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Have clinical trials properly assessed c-Met inhibitors?

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Abstract

The Met/HGF pathway is implicated in cancer progression and dissemination. Many inhibitors have been developed to target this pathway. Unfortunately, most trials have failed to demonstrate efficacy. Clinical trials, however, have not adequately tested the concept of Met pathway inhibition due to lack of appropriate patient selection criteria.

Keywords

clinical trials; c-Met; inhibitor; cancer

C-Met as a target of small molecule inhibitors

C-Met has been an intriguing target in the development pipeline of small molecule inhibitors. The c-Met pathway is dysregulated in cancer and associates with metastasis [1], and C-Met inhibition is effective in reducing c-Met signaling and metastatic phenotype in a range of preclinical models. Several c-Met inhibitors entered clinical evaluation, and 14 moved to or are currently in phase II or III trials (Table 1). Of these, 2 drugs gained FDA approval, neither being a specific inhibitor of c-Met.

Utility of total protein as a selection criterion

Small molecule inhibitors target specific proteins, and selecting patients whose tumors bear these proteins is necessary, though not sufficient, for efficacy. This is clear from clinical experience with Epidermal Growth Factor Receptor (EGFR) inhibitors. In clinical trials for non-small cell lung cancer [2, 3], the patient response to EGFR drugs varied, and the expression levels of EGFR protein in tumors did not predict patient outcome [4]. Women, Asians, and patients with adenocarcinoma fared best. Further investigation showed that EGFR mutations, not total protein expression, conferred sensitivity to the inhibitor [5]. In the case of c-Met inhibitors, gene mutations and amplifications, or overexpression of total protein have been used as markers for patient selection.

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Assessment of Markers

Perhaps the most iconic c-Met mutation is an exon 14 skip, resulting in delayed degradation and prolonged signaling [6]. However, exon 14 mutations are rare, occurring in only 3–4% of non-small cell lung carcinomas (NSCLC), and at even lesser frequency in other neoplasms such as in 2.3% of lung neoplasms (non NSCLC), 0.4% of gliomas, 0.4% of tumors of unknown primary origin, and in <0.1% of other tumor types [7]. Exon 14 skipping was not found in female reproductive, colorectal, or pancreatic tumors [7]. There are several other c-Met mutations, but the most common are generally regarded as passenger mutations [8]. Thus, c-Met mutations appear to contribute to a minor proportion of Met activity in cancer patients. As such, amplification and overexpression of c-Met are more commonly investigated as markers for patient enrollment in clinical trials.

Gene amplification is commonly believed to be associated with protein overexpression and pathway activity. However, amplification of *MET* does not directly correlate with protein expression. In NSCLC, only 28.8% of c-Met positive samples were also *MET* amplified. Furthermore, only 30% of phospho-Met positive cases displayed gene amplification [9]. A study in gliomas revealed c-Met overexpression in 13.1% of samples, but only 38.9% of the c-Met positive samples concurrently displayed gene amplification [10]. Thus, amplification of Met may not be a strong predictor of Met pathway activation. Although protein overexpression is often considered synonymous with protein activity, this appears not to be the case for c-Met. In in vitro studies of glioblastoma, no correlation was seen between levels of total Met and phospho-Met [11].

Despite the association between c-Met expression and cancer, results from most trials testing Met inhibitors have been disappointing. The results of Phase II and III clinical trials (not including trials of Crizotinib in ALK-positive NSCLC patients) showed no difference in progression free survival or overall survival, despite some of those trials selecting patients for protein overexpression or gene amplification. In the few trials that did meet the primary objective of improved progression free or overall survival, the improvements were modest at best. No selective c-Met inhibitor has demonstrated efficacy in human trials.

C-Met in clinical trials – patient selection criteria and surrogate markers

A closer examination of c-Met trials raises the question of whether the lack of tumor response is a true test of the validity of c-Met as a target in cancer. The key issue concerns patient selection. Table 2 compiles anti-c-Met or anti-HGF agents in phase II and III clinical trials. Only 16.6% required evidence of total protein expression, 8.9% required evidence of gene amplification, and 6.4% required evidence of mutation for patient inclusion. In 157 c-Met trials, 70.7% do not indicate the use of gene or protein markers.

Most importantly, no clinical trial required evidence of phosphorylation of Met. Yet, pathway activity is critical to demonstrating efficacy of small molecule drugs. C-Met overexpression and amplification are not proven to correlate with pathway activity. Thus, we would argue that even in the clinical trials that required evidence of total c-Met expression or gene amplification for patient inclusion (Table 2), these markers are unlikely to have

identified tumors with an active c-Met pathway. This leads us to believe that determination of total protein has little-to-no merit as an indicator of pathway activity for c-Met.

Summary

The success of small molecules such as EGFR inhibitors proved that identification of a correct target in cancer patients is crucial for success of therapy. In the case of c-Met inhibition, clinical trials have yielded little benefit to patients. The failure of clinical trials raises the common concern to many targeting approaches of whether the appropriate patient population was selected. Met inhibitors are designed to reduce phosphorylation of c-Met, and thus, reduce signaling and pathway activity. We would argue the selection criteria of tumor type, total protein expression, and gene amplification have not been shown to correlate to pathway activity. Trials that utilized c-Met mutation as an inclusion criterion have utilized a marker shown to correlate with pathway activity. Still, c-Met mutations are relatively rare, resulting in the vast majority of trials not utilizing an appropriate marker. Furthermore, to date no Met clinical trial used c-Met phosphorylation in the selection of patients for clinical trial participation, which we believe to be the most accurate biomarker. Inhibitors of c-Met have can be of value in patients with elevated c-Met activity, however, this has not been adequately evaluated in the clinic.

Signal transduction inhibitors can be highly efficacious cancer therapeutics. However, agents can appear to lack efficacy if evaluated in unselected or improperly selected group of patients. Using total protein or other surrogate marker as an indicator for pathway activity in selecting patients for clinical trials is likely to lead to the inclusion of a large proportion of patients who will not benefit from the agent, resulting in failed clinical trials. Pathway activity should be verified in patients using an appropriate biomarker, yet biomarkers are rarely validated. A validated phospho-Met immunoassay has been developed, however, it is not currently used in clinical trials [12]. Assays like this must be utilized if we are to advance therapeutics. Enrolling patients whose tumors do not express phospho-Met in a clinical trial of c-Met inhibition is unlikely to have a positive outcome, and is unjust to the patients. Ultimately, potentially beneficial drugs may be discarded.

Acknowledgments

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Table 1

C-Met/HGF inhibitors in phase II and III clinical trials

c-Met inhibitor	Name	Type	Targets	FDA approval status
ARQ 197	Tivantinib	non-ATP-competitive small molecule	c-Met, microtubule	None
GSK1363089/XL880	Foretinib	ATP-competitive small molecule	c-Met, VEGFR-2	None
XL184	Cabozantinib	ATP-competitive small molecule	c-Met, VEGFR, and Axl	Metastatic medullary thyroid cancer. Advanced renal cell carcinoma with prior anti-angiogenics treatment.
PF2341066	Crizotinib	ATP-competitive small molecule	c-Met, ALK, ROS1, and RON	ALK-positive advanced NSCLC
INC280	Capmatinib	ATP-competitive small molecule	c-Met. Little activity against EGFR and HER-3	None
AMG337		ATP-competitive small molecule	c-Met	None
AZD6094	Volitinib/Savolitinib	ATP-competitive small molecule	c-Met	None
BMS 777607/ASLAN002		ATP-competitive small molecule	c-Met, Axl, Tyro3, RON	None
MGCD265	Glesatinib	ATP-competitive small molecule	c-Met, Axl	None
MSC2156119J	Tepotinib	ATP-competitive small molecule	c-Met	None
PRO-142966	Onartuzumab	anti-c-Met monovalent antibody	c-Met	None
AMG-102	Rilotumumab	anti-c-Met monovalent antibody	c-Met	None
AV-299/SCH900105	Ficlatuzumab	anti-HGF monovalent antibody	HGF	None
LY2875358/LA480	Emibetuzumab	anti-HGF bivalent antibody	HGF	None

Table 2

Patient selection criteria used in phase II and III c-Met/HGF inhibitor clinical trials.

Inhibitor	# of cancer clinical trials	# of studies that used no marker	# of studies that used total Met expression	# of studies that used p-Met expression	# of studies that used Met amplification	# of studies that used Met mutation
ARQ 197	25	22	3	0	0	0
GSK1363089/XL880	7	7	0	0	0	0
XL184	44	42	1	0	2	1
PF2341066	15	8	2	0	3	2
INC280	15	4	2	0	4	3
AMG337	3	0	1	0	2	0
AZD6094	8	2	1	0	2	3
BMS 777607/ASLAN002	1	1	0	0	0	0
MGCD265	2	1	0	0	1	1
MSC2156119J	3	3	3	0	0	0
PRO-142966	13	3	3	0	0	0
AMG-102	15	11	4	0	0	0
AV-299/SCH900105	2	2	0	0	0	0
LY2875358/LA480	4	2	2	0	0	0
Total # of studies	157	111	26	0	14	10
% of total	-	70.7	16.6	0.0	8.9	6.4

Clinical trials do not include ALK-specific studies of PF2341066.