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MONOGRAPH

LINSITINIB

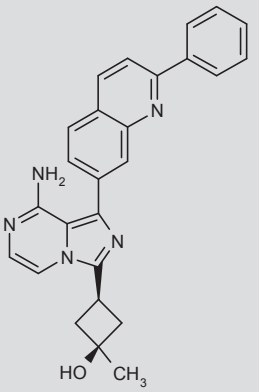
Prop INN; USAN

Insulin-like Growth Factor 1 Receptor Antagonist
Insulin Receptor Antagonist
Oncolytic

OSI-906

cis-3-[8-Amino-1-(2-phenylquinolin-7-yl)imidazo[1,5-*a*]pyrazin-3-yl]-1-methylcyclobutanol

InChI: 1S/C26H23N5O/c1-26(32)14-19(15-26)25-30-22(23-24(27)28-11-12-31(23)25)18-8-7-17-9-10-20(29-21(17)13-18)16-5-3-2-4-6-16/h2-13,19,32H,14-15H2,1H3,(H2,27,28)/t19-,26+



$C_{26}H_{23}N_5O$
Mol wt: 421.4937
CAS: 867160-71-2
EN: 637421

SUMMARY

Linsitinib (OSI-906) is a novel, small-molecule, dual inhibitor of insulin-like growth factor 1 receptor (IGF-I receptor) and insulin receptor (IR). There is ample evidence that the IGF-I receptor is overexpressed in several epithelial and mesenchymal malignancies. Preclinical data support linsitinib as a single agent or in combination with cytotoxic chemotherapy for colorectal carcinoma, adrenocortical carcinoma and breast carcinoma, among other cancers. This review will evaluate the preclinical pharmacology, pharmacokinetics, drug interactions and clinical activity in phase I through phase III studies.

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SYNTHESIS*

Linsitinib can be prepared by three different strategies, as described below:

In one strategy, condensation of amine (I) with 3-methylenecyclobutanecarboxylic acid (II) in the presence of EDC and HOBt in CH_2Cl_2 yields amide (III), which then undergoes cyclization to the imidazo[1,5-*a*]pyrazine derivative (IV) upon heating with $POCl_3$ in DMF. Oxidation of alkene (IV) by means of $K_2OsO_4 \cdot 2H_2O$ in the presence of NMMO in THF/H_2O furnishes the 1-(hydroxymethyl)cyclobutanol (V), which is then subjected to chloride displacement with NH_3 in *i*-PrOH to produce the 8-aminoimidazo[1,5-*a*]pyrazine derivative (VI). Oxidative cleavage of diol (VI) by means of $NaIO_4$ in THF/H_2O yields the cyclobutanone (VII), which upon addition of MeLi in THF and subsequent separation of the obtained isomers using TLC affords linsitinib (1). Scheme 1.

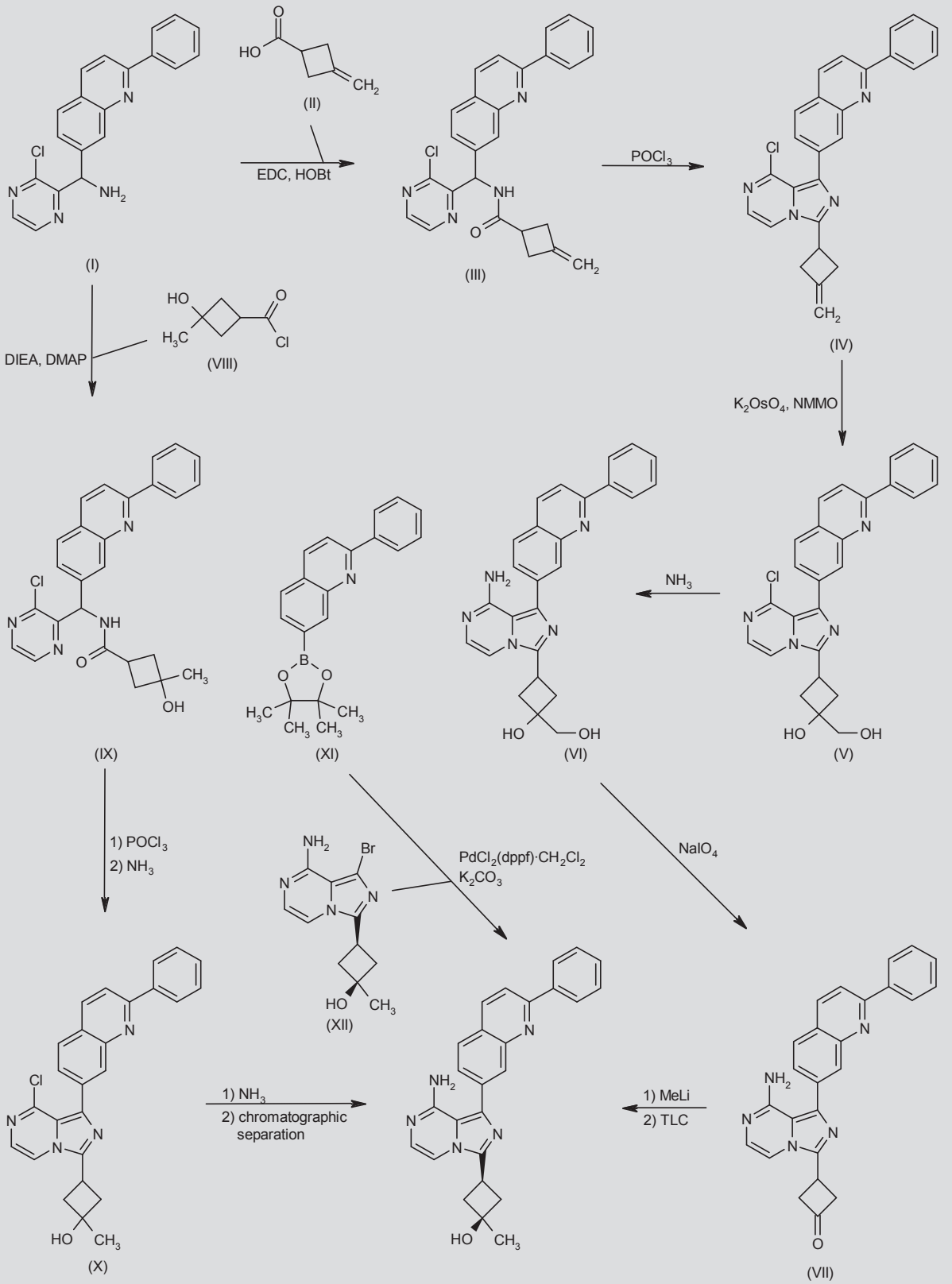
In another strategy, condensation of amine (I) with 3-hydroxy-3-methylcyclobutanecarbonyl chloride (VIII) in the presence of DIEA and DMAP in CH_2Cl_2 produces carboxamide (IX). Cyclization of amide (IX) with $POCl_3$ at 70 °C followed by treatment with NH_3 then leads to the imidazo[1,5-*a*]pyrazine derivative (X). Displacement of the 8-chloroimidazo[1,5-*a*]pyrazine derivative (X) with NH_3 at 110 °C and subsequent chromatographic separation of the isomers provides linsitinib (1). Scheme 1.

In the third strategy, linsitinib is obtained by Suzuki coupling of the quinolinylboronate (XI) with the 1-bromoimidazo[1,5-*a*]pyrazine derivative (XII) in the presence of $PdCl_2(dppf) \cdot CH_2Cl_2$ and K_2CO_3 at 90 °C (2). Scheme 1.

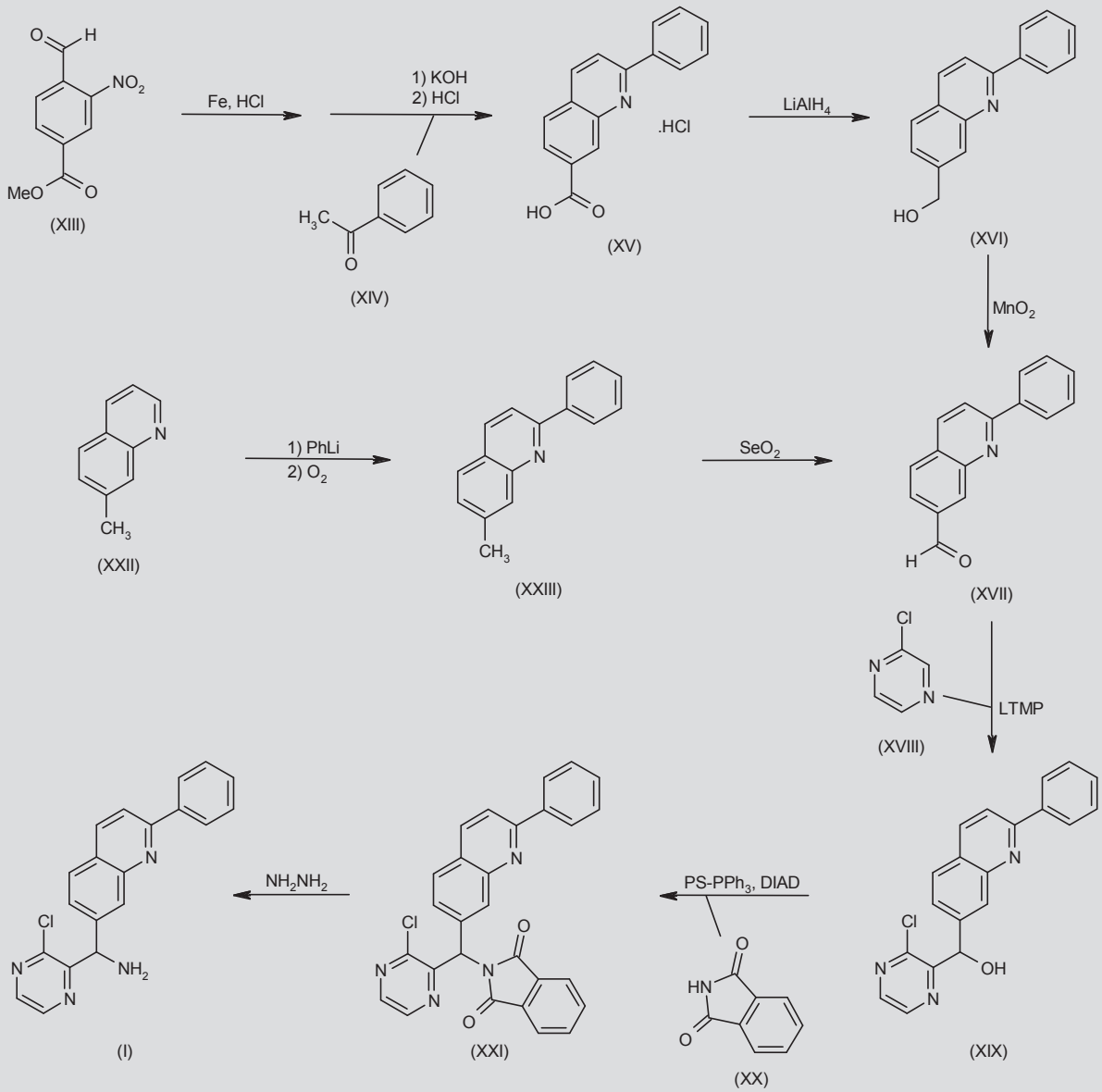
Intermediate (I) is synthesized as follows:

Reduction of methyl 4-formyl-3-nitrobenzoate (XIII) by means of Fe and HCl in EtOH, followed by Friedländer condensation of the resulting aminoaldehyde with acetophenone (XIV) in the presence of KOH at 95 °C, and treatment with HCl, yields 2-phenylquinoline-7-carboxylic acid hydrochloride (XV). Reduction of acid (XV) with $LiAlH_4$ in THF gives alcohol (XVI), which is then oxidized by means of MnO_2 in $CHCl_3$ to give 2-phenylquinoline-7-carbaldehyde (XVII). Coupling of carbaldehyde (XVII) with the metalated derivative of 2-chloropyrazine (XVIII) in the presence LTMP (prepared from BuLi

Scheme 1. Synthesis of Linsitinib



Scheme 2. Synthesis of Intermediate (I)



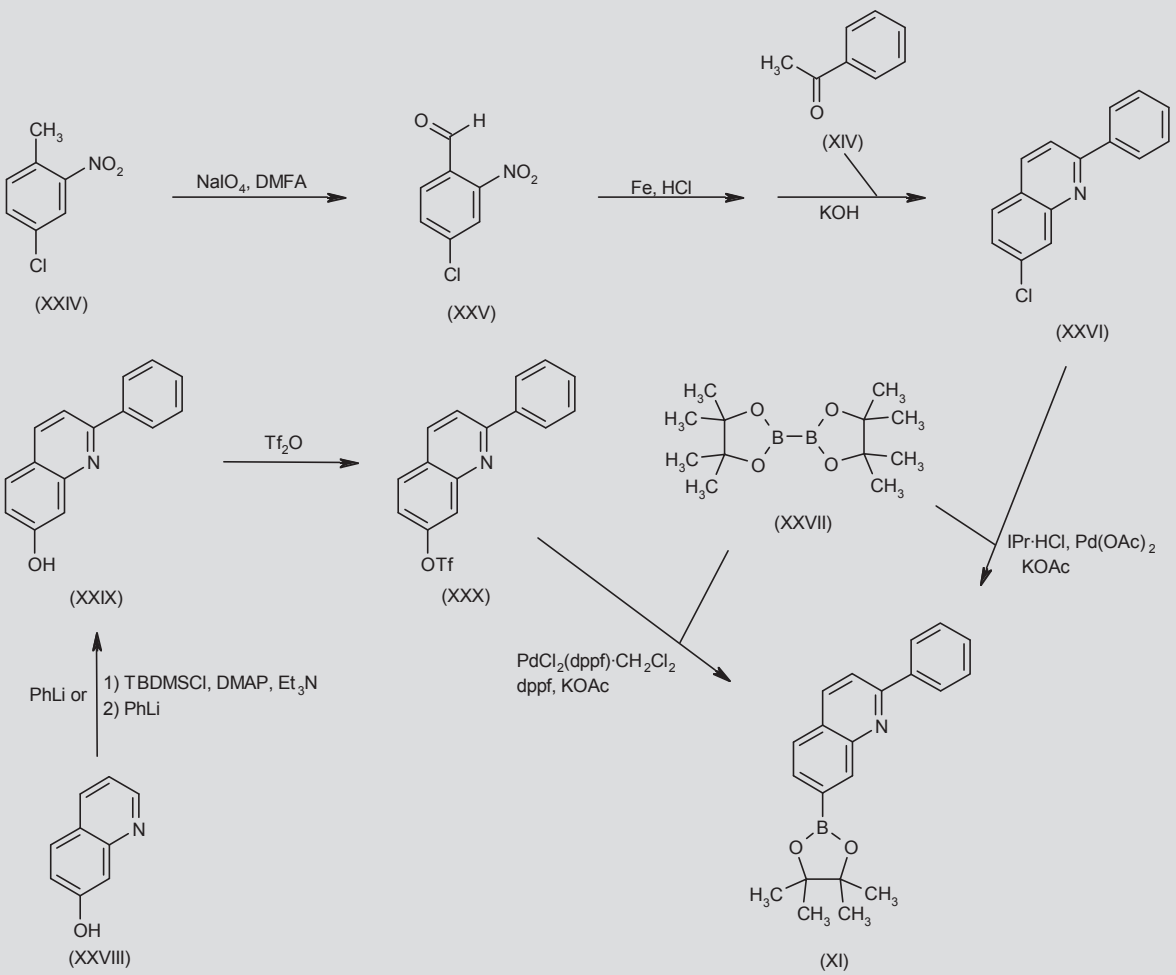
and TMP) in THF yields the diaryl carbinol (XIX), which is then subjected to Mitsunobu reaction with phthalimide (XX) in the presence of PS-PPh_3 and DIAD in THF to provide the *N*-substituted phthalimide (XXI). Hydrazinolysis of phthalimide (XXI) with NH_2NH_2 in EtOH/CH_2Cl_2 then affords amine (I). Scheme 2.

Alternatively, carbaldehyde (XVII) can be prepared by arylation of 7-methylquinoline (XXII) with phenyl lithium in THF, followed by air oxidation to produce 7-methyl-2-phenylquinoline (XXIII). Side chain oxidation of (XXIII) using SeO_2 at 160 °C provides the target aldehyde (XVII) (1). Scheme 2.

Intermediate (XI) can be prepared by the following two methods:

In one method, oxidation of 4-chloro-2-nitrotoluene (XXIV) with $NaIO_4$ in the presence of DMFA in DMF at 135 °C yields 4-chloro-2-nitrobenzaldehyde (XXV). Reduction of the nitro group in compound (XXV) with Fe and HCl in EtOH/H_2O, followed by Friedländer condensation of the resulting aminoaldehyde with acetophenone (XIV)

Scheme 3. Synthesis of Intermediate (XI)



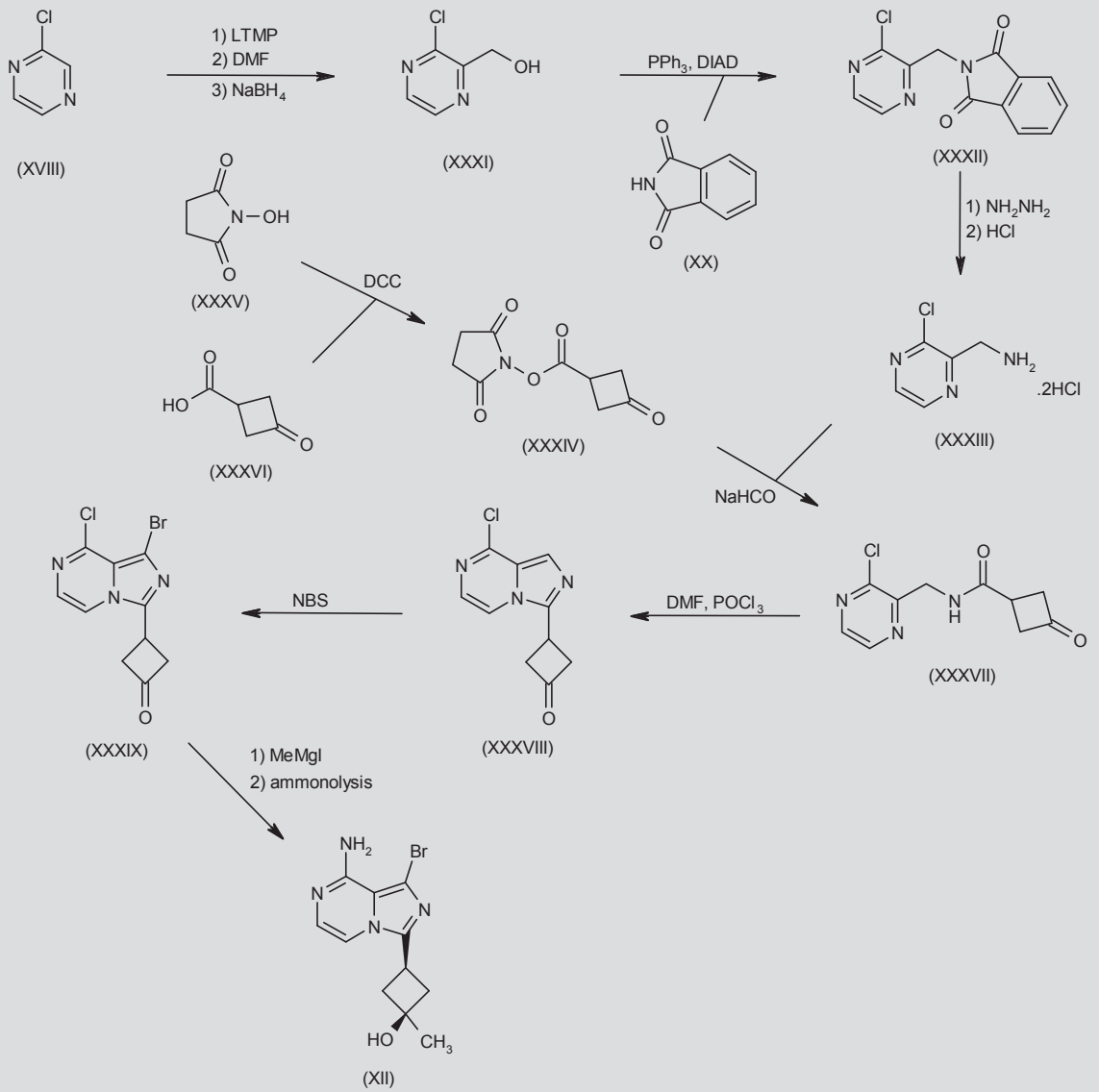
using KOH at reflux gives 7-chloro-2-phenylquinoline (XXVI). Miyaura borylation of chloroquinoline (XXVI) with bis(pinacolato)diboron (XXVII) in the presence of 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride [IPr·HCl], $Pd(OAc)_2$ and KOAc in refluxing THF furnishes boronate ester (XI). Scheme 3.

In another method, arylation of 7-quinolinol (XXVIII) using phenyl lithium in THF, optionally after protection of the hydroxyl group with TBDMSCl in the presence of DMAP and Et_3N in CH_2Cl_2, leads to 2-phenyl-7-quinolinol (XXIX). Quinolinol (XXIX) is then activated by Tf_2O in pyr/CH_2Cl_2 to produce the aryl triflate (XXX), which condenses with bis(pinacolato)diboron (XXVII) in the presence of $PdCl_2$(dppf) CH_2Cl_2, dppf and KOAc in 1,4-dioxane to afford the dioxaborolane derivative (XI) (1). Scheme 3.

Intermediate (XII) can be synthesized as follows:

Metalation of 2-chloropyrazine (XVIII) with LTMP (prepared from BuLi and TMP) in THF, followed by formylation with DMF and subsequent reduction with $NaBH_4$ yields (3-chloro-2-pyrazinyl)methanol (XXXI). Mitsunobu coupling of alcohol (XXXI) with phthalimide (XX) in the presence of PPh_3 and DIAD in THF gives the *N*-substituted phthalimide (XXXII), which is then subjected to hydrazinolysis with NH_2NH_2 in CH_2Cl_2 to provide, after treatment with HCl, (3-chloro-2-pyrazinyl)methylamine dihydrochloride (XXXIII) (1, 2). Coupling of amine (XXXIII) with succinimidyl ester (XXXIV) (prepared by condensation of 3-oxocyclobutanecarboxylic acid [XXXVI] with *N*-hydroxysuccinimide [XXXV] using DCC in isopropyl acetate [3]) in the presence of $NaHCO_3$ in THF/H_2O produces the 3-oxocyclobutanecarboxamide (XXXVII). Cyclization of amide (XXXVII) in the presence $POCl_3$ and DMF in EtOAc affords 3-(8-chloroimidazo[1,5-*a*]pyrazin-3-yl)cyclobutanone (XXXVIII), which is then brominated by means of

Scheme 4. Synthesis of Intermediate (XII)



NBS in DMF to yield the 1-bromo derivative (XXXIX) (2, 3). Addition of CH_3MgI to ketone (XXXIX) in THF, followed by chloride substitution with NH_3, gives rise to *cis*-3-(8-amino-1-bromoimidazo[1,5-*a*]pyrazin-3-yl)-1-methylcyclobutanol (XII) (2). Scheme 4.

BACKGROUND

The insulin-like growth factor 1 receptor (IGF-I receptor) is a transmembrane receptor tyrosine kinase that has been implicated in the development and progression of several human cancers (4-6). The IGF-I receptor is composed of an extracellular α-subunit and a β-subunit comprising a transmembrane and intracellular portion. The extracellular α-subunit is responsible for binding soluble IGF-I receptor ligands such as insulin-like growth factors I (IGF-I) and II (IGF-II), whereas the β-subunit is responsible for the cytoplasmic receptor tyrosine kinase activity (7). The IGF-I receptor is constitutively expressed as a homodimer. Upon ligand binding, IGF-I receptor homodimers or IGF-I receptor:receptor tyrosine kinase heterodimers undergo autophosphorylation and activate the downstream phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/Akt/serine/threonine-protein kinase mTOR and Ras/mitogen-activated protein kinase (MAPK) pathways (4). The end result is

decreased apoptosis, increased cell growth and increased mobility, leading to tumor growth and metastasis (4, 5). Oncogenic mutations in the IGF-I receptor have not been identified; however, increased IGF-I receptor expression has been recognized in breast, colon, lung and prostate cancers, and sarcomas, among other malignancies (5, 8-11). For instance, in colorectal cancer (CRC) the IGF-I receptor is expressed nine times more than in neighboring normal tissue (12). Similarly, patients with increased IGF-I receptor levels have been found to be at higher risk of developing cancers of the colon, breast, lung, prostate and bladder (9, 13-15). IGF-I receptor overexpression and signaling activity have been correlated with resistance to therapy in solid tumors and acute myeloid leukemia (16-19).

The insulin receptor (IR) has also been implicated in the development and proliferation of human malignancies. The IR is structurally similar to the IGF-I receptor, sharing 80% identity with the catalytic domain and having a similar tertiary structure (20). Ectopic expression of IR in mammary epithelial cells and NIH/3T3 fibroblasts causes malignant transformation in cell culture (21, 22). IR expression is seen in breast, prostate and ovarian cancers, among others, and may be associated with worse prognosis (23-25). Moreover, diabetes, insulin resistance and high circulating insulin levels may be associated with the development of breast, colorectal, hepatocellular and prostate carcinoma (23, 26-28). Due to their potential roles in the development and proliferation of human cancers, the IGF-I receptor and IR are attractive targets for anticancer therapy.

The two general strategies for targeting the IGF-I receptor have been antibodies against the receptor and small-molecule inhibitors that bind to the ATP binding site. At present, there are over 20 anti-IGF-I receptor antibodies and small-molecule inhibitors in various stages of preclinical and clinical testing (29). Monoclonal antibodies are further along in clinical development than small-molecule IGF-I receptor inhibitors and have shown mixed results. In phase I studies, several anti-IGF-I receptor antibodies have caused prolonged responses in patients with Ewing's sarcoma and have been associated with reasonable toxicity profiles, including conatumumab (AMG-479; Amgen), R-1507 (Roche) and figitumumab (CP-751; Pfizer) (30-32). Phase I or II studies with dalotuzumab (MK-0646M; Merck), cixutumumab (IMC-A12; ImClone), AVE-1642 (Sanofi) and Sch-717454 (Merck) have also demonstrated a favorable toxicity profile, with some antitumor activity in soft tissue sarcomas, non-small cell lung cancer (NSCLC) and other malignancies (29, 33, 34). A phase II study of figitumumab combined with carboplatin and paclitaxel in advanced NSCLC showed a 54% response rate for the three-drug combination compared to 42% with carboplatin and paclitaxel alone (35).

Unfortunately, several other phase II and III studies have thus far been disappointing. A randomized phase II study of IMC-A12 with or without cetuximab for patients with metastatic colorectal cancer refractory to epidermal growth factor receptor (EGFR) inhibition did not demonstrate any benefit (36). Two large phase III studies combining figitumumab, a fully human IgG_2 monoclonal antibody, with carboplatin plus paclitaxel or the EGFR tyrosine kinase inhibitor erlotinib in patients with advanced NSCLC were stopped early after an interim analysis indicated futility and potentially increased harm, although patients with high circulating free IGF-I may have shown some benefit (37). At this point, enthusiasm for IGF-I receptor antibodies is somewhat tempered; however, numerous other clinical trials using IGF-I receptor antibodies as single agents or in combination with other drugs are currently enrolling.

Small-molecule tyrosine kinase inhibitors (TKIs) are another strategy for inhibiting the IGF-I receptor. TKIs have some theoretical advantages over monoclonal antibodies that may improve their efficacy and safety. Owing to the close homology between ATP binding sites, small-molecule inhibitors may bind both the IGF-I receptor and IR. This dual inhibition could further decrease the cross-talk between IGF-I receptor- and IR-activated pathways. Small-molecule inhibitors typically have shorter half-lives than monoclonal antibodies. The shorter half-life may increase dosing flexibility, which in turn may be used to manage toxicity and enhance efficacy. In preclinical models, flexibility in drug dosing and sequencing changed antitumor activity. Breast cancer xenografts allowed to recover IGF-I receptor signaling prior to treatment with doxorubicin showed a greater response than those where IGF-I receptor signaling was suppressed during or after receiving chemotherapy (38). While not tested in this model, it may be easier to inhibit and restore IGF-I receptor signaling with TKIs than with antibodies due to their shorter half-lives. Lastly, IGF-I receptor small molecules may have the benefit of off-target tyrosine kinase inhibition.

As of May 2011, there were at least five different IGF-I receptor TKIs in clinical trials according to www.clinicaltrials.gov (Table I). The drugs differ significantly in their potency and IGF-I receptor specificity. AXL-1717 (Axelar AB) and linsitinib (OSI-906; Astellas Pharma) are the most specific for the IGF-I receptor, although linsitinib also binds to the IR (39, 40). XL-228 (Exelixis) has the greatest potency against the IGF-I receptor but also inhibits many other kinases with significant potency, such as Aurora kinase B (IC_{50} = 0.6 nM), fibroblast growth factor receptor 2 (FGFR-2; IC_{50} = 2 nM) and proto-oncogene tyrosine-protein kinase Src (IC_{50} = 5 nM) (41). BMS-754807 and INSM-18 also have significant off-target activity (42, 43). Of the IGF-I receptor TKIs in clinical testing, linsitinib is the most advanced and will be the focus of this review.

PRECLINICAL PHARMACOLOGY

Linsitinib is a rationally designed, small-molecule dual inhibitor of IGF-I receptor and IR with excellent preclinical selectivity and antitumor activity in vitro and in vivo. It binds competitively at the ATP binding site to inhibit autophosphorylation. The principal pharmacological characterization of linsitinib occurred using the 3T3/hulGF IR cell line (LISN), a line of sarcoma cells overexpressing the IGF-I receptor. In cell cultures, escalating doses of linsitinib resulted in concentration-dependent inhibition of IGF-I-stimulated tumor growth and phosphorylation of Akt, ribosomal protein S6 kinase (S6K; a downstream target of mTOR) and ERK-1/2 (MAPK). In vitro the IC_{50} was 0.024 μM for IGF-I receptor, 0.13 μM for pAkt, 0.06 μM for pS6K and 0.028 μM for pERK (39). Selectivity for the IGF-I receptor and IR was then determined using a panel of purified protein kinases from the ProfilerPro® Kinase Selectivity Assay Kit (Caliper Life Sciences, Hopkinton, MA). Using this system, the IC_{50} for the IGF-I receptor was 0.035 μM and 0.075 μM for IR. The IC_{50} was > 10 μM for 85 other kinases, including Akt, EGFR, ERK-1/2, tyrosine-protein kinase JAK2, Aurora kinase A/B, platelet-derived growth factor receptor (PDGFR)-alpha/beta, FGFR, ALK tyrosine kinase receptor

Table I. *Small-molecule antagonists of insulin-like growth factor 1 receptor (IGF-I receptor) in clinical trials.*

Drug	Company	Clinical Status	Special comments
AXL-1717 (40)	Axelar AB	Phase I/II trial	Selective, non-ATP-competitive IGF-I receptor antagonist (IC_{50} = 40 nM) No IR inhibition
BMS-754807 (43)	Bristol-Myers Squibb	Phase I and II trials	Reversible, ATP-competitive, dual IGF-I receptor/IR antagonist (IC_{50} = 14 nM) Off-target activity against Aurora kinase A/B, c-Met, macrophage-stimulating protein receptor (*RON*), receptor tyrosine kinase A
INSM-18 (50)	Insmed	Phase II trial	Combined IGF-I receptor/IR inhibitor (IC_{50} = 20-30 nM) Off-target activity against receptor tyrosine-protein kinase erbB-2 (HER2) and 15-lipoxygenase
Linsitinib (49)	Astellas	Phase I, II and III trials	Reversible, ATP-competitive dual IGF-I receptor/IR inhibitor (IC_{50} = 24 nM) Highly selective, with little activity against other kinases
XL-228 (41)	Exelixis	Phase I trial	High-potency IGF-I receptor inhibitor (IC_{50} = 2 nM) Multi-targeted kinase inhibitor with activity against Aurora kinase A/B, BCR-ABL, fibroblast growth factor receptor (FGFR), Src family kinases

BCR-ABL, breakpoint cluster-region-Abelson murine leukemia fusion protein; IR, insulin receptor.

and hepatocyte growth factor receptor (proto-oncogene c-Met). These data were confirmed in the mouse-derived hepatocellular carcinoma Hepa1 cell line, where the IC_{50} for inhibiting IR was 0.039 μM. PQIP, an advanced lead compound, was evaluated against 42 different receptor tyrosine kinases in another study (44). The proteome arrays showed that phosphorylated IGF-I receptor decreased after 24-hour exposure to drug in all cell lines. IR phosphorylation was also reduced, yet no other kinases were affected. Combined, these studies have established and confirmed that linsitinib is a selective dual inhibitor of the IGF-I receptor and IR.

Preclinical antitumor effects have been established in several models. In vitro growth proliferation studies were performed in a wide variety of tumor cell lines (Table II). In general, the EC_{50} ranged from highly sensitive (0.021 μM) to insensitive (> 10 μM). In vivo models also support linsitinib's antitumor properties. In a GEO cell colorectal carcinoma xenograft model, a single oral dose of PQIP of 25 mg/kg yielded 57% inhibition of tumor IGF-I receptor phosphorylation by 4 hours, whereas 80% inhibition was achieved at 16 hours and was maintained for at least 24 hours. If the dose was increased to 100 mg/kg, 90% inhibition of IGF-I receptor phosphorylation was maintained for at least 24 hours. Tumor growth inhibition was greater with escalating doses of drug, although xenografts treated daily with 25, 50 or 100 mg/kg all had tumor growth < 50% of control. This pattern held for xenografts harboring 3T3/huIGF1R fibrosarcoma cells treated with PQIP (45). In a LISN xenograft model treated with linsitinib, dose-dependent tumor growth inhibition was also observed. Tumor growth inhibition was 100% in xenografts treated with 75 mg/kg/day and 55% of tumors showed evidence of regression. The drug plasma levels were greater than the IC_{50} from 4 to 24 hours post-dose. On the contrary, daily doses of 25 mg/kg yielded adequate drug levels from 4 to 16 hours only. Xenografts treated with 25 mg/kg daily showed 60% tumor growth inhibition but no tumor regression (39).

Table II. *In vitro antitumor effects of linsitinib.*

Tumor type	Cell line	EC_{50} (μM)
Breast	DU4475	0.086
	MCF7	0.177
Colorectal	SW620	0.021
	HT-29	0.21
	COLO 205	0.32
	RKO	> 10
Non-small cell lung	NCI-H292	0.78
	NCI-H358	0.81
	NCI-H1703	> 10
Pancreatic	BxPC-3	0.15
Rhabdomyosarcoma	A673	0.153

BCR-ABL, breakpoint cluster-region-Abelson murine leukemia fusion protein; IR, insulin receptor.

Efforts have been undertaken to better characterize which CRCs are sensitive and resistant to linsitinib. Twenty-seven CRC cell lines were exposed to linsitinib and classified by IC_{50} as sensitive (≤ 1.5 μM/L) or resistant (> 5 μM/L) (46). Six cell lines were classified as sensitive and the remaining 21 were resistant. Cell lines were then analyzed for IGF-I receptor pathway activity by immunoblotting and immunohistochemistry, IGF-I receptor (*IGF1R*) gene copy number by florescence in situ hybridization (FISH), gene mutation status (*KRAS, BRAF, PIK3*) and gene expression profiles. No single predictive marker could be identified. However, an integrated genomic classifier was developed combining gene array data, IGF-I receptor FISH results

and *KRAS* mutation status. When this classifier was applied prospectively to eight human CRC direct tumor xenografts, it predicted response to linsitinib with 100% accuracy. The two CRC direct tumor explants predicted to respond to linsitinib showed 21-28% tumor growth compared to control, whereas the six xenografts predicted to be resistant showed 76-178% growth.

Linsitinib may be more effective in combination with other agents than as a single agent. PQIP was tested as a single agent against 29 CRC cell lines and the lines were classified by IC_{50} as sensitive (≤ 1.5 μM/L) or resistant (> 5 μM/L) (44). Five sensitive cell lines were identified. Interestingly, in representative sensitive and resistant serum-starved cells, 3-hour exposure to PQIP almost completely inhibited IGF-II-induced tyrosine autophosphorylation of the IGF-I receptor. Sensitive and resistant cell lines were then exposed to PQIP (0.1, 0.4 and 1.6 μmol/L), SN-38, the active metabolite of irinotecan (2.0, 4.0 and 8.0 nmol/L), oxaliplatin (0.5, 1.0 and 5.0 μmol/L) and 5-fluorouracil (3.125, 6.25 and 12.5 μmol/L). In cell lines known to be sensitive to PQIP, synergy with cytotoxic agents was observed, whereas an additive effect was seen in resistant lines. The enhanced effects of combined therapy appeared to be due to induction of cell cycle arrest in the $G_{0/1}$ phase and decreased phosphorylation of Akt rather than induction of apoptosis. Synergy was seen between the clinical compound linsitinib and irinotecan in a CRC xenograft of the linsitinib-resistant RKO cell line as well. Treatment with linsitinib alone inhibited tumor growth by 25% compared to control. Treatment with single-agent irinotecan inhibited tumor growth by 59% compared to control, and the combination of linsitinib and irinotecan yielded 85% growth inhibition compared to control. These data support studies combining linsitinib and cytotoxic chemotherapies in humans with CRC.

PHARMACOKINETICS AND METABOLISM

As described above, linsitinib was designed to optimize absorption, distribution, metabolism and excretion. Initial pharmacokinetic studies were reported with the lead compound PQIP. Mice were given oral (p.o.) or intravenous (i.v.) PQIP and similar bioavailability was seen. The maximum concentration (C_{max}) increased in a linear fashion up to doses > 250 mg/kg, at which point this was no longer dose-proportional. For each dose, area under the concentration–time curve (AUC) values were used to estimate bioequivalence of p.o. to i.v. doses as a ratio, with approximately 100% bioavailability observed after a dose of 10 mg/kg (45).

Linsitinib has undergone preclinical pharmacokinetic evaluation as well. The bioavailability of once-daily doses was as high as 92%. At doses of 5 or 10 mg i.v. in mice and rats, the half-life ($t_{1/2}$) was 5 and 20 hours, respectively (39). The oral dose of 25 mg was compared in each species, showing $t_{1/2}$ values of 23.6 and 28.7 hours, respectively, in mice and rats. The rate of clearance was 19 and 16 mL/min/kg, respectively, and the volume of distribution was 8 and 21 L/kg, respectively. When linsitinib was administered to beagle dogs, the $t_{1/2}$ was 1 hour, with a clearance of 39 mL/min/kg, which is equivalent to liver blood flow. The plasma protein binding in mouse, rat, dog, monkey or human plasma was greatest in mouse models and lowest in human models. The volume of distribution in all species studied was < 5 L/kg. Most metabolism of linsitinib occurs in the liver via the cytochrome P450 system. The main metabolite of linsitinib is OSI-420.

Initial human pharmacokinetic data have been reported from phase I clinical trials. Results with intermittent oral dosing indicate linear exposure of linsitinib, with median t_{max} and $t_{3/4}$ values of 1-8 and 2-5 hours, respectively. Plasma linsitinib concentrations were above the predicted effective concentration (1 μM) at the maximal tolerated dose (MTD). For continuous oral dosing, the median t_{max} and $t_{3/4}$ values were 2-4 hours. Steady-state plasma concentrations were obtained by day 8 with twice-daily dosing (47). Pharmacokinetic characteristics of continuous linsitinib dosing were not altered by coadministration with erlotinib (48).

SAFETY

Preliminary safety data for linsitinib and PQIP are available from preclinical and phase I studies. In a study of PQIP combined with SN-38, no significant loss of body weight was seen in mouse colorectal cancer xenograft models compared to untreated mice (44). Animals with xenografts treated with lower doses of linsitinib (25 mg/kg/day) did not experience significant weight loss, but those treated with higher doses (75 mg/kg/day) lost an average of 16% of body weight in some studies (39). However, elevations in plasma glucose levels have been seen in xenograft-bearing animals treated with PQIP and linsitinib (39, 45).

Safety data for linsitinib alone and in combination with other agents from phase I trials are available and discussed below. In general, hyperglycemia, QT_c prolongation and liver function abnormalities were the major adverse events.

CLINICAL STUDIES

Linsitinib has been evaluated in numerous phase I, II and III trials as a single agent or in combination with other drugs. According to www.clinicaltrials.gov, several trials using linsitinib are actively enrolling. We will review the key findings of currently available studies.

Two phase I single-agent trials have been completed evaluating linsitinib in patients with advanced solid tumors. The two studies used different dosing schedules and dose levels and have been reported in abstract form. In the intermittent dosing schedule trial (NCT00514306), 61 patients were treated at regimens from 10 mg for 3 consecutive days every 14 days to 600 mg for 7 consecutive days every 14 days (49). Dose-limiting toxicity (DLT) was seen in seven patients and four patients had grade 3 hyperglycemia. The other DLTs were grade 4 fatigue, grade 3 QT_c prolongation and grade 3 vomiting. The most common adverse events of any grade were nausea (21%), vomiting (17%) and diarrhea (11%). Antitumor effects were seen in numerous tumor types. Stable disease for ≥ 12 weeks was seen in 24 patients (39%), including 4 of 11 patients with adrenocortical carcinoma. One patient with metastatic adrenocortical carcinoma had a partial response according to RECIST criteria. The intermittent schedule maximal tolerated dose (MTD) was established as 600 mg for 3 or 7 consecutive days on a 14-day cycle.

Linsitinib was given continuously (NCT00514007) at dose levels ranging from 10 mg to 450 mg daily and 20 mg to 200 mg twice daily in another phase I study (47). Of the 57 patients treated, 6 had DLTs, including grade 3 hyperglycemia (2 patients), grade 3 or 4 elevated AST/ALT (1 each), grade 3 prolonged QT_c and grade 3 inability to complete treatment period 1. Hyperglycemia of all grades was seen in 6 of 54 (11%) of patients. Nausea (20%), vomiting (20%) and

fatigue or lethargy (19%) were also observed. Stable disease was seen in 18 of 43 evaluable patients and the MTD was defined as 400 mg daily or 150 mg twice daily.

Linsitinib and erlotinib (NCT00739453) were combined in patients with advanced solid tumors. Patients were treated with 100 mg of erlotinib daily and either escalating doses of linsitinib as intermittent (50-600 mg for 3 consecutive days every 7 days) or continuous (50 or 100 mg) dosing schedules (44). Grade 4 ALT/AST and grade 3 hyperglycemia were seen in 2 of 26 evaluable patients. Grade 1 or 2 hyperglycemia was seen in 12 (46%) patients. Other grade 1 or 2 adverse events observed in two or more patients included diarrhea (31%), fatigue (31%), anorexia (12%), nausea (15%), vomiting (8%), dyspepsia (8%) and dysgeusia (8%). Erlotinib-related skin rash was observed in 85% of patients, with 4% of patients experiencing grade 3 rash. Stable disease for ≥ 12 weeks was seen in 4 of 7 patients on continuous linsitinib dosing (48). The study remains active and an MTD has not yet been reported; however, 150 mg of linsitinib twice daily is the dose carried forward in phase II studies in combination with erlotinib.

Three other phase I or phase I/II combination trials with linsitinib are currently enrolling. Linsitinib and irinotecan (NCT01016860) are combined in a phase I/IIb study at the University of Colorado Cancer Center evaluating their safety and efficacy in advanced solid tumors, with an expanded cohort stratified by an integrated classifier (46). The Sarah Cannon Research Institute is evaluating linsitinib and everolimus (NCT01154335) for patients with metastatic colorectal carcinoma. Paclitaxel and linsitinib (NCT00889382) are combined in a phase I study in patients with advanced solid tumors with a preplanned phase II study for ovarian cancer to follow.

There are a number of phase II studies currently enrolling and evaluating single-agent linsitinib or the drug in combination with other anticancer therapies. The only single-agent study is a randomized, double-blind trial of linsitinib (150 mg twice daily) versus placebo in patients with advanced hepatocellular carcinoma that has progressed on sorafenib (NCT01101906). For combination studies, continuous linsitinib at two different dose levels is combined with erlotinib and anti-estrogen therapy in patients with hormone-sensitive metastatic breast cancer (NCT01205685). There are two studies of linsitinib combined with erlotinib in NSCLC. The first is a study of linsitinib (150 mg twice daily) or placebo plus erlotinib (150 mg daily) for patients with EGFR-activating mutations (NCT01221077), and the second is a maintenance study of linsitinib (150 mg twice daily) or placebo combined with erlotinib (150 mg daily) in patients with metastatic NSCLC who did not have progression after four cycles of platinum-based chemotherapy (NCT01186861). Finally, a single-arm study of linsitinib (150 mg twice daily) combined with sorafenib (400 mg twice daily) is under way in patients with hepatocellular carcinoma (NCT01334710).

The GALACCTIC study is a randomized, double-blind, placebo-controlled trial of linsitinib (150 mg twice daily) in patients with locally advanced or metastatic ACC (NCT00924989). This study is open and enrolling at 43 centers in North America, Europe and Australia.

DRUG INTERACTIONS

In clinical studies, linsitinib has been combined with other targeted therapies (erlotinib and everolimus) and cytotoxic agents (irinotecan and paclitaxel). In the phase I study of linsitinib combined with erlotinib, no clear changes were reported in pharmacokinetics, pharmacodynamics or toxicity (48). Drug interaction data are not available for the other combination studies at this time. The greatest theoretical concern for drug interactions would be for drugs that cause hyperglycemia, QT_c prolongation and elevation in AST/ALT, mimicking the toxicity of linsitinib.

CONCLUSION

Linsitinib is a novel, small-molecule dual inhibitor of IGF-I receptor and IR. It has demonstrated significant preclinical activity in a number of different epithelial and mesenchymal malignancies, as well as linear pharmacokinetics and good oral bioavailability. Several phase I and II single-agent and combination studies are ongoing and a phase III trial of single-agent linsitinib is enrolling patients with adrenocortical carcinoma. In the next several years it should become clear whether linsitinib has a place in contemporary oncological care.

SOURCE

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DISCLOSURES

The authors state no conflicts of interest.

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