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The research progress of c-Met inhibitors in clinical trials

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Abstract: **Mesenchymal-epithelial transition factor gene (Met) is a protein encoded by c-Met proto-oncogene, which involved in the formation, transfer, and invasion of a variety of tumors. Increased c-Met expression in several human malignancies is related to increased tumor progression and is a new potential drug target for several types of cancers. Recently, there are two c-met inhibitor drugs have been approved for marketing, meanwhile, lots of c-Met inhibitors are in clinical research. Some of them showed good potential to reach market. The purpose of this paper is to summarize the structure and biological of c-Met inhibitors in the clinical research.**

Keywords: c-Met; anticancer; Inhibitor; Clinical research; Structure

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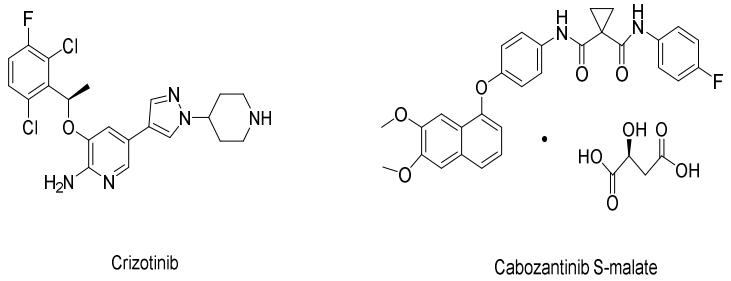
1. Introduction

Met is the N-methyl-N'-nitroso-gua-nidine human osteosarcoma transforming gene, which is a proto-oncogene encoding a receptor tyrosine kinase c-Met for hepatocyte growth factor (HGF)[1]. c-Met is the only known high-affinity receptor for HGF widely expressing in cells of epithelial- endothelial origin, containing liver cells, fibroblasts, hematopoietic cells, and keratinocytes[2]. The binding of active HGF to c-Met can result in downstream signaling for motility, proliferation, survival, morphogenesis, receptor dimerization/multimerization, and multiple tyrosine residue phosphorylation in the intracellular region[3-4].

The deregulation and activation of c-Met leads to unregulated cell growth and differentiation, and c-Met over expression or enhanced activation relative to normal tissues has been detected in many types of human cancer, for instance, liver, colorectal, gastric, pancreatic, lung, head and neck, ovarian, renal, prostate, and breast[5]. Recently, lots of c-Met target drugs were researched in clinical trial, Pfizer's crizotinib[6] and cabozantinib S-malate[7] (Figure 1) have been approved for marketing, meanwhile cabozantinib got FDA breakthrough designation in May 29 of 2018. This is the first time that c-Met inhibitor got the designation. It indicated c-Met inhibitor has good development prospects. This paper is to summarize the structure and biological of c-met inhibitors in the clinical research, some multi-target c-Met drugs were included.



Crizotinib Cabozantinib S-malate

Figure 1. The structures of crizotinib and cabozantinib.

2. The clinical research of c-met inhibitors

2.1. The c-met inhibitors in clinical phase III

There are six c-Met inhibitors were in clinical phase III. Onartuzumab[9] is a humanized monoclonal antibody targeted at human hepatocyte growth factor, which were researched by Genentech, it once has been approved by the FDA as an orphan drug for liver cancer in 2013, but it has been terminated because lack of clinical validity. Another antibody drug targeted at c-Met/HGFR is Pudk-HGF, also called recombinant plasmid-hepatocyte growth factor[10], which was researched by Humanwell Healthcare of Chinese, used as treating ischemic disease. Tivantinib[11], volitinib[12] and capmatinib[13] (Figure 2) are small molecular anticancer drugs targeted at c-Met/HGFR in clinical phase III, volitinib is a China's novel anticancer drug. Another small molecular drug targeted at c-Met/HGFR is refanalin[14], used as treating delayed functional recovery after transplantation, the structure information of refanalin is undisclosed.

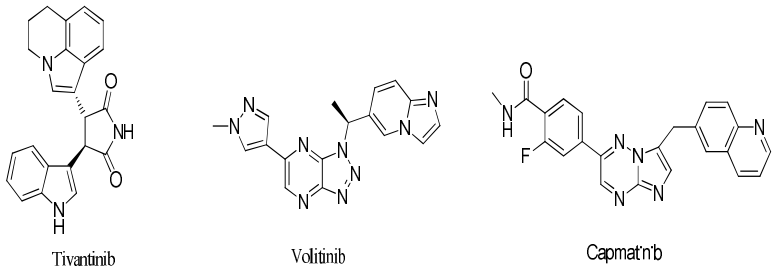


Figure 2. The structures of tivantinib and volitinib.

2.2. The c-met inhibitors in clinical phase II

There are twenty c-Met inhibitors in clinical phase II, some of them have ended research or didn't have more research information, ongoing clinical study drugs were listed in Table 1, and parts of the structures were listed in Figure 3. GM-604[15] was used in amyotrophic lateral sclerosis (ALS), in Phase 2A double-blind, randomized, placebo controlled clinical trial study, it was demonstrated that GM-604 can modulate protein expression. ASLAN-002[16] is a potent small inhibitor of Met (IC_{50}=3.9 nM) and RON (IC_{50}=1.8 nM) as well as related kinases inhibitor. The phase I dose escalation study was conducted to determine the safety and pharmacokinetics of ASLAN-002 with advanced cancer patients. The results showed ASLAN-002 was well tolerated at 300 mg BID. Tepotinib (EMD 1214063)[17] is a potent and selective c-Met inhibitor in IC_{50} of 4 nM, the phase I results showed more than 57 % patients were response positive to tepotinib. SAR125844[18] is a potent and highly selective c-Met inhibitor with potential antineoplastic activity. SAR125844 displayed nanomolar activity against the wild-type kinase (IC_{50}= 4.2 nM) and the M1250T and Y1235D mutants. AMG-337[19] is also a potent and highly selective small molecule ATP-competitive MET kinase inhibitor with IC_{50} < 5 nM in enzymatic assays. The phase study shows AMG-337 has good activity against gastric cancer and novel research shows AMG-337 is also a potential anti-liver cancer inhibitor. From the above data, large amount of c-Met inhibitors are ongoing in clinical study. We maintain a positive attitude with c-Met inhibitors; hope c-Met inhibitors will get a big achievement in anticancer.

Table 1. The c-met inhibitors in clinical phase II

No.	Name	Target	Treatment	Company	Structure
1	Emibetuzumab	c-Met/HGFR	stomach cancer, NSCLC	Lilly	Antibody
2	GM-604	Class I PI3K, INSR, c-Met/HGFR	amyotrophic lateral sclerosis, parkinson's disease, ischemic stroke	Genervon	Figure 3
3	ASLAN-002	MSI1R, c-Met/HGFR	stomach cancer, breast cancer	BMS, Asian	Figure 3
4	APG-8361	c-Met/HGFR	solid tumor	Yasheng	Undisclosed
5	SAR-125844	c-Met/HGFR	NSCLC	Sanofi	Figure 3
6	MK-2461	c-Met/HGFR	solid tumor	Merck	Figure 3
7	S-49076	FGFR2,UFO,c-Met/HGFR,FGFR3,FGFR1	NSCLC, glioblastoma	Servier	Figure 3
8	BPI-9016M	UFO, c-Met/HGFR	NSCLC, solid tumor	Beta	Undisclosed
9	Sym-015	c-Met/HGFR	solid tumor	Symphogen	Undisclosed
10	Glesatinib	VEGFR3, MST1R, VEGFR2, c-Met/HGFR	NSCLC, solid tumor	Mirati Therapeutics	Figure 3
11	Sitravatinib	VEGFR3, VEGFR2, TIE2, c-Met/HGFR	NSCLC, liposarcoma, soft tissue sarcoma	Mirati Therapeutics	Figure 3
12	Merestinib	c-Met/HGFR	solid tumor	Lilly	Figure 3
13	AMG-337	c-Met/HGFR	gastric cancer, esophageal cancer, solid tumor	Amgen	Figure 3
14	Tepotinib	c-Met/HGFR	NSCLC, hepatocellular carcinoma	Merck Serono	Figure 3

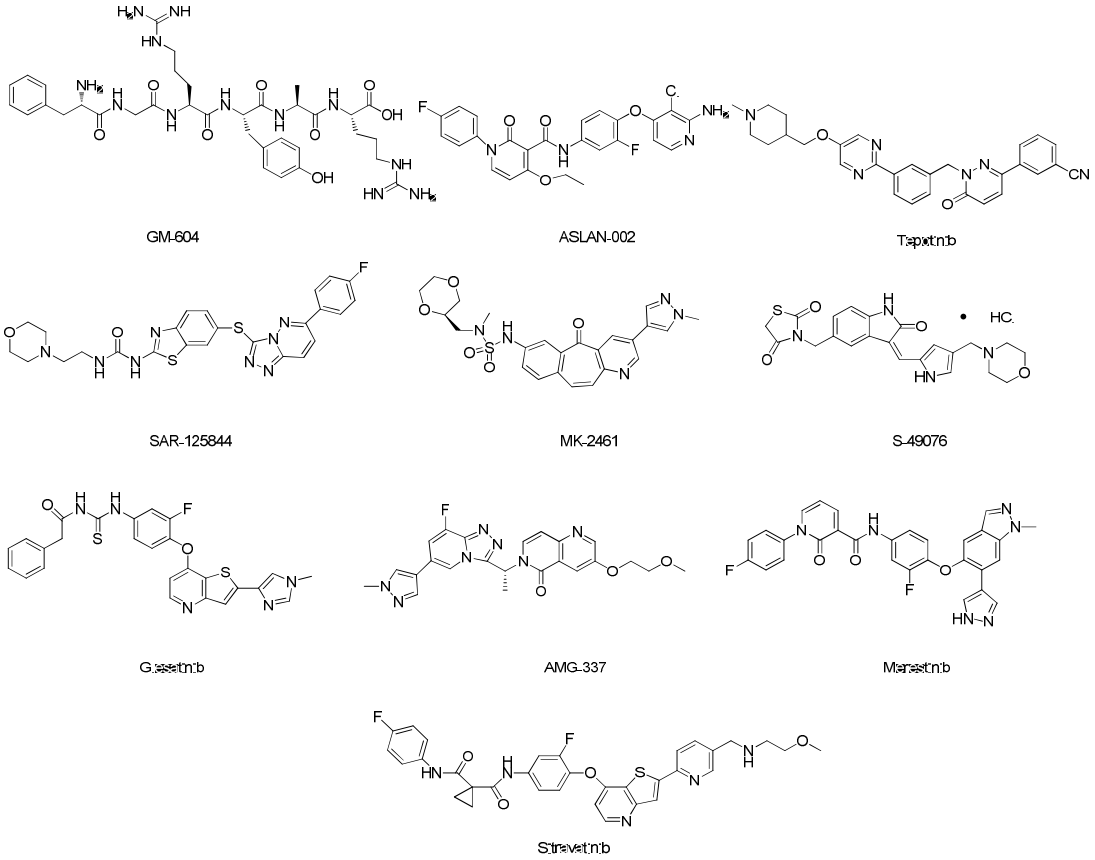


Figure 3. The structures of c-met inhibitors in clinical phase II.

Table 2. The c-met inhibitors in clinical phase I

No.	Name	Target	Treatment	Company	Structure
1	CM-118	c-Met/HGFR	NSCLC, malignant tumor	Xcovery, Kananji	Undisclosed
2	Boxitinib Hydrochloride	c-Met/HGFR	glioma, stomach cancer, breast cancer, lung cancer, kidney cancer	HEC	Undisclosed
3	HS-10241	c-Met/HGFR	stomach cancer, solid tumors, lung cancer, liver cancer	Jiangsu Haosen	Undisclosed
4	Altiratinib	NTRK3, TRKA, VEGFR2, TIE2, c-Met/HGFR, NTRK2	solid tumors	Deciphera	Figure 4
5	Ningetinib Tosylate	UFO, VEGFR2, c-Met/HGFR	glioma, gastric cancer, NSCLC, breast cancer, acute myeloid leukemia, liver cancer, bladder cancer, ovarian cancer, kidney cancer	HEC	Figure 4
6	LY-3164530	EGFR, c-Met/HGFR	solid tumor	Lilly	Undisclosed
7	DBPR-114	Chk2, TRKA, c-Met/HGFR	cancer	National Health Research Institutes	Undisclosed

8	Glumetinib	c-Met/HGFR	solid tumor	Shanghai institute of medicine, Shanghai lugu	Figure 4
9	SPH3348	c-Met/HGFR	gastric cancer, lung cancer, liver cancer	Shanghai Med. Pharm.	Undisclosed
10	Anti-cMet SIMPLE Antibody	c-Met/HGFR	solid tumor	ArGEN-X	Undisclosed
11	Metatinib Trometamol	VEGFR2, c-Met/HGFR	stomach cancer, prostate cancer, esophageal cancer	Bristol-Myers Squibb, Simcere	Figure 4
12	Kanitinib	VEGFR2, c-Met/HGFR	metastatic prostate cancer, gastric esophageal junction adenocarcinoma	Beijing Kang Chen	Undisclosed
13	Bozitinib	c-Met/HGFR	stomach cancer, NSCLC	Sichuan Hengkang	Undisclosed
14	SHR-A1403	c-Met/HGFR	solid tumor	Jiangsu hengrui	Antibody
15	HQP8361	c-Met/HGFR	malignant tumor	Guangzhou Shunjian	Undisclosed
16	JNJ-38877618	c-Met/HGFR	solid tumor	Johnson	Figure 4
17	TAS-115	VEGFR2, c-Met/HGFR	solid tumor	Otsuka	Figure 4
18	Telisotuzumab vedotin	c-Met/HGFR	solid tumor	AbbVie	Undisclosed
19	JNJ-61186372	HERs, c-Met/HGFR	NSCLC	Genmab, Janssen	Undisclosed
20	AL-2846	c-Met/HGFR	Glioma, NSCLC, gastric cancer, prostate cancer, thyroid myeloid cancer, liver cancer	Jiangsu Chia Tai-Tianqing	Undisclosed

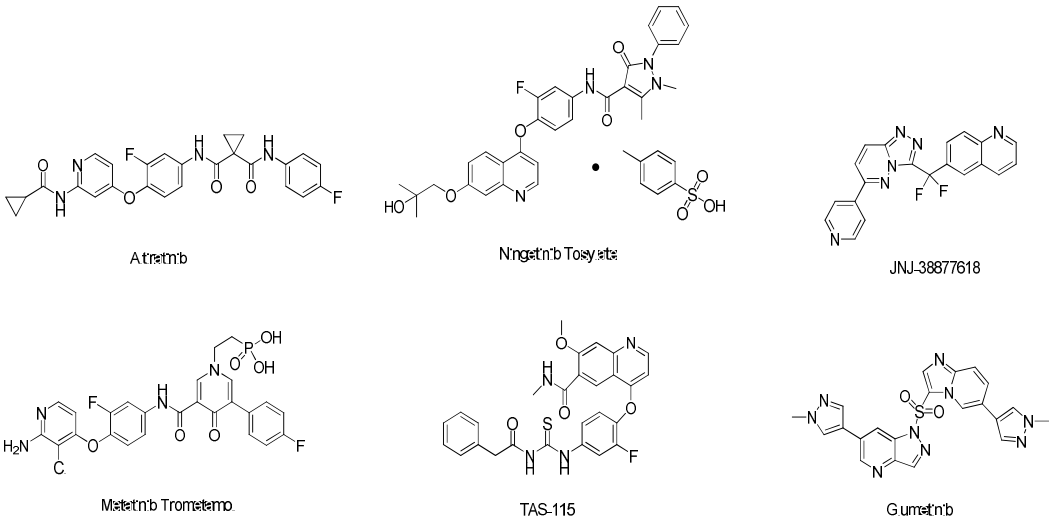


Figure 4. The structures of c-met inhibitors in clinical phase I.

2.3. The c-met inhibitors in clinical phase I

There are twenty ongoing c-Met inhibitors in clinical phase I, their basic information were listed in Table 2, and only six structures were published until now, listed in Figure 4. From table 2, we can find eight inhibitors are researched by Chinese company, which means more and more Chinese pharmaceutical company pay attention to innovation of new drugs.

3. Conclusion

There are lots of c-Met inhibitors in clinical trial, some of them showed excellent anticancer activity, market drugs crizotinib and cabozantinib showed broad-spectrum anticancer activity, which indicated c-Met targets were worth further study. Let's wait and see, hope c-Met inhibitor will bring big surprise to patients.

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