Drugs of the Future 2011, 36(12): 893-898

CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.12.1624326

MONOGRAPH

TIVANTINIB

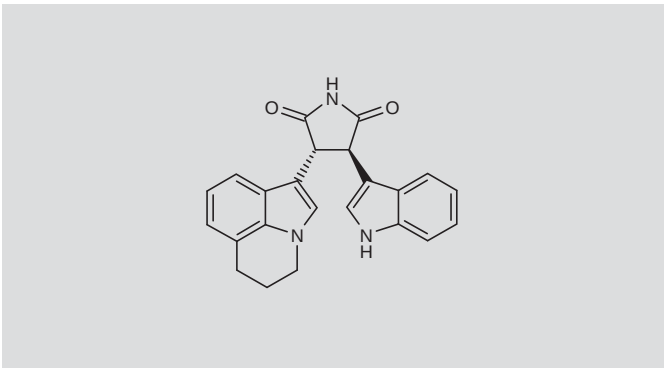
Prop INN; USAN

Proto-oncogene c-Met Inhibitor
Hepatocyte Growth Factor Receptor Inhibitor
Oncolytic

ARQ-197

(–)-3(*R*)-(5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)-4(*R*)-(1*H*-indol-3-yl)pyrrolidine-2,5-dione

InChI: 1S/C23H19N3O2/c27-22-19(16-11-24-18-9-2-1-7-14(16)18)20(23(28)25-22)17-12-26-10-4-6-13-5-3-8-15(17)21(13)26/h1-3,5,7-9,11-12,19-20,24H,4,6,10H2,(H,25,27,28)/t19-,20-/m0/s1



$C_{23}H_{19}N_3O_2$
Mol wt: 369.4159
CAS: 905854-02-6
EN: 432842

SUMMARY

As an oncogene, hepatocyte growth factor receptor (proto-oncogene c-Met; MET) is known to be overexpressed and/or mutated in many types of cancer and plays a critical role in cancer cell survival, proliferation, angiogenesis, invasion and metastasis. c-Met encodes for a tyrosine-protein kinase receptor that is activated by hepatocyte growth factor (HGF). Tivantinib is a selective, orally active c-Met inhibitor. Tivantinib binds directly to the c-Met protein in a selective manner and disrupts the c-Met signal transduction pathway. Preclinical studies have demonstrated unique inhibition of c-Met activation in numerous human cancer cell lines. Phase I and II clinical trials indicate that this c-Met inhibitor shows clinical promise in terms of safety, tolerability and efficacy for the treatment of c-Met-associated cancers.

J. Thomas Pento, PhD. Department of Pharmaceutical Sciences, College of Pharmacy, University of Oklahoma, Health Sciences Center, Oklahoma City, OK 73117, USA. E-mail: tom-pento@ouhsc.edu.
*Synthesis prepared by C. Estivill, J. Bolòs, R. Castañer. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

SYNTHESIS*

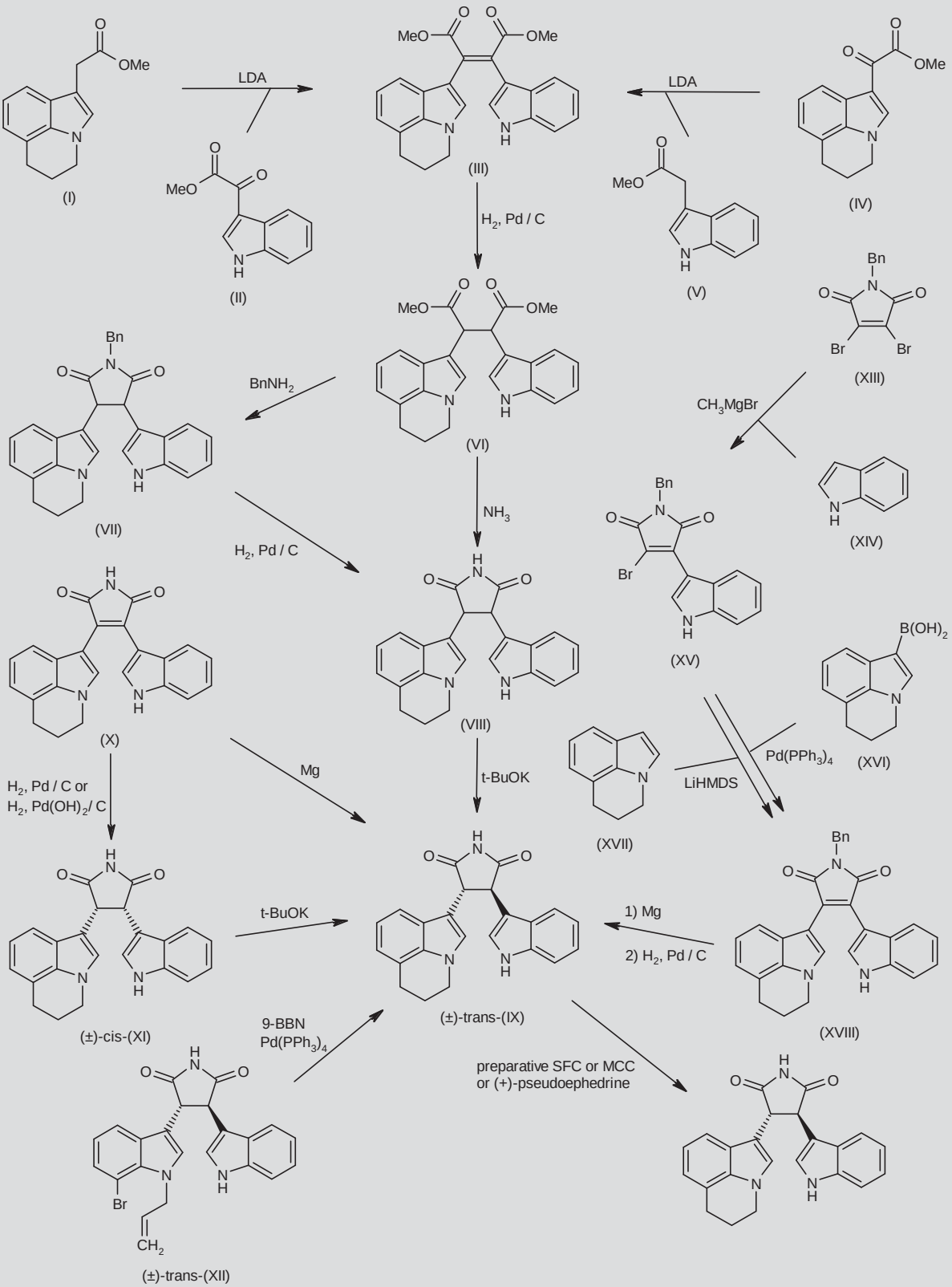
Tivantinib can be obtained by several different ways:

Condensation of methyl 5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-1-yl-acetate (I) with methyl (3-indolyl)glyoxylate (II) in the presence of LDA in THF affords the butenedioate derivative (III), which can also be prepared by condensation of methyl 5,6-dihydropyrrolo[3,2,1-*ij*]quinoline-1-glyoxylate (IV) with methyl 3-indolylacetate (V) in the presence of LDA in THF. Hydrogenation of alkene (III) over Pd/C gives the saturated diester (VI), which upon cyclocondensation with benzylamine in THF yields the 1-benzyl-2,5-pyrrolidinedione derivative (VII). Debenzylation of compound (VII) by means of H_2 over Pd/C then provides the 2,3-diarylsuccinimide (VIII) as a *cis/trans* mixture. Alternatively, succinimide (VIII) can be produced by the direct cyclocondensation of diester (VI) with NH_3 in MeOH at elevated temperature. Isomerization of intermediate (VIII) with *t*-BuOK in *t*-BuOH or THF/*t*-BuOH leads to the (±)-*trans*-isomer, racemic tivantinib (IX) (1, 2). Resolution of racemate (IX) can be effected by means of chiral preparative SFC (1, 2) or MCC (3), or by fractional crystallization with (1*S*,2*S*)-(+)-pseudoephedrine (3). Scheme 1.

Racemic tivantinib (IX) can also be obtained by the following methods:

Reduction of the maleimide derivative (X) with Mg in refluxing MeOH produces the *trans*-succinimide (IX) (1, 2). Alternatively, the reduction of maleimide (X) by catalytic hydrogenation over Pd/C in MeOH (1, 2) or $Pd(OH)_2$/C in toluene (3) provides the (±)-*cis*-succinimide (XI), which can be isomerized to the corresponding *trans*-succinimide (IX) by treatment with *t*-BuOK in *t*-BuOH at 50 °C (1-3). Similarly, reduction of the maleimide (X) with Zn(Hg) in HCl/EtOH leads to a mixture of *cis*- and *trans*-maleimides (1, 2). The tricyclic compound (IX) can also be obtained by intramolecular Heck reaction of the 1-allyl-7-bromoindole derivative (XII) in the presence of 9-BBN and $Pd(PPh_3)_4$ (1, 2). In a further method, condensation of 1-benzyl-3,4-dibromopyrrole-2,5-dione (XIII) with indole (XIV) using methyl magnesium bromide yields 1-benzyl-3-bromo-4-(3-indolyl)pyrrole-2,5-dione (XV), which by Suzuki coupling with 5,6-dihydropyrrolo[3,2,1-*ij*]quinolin-1-ylboronic acid (XVI) in the presence of $Pd(PPh_3)_4$ or by condensation with 5,6-dihydropyrrolo[3,2,1-*ij*]quinoline (XVII) by means of LiHMDS affords the maleimide (XVIII). Finally, adduct (XVIII) is reduced with Mg in refluxing MeOH, followed by debenzylation with H_2 over Pd/C in MeOH (IX) (1, 2). Scheme 1.

Scheme 1. Synthesis of Tivantinib



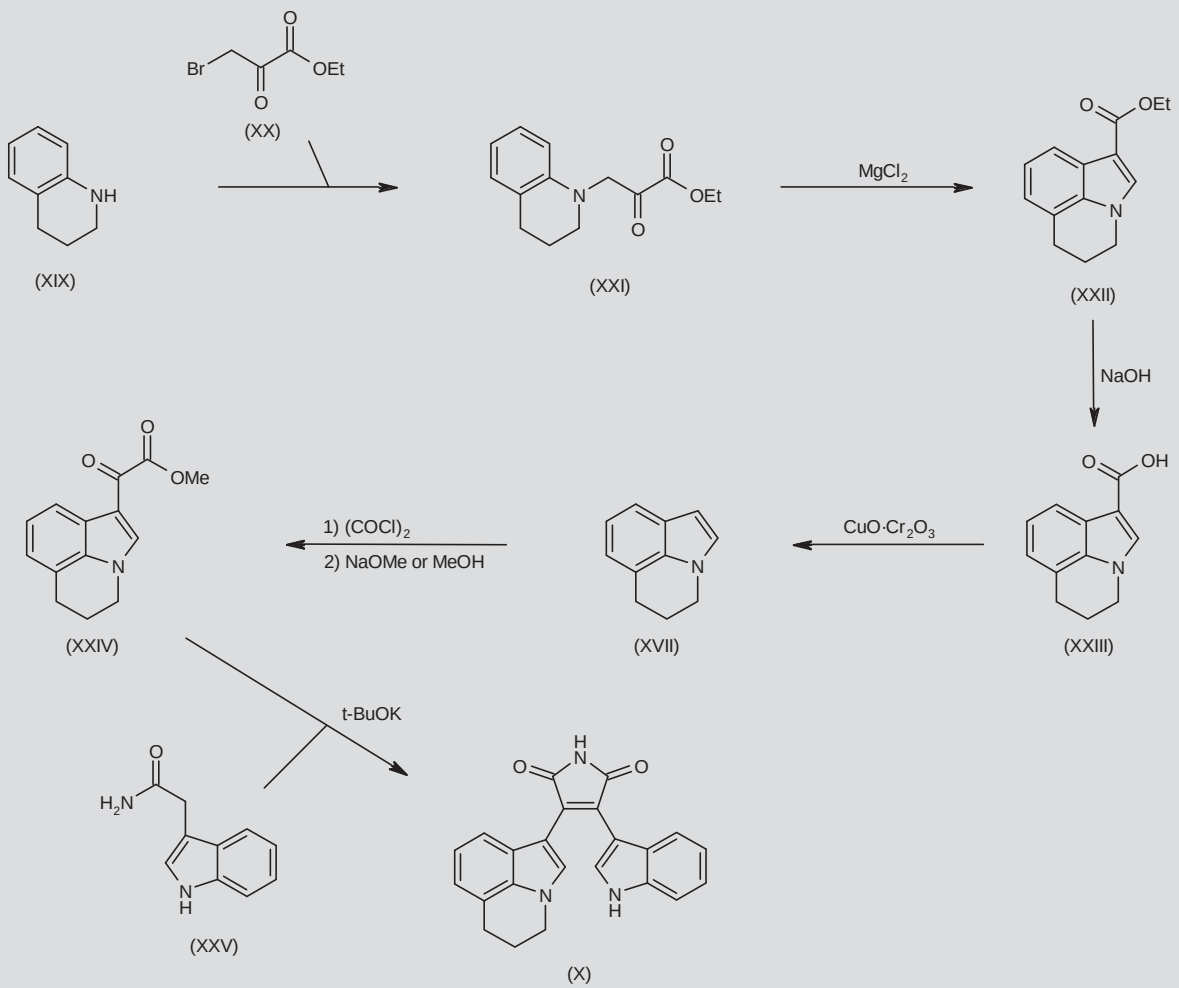
The 2,3-disubstituted maleimide intermediate (X) is prepared by *N*-alkylation of 1,2,3,4-tetrahydroquinoline (XIX) with ethyl 3-bromopyruvate (XX) in THF to give ethyl 3-(3,4-dihydro-2*H*-quinolin-1-yl)-2-oxopropionate (XXI), which by intramolecular cyclocondensation by means of $MgCl_2$ in 2-methoxyethanol at 125 °C affords ethyl 5,6-dihydropyrrolo[3,2,1-*ij*]quinoline-1-carboxylate (XXII). Hydrolysis of ethyl ester (XXII) with NaOH in EtOH/H_2O provides the corresponding carboxylic acid (XXIII), which is then decarboxylated to 5,6-dihydropyrrolo[3,2,1-*ij*]quinoline (lilolidine) (XVII) by heating to 185 °C in quinoline in the presence of $CuO{\cdot}Cr_2O_3$ (1, 2). Acylation of lilolidine (XVII) with $(COCl)_2$ in Et_2O, and subsequent quenching of the resulting glyoxylyl chloride with MeOH or NaOMe/MeOH affords the oxoester (XXIV), which is finally cyclocondensed with indole-3-acetamide (XXV) in the presence of *t*-BuOK in THF (1-3). Scheme 2.

The allyl-indole intermediate (XII) is obtained by acylation of 1-allyl-7-bromoindole (XXVI) with $(COCl)_2$ in CH_2Cl_2, followed by treatment with NaOMe to afford the oxoester (XXVII), which upon cyclocondensation with (3-indolyl)acetamide (XXV) in the presence of *t*-BuOK in THF furnishes the pyrrole-2,5-dione derivative (XXVIII). Finally, the maleimide derivative (XXVIII) is reduced by means of Mg in refluxing MeOH (1, 2). Scheme 3.

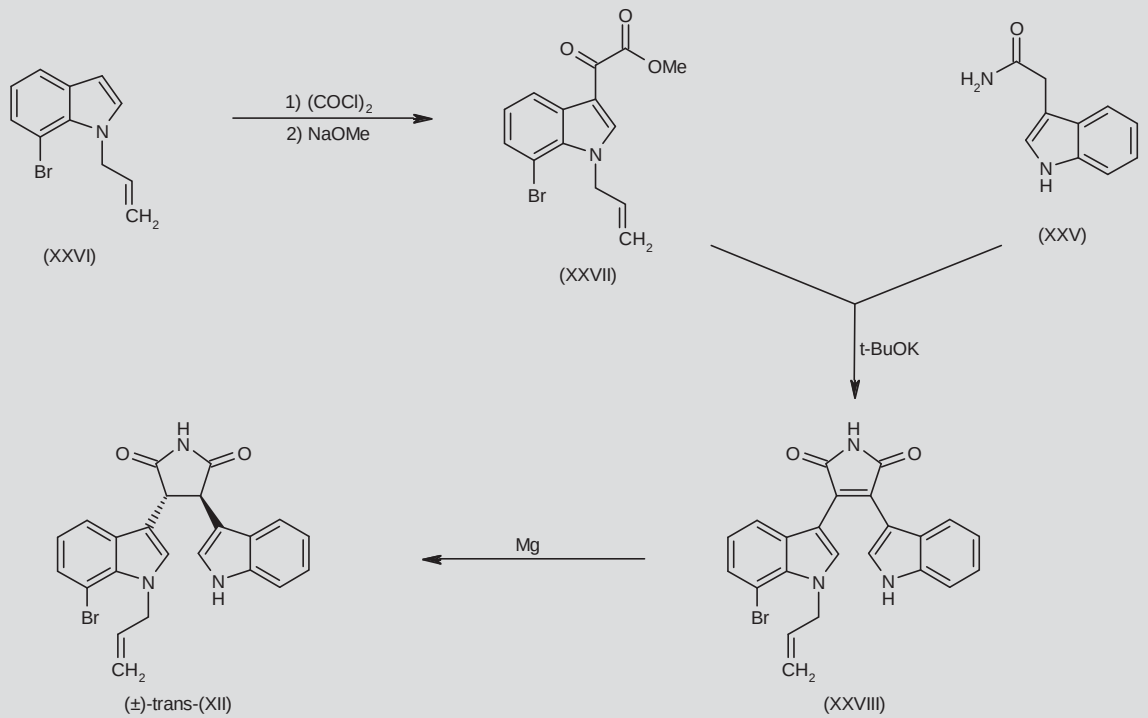
BACKGROUND

c-Met is a proto-oncogene that encodes a receptor tyrosine kinase protein that functions as the receptor for hepatocyte growth factor (HGF) (4, 5). HGF activity via c-Met activation is known to be involved in several important aspects of embryonic development, as well as wound healing in adults. HGF is expressed by mesenchymal cells, while c-Met is expressed exclusively by cells of epithelial origin (6). HGF activation of the c-Met receptor produces a collective group of biological responses, which include cancer cell proliferation, cell

Scheme 2. Synthesis of Intermediate (X)



Scheme 3. Synthesis of Intermediate (XII)



migration, resistance to apoptosis, invasion of surrounding tissues and neovascularization or the sprouting of new blood vessels in hypoxic tumor tissue (7). All of these biological responses are known to be associated with aggressive cancer progression and metastasis (8). Moreover, overexpression of HGF, c-Met and/or *MET* mutations are often associated with the initiation of tumor growth, angiogenesis and metastasis (8-10). Activation of c-Met is known to signal through multiple signaling pathways, including, Ras pathway intermediates (11), the phosphatidylinositol-4-phosphate 3-kinase (PI3K) pathway (6), the signal transducer and activator of transcription (STAT) pathway (12), β-catenin, which is part of the Wnt pathway (13) and the Notch pathway (14). Accordingly, it has been reported that aberrant c-Met signaling is observed in a wide variety of human malignancies, such as breast, colon, gastric, liver, ovarian, renal, thyroid and non-small cell lung cancer (NSCLC) (15-17).

c-Met overexpression and/or mutation in cancer patients has been correlated with aggressive cancer progression and a poor prognosis (8, 9). Thus, selective inhibition of c-Met activation and signaling holds the potential to significantly improve the treatment of many types of cancer. In addition, it has been reported that in NSCLC there appears to be an interaction between c-Met and epidermal growth factor receptor (EGFR) (both tyrosine kinase receptors), resulting in lateral signaling, which enhances the growth and progression of this cancer, thereby suggesting that combined targeting with c-Met and EGFR inhibitors may improve therapeutic responsiveness (18).

PRECLINICAL PHARMACOLOGY

Tyrosine kinase inhibitors are typically low-molecular-weight molecules that selectively compete with endogenous growth factors for the ATP binding pocket in the membrane receptor, thereby preventing receptor activation, *trans*-phosphorylation and downstream signaling. A number of c-Met inhibitors, such as K-252a (19), SU-11274 (20, 21) and PHA-665752 (22), have been identified and tested. However, tivantinib (ARQ-197) appears to be unique among the c-Met tyrosine kinase inhibitors, since it is known to be a highly selective c-Met inhibitor that acts in a non-ATP-competitive manner and shows promise as a therapeutic agent for the treatment of various cancers (23).

Tivantinib binds selectively to the inactive or non-phosphorylated form of the c-Met receptor, and thus prevents receptor activation by HGF or other growth factors (8). Munshi et al. (24) have reported that tivantinib inhibits both the proliferation of and caspase-dependent apoptosis in c-Met-expressing or -overexpressing cancer cell lines, including human colon adenocarcinoma HT-29, gastric cancer MKN-45 and breast adenocarcinoma MDA-MB-231 cells. Furthermore, they have demonstrated that oral administration of tivantinib effectively inhibits the growth of tumors in mouse

xenograft experiments utilizing these cancer cell lines. The results indicated that cancer cell death and arrest of tumor growth were associated with an effect of tivantinib on the caspase-dependent intrinsic apoptotic pathway.

Recently, Chen et al. (25) examined the combination of tivantinib and gemcitabine to establish a more effective treatment strategy for future clinical trials. Both tivantinib and gemcitabine induce cell cycle arrest of cancer cells; however, these agents act at different phases of the cell cycle. Therefore, it was postulated that the combination of these agents, using selective cell cycle pulsatile treatment, could potentially enhance anticancer treatment effectiveness. In this study, cancer cells were treated for a total of 7 days; cells were seeded on day 0, treated with gemcitabine for 24 hours on day 2, drug-free media was added on day 3 and the cells were treated with tivantinib for 24 hours on day 5, with cell viability testing on day 7. This combinatorial pulsatile treatment schedule was found to enhance the cytotoxicity of the following cancer cells: bladder, pancreatic, breast, ovarian and uterine carcinomas and NSCLC. In addition, drug potentiation was also observed when cancer cell exposure to tivantinib preceded gemcitabine treatment in these experiments.

CLINICAL STUDIES

Garcia et al. (26) completed a phase I dose-escalation study to determine the safety, tolerability, recommended phase II dose, pharmacokinetics and pharmacodynamic activity of tivantinib. The study was conducted in 38 patients with metastatic cancer in whom standard anticancer therapy had failed. Treatment consisted of twice-daily oral dosing for 2 of 3 weeks with doses ranging from 10 to 360 mg/day. The results of this study demonstrated that tivantinib was well tolerated. Adverse events were generally not observed, with fatigue (24%), diarrhea (21%) and constipation (21%) being the most common. Of the 38 patients enrolled in this study, 33 could be evaluated for tivantinib efficacy and it was observed that 1 patient had a partial remission and in 19 patients the cancer had stabilized for up to 34 weeks. Based upon the pharmacokinetic results, it was determined that the recommended phase II dose for this agent is 120 mg b.i.d.

In a separate phase I study, Yap et al. (27) examined the safety, tolerability and tumor targeting of tivantinib employing biopsy samples to determine intratumoral c-Met signaling, apoptosis and angiogenesis. Serial biopsies of patients with solid tumors were evaluated with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and quantitation of circulating endothelial cells (CECs) and circulating tumor cells (CTCs) to examine the cancer selectivity of the compound. In this study, 51 patients received 100-400 mg of tivantinib twice daily. The drug was generally well tolerated, with grade 1-2 fatigue, nausea and vomiting being the most common adverse events. Dose-limiting adverse events included grade 3 fatigue at a dose of 200 mg b.i.d. in one patient, grade 3 mucositis, erythrodysesthesia and hypokalemia at a dose of 400 mg b.i.d. in one patient, and grade 3-4 febrile neutropenia at a dose of 360-400 mg b.i.d. in three patients. Tivantinib treatment was found to decrease c-Met and focal adhesion kinase phosphorylation and decreased apoptosis in biopsies from 15 patients. Treatment produced a 30% or greater decline in CTCs in 53% of the patients with detectable CTCs (15 total); while CECs were found to decrease in 58% of all patients, little or no change in DCE-MRI imaging was observed with tivantinib treatment. Stable disease for 4 months or greater was observed in 14 patients and minor regression was found in gastric and Merkel cell cancer patients. The recommended phase II dose was determined to be 360 mg b.i.d. from the results of this study.

In addition, phase II clinical trials examining the efficacy of tivantinib for the treatment of non-CNS germ cell carcinomas have been initiated (http://www.arqule.com/res/onc/).

CONCLUSION

Tivantinib is a selective c-Met inhibitor that appears to effectively inhibit the growth, invasiveness and metastatic potential of a number of clinically important cancers. Initial clinical trials indicate that this agent is well tolerated and has the potential to be used effectively for the treatment of a broad range of human cancers.

SOURCES

Developed by ArQule, Inc. (US) in partnership with Daiichi Sankyo Co., Ltd. (JP) and Asian licensee Kyowa Hakko Kogyo Co., Ltd. (JP).

REFERENCES

1. Li, C.J., Ashwell, M.A., Hill, J., Moussa, M.M., Munshi, N. (ArQule, Inc.). *Maleimide derivatives, pharmaceutical compositions and methods for treatment of cancer.* CN 10194970, EP 1846406, EP 2289892, JP 2008530026, US 2006223760, US 7713969, WO 2006086484.
2. Chan, T.C.K., France, D.S., Ishii, K. (ArQule, Inc.; Kyowa Hakko Kirin Co., Ltd.). *Combinational compositions and methods for treatment of cancer.* KR 2011118817, US 2010297075, WO 2010093789.
3. Reed, D.P., Barnes, N.R., Kane, J.C., Lee, C.A., Chen, J.-X., Redmon, M.P. (ArQule, Inc.). *Purified pyrroloquinolinyl-pyrrolidine-2,5-dione compositions and methods for preparing and using same.* US 2011116022, WO 2011079142.
4. Bottaro, D.P., Rubin, J.S., Faletto, D.L. et al. *Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product.* Science 1991, 251(4995): 802-4.
5. Cooper, C.S. *The met oncogene: From detection by transfection to transmembrane receptor for hepatocyte growth factor.* Oncogene 1992, 7(1): 3-7.
6. Gentile, A., Trusolino, L., Comoglio, P.M. *The Met tyrosine kinase receptor in development and cancer.* Cancer Metastasis Rev 2008, 27(1): 85-94.
7. Folkman, J. *Angiogenesis.* Annu Rev Med 2006, 57: 1-18.
8. Adjei, A.A., Schwartz, B., Garmey, E. *Early clinical development of ARQ 197, a selective, non-ATP-competitive inhibitor targeting MET tyrosine kinase for the treatment of advanced cancers.* Oncologist 2011, 16(6): 788-99.
9. Birchmeier, C., Birchmeier, W., Gherardi, E., Vande Woude, G.F. *Met, metastasis, motility and more.* Nat Rev Mol Cell Biol 2003, 4(12): 915-25.
10. Gentile, A., D'Alessandro, L., Lazzari, L. et al. *Met-driven invasive growth involves transcriptional regulation of Arhgap12*. Oncogene 2008, 27(42): 5590-8.
11. Marshall, C.J. *Specificity of receptor tyrosine kinase signaling: Transient versus sustained extracellular signal-regulated kinase activation*. Cell 1995, 80(2): 179-85.
12. Boccaccio, C., Ando, M., Tamagnone, L., Bardelli, A., Michieli, P., Battistini, C., Comoglio, P.M. *Induction of epithelial tubules by growth factor HGF depends on the STAT pathway.* Nature 1998, 391(6664): 285-8.
13. Monga, S.P., Mars, W.M., Pediaditakis, P. et al. *Hepatocyte growth factor induces Wnt-independent nuclear translocation of beta-catenin after Met-beta-catenin dissociation in hepatocytes.* Cancer Res 2002, 62(7): 2064-71.

14. Abounader, R., Reznik, T., Colantuoni, C., Martinez-Murillo, F., Rosen, E.M., Laterra, J. *Regulation of c-Met-dependent gene expression by PTEN*. Oncogene 2004, 23(57): 9173-82.
15. Asaoka, Y., Ikenoue, T., Koike, K. *New targeted therapies for gastric cancer.* Expert Opin Investig Drugs 2011, 20(5): 595-604.
16. Eder, J.P., Vande Woude, G.F., Boerner, S.A., LoRusso, P.M. *Novel therapeutic inhibitors of the c-Met signaling pathway in cancer.* Clin Cancer Res 2009, 15(7): 2207-14.
17. Wojtalla, A., Arcaro, A. *Targeting phosphoinositide 3-kinase signalling in lung cancer*. Crit Rev Oncol Hematol 2011, 80(2): 278-90.
18. Dulak, A.M., Gubish, C.T., Stabile, L.P., Henry, C., Siegfried, J.M. *HGF-independent potentiation of EGFR action by c-Met.* Oncogene 2011, 30(33): 3625-35.
19. Morotti, A., Mila, S., Accornero, P., Tagliabue, E., Ponzetto, C. *K252a inhibits the oncogenic properties of Met, the HGF receptor.* Oncogene 2002, 21(32): 4885-93.
20. Berthou, S., Aebersold, D.M., Schmidt, L.S. et al. *The Met kinase inhibitor SU11274 exhibits a selective inhibition pattern toward different receptor mutated variants.* Oncogene 2004, 23(31): 5387-93.
21. Wang, X., Le, P., Liang, C. et al. *Potent and selective inhibitors of the Met [hepatocyte growth factor/scatter factor (HGF/SF) receptor] tyrosine kinase block HGF/SF-induced tumor cell growth and invasion.* Mol Cancer Ther 2003, 2(11): 1085-92.
22. Smolen, G.A., Sordella, R., Muir, B. et al. *Amplification of MET may identify a subset of cancers with extreme sensitivity to the selective tyrosine kinase inhibitor PHA-665752.* Proc Natl Acad Sci U S A 2006, 103(7): 2316-21.
23. Bagai, R., Fan, W., Ma, P.C. *ARQ-197, an oral small-molecule inhibitor of c-Met for the treatment of solid tumors.* IDrugs 2010, 13(6): 404-14.
24. Munshi, N., Jeay, S., Li, Y. et al. *ARQ 197, a novel and selective inhibitor of the human c-Met receptor tyrosine kinase with antitumor activity.* Mol Cancer Ther 2010, 9(6): 1544-53.
25. Chen, C.R., Abbadessa, G., McSweeney, D., Szwaya, J., Chan, T.C., France, D.S. *Potentiation of the anti-proliferative and cytotoxic activity of ARQ 197 & gemcitabine with a pulsitile exposure regimen*. Proc Am Assoc Cancer Res (AACR) 2011, Abst 5376.
26. Garcia, A., Rosen, L., Cunningham, C.C. et al. *Phase 1 study of ARQ 197, a selective inhibitor of c-Met RTK in patients with metastatic solid tumors reaches recommended phase 2 dose.* J Clin Oncol [43rd Annu Meet Am Soc Clin Oncol (ASCO) (June 1-5, Chicago) 2007] 2007, 25(18, Suppl.): Abst 3525.
27. Yap, T.A., Olmos, D., Brunetto, A.T. et al. *Phase I trial of a selective c-MET inhibitor ARQ 197 incorporating proof of mechanism pharmacodynamic studies.* J Clin Oncol 2011, 29(10): 1271-9.