Drugs of the Future 2010, 35(8): 621-628

CCC: 0377-8282/2010
DOI: 10.1358/dof.2010.35.8.1514126

MONOGRAPH

NERATINIB

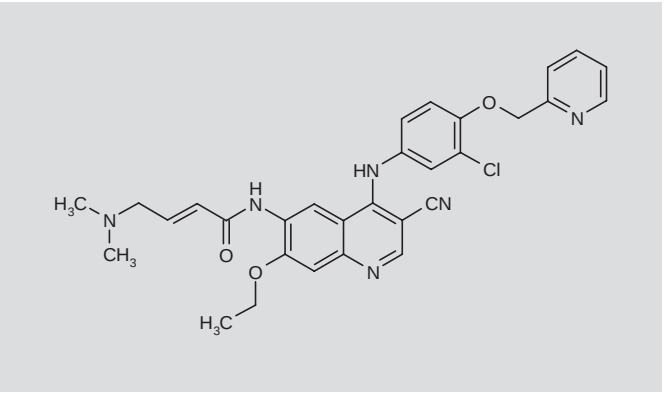
Rec INN; USAN

Pan-erbB Inhibitor
Oncolytic

HKI-272
WAY-179272

N-[4-[3-Chloro-4-(pyridin-2-ylmethoxy)phenylamino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)-2(*E*)-butenamide

InChI: 1S/C30H29ClN6O3/c1-4-39-28-16-25-23(15-26(28)36-29(38)9-7-13-37(2)3)30(20(17-32)18-34-25)35-21-10-11-27(24(31)14-21)40-19-22-8-5-6-12-33-22/h5-12,14-16,18H,4,13,19H2,1-3H3,(H,34,35)(H,36,38)/b9-7+



$C_{30}H_{29}ClN_6O_3$
Mol wt: 557.043
CAS: 698387-09-6
EN: 343722

SUMMARY

The erbB receptors are a family of transmembrane receptors that ultimately lead to the expression of different genes responsible for specific cellular functions, including increased proliferation and inhibition of apoptosis. Deregulation and hyperactivation of these receptors play an important role in the oncogenesis of various cancers. Neratinib is a 4-anilino-3-cyanoquinoline derivative that functions as an irreversible pan-erbB inhibitor. Preclinical studies have shown a statistically significant inhibition of tumor cell proliferation and decrease in tumor burden. Similarly, early clinical trials have shown that neratinib is well tolerated, with minimal adverse events. The most frequent adverse event was diarrhea, leading to a dose reduction in 33% of phase II trial participants. A phase I and two phase II trials have been completed with promising results. While the use of neratinib has been evaluated in both non-small cell lung cancer and breast cancer, it appears to hold the most promise in the treatment of breast cancer.

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*Synthesis prepared by R. Pandian, J. Bolòs, R. Castañer. Thomson Reuters, Provença 388, 08025 Barcelona, Spain.

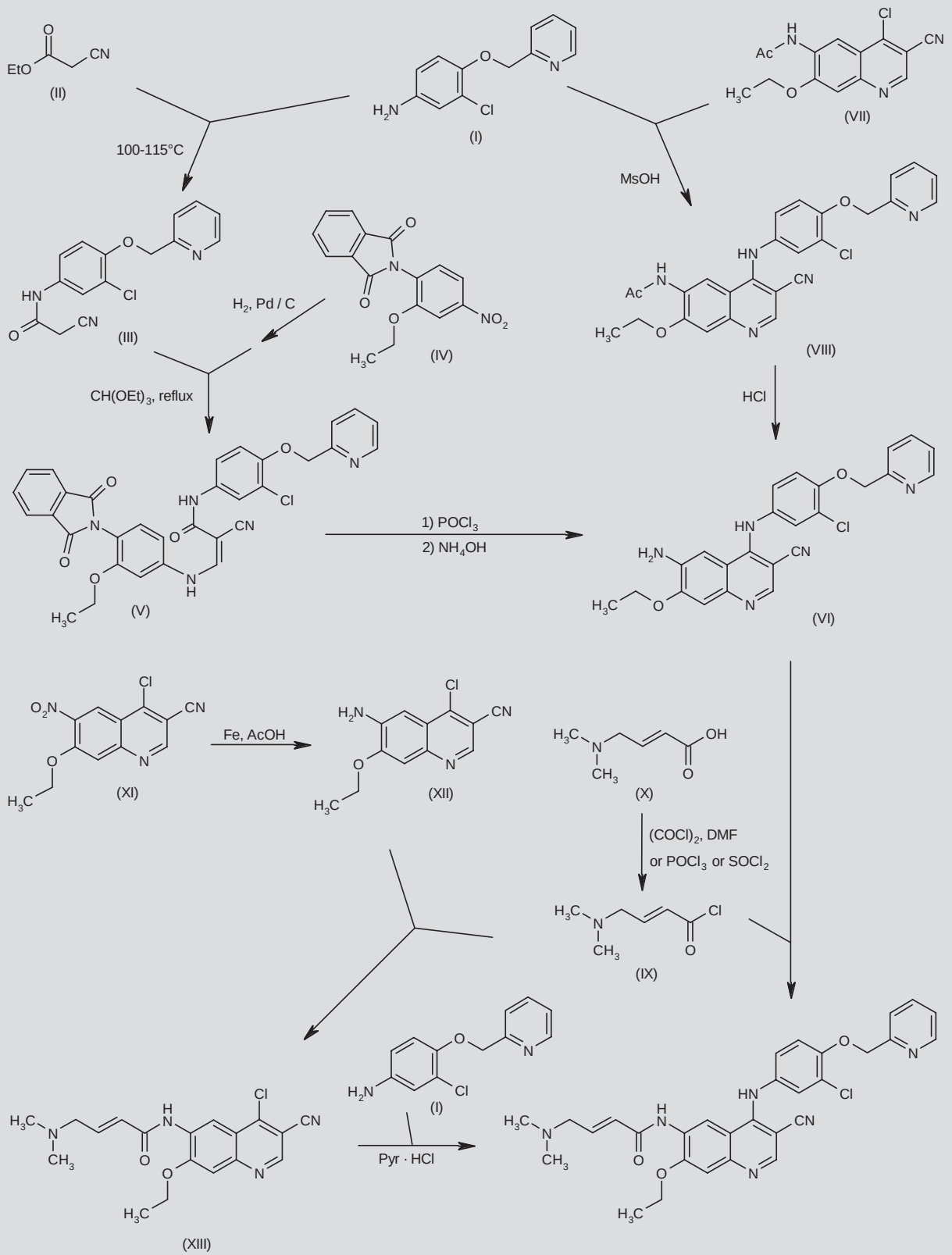
SYNTHESIS*

Neratinib can be prepared as follows:

3-Chloro-4-(2-pyridylmethoxy)aniline (I) is condensed with ethyl cyanoacetate (II) at 100-115 °C to give the *N*-aryl 2-cyanoacetamide (III). Reduction of 3-ethoxy-4-phthalimido-1-nitrobenzene (IV) with H_2 over Pd/C in THF at 50 °C followed by coupling of the resulting aniline with the cyano amide (III) by means of triethyl orthoformate in refluxing propanol affords the 3-amino-2-cyanopropenamide derivative (V). After intramolecular cyclization of propenamide (V) by means of $POCl_3$ in acetonitrile at 60-70 °C, the obtained 6-phthalimidoquinoline derivative is hydrolyzed by means of NH_4OH in EtOH at 62-68 °C to give the 6-aminoquinoline (VI) (1). Alternatively, the aminoquinoline (VI) can be obtained by condensation of the aniline derivative (I) with 6-acetamido-4-chloro-7-ethoxyquinoline-3-carbonitrile (VII) in the presence of methanesulfonic acid at 70-75 °C, affording the diarylamine (VIII), which is then deacetylated to the aminoquinoline (VI) by hydrolysis with HCl (2-5). Finally, compound (VI) is acylated with 4-(dimethylamino)-2-butenoyl chloride (IX) (1-4, 6), obtained by chlorination of the corresponding free acid (X) or its hydrochloride salt with either $(COCl)_2$ by means of DMF in THF or DMF/*i*-PrOAc (1-6), $POCl_3$ in DMAc, or $SOCl_2$ in DMAc (6), in the presence of NMP (1-7). Scheme 1.

In a related strategy, 4-chloro-7-ethoxy-6-nitroquinoline-3-carbonitrile (XI) is reduced to the corresponding amine (XII) by means of Fe and acetic acid in refluxing methanol. Subsequent acylation of (XII) with 4-(dimethylamino)-2-butenoyl chloride (IX) in the presence of NMP in acetonitrile or DMF yields carboxamide (XIII), which is finally coupled with 3-chloro-4-(2-pyridylmethoxy)aniline (I) by means of pyridinium chloride in refluxing isopropanol or 2-methoxyethanol (8). Scheme 1.

Scheme 1. Synthesis of Neratinib



The precursor 3-chloro-4-(2-pyridylmethoxy)aniline (I) is prepared by coupling of 2-chloro-1-fluoro-4-nitrobenzene (XIV) with 2-pyridylmethanol (XV) by means of KOH in acetonitrile to give the 2-chloro-4-nitrophenyl ether (XVI) (1-4), which is then reduced to the corresponding aniline (I) by means of H_2 over Pt/C (1) or Pd/C (2) in THF, or Zn and NH_4Cl in EtOH (3, 4). Scheme 2.

The intermediate *N*-(2-ethoxy-4-nitrophenyl)phthalimide (IV) is prepared by *N*-protection of 2-amino-5-nitrophenol (XVII) with phthalic anhydride (XVIII) in the presence of AcOH at 115-120 °C to give the corresponding phthalimide (XIX), which is then alkylated at the phenolic hydroxyl with ethyl bromide (XX) in the presence of K_2CO_3 in DMF (1). Scheme 3.

The 4-chloroquinoline building block (VII) can be prepared by two alternative methods:

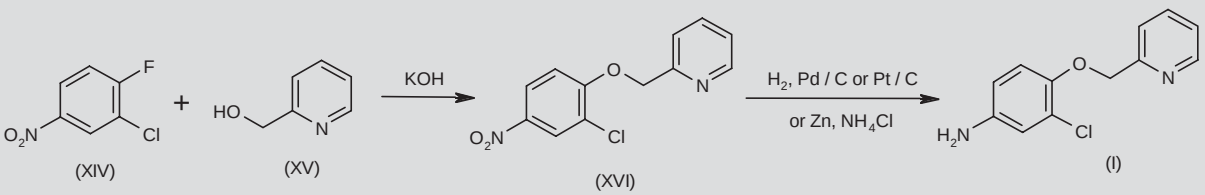
N-Protection of 2-amino-5-nitrophenol (XVII) with Ac_2O in the presence of AcOH gives *N*-(2-hydroxy-4-nitrophenyl)acetamide (XXI), which upon *O*-alkylation with ethyl bromide (XX) in the presence of K_2CO_3 in DMF at 60 °C affords *N*-(2-ethoxy-4-nitrophenyl) acetamide (XXII). Reduction of the nitro derivative (XXII) with H_2 over Pd/C in THF furnishes the corresponding aniline (XXIII), which by condensation with ethyl 2-cyano-3-ethoxy-2-propenoate (XXIV) at reflux produces enamine (XXV). Thermal cyclization of enamino ester (XXV) in Dowtherm at 250 °C then yields 4-hydroxyquinoline derivative (XXVI) (2, 3), which upon chlorination with $POCl_3$ in 1,2-diethoxyethane at 80-85 °C affords *N*-(4-chloro-3-cyano-7-ethoxyquinolin-6-yl)acetamide (VII) (2, 3, 9). Alternatively, condensation of ethyl cyanoacetate (II) with morpholine (XXVII) at 100-110 °C gives 4-(cyanoacetyl)morpholine (XXVIII), which after coupling with 4-acetamido-3-ethoxyaniline (XXIII) in the presence of triethyl orthoformate in *i*-PrOH at 50-60 °C produces the arylamino propenamide (XXIX). Finally, cyclization of (XXIX) in the presence of $POCl_3$ in acetonitrile at 60-65 °C then leads to the target intermediate (VII) (10). Scheme 4.

BACKGROUND

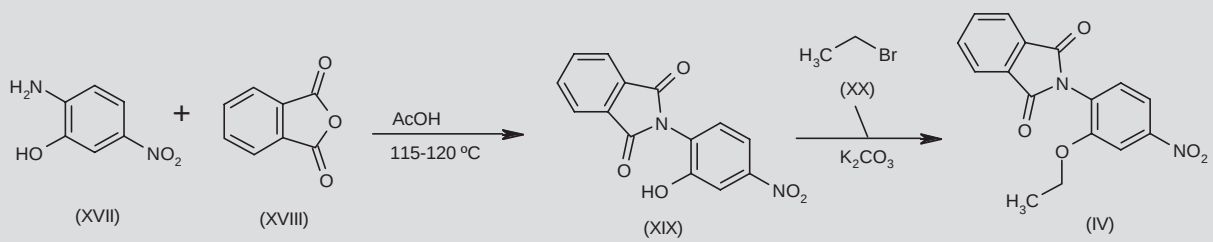
Breast cancer is the most common cause of cancer in women and the second leading cause of cancer-related deaths in this population. Similarly, lung cancer is the second most common cancer in both women and men, and the leading cause of cancer-related deaths in both genders. According to the National Cancer Institute's SEER incidence statistics, the incidence of lung cancer is 62.5 men and women per 100,000 per year, with a mean 5-year survival of only 16%. The annual incidence for breast cancer is 123 women per 100,000 per year. Although breast cancer has a higher incidence, the 5-year survival is more favorable at 89% (11).

Oncoprotein-targeted therapies for the treatment of various cancers are a novel approach that has been under investigation for a number of years. For example, the epidermal growth factor receptor (EGFR) signaling cascade has been shown to play an important role in the formation, maintenance and survival of cancer cells (12). EGFR, also known as erbB-1, is a member of the erbB family. Other members include HER2 (erbB-2), HER3 (erbB-3) and HER4 (erbB-4). These proteins are transmembrane receptors that consist of an extracellular ligand-binding domain, a transmembrane segment and an intracellular tyrosine kinase domain. When a ligand binds to the extracellular domain, homo- or heterodimerization of the receptor occurs, leading to the autophosphorylation of the cytoplasmic domain. This conformational change results in activation of intracel-

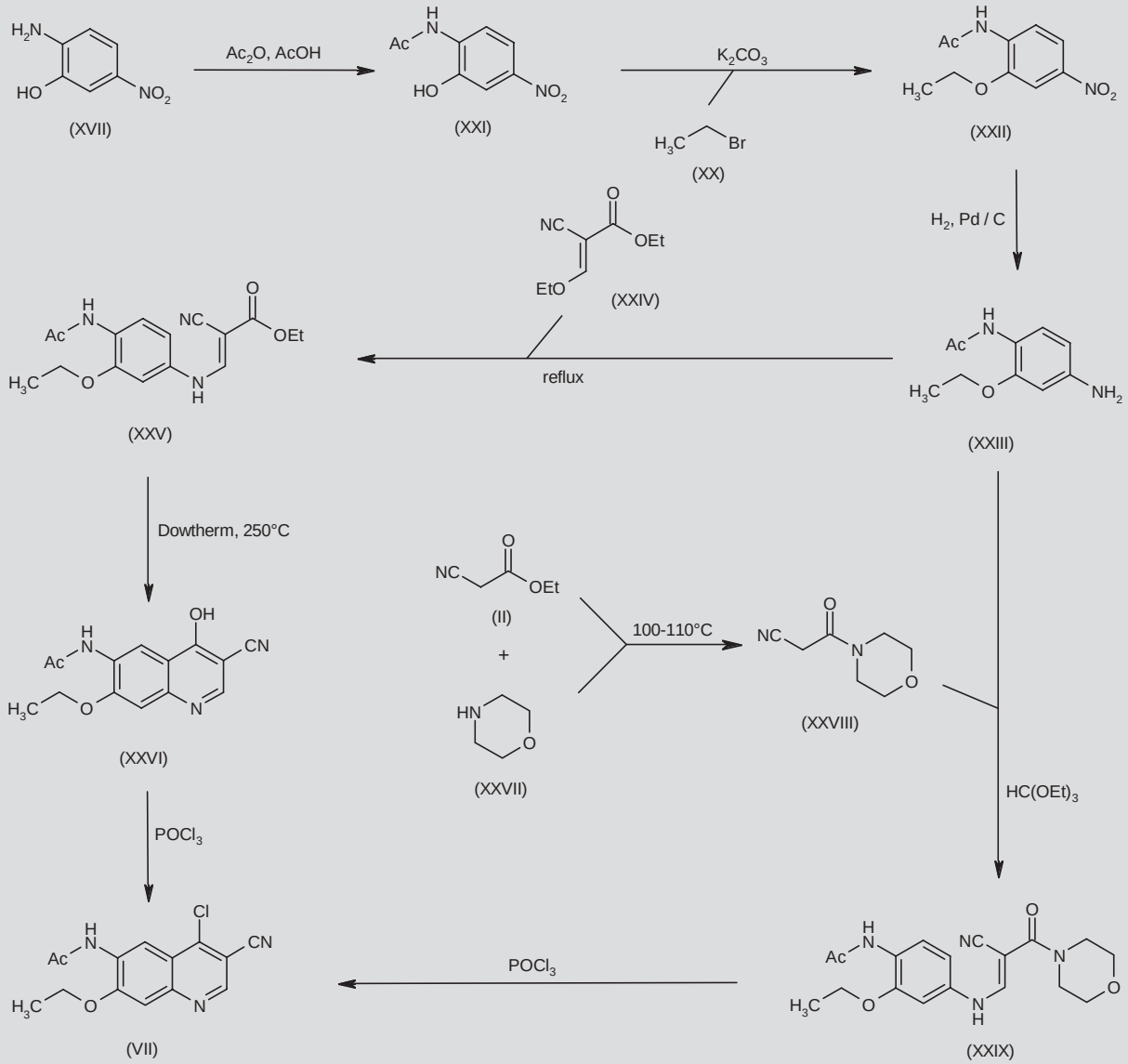
Scheme 2. Synthesis of Precursor (I)



Scheme 3. Synthesis of Intermediate (IV)



Scheme 4. Synthesis of Building Block (VII)



lular signaling cascades and the production of downstream mediators. The end result is the expression of different genes responsible for specific cellular functions, including increased proliferation and inhibition of apoptosis (13).

HER2 and HER3 are exceptions to the common pathway. HER2 has no known extracellular ligand; however, it is the preferred coreceptor for the heterodimerization of other erbB receptors. In conjunction with EGFR, HER2 functions to increase the binding affinity of its ligand, decrease degradation and enhance receptor recycling. In addition, HER2 can participate in homodimerization when overexpressed, leading to activation of downstream signaling cascades independent of ligand binding. Similarly, HER3 lacks tyrosine kinase activity and therefore functions only as a coreceptor in heterodimerization of other erbB receptors (13).

The erbB family of receptors is important because receptor deregulation and hyperactivation have been shown to play a role in oncogenesis. Mutation, rearrangement, overexpression and gene amplification leading to aberrant EGFR activation have all been implicated in several malignancies. The two most studied of these malignancies are lung and breast cancer. HER2 overexpression is demonstrated in

20% of breast cancers and is associated with a poor prognosis (13). This overexpression has led to the development of targeted therapies against HER2. Trastuzumab (Herceptin®; Genentech) was approved by the FDA in 1998. It is a monoclonal antibody that binds to and inhibits the extracellular domain of the receptor. Specifically, it binds to domain IV and renders the receptor inactive, primarily when it has undergone dimerization with HER3 (14). The NSABP B-31 trial compared adjuvant chemotherapy with and without the addition of trastuzumab in HER2-positive breast cancer patients. In this study, adjuvant trastuzumab decreased the risk of treatment failure by 52% and the risk of death by 33%, making its administration now standard of care (15). However, not all HER2-positive tumors respond to trastuzumab, and HER2 status may be discordant when tested by different laboratories or using different molecular assays (i.e., immunohistochemistry or fluorescence in situ hybridization [FISH]). Only a 15% response rate was achieved when trastuzumab was used as monotherapy. Furthermore, response rates only increased to 49% when used in combination with paclitaxel, emphasizing the need for further alternative therapies (16).

Further research endeavors targeting EGFR and the erbB family of receptors have led to significant biological and therapeutic advances. For example, overexpression of EGFR has also been demonstrated in over 80% of non-small cell lung cancers (NSCLC) (17). While trastuzumab targeted the receptor itself, a second class of drugs was designed to interfere with the tyrosine kinase pathway and prevent further downstream signaling cascades. Gefitinib and erlotinib were the first generation of reversible tyrosine kinase inhibitors developed. They function specifically by competitively binding to ATP within the kinase domain (12). While gefitinib showed no statistically significant improvement in disease progression or overall survival, erlotinib did demonstrate a small, statistically significant survival benefit in NSCLC patients (18). However, the overall response rate was low, with only 10-20% of tumors responding (17).

Acquired resistance is most commonly caused by the T790M mutation. There are two theories as to how this mutation affects binding of erlotinib and gefitinib. The first is that T790M contains a bulky methionine side-chain found at the ATP binding site within the kinase domain. This changes the ATP binding pocket and sterically hinders binding of the drug (19). More recently, however, it was demonstrated that the combination of EGFR and T790M led to increased affinity for ATP, therefore decreasing binding of erlotinib and gefitinib secondary to competitive inhibition (18).

The short duration of response and almost universal development of resistance directed new investigations to discover a compound that could overcome these problems. This facilitated the development of irreversible tyrosine kinase inhibitors. These second-generation inhibitors form covalent or permanent bonds with the ATP of the kinase domain (20). This leads to prolonged inhibition that exists for the entire lifespan of the receptor, overcome only by the generation of a new receptor. The most promising of these inhibitors is neratinib (HKI-272, WAY-179272; Pfizer).

PRECLINICAL PHARMACOLOGY

Neratinib, a 4-anilino-3-cyanoquinoline derivative, was developed by Pfizer (8). Its precursor compound, EKB-569, was found to be a strong inhibitor of EGFR but was not as effective against HER2. By varying the *para*-position of the 4-anilino substituent, Pfizer researchers produced a compound that was able to inhibit both EGFR and HER2 effectively and at comparable concentrations (21). Neratinib functions as a pan-erbB inhibitor, irreversibly binding to erbB-1, -2 and -4. It develops a covalent complex with a conserved cysteine residue (Cys 797) located within the erbB kinase domain (22). This leads to subsequent inhibition of tyrosine kinase activity and further cell regulatory pathways. Specifically, it causes arrest of the cell cycle at the G_1-S phase transition, impeding cell proliferation. Other functions include inhibition of autophosphorylation of the HER2 receptor and induction of apoptosis (16, 23).

Research efforts have shown promising preclinical results. An in vitro study performed by Kwak et al. demonstrated that neratinib was able to circumvent the T790M mutation, as well as alterations in receptor trafficking. They noted that resistance to the irreversible inhibitors was rare and speculated that this was in part secondary to crosslinking of the receptor (24). Furthermore, an in vivo study by Li et al. established that neratinib in combination with rapamycin led to significant regression of both bronchial and peripheral lung tumors in a mouse model (25).

Investigators have further examined additional mutations seen in NSCLC and their response to neratinib. For example, erbB-2 or HER2 mutations have recently been elucidated in 2-4% of NSCLC (27). However, these tumors have shown minimal response to trastuzumab. Both in vitro and in vivo studies have shown these tumors to be sensitive to neratinib (23, 26). In addition, 5% of squamous cell cancers of the lung harbor an EGFR vIII mutation that has shown little response to erlotinib or gefitinib. A dramatic reduction in the size of these tumors was seen with neratinib in a murine model (27).

PHARMACOKINETICS AND METABOLISM

An in vivo study by Rabindran et al. estimated 5-10 mg/kg/day as the minimum dose required for statistically significant inhibition of tumor proliferation. Similarly, concentrations of 28 ng/mL or more demonstrated inhibition of receptor autophosphorylation. The terminal half-life is approximately 4 h after a single dose of 20 mg/kg in nude mice, correlating with irreversible inhibition of the target (16).

A phase I trial completed by Wong et al. demonstrated relatively slow absorption of neratinib, with a median of 3-6.5 h for a dose range of 40-400 mg. At steady state, the mean peak concentration ranged from 5.8 to 199 ng/mL and the mean AUC ranged from 76 to 1704 ng.h/mL. Furthermore, their analyses revealed that steady-state mean peak concentration and AUC increased in a dose-dependent manner from 40 to 320 mg, but plateaued from 320 to 400 mg. In this study, 320 mg was determined to be the maximum tolerated dose. However, because 36% of patients required dose reduction, Wong et al. designated 240 mg of neratinib as the recommended therapeutic dose for phase II trials. Using a 240-mg oral daily dose, the mean accumulation value was 1.14, indicating no major accumulation, with a mean elimination half-life of 14 h (22).

SAFETY

Neratinib is well tolerated overall. Adverse events are most often gastrointestinal in nature, with diarrhea being the most frequent. In the phase I study by Wong et al., all 72 patients experienced some

form of neratinib-related adverse event, although only 39% had a grade 3 or higher event. Diarrhea (88%), nausea (64%), fatigue (63%) and vomiting (50%) were the most common. The median onset of diarrhea was 8.5 days, with a range of 1-22 days. In 14% of the patients, diarrhea led to discontinuation of the drug. Other reasons for discontinuation included all adverse events (18%), disease progression (56%) and symptomatic deterioration (10%). Fifteen of 72 patients died during the study and all deaths were attributed to disease progression and not neratinib use (22).

In addition, in a phase II trial completed by Burstein et al., similar adverse events were noted. The only grade 3 or 4 adverse event to occur at a daily dose of 240 mg was diarrhea in 10% of patients. Median time to onset of diarrhea was 2-3 days, with a median duration of 5-7 days. However, the severity of the diarrhea subsided as treatment continued. A total of 99% of the participants were able to continue the drug with antidiarrheals and dose reduction in 33% (28).

CLINICAL STUDIES

Currently there are 18 clinical trials registered at clinicaltrials.gov. Three have been completed and published (Table I), with the remainder close to completion or ongoing. As described previously, a phase I trial was completed in 2009 by Wong et al. This open-label, dose-escalation study included 72 patients with advanced-stage erbB-1- or erbB-2-positive cancers who had failed standard therapy. The two predominant cancers were breast and lung cancer at 40% and 21%, respectively. A daily dose of 320 mg was established as the maximum tolerated dose. Diarrhea was the most common adverse event recorded, leading to discontinuation of therapy in 14% of patients. Furthermore, a favorable tumor response was noted, with a partial response seen in 32% (8/25) of the breast cancer patients. Similarly, 6 of 14 NSCLC and 1 breast cancer patient were free of disease progression for over 24 weeks. For the breast cancer patients, the median duration of response was 4.8 months and the median duration of stable disease was 5.8 months. For the lung cancer patients, the median duration of stable disease was 9 months. The median progression-free survival (PFS) for breast and lung cancer patients was 3.6 and 3.5 months, respectively (22).

Two phase II trials have been completed. The first was a multicenter study to evaluate the efficacy and safety of neratinib in patients with advanced erbB-2-positive breast cancer. Two cohorts of patients, one with prior trastuzumab therapy and the second without, were given 240 mg once daily with the primary endpoint of 16-week PFS. There were 136 patients, 66 with prior trastuzumab therapy and 70 without. A 16-week PFS was obtained in 59% of patients with prior therapy and 78% of patients with no prior trastuzumab exposure. The median PFS was 22.3 and 39.6 weeks, respectively, with observed response rates of 24% and 56%, respectively. For patients with previous trastuzumab therapy, the median duration of response was 39.3 weeks and 52.4 weeks for those who had received no prior trastuzumab. Fourteen patients from both arms had at least 24 weeks free of disease progression (28).

The second phase II trial evaluated neratinib in patients with advanced NSCLC who had previously responded to the tyrosine kinase inhibitors erlotinib and gefitinib. In addition, EGFR sequencing was completed at enrollment to determine if somatic mutations were present. A total of 167 patients were divided into 3 arms. Arm A included patients who had received over 12 weeks of prior tyrosine kinase inhibitor therapy and had an EGFR mutation present. Arm B also included patients who had received prior erlotinib therapy, but who had wild-type tumors. Lastly, the third arm, or arm C, contained patients who were naïve to tyrosine kinase inhibitors. The initial starting dose of neratinib was 320 mg. However, this was subsequently decreased to 240 mg due to excessive diarrhea. All patients received once-daily dosing. Unfortunately, response rates were poor, with only 3% of patients in arm A having an objective response and no patients in arms B or C showing a response. However, 50% in arm A, 64% in arm B and 32% in arm C showed stable disease, with a median PFS of 15.3 weeks. Furthermore, of the 167 patients enrolled, 7% had a documented T790M mutation and none of these patients responded to neratinib therapy (29). This is in contradiction to the previously described in vitro study by Kwak et al. (24).

In addition, eight abstracts have been presented at national conferences, four at the 2009 American Society of Clinical Oncology (ASCO) meeting and four at the 2009 San Antonio Breast Cancer

Table I. *Summary of completed phase I and II trials.*

Study title	Study type	Authors	Number of patients	Types of cancer	Median progression-free survival
A phase I study with neratinib (HKI-272), an irreversible pan ErbB receptor tyrosine kinase inhibitor, in patients with solid tumors (22)	Phase I	Wong et al.	73	Breast, NSCLC, ovarian, colorectal, glioblastoma, renal, pancreatic	3.6 months for breast cancer, 3.5 months for lung cancer patients
Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer (28)	Phase II	Burstein et al.	136	Breast	22.3 weeks for trastuzumab non-naïve, 39.6 weeks for trastuzumab-naïve patients
Neratinib, an irreversible pan ErbB receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced NSCLC (29)	Phase II	Sequist et al.	167	NSCLC	15.3 weeks

NSCLC, non-small cell lung cancer.

Symposium (SABCS). Of the abstracts presented at ASCO, three examined the efficacy and safety of neratinib in combination with other anticancer medications. For example, Chow et al. examined neratinib in conjunction with paclitaxel in patients with solid tumors. They found no dose-limiting toxicities at 240 mg of neratinib plus 80 mg/m^2 of paclitaxel, with five participants showing a partial response (30). Similarly, Limentani et al. demonstrated that neratinib together with vinorelbine was well tolerated (31). The third abstract examined the effect of neratinib with trastuzumab. These results were promising, with a 27% objective response rate, a 47% 16-week PFS and a 19-week median PFS (32).

The 2009 SABCS abstracts also evaluated neratinib in conjunction with capecitabine (33), vinorelbine (34) and paclitaxel (35). Each drug combination was well tolerated and showed promising antitumor activity.

CONCLUSIONS

In conclusion, neratinib is an oncoprotein-targeted therapy that functions by irreversibly inhibiting the erbB family of transmembrane receptors and their tyrosine kinase activity. It has been most widely investigated for use in the treatment of NSCLC and breast cancer. While the results have been mixed with regards to its efficacy in NSCLC, neratinib does appear to have some promising effects in the treatment of breast cancer, although further studies are warranted. There are a number of ongoing studies, as well as three phase III trials currently recruiting participants to further evaluate the role of neratinib in the treatment of breast cancer. Of note, neratinib will also be included as one of the investigational agents in the phase II multicenter I-SPY2 trial. This trial is likely to provide considerable information on the efficacy of neratinib in locally advanced nonmetastatic breast cancer patients. Although treatment with neratinib does appear beneficial in breast cancer, its full potential will not be known until these studies have been completed.

SOURCE

Pfizer, Inc. (US).

DISCLOSURES

The authors state no conflicts of interest.

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