunohistochemistry.

Subsequent to this report, a number of investigators have published similar findings in NSCLC and breast cancer (14, 15). Additionally, an earlier paper found that the addition of celecoxib to interferon alfa in advanced renal cell carcinoma was most active in patients with higher levels of COX-2 (16). The authors remarked that this was surprising, as these patients would normally be expected to have an inferior outcome.

A major problem with the use of immunohistochemistry is the requirement for a tumor specimen. In many cases, an adequate specimen will require an invasive procedure or was obtained at a substantially earlier time (for example, a specimen obtained at the time of a curative intent resection, which may precede relapse by years). An alternative approach to evaluating the role of COX-2 in a specific patient's disease is to measure suppression of urinary PGE metabolite. Prostaglandins are derived from the endoperoxide intermediate prostaglandin H_2 (PGH_2), which is generated from the precursor arachidonic acid by the action of COX enzymes. PGE_2 has been identified as the prostaglandin most involved in the neoplastic process (17). PGE_2 can be readily quantified in cell culture using a variety of approaches, such as immunoassay, high-performance liquid chromatography (HPLC) and mass spectrometry. PGE_2 quantification is more difficult in animals and humans. The most generally accepted way of measuring endogenous PGE_2 production is by determination of urinary metabolites. A methodology has been established for determination of the urinary metabolite of PGE_2, termed PGE-M, that can be used clinically. This allows for selection of patients based on PGE_2 without the need for tumor biopsies. It also allows for repeated determinations during the treatment period. Csiki et al. have shown that while baseline urinary PGE-M was not predictive, serial evaluations of urinary PGE-M were useful. The greater the drop of PGE-M after 1 week of treatment with celecoxib relative to baseline, the longer the survival (18).

The rationale for COX-2 inhibition and methods of assessing the role of COX-2 in a specific patient's disease is critical for an understanding of the current development plan for apricoxib. Apricoxib (CS-706, TG-01, Capoxigem®) is a selective oral COX-2 inhibitor under development for pain and cancer by Tragara Pharmaceuticals. The drug is selective for COX-2, with an IC_{50} of 0.31 μM for COX-2 versus 2.2 μM for COX-1 in a human white blood cell assay (19).

PRECLINICAL PHARMACOLOGY

A number of preclinical studies have evaluated apricoxib as a single agent and in combination with chemotherapy in vitro and in animal models of cancer. In a series of pancreatic cancer cell lines, apricoxib improved responsiveness to treatment with gemcitabine and erlotinib.

In animal models of pancreatic cancer the data are conflicting. Apricoxib demonstrated significant benefit, with reduction of tumor size and metastatic potential in one xenograft model, but not in another (20). In other models of gastrointestinal cancer, apricoxib as a single

agent prevented the development of gallbladder carcinoma or inhibited its progression. Apricoxib in combination with cisplatin demonstrated superiority in animal models of colorectal cancer and gallbladder carcinoma (21).

In the human NSCLC NCI-H460 tumor xenograft model, apricoxib and celecoxib were evaluated as monotherapy and in combination with docetaxel (22). This tumor model was selected for the combination study as it is only moderately sensitive to docetaxel at the maximally tolerated dose. Thus, potentiation by a COX-2 inhibitor should be readily assessable in this model. Monotherapy with both apricoxib and celecoxib significantly delayed tumor growth at two different dose levels each. The maximum tumor growth delay was 30% with apricoxib and 22% with celecoxib, and proved to be statistically significant due to the small variation in both treated and control groups. In the same experiment, the putative maximum tolerated dose (MTD) of docetaxel was evaluated in combination with either apricoxib or celecoxib. The combinations were no more effective than monotherapy with docetaxel. The longest tumor growth delay was seen with docetaxel plus the lowest dose of apricoxib.

Apricoxib and celecoxib were tested alone and in combination with pemetrexed in human breast carcinoma MX-1 implanted in nude mice (23). This model was chosen as it is one of very few tumor models, both human and murine, that has been reported to be sensitive to pemetrexed in vivo. The high level of serum thymidine and reduced folate pools in rodents makes the evaluation of agents such as pemetrexed problematic in these species. In contrast to a prior report, pemetrexed given at a high dose on a daily x 7 regimen failed to delay the growth of MX-1 tumors. Monotherapy with either apricoxib or celecoxib did not delay tumor growth significantly in this breast tumor model. Despite the fact that there was no significant activity seen with monotherapy with either pemetrexed or either of the COX-2 inhibitors, the combination of either apricoxib or celecoxib with pemetrexed produced significant tumor growth delay when compared to the untreated control or pemetrexed alone. There was a significant delay at both dose levels of apricoxib tested and at the higher of the two doses of celecoxib. The tumor growth delay for the combination with either of the COX-2 inhibitors was 51-56% above that of pemetrexed alone.

PHARMACOKINETICS AND METABOLISM

The pharmacokinetics of apricoxib are best described utilizing a two-compartment model (24). Drug distribution and elimination occur from a central compartment, with a linked peripheral compartment. In the predicted dose range (up to 200 mg) elimination kinetics are linear, with decreasing clearance at higher (and not clinically relevant) doses. Oral bioavailability also decreases with increasing dose. There is approximately 50% saturation at a dose of 221 mg. The half-life of the drug is 15-18 hours, allowing for daily dosing (25). However, AUC data indicate that exposure to drug is greater with twice-daily dosing. In vitro data indicate that apricoxib is a substrate for cytochrome P450 CYP2D6, CYP2C9, CYP3A4 and CYP1A2. In clinical testing, CYP2D6 emerged as an important determinant of clearance. Patients with the CYP2D6 phenotype indicative of poor or intermediate metabolism had decreased oral clearance. Oral clearance is decreased by 15% in individuals expressing the reduced hydroxylator CYP2C9 phenotype compared to intermediate or normal phenotypes. Another important determinant of clearance is sex. Female subjects display 38.4% lower clearance. Ethnicity may also be an important aspect of clearance; for example, Japanese subjects have a reduced incidence of poor metabolizers compared with Caucasians.

Pharmacodynamic models demonstrated that there is an approximately 20:1 ratio of COX-2:COX-1 inhibition seen in vivo (26). This level of effect is comparable to that of other selective COX-2 inhibitors and in contrast to the approximately 1:1 ratio seen with nonselective inhibitors (Table I). Inhibition of both COX-1 and COX-2 enzymes occurs in a dose-dependent manner, without any evidence of differences between Japanese and Caucasian patients.

SAFETY

A major concern regarding NSAIDs in general and COX-2-specific inhibitors in particular is the question of cardiovascular toxicity. As noted above, this emerged as a consequence of the cardiovascular toxicity seen with rofecoxib (27). It is important to recognize that considerable epidemiological and trial data indicate that cardiovascular risk varies considerably among both selective and nonselective COX inhibitors, with rofecoxib carrying the greatest risk (28-30). This risk appears to be most pronounced in those with an existing history of atherosclerotic cardiovascular disease (31). The etiology of cardiovascular toxicity due to rofecoxib and COX inhibitors in general appears to be multifactorial and has been linked to blockade of prostacyclin production without inhibition of thromboxane A2, as well as other deleterious alterations in the balance of cardioprotective arachidonic acid metabolites (32). In addition, there may be effects on vascular smooth muscle ion channels and other effects on the arterial wall (33). To date, significant cardiovascular toxicity has not been observed with apricoxib in the randomized trials in pancreatic cancer and NSCLC (34, 35). One possible reason is that apricoxib (and celecoxib), in contrast to rofecoxib, does not bind to arterial wall elastin (36).

Another major concern, and one of the original rationales for the development of COX-2 inhibitors, is the potential for reduction of GI toxicity, and specifically, GI ulceration and bleeding. A corporate-sponsored evaluation of apricoxib versus naproxen on acute GI mucosal injury in healthy men and women (N = 160) without evidence of underlying gastroduodenal lesions was performed. Sub-

Table I. *Pharmacodynamics of apricoxib and other COX inhibitors (33).*

Agent	IC_{50} for COX-1 (μM with 95% CI)	IC_{50} for COX-2 (μM with 95% CI)
Apricoxib	2.8 (1.7-3.9)	0.36 (0.10-0.62)
Celecoxib	8.3 (5.9-13)	0.93 (0.47-28)
Rofecoxib	6.5 (3.0-11)	0.20 (0.15-0.26)
Valdecoxib	28 (7.3-74)	0.6 (0.46-0.79)
Tiracoxib	71 (44-190)	37 (27-52)
Etoricoxib	49 (32-84)	0.35 (0.27-0.43)
Meloxicam	1.6 (0.89-2.6)	0.93 (0.69-1.4)
R-132149 (metabolite)*	28	2.3
R-111589 (metabolite)*	39	18

*Apricoxib metabolites. CI, confidence interval.

jects were randomized to placebo, 100 mg apricoxib once daily, 200 mg apricoxib once daily or 500 mg naproxen twice daily, administered for 7 days. On day 8, subjects underwent a post-treatment upper GI endoscopy to assess the development of gastroduodenal petechiae, erosions and ulcers. The extent of upper GI mucosal injury for both apricoxib dose groups was statistically significantly less than that for naproxen ($P < 0.001$) and was similar to placebo ($P = 0.615$ and $P = 0.115$ for 100 and 200 mg apricoxib, respectively). There was numerically greater GI injury seen in the apricoxib 200 mg compared to the 100 mg group. No subject in the placebo or either apricoxib treatment group had gastroduodenal ulcers, compared with 11 (28.2%) subjects treated with naproxen ($P < 0.001$). Subsets of each of the groups were analyzed for COX-1 and COX-2 inhibition. Both doses of apricoxib inhibited COX-2 activity to a similar extent as naproxen, whereas neither dose of apricoxib showed meaningful inhibition of platelet COX-1. In contrast, naproxen nearly completely inhibited COX-1 over the dosing interval (37).

CLINICAL STUDIES

Apricoxib has been evaluated as a single agent for the treatment of dental pain. A randomized, double-blind, double-dummy, placebo-controlled study was conducted in healthy male and female subjects who were undergoing dental extractions associated with moderate to severe pain intensity. Patients were randomized (approximately 50 per group) to receive a single oral dose of apricoxib 10, 50, 100 or 200 mg, celecoxib 400 mg or placebo. Pain intensity and pain relief were measured on categorical and visual analog scales for 24 hours after the dose. Virtually all doses of apricoxib were superior to celecoxib or placebo in multiple measures of analgesic effect. The onset of analgesia for all apricoxib doses occurred within 1 hour after dosing ($P < 0.001$ vs. placebo). The incidence and severity of adverse events were similar among all treatment groups. Adverse events occurring in ≥ 5% of subjects in any treatment group were nausea, vomiting, dry socket, dizziness, headache and paresthesia (38).

The mechanism of and preclinical data for apricoxib indicate that it is unlikely to have major single-agent activity in established cancer. To date, all trials with the agent in cancer have combined it with other drugs. Reckamp conducted a phase I dose-escalation pharmacokinetic and pharmacodynamic study of apricoxib + erlotinib (AP/E) in patients with advanced NSCLC (39). The primary objective of the study was to determine the recommended phase II dose of AP/E, defined as the optimum biological dose or the MTD of the combination. The optimal biological dose was defined as the highest dose level where the inhibition of urinary PGE-M was at least > 75% and there was ≤ 1 dose-limiting toxicity in 3 of 6 patients. The combination of AP/E was administered daily on 28-day cycles. The daily dose of erlotinib was 150 mg. The apricoxib dose was escalated by cohort starting with a dose of 100 mg/day. Twenty patients were treated and the combination was well tolerated. Four patients had grade ≥ 3 drug-related adverse events (diarrhea, perforated duodenal ulcer, hypophosphatemia and deep vein thrombosis). One patient had a partial response and 11 had stable disease. Stable disease was observed in patients who had received prior EGFR inhibitor therapy, but was greater in patients not previously treated with an EGFR inhibitor. Seventeen patients had elevated urinary PGE-M at baseline and 14 (70%) had a decrease from baseline, which was associated with disease control. The recommended phase II dose of apricoxib was 400 mg daily.

Four trials have been initiated testing the activity of apricoxib in advanced, COX-2-dependent malignancies (Table II). COX-2 dependence has been evaluated by the use of urinary PGE-M suppression. All of the trials share a randomized phase II design and have a primary endpoint of PFS. Three trials are directly coordinated by Tragara Pharmaceuticals and are known as the "APRiCOT" (Apricoxib in Combination Oncology Treatment) studies. One of these, termed APRiCOT-B (breast), was designed to evaluate apricoxib in combination with lapatinib and capecitabine in the treatment of HER2/Neu$^+$ breast cancer but was terminated before completion. APRiCOT-P (pancreas) is comparing the antitumor efficacy of first-line chemotherapy with apricoxib and gemcitabine/erlotinib as opposed to placebo and gemcitabine/erlotinib. The primary endpoint is PFS. A preliminary report detailing adverse events in the first 46 (of a planned 110) patients enrolled was presented in 2010 (33). APRiCOT-L (lung) compared the antitumor efficacy of apricoxib and erlotinib with placebo and erlotinib in advanced, previously treated NSCLC, as measured by time to disease progression, to test the hypothesis that downregulation of COX-2 and EGFR pathways in patients with upregulated COX-2 expression in tumors will have a clinical benefit compared with erlotinib alone. Preliminary results of APRICOT-L were reported in June 2011 (34). While the study failed to meet its primary endpoint of improved survival, a prespecified subset analysis of patients < 65 years of age did demonstrate improved outcome in terms of disease control, time to progression and overall survival. Analysis of the > 65-year-old subgroup demonstrated increased toxicity, including GI bleeding. This increased toxicity was confined to patients with low albumin (< 2.5 mg/dL). A phase III trial is planned.

A fourth trial, UMGCC 0822, is being conducted independently by the University of Maryland. This multicenter, randomized phase II study is evaluating the role of apricoxib in addition to either docetaxel or pemetrexed for the second-line treatment of advanced NSCLC. This trial is expected to complete accrual during the summer of 2011 and results will be presented in 2012.

CONCLUSIONS

Apricoxib is a well-tolerated, highly selective COX-2 inhibitor currently undergoing evaluation as an anticancer agent. Preclinical evidence has demonstrated both single-agent activity and a significant ability to potentiate existing agents, including widely used cytotoxic agents such as cisplatin, docetaxel and pemetrexed, as well as the EGFR tyrosine kinase inhibitor erlotinib. It has become clear that the optimum use of COX-2 inhibitors, including apricoxib, requires a strategy to select patients who have tumors that demonstrate some dependency upon COX-2. This can be accomplished either with immunohistochemistry of biopsy specimens or suppression of urinary PGE-M by a brief course of the inhibitor. Currently, several trials in advanced cancer are either in progress or have been completed and about to be reported. Depending on the results of these studies, apricoxib may have a place as an anticancer drug. Furthermore, its favorable toxicity profile and daily dosing would be of potential value as a chemopreventive agent as well.

Table II. *Clinical trials of apricoxib.*

Trial	ClinicalTrials.gov	Disease	Design	Projected N	Projected completion
APRiCOT-P: Study to Evaluate the Safety and Efficacy of Apricoxib With Gemcitabine and Erlotinib in the Treatment of Patients With Advanced Pancreatic Cancer	NCT00709826	Pancreatic cancer	Randomized phase II	110	June 2011
APRiCOT-L: Study to Evaluate Efficacy and Safety of Apricoxib With Erlotinib in Patients With Non-small Cell Lung Cancer	NCT00652340	NSCLC	Randomized phase II	122	Completed
APRiCOT-B: A Phase 2 Study of the Efficacy and Safety of Apricoxibin Combination With Lapatinib and Capecitabine in the Treatment of Patients With HER2/Neu+ Breast Cancer Who Have Failed Trastuzumab and Chemotherapy Including a Taxane	NCT00657137	Breast cancer	Randomized phase II	120	Terminated
UMGCC 0822: Randomized, Double-Blind, Placebo-Controlled Multicenter Phase 2 Study of the Efficacy and Safety of Apricoxib in Combination With Either Docetaxel or Pemetrexed in Non-Small Cell Lung Cancer Patients	NCT00771953	NSCLC	Randomized phase II	70	August 2011

SOURCES

Tragara Pharmaceuticals, Inc. (US); licensed from Daiichi Sankyo, Inc. (JP).

DISCLOSURES

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