Seminars in clinical pharmacology: an introduction to MET inhibitors for the medical oncologist

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MET is a tyrosine kinase receptor for hepatocyte growth factor (HGF), primarily expressed on epithelial cells; the activation of MET induces several biological responses relevant for the development and growth of many human cancers. Several human malignancies present altered expression of MET and this is usually associated with poor prognosis and aggressive phenotype. The majority of MET inhibitors in clinical development target directly the receptor through the use of monoclonal antibodies (MAbs) or through small molecule inhibitors of MET kinase activity; small molecule inhibitors are very potent but less specific than MAbs. MET inhibitors are of great clinical interest because of the extensive crosstalk of the HGF/MET axis with many other signaling pathways, including growth factor-dependent pathways (like PI3K/AKT/mTOR, RAS/RAF/ERK) and vascular endothelial growth factor (VEGF) axis. In preclinical studies, the treatment with MET inhibitors could prevent or reverse resistance to inhibitors of growth factor-dependent signaling; this hypothesis is currently tested in phase III trials with anti-epidermal growth factor receptor (EGFR) inhibitors in non-small-cell lung cancer (NSCLC). Based on preclinical and preliminary clinical results, a rational strategy for the clinical development of MET antagonists should include a selection of the tumors with MET overexpression, the identification of prognostic/predictive biomarkers, the evaluation of combinations with anti-VEGF compounds.

Key words: inhibitors, MET, MET receptor, molecule-targeted treatment, target

introduction

MET is a tyrosine kinase receptor for the hepatocyte growth factor (HGF). Structurally, MET is formed by an entirely extracellular α-subunit linked to a transmembrane β-subunit which contains the intracellular catalytic activity.

The extracellular part consists of three functional domains; the intracellular part consists of three distinct regions, a juxtamembrane sequence which has the function of downregulating the kinase activity, a catalytic region in which there are activating phosphorylation sites (tyrosine residues 1234 and 1235) and a C-terminal domain which contains the docking site for the interaction with adaptors and transducers (tyrosines 1349 and 1356) [1, 2]. Upon binding of the ligand, the kinase activity of MET is turned on, leading to the autophosphorylation of the two sites present in the C-terminal part which represents the signal for the recruitment of adaptor and transducer proteins. Among the effectors recruited to the intracellular part of MET, there are several SH2-containing effectors like Src, PI3K and GRB2.

MET is primarily expressed on epithelial cells and its activation induces several biological responses essential for the development and progression of many human cancers. Several human malignancies present aberrant expression of MET and this is usually associated with poor prognosis, aggressive phenotype and increased metastasis. Alterations of MET expression could be also associated with drug resistance. The most frequent alteration of MET is overexpression, mostly due to increased transcription and, to a lesser extent, to gene amplification. Some tumors, like hereditary and spontaneous renal carcinoma and hepatocellular carcinoma in children, present activating point mutations in the coding region of the gene (see for more details [2–6]). Overall, these molecular alterations provide a proof of concept for the role of MET in human cancers.

The preclinical data clearly indicated that MET was an attractive target for anticancer treatment and several molecules have been designed to block its activation.

targeting MET

The majority of the compounds in development target directly the receptor, through the use of either monoclonal antibodies (MAbs) or small molecule inhibitors.

Small molecule inhibitors can act in an ATP-competitive or non-competitive fashion. ATP-competitive inhibitors are very potent but often (due to the structure similarity between the
ATP pocket of MET and that of other kinases) less specific, since they inhibit other kinases at concentrations not so different from those inhibiting MET. The non-competitive inhibitors could be more specific since they are not in general directly interacting with the ATP pocket but rather with allosteric sites of the receptor, which are not shared by other kinases. Binding to the allosteric sites leads to changes in the conformation of the active site, which alters the binding of the ligand HGF. Non-competitive inhibitors, on the other hand, might not completely block the activity of the receptor.

MET is the prototype of a family of receptor tyrosine kinases to which RON (Recepteur d’Origine Nantais) belongs. MET and the macrophage-stimulating protein (MSP) receptor RON are structurally related, and human MET and RON share >60% amino acid sequence homology. Like MET, RON is frequently overexpressed in various human cancers [7] and signals through mechanisms analogous to MET, generating similar biological responses. Because of the structure similarity, it is expected that some of the small molecule inhibitors could inhibit both MET and RON with potential advantages.

MAbs are specific for MET, and block the interaction between the ligand HGF and MET. MAbs can target HGF, thus blocking its binding to MET, or can target the receptor itself preventing its ligand-dependent activation or inducing receptor internalization and degradation.

MAbs that bind the ligand or target MET but do not cause its degradation are likely to be inactive in tumors with constitutive activation of MET due to the presence of mutations. On the contrary, if the MAb causes the internalization and degradation of the receptor, it could be active also in tumors in which MET is constitutively activated in a ligand-independent way.

An additional interesting application is the use of MET inhibitors in combination. In several models, the amplification of MET has been shown to be a mechanism of resistance to targeted therapy, like in non-small-cell lung cancer (NSCLC) following gefitinib therapy. In these resistant tumors, inhibition of MET signaling was able, at least at the preclinical level, to restore sensitivity to epidermal growth factor receptor (EGFR) antagonists [8, 9]. These data have been the main rationale for carrying out clinical studies with combinations of MET and EGFR inhibitors in NSCLC.

**Preclinical development**

The main features of MET inhibitors are given in Table 1.

**Non-competitive ATP inhibitors**

Tivantinib (ArQule) is an oral small molecule with high specificity for MET; tivantinib inhibited MET with no appreciable inhibitory effects against the majority of the other 229 human kinases tested, including RON [10].

A distinctive feature of tivantinib is the selective targeting of the inactive form of the kinase, which prevents MET autophosphorylation, the initial step for the full activation of the kinase [11].

In an in vitro panel of 12 human cancer cell lines, tivantinib showed high cytotoxicity in all the nine cell lines with active MET; the activity was correlated to the inhibition of MET phosphorylation, with inhibition of downstream MET effectors [10]. The antitumor activity was also observed in vivo at non-toxic doses. Tivantinib was also able to delay the onset of bone metastases in a breast murine model, at doses which did not have a cytotoxic effect [12].

**Competitive ATP inhibitors**

Several ATP-competitive inhibitors have been developed. All these compounds have shown potent activity in vitro and in vivo in preclinical models, including human MET-driven tumors. The majority of these compounds have a reduced selectivity for MET, being able to inhibit also other kinases, and the differences in their spectrum of activity might be the criteria for selection (Figure 1).

**Cabozantinib**

Cabozantinib (Exelixis) inhibits MET, VEGF 1–3, Ret, Kit and has shown antitumor activity in several xenograft models [13]. The compound showed activity also in tumors non-MET-dependent (that are in fact poorly responsive in vitro to MET inhibition), suggesting that the broad antitumor activity results from the inhibition of both MET and, most likely, vascular endothelial growth factor receptor (VEGFR) [13].

Cabozantinib was able to inhibit the formation of metastasis in experimental models [13, 14]; this antitumor activity is particularly interesting because of the experimental evidence that VEGFR inhibitors could increase the metastatic potential of tumors [15, 16].

**Foretinib**

Foretinib (Glaxo) was tested in a panel of human gastric cancer cell lines, showing activity only in those with amplification of MET or VEGFR2. The putative mechanism was postulated to be the inhibition of the interkinase network signaling where MET and VEGFR2 play a central role [17]. Foretinib showed a good antitumor activity in different models, both in vitro and in vivo [18].

**Crizotinib**

Crizotinib (Pfizer) is already at an advanced stage of clinical development as ALK inhibitor; an objective response rate of 57% has been reported in NSCLC patients with EMLA-ALK translocation, which is present in ~2%–7% of cases [19].

The in vitro cytotoxicity of crizotinib is higher in cells with MET amplification [20] and clinical studies with crizotinib as MET inhibitor are ongoing.

**Monoclonal antibodies**

Three MAbs, one directly targeting MET (MetMAb, onartuzumab, Genentech) and the others targeting the ligand HGF (rilotumumab, Amgen and ficlatuzumab, AVEO), are currently in clinical trials.

**Onartuzumab**

Onartuzumab is a mono MAb which inhibits the binding of HGF to the receptor and, differently from a bivalent antibody, does not have agonistic effects. Onartuzumab showed a high antitumor activity against an orthotopically implanted glioblastoma [21], the growth of which was dependent on HGF/MET. Onartuzumab also showed a good antitumor activity in pancreatic xenograft models dependent on the HGF/MET axis.
growing orthotopically or subcutaneously [22]. The antitumor activity was observed in both early- and late-stage tumors, the latter situation being more representative of the clinical one [22].

Rilotumumab
Rilotumumab is a fully human MAb which selectively targets HGF preventing its binding to MET. Rilotumumab has been shown to enhance the activity of temozolomide and docetaxel (Taxotere) in vitro and in vivo in preclinical models of human glioblastoma with upregulation of HGF/MET [23].

Ficlatuzumab
Ficlatuzumab is a humanized anti-HGF antibody with activity in vitro and in vivo in xenograft models; ficlatuzumab demonstrated additive activity when given in combination with erlotinib, cetuximab and temozolomide and is currently in phase II clinical studies.

Preclinical data on both rilotumumab and ficlatuzumab are scant due to their lack of binding and functional activity on mouse, rat or rabbit HGF, thus precluding the use of these species in the preclinical evaluation of safety [24].
clinical development

non-competitive ATP inhibitors
tivantinib (ARQ197)

phase I studies. Tivantinib was administered orally at 100–400 mg twice per day (BID) continuously to 51 patients with advanced solid tumors [25]. Patients were neither selected nor systematically assessed for molecular dysregulation of MET. The recommended phase II dose was 360 mg BID. The most common (>10%) drug-related adverse events (AEs) were mild-to-moderate grade 1–2 fatigue, nausea, vomiting and diarrhea.

Concomitant pharmacokinetic (PK) and pharmacodynamic analyses were done by evaluating MET expression by immunohistochemistry (IHC) (total and phosphorylated in repeated tumor biopsies), changes in circulating tumor and endothelial cells (CTC and CEC) and changes in tumor blood flow by dynamic contrast-enhanced magnetic resonance (DCE-MRI), to prove the expected biological effects. There was a decrease in the intratumoral MET levels, >30% decrease in CTC and up to 100% decrease in CEC in 58% patients with no changes in DCE-MRI parameters.

phase II studies. Many preclinical data supported the clinical development of MET and EGFR inhibitors in NSCLC [8, 9]. In a double-blind, randomized, phase II study, the combination of erlotinib plus tivantinib (ET) was compared with erlotinib plus placebo (EP) in 167 erlotinib naïve NSCLC patients [26]. At progression, patients were allowed to cross-over from placebo to tivantinib. The primary endpoint was progression-free survival (PFS) (Table 2). All patients were retrospectively assessed for EGFR, KRAS mutations and MET amplification. PFS and overall survival (OS) were not significantly longer after ET; however, in a preplanned exploratory survival analysis, PFS and OS were longer in patients with non-squamous histology, in patients with wild-type EGFR and in patients with KRAS mutation. ET is now compared with EP in a randomized, double-blind, phase III study in chemotherapy-pretreated, non-squamous NSCLC with OS as the primary end-point. Tumor tissues are collected and the patients are stratified by EGFR and KRAS mutational status [27].

In a randomized, placebo-controlled phase II study in 107 patients with unresectable hepatocellular carcinoma pretreated with chemotherapy, tivantinib induced a longer median time to progression in patients with high MET expression (defined as MET >2+ in >50% of tumor cells by IHC) (Table 2) [28].

competitive ATP inhibitors
cabozantinib (XL184)

phase I studies. Cabozantinib was given to 85 patients with advanced malignancies, including 37 with medullary thyroid carcinoma (MTC). Cabozantinib was given on two different schedules (intermittent days 1–5 and continuously) [29].

Hand and foot syndrome (HFS), and elevation of AST and ALT were the dose-limiting toxic effects; the most frequent AEs were diarrhea, fatigue and decreased appetite. Overall, 20% of patients achieved a partial response (PR), raising to 29% in the group of MTC.

phase II studies. The efficacy of cabozantinib was evaluated in a phase II, randomized discontinuation study in patients with different solid tumors, of which the most promising results were those achieved in advanced ovarian cancer (OC) [30] and castration-resistant prostate cancer (CRPC) patients [31].

All patients received cabozantinib 100 mg daily for 12 weeks followed by tumor evaluation; patients with tumor progression went off study, while partial responders continued on cabozantinib. Patients with stable disease (SD) were randomly assigned to cabozantinib or placebo.

The accrual in the OC study was stopped after 68 patients had been treated because of the high overall response rate (ORR) (24%) (18% in platinum-resistant and 29% in platinum-sensitive patients); the overall disease control rate (PR + SD) (DCR) was 58% [30].

The accrual in the prostate cancer study was discontinued after 168 patients had been treated, again because of the

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tumor type</th>
<th>Study design</th>
<th>Patients selection</th>
<th>Results</th>
<th>Predictive biomarkers</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tivantinib (T)</td>
<td>Pretreated NSCLC</td>
<td>Erlotinib + T (ET), versus erlotinib + placebo (EP)</td>
<td>None</td>
<td>PFS: 3.8 (ET) versus 2.3 (EP) mos</td>
<td>None</td>
<td>[26]</td>
</tr>
<tr>
<td></td>
<td>Pretreated HCC</td>
<td>Randomized 2:1 T (360 mg/BID); T (240 mg/BID); P</td>
<td>None</td>
<td>In high MET-positive PFS: 11.7 weeks (T) versus 6.1 weeks; OS: 7.2 mos versus 3.8 mos</td>
<td>High MET-positive (IHC)</td>
<td>[28]</td>
</tr>
<tr>
<td>Cabozantinib (C)</td>
<td>MTC</td>
<td>Expansion phase I</td>
<td>None</td>
<td>10 PR/35 patients (29%)</td>
<td>None</td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td>OC, CRPC</td>
<td>Randomized discontinuation design</td>
<td>None</td>
<td>OC (68 patients): ORR 24% (18% in platinum resistant patients), DCR 58%; CRPC (168 patients): ORR 4%, DCR 71%, pain improvement 67%</td>
<td>None</td>
<td>[30, 31]</td>
</tr>
<tr>
<td>Foretinib (F)</td>
<td>Gastric, H &amp; N, papillary renal</td>
<td>Phase II</td>
<td>None</td>
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OS, overall survival; MTC, medullary thyroid cancer; OC, ovarian cancer; CRPC, castration-resistant prostate cancer; DCR, disease control rate; ORR, overall response rate; HCC, hepatocellular carcinoma; PFS, progression-free survival; PR, partial response.

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Table 2. Phase II development of MET inhibitors: kinase inhibitors
relevant rate of clinical activity, regardless of prior treatment with docetaxel [31]. In 100 assessable patients, the 12-week DCR was 71%; 86% of patients assessable by bone scan had complete or partial resolution of bone lesions, 12% had SD and 2% had progressive disease (PD) (Table 2).

Dose reductions and discontinuations for AEs occurred in 51% and 10% of patients, respectively, the main toxic effects being HFS, diarrhea and fatigue.

Phase III studies are ongoing in advanced MTC and in CRPC patients pretreated with docetaxel and abiraterone or MDV 3100.

foretinib (XL880)

Foretinib was given for five consecutive days every 2 weeks to 40 patients with advanced solid tumors refractory to standard chemotherapy [32] (Table 1). The main toxic effects were hypertension, diarrhea and fatigue. PK data showed a long half-life, with dose proportional accumulation and continued plasma exposure during the off-treatment period. Repeated tumor biopsies of three patients with different tumor types (melanoma, MTC and triple-negative breast cancer) showed a decrease of pMET, pRON, pAKT and pERK 4 h after dosing. Three patients achieved a PR (Table 1). Phase II studies have been recently completed (gastric, papillary renal and H&N) and the results are awaited.

monoclonal antibodies

onartuzumab

Escalating doses of onartuzumab were given to 21 patients with a variety of solid tumors, with fatigue, nausea and peripheral edema as main toxic effects [33]. A durable CR has been observed in a patient with metastatic chemorefractory gastric cancer; the analysis for MET gene copy number from the primary tumor showed a high polisomy and MET protein expression by IHC [34]. A randomized, placebo-controlled, phase III study of onartuzumab in combination with FOLFOX was mandatory. MET-positive patients were defined as those with moderate or strong expression in >50% of tumor cells.

In MET-positive patients, PFS and OS were longer after EO than after EP, while patients MET-negative had shorter PFS after EO (Table 3). The most common AEs were rash, diarrhea, fatigue, anorexia, nausea and vomiting and were comparable in the two treatment groups. The incidence of peripheral edema was higher with EO (23.2% versus 7.5%).

A phase III study is ongoing in MET-positive patients.

rilotumumab

Rilotumumab is a fully human anti-HGF IgG2 antibody with a favorable toxicity profile with fatigue, nausea, myalgia, edema and hypertension as main toxic effects [35] (Table 1).

The existence of interactions between VEGF and HGF/SF (Scatter Factor) pathways in animal models was the rationale for studying the combination of rilotumumab with bevacizumab or motesanib [36]. Rilotumumab with bevacizumab full doses was well tolerated with fatigue, nausea and peripheral edema as main toxic effects.

In the locally advanced or metastatic gastric or esophageal cancer, a combination of rilotumumab with epirubicin, cisplatin and capecitabine was associated with a longer OS only in patients with high MET expression (>50% tumor cells positive) by IHC [37] (Table 3).

ficlatuzumab

Ficlatuzumab in a phase I study was given as a single agent at escalating doses and in combination with erlotinib at the recommended dose [38].

Comments and perspectives

MET inhibitors are compounds of great clinical interest for the following reasons:

- the existence of an extensive crosstalk of the HGF/MET axis with many other signaling pathways;
- the presence of dysregulations of the receptor, important for the development and progression of many human cancers;
- the antimitastatic effect observed in animal models;
- the potential of preventing or reversing resistance to inhibitors of growth factor-dependent pathways (like EGFR in NSCLC). The latter finding was the rationale for phase II, now phase III ongoing studies, with MET inhibitors and erlotinib or gefitinib.

Table 3. Phase II development of MET inhibitors: monoclonal antibodies (MAbs)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Onartuzumab (O)</td>
<td>Pretreated NSCLC</td>
<td>Randomized placebo controlled erlotinib + O versus erlotinib + P</td>
<td>None</td>
<td>Met-positive PFS: 2.9 versus 1.5 mos; OS: 12.6 versus 2.8 mos</td>
<td>MET positive (IHC)</td>
<td>[39]</td>
</tr>
<tr>
<td>Rilotumumab (R)</td>
<td>Untreated esophagogastrectomy (GEC)</td>
<td>Randomized placebo controlled R + ECx versus P + ECx</td>
<td>None</td>
<td>Met high positive OS: 11.1 versus 5.7 mo</td>
<td>Met positive (IHC)</td>
<td>[37]</td>
</tr>
<tr>
<td>Ficlatuzumab (F)</td>
<td>Untreated NSCLC</td>
<td>F + gefitinib versus gefitinib</td>
<td>Asian patients</td>
<td>Ongoing</td>
<td>To be evaluated</td>
<td>[41]</td>
</tr>
</tbody>
</table>

NSCLC, non-small cell lung cancer; IHC, immunochemistry; OS, overall survival; PFS, progression-free survival; ECx, epirubicin, cisplatin, capecitabine; P, placebo.
The preclinical data on the antitumor activity in a variety of tumor models indicated that in tumors with a constitutive activation of MET or in tumors with an autocrine expression of MET and HGF by tumor cells, the inhibition of MET was associated with antitumor activity. These findings clearly indicate the need to select tumor types and patients to achieve an antitumor effect with MET inhibitors both as single agents and in combination. This strategy of clinical development has been already confirmed by the preliminary results of phase III with erlotinib with/without onartuzumab in NSCLC [39], of phase II with tivantinib in HCC [28] and by the recent report of a durable complete response to onartuzumab in a patient with chemotherapy-refractory metastatic gastric cancer with high MET gene polisomy and a high level of MET and HGF expression by IHC in the primary tumor [34].

These findings are particularly relevant because the determination of MET expression by IHC (compared with FISH and sequencing) is feasible in almost all laboratories and relatively inexpensive. There is a need, however, to standardize as much as possible the criteria used to determine overexpression, similarly to what has been done for EGFR and HER-2.

A variety of tumor models have been tested to elucidate the different mechanisms by which MET is activated in human tumors (paracrine activation by HGF expressed by tumor-associated mesenchymal tissues; autocrine expression of MET by tumor cells; constitutively active MET). Overall, these studies indicated that in the evaluation of the target and of the potential predictive factors both MET and HGF expression should be considered. From this point of view, the strategy of clinical development has been rationale with the identification of predictive/prognostic biomarkers, possibly including HGF in plasma and VEGF for a broad spectrum of small-molecule MET inhibitors.

From the clinical point of view, the most interesting and promising field of investigations is related to the possibility of the HGF/MET axis to interfere with many signaling pathways. Combinations with MET inhibitors should be tailored to the particular tumor type by combining selective MET inhibitors with cytotoxics of known antitumor activity or with targeted agents of pathways of relevance for the tumor type.

The combination with VEGF/VEGFR inhibitors is very promising because of the preliminary results achieved with cabozantinib, the suggested mechanism of resistance to VEGF and the way to overcome it. The toxicity profile of cabozantinib, however, might affect a broad clinical development; combinations of MET inhibitors and antiangiogenics might have a better therapeutic index because of a more favorable safety profile and of the possibility to improve antitumor activity by selecting the best sequence of administration in preclinical studies.

disclosure
The authors have declared no conflicts of interest.

references
Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer

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Background: Previous studies have demonstrated the efficacy and safety of bevacizumab in the treatment of non-small-cell lung cancer (NSCLC).


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