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cMet signaling pathway in cancer

Scientific overview and clinical trials management

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cMet is deregulated in many types of human malignancies and this has been correlated with poor clinical outcome; cMet remains an attractive drug target in oncology with many small molecule and biologic programs currently underway.

This white paper presents a comprehensive scientific overview of the cMet pathway and drugs under clinical development integrated with operational considerations on how to manage clinical trials in this indication.

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Executive summary

Receptor tyrosine kinases are a group of molecules that can enhance cellular proliferation, cell motility and migration, and eventual metastasis. cMet receptor tyrosine kinase has a significant biological and biochemical effect on cancer cells, and appears to be an important therapeutic target.

cMet has a complex biology that involves multiple cellular and tissue functions beyond epithelial cell growth and survival. cMet also presents with a range of molecular alterations, including amplification, mutation, rearrangement, expression and phosphorylation and this adds to the complexity of developing potential new drugs.

Abnormal cMet activation in cancer correlates with poor prognosis, where aberrantly active cMet triggers tumor growth, formation of new blood vessels (angiogenesis) that supply the tumor with nutrients, and cancer spread to other organs (metastasis).

cMet is therefore an attractive drug target in oncology with many small molecule and biologic programs currently underway.

This white paper provides a detailed analysis of the cMet signaling pathway in cancer from the scientific and clinical trial management perspective.

Section 1 provides a comprehensive scientific overview, including the current biomarker strategies, the clinical aspects and a summary of the compounds in clinical development.

Section 2 is focused on the operational and challenging aspects of conducting a clinical trial targeting cMet patients and presents innovative ways to manage study complexity.

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Section 1: Scientific overview

Biomarker considerations for cMet-targeted drug development in oncology

The cMet oncogene has been an important focus for targeted oncology drug development and associated biomarker research since the early 1990's and continues to challenge researchers hoping to identify and target patients most likely to respond to agents such as tivantinib and MetMab. The cMet receptor tyrosine kinase (RTK) may be compared to other, better known RTK's such as erbB2/HER2 and erbB1/EGFR that drive epithelial tumor development. However, cMet has a complex biology that involves multiple cellular and tissue functions beyond epithelial cell growth and survival. In addition, the complex range of cMet molecular alterations, including amplification, mutation, rearrangement, expression and phosphorylation continues to confound drug developers as contrasted with HER2 and EGFR overexpression, where patient selection is more straightforward. This section reviews the progress that has been made in biomarker strategies to support cMet inhibitor clinical development, including pharmacodynamic and predictive biomarkers.

The pharmacodynamic (PD) analysis of a drug's target engagement and inhibition and biological activity is an important priority and milestone for early clinical research. The results of the PD analysis should support the proof of concept of the agent and may provide data to direct dosing in later studies. Similar to other RTK's, target engagement of cMet is typically demonstrated by inhibition of cMet phosphorylation using phospho-specific immunoassays.[1] Analysis of receptor internalization and degradation may provide further evidence of target engagement.[2] Drug impact on downstream cellular signaling may be determined by additional phospho-assay analyses targeting S6-ribosomal protein or other common signaling molecules.

The pharmacodynamic biomarker strategy extends to biological activity and disease biomarkers. cMet biology presents many potential markers of biological activity including circulating HGF and soluble cMet receptor levels and more distal circulating growth factors such as VEGF. Markers of EMT and angiogenesis, cellular functions linked to cMet activity, may also be followed including expression of adhesion and structural proteins (e-cadherin and vimentin) and endothelial markers (CD31). Another promising area for testing is the activation of parallel RTK's known to interact with cMet including EGFR and IGF-IR. It may also be important to determine the impact of drug exposure on alternative targets, depending on the specificity of the drug. For example, many of the cMet inhibitors that have been developed also have activity against type III RTK's such as PDGFR, VEGFR and Kit. The overall goal of the PD strategy is to link target engagement with impact on disease biology that may lead to patient response.

The search for robust predictive biomarkers for cMet inhibitor clinical development and patient use has challenged researchers and pathologists. cMet is overexpressed, phosphorylated, amplified, rearranged and/or mutated in a wide number of malignancies. These alterations have been investigated as possible predictive biomarkers with no clear results in favor of a single alteration in a specific indication. cMet amplification, as determined by FISH, versus cMet overexpression, tested by IHC, has been the primary focus of research in many studies. This research has been made more difficult by technical difficulties for patient testing including changing FISH probe sets, uncertain FISH gene copy number cut-offs, multiple cMet and phospho-cMet IHC tests and IHC scoring methods. In some indications and study designs, such as non-small cell lung cancer (NSCLC) and relapsed patients, sample access may also be difficult. This has led to the development of alternative sample sources such as circulating tumor cells and circulating tumor DNA. These approaches promise to make patient testing for cMet alterations much more feasible.

Two cancer indications highlight the complexity and range of biomarker strategies that have been used for cMet inhibitor clinical development. In particular, the clinical development of cMet inhibitors in hepatocellular carcinoma (HCC) focuses on certain cMet biomarkers and aspects of biology that are distinct from those seen in NSCLC. cMet is overexpressed (protein and RNA) in HCC but amplification is rare.[3] cMet mutations have only been reported in pediatric cases of HCC.[3] Therefore, cMet overexpression has been the focus for predictive biomarker testing in HCC. Interestingly, circulating levels of HGF may be prognostic but have not been shown to be predictive of response to cMet inhibitors.[3] Any biomarker strategy in HCC is complicated by the potential impact of liver disease such as cirrhosis that also involves HGF and cMet signaling. PD analysis has included testing for cMet phosphorylation as well as downstream targets such as AKT and ERK. Importantly, cMet's role in HCC appears to involve angiogenesis, including cross-talk with the VEGF receptors. Therefore, HCC biomarker strategies must include markers of angiogenesis such as circulating VEGF or staining for CD31-positive endothelial cells. A number of small molecule inhibitors targeting HGF or cMet are currently in clinical trials (clinicaltrial.gov). It is noteworthy that Cabozantinib is in a Phase III trial in HCC patients following sorafenib therapy without selection for high cMet expression. In comparison, Tivantinib is in a Phase III study in patients with inoperable HCC and selects for patients with high cMet expression by IHC. It is important to note that Cabozantinib also targets VEGFR. These two contrasting studies highlight the multiple variables that impact biomarkers strategies for specific compounds in HCC.

cMet is overexpressed, phosphorylated, amplified, rearranged and/or mutated in a wide number of malignancies. These alterations have been investigated as possible predictive biomarkers with no clear results in favor of a single alteration in a specific indication.

High expression of cMet and HGF has been shown to be prognostic in NSCLC suggesting that cMet signaling is an important driver of oncogenesis in this indication.[4] In contrast to HCC, cMet amplification has been observed in a significant percentage of NSCLC patients.[4] In addition, cMet mutations have also been found in a small number of patients. However, it has yet to be determined whether the known mutations are activating or drive tumor proliferation. Importantly, cMet activation has been shown to be an important resistance mechanism for EGFR inhibitors in NSCLC and the level of cMet overexpression or amplification increases in relapse patients exposed to an EGFR targeted drug. A number of cMet-targeted drugs are in trials for relapse patients due to activation of this pathway. While multiple small molecule TKI's, including Tivantinib and Cabozantinib, are in late phase clinical trials in NSCLC, much of the focus has been on antibodies directed to HGF or cMet. These programs have also used cMet amplification by FISH or expression by IHC as a selection and predictive biomarker with limited success. One notable example of a biologic approach is the MetMab program from Genentech/Roche. Both IHC and FISH testing have been explored in MetMab NSCLC studies with results suggesting that expression and IHC was the more predictive approach.[5] Roche/Genentech halted development of the agent during a Phase III trial targeting NCLSC patients that overexpress cMet by IHC when an interim analysis failed to find meaningful efficacy. Development of Tivantinib in NSCLC has also shown mixed results with one large Phase III study that targeted patients with high cMet expression being halted due to lack of efficacy.[6] Continued subgroup analysis may still identify a response patient population from these studies. Setbacks such as these highlight the challenges in targeting cMet in NSCLC using cMet expression as a selection criteria.

cMet remains an attractive drug target in oncology with many small molecule and biologic programs currently underway. Clearly existing strategies for predictive biomarkers and patient selection have not led to the identification of therapeutic benefit, although many factors influence trial outcomes. Technical advances in testing approaches including the use of NGS genomic patient screening to better identify patients with cMet alterations will likely have a significant impact on the success rate of studies using these alterations as a selection criteria. A greater understanding of cMet biology and its role in tumor proliferation and survival as well as angiogenesis, hypoxia, EMT and cell migration will better inform drug targeting and biomarker strategies. It is also important that trials be designed to enable robust retrospective biomarker analysis from both a sample access, banking and consent perspective and a statistical perspective. It is likely that retrospective subgroup analysis will be crucial for advancing cMet biomarker strategies in the future.

> *Clearly existing strategies for predictive biomarkers and patient selection have not led to the identification of therapeutic benefit, although many factors influence trial outcomes.*

Medical review

A. cMet overexpression correlated with poor clinical outcome and resistance

Abnormal cMet activation in cancer correlates with poor prognosis, where aberrantly active cMet triggers tumor growth, formation of new blood vessels (angiogenesis) that supply the tumor with nutrients, and cancer spread to other organs (metastasis). cMet is deregulated in many types of human malignancies, including cancers of kidney, liver, stomach, breast and brain. Normally, only stem cells and progenitor cells express MET, which allows these cells to grow invasively in order to generate new tissues in an embryo or regenerate damaged tissues in an adult. However, cancer stem cells are thought to hijack the ability of normal stem cells to express MET, and thus become the cause of cancer persistence and spread to other sites in the body.[7]

In several clinical studies, aberrant MET over-expression has been correlated with poor clinical outcome, exemplified by rapid dissemination of disease and short survival. Over-expression of MET and HGF are also thought to result in resistance of tumor cells to chemotherapy and radiotherapy and correlates with the development of distant metastases and with shorter metastasis-free survival.[8]

B. Drugs under clinical development[8,9,10]

Receptor tyrosine kinases are a group of molecules that can enhance cellular proliferation, cell motility and migration, and eventual metastasis. cMet receptor tyrosine kinase has a significant biological and biochemical effect on cancer cells, and appears to be an important therapeutic target. In many cancers, cMet (which can be activated by its ligand hepatocyte growth factor, HGF) can be overexpressed, activated, amplified and/or mutated.

Several MET pathway inhibitors are currently being studied in the clinic. These agents focus on the serial steps that lead to activation of Met:

1. HGF specific binding to Met can be prevented by competitors that prevent HGF ligand from interacting with the Met receptor, blocking downstream activation of the pathway;

2. Met receptor activation can be prevented by receptor blockage by specific monoclonal antibodies that bind to and degrade the receptor;

3. Met receptor activation can also be targeted by selective Met kinase inhibitors, which have specific selectivity for Met receptor tyrosine kinase, or nonselective Met kinase inhibitors, which have broad activity against Met and other receptor tyrosine kinases that have also been shown to be important in cancer.

Table 1 provides a summary of some selected examples of cMet inhibitors from two angles: Monoclonal Antibodies and Tyrosine Kinase Inhibitors. This is not meant to be a fully comprehensive list; of note, several other compounds not listed in table one are in early phase of clinical development and some of them targets multiple genes but cMet is currently not their main target.

Table 1: Selected examples of MET inhibitors in clinical development

Drug name	Stage of development	Drug target	Comments
Monoclonal antibodies			
Rilotumumab (AMG102)	Phase I/II/III	HGF IgG2 Mab	NSCLC/CRC/Prostate cancer/ SCLC/Solid tumours combination
Ficlatuzumab (AV-199)	Phase I/II	HGF IgG2 Mab	NSCLC/Solid tumours/lymphoma/ myeloma Combination/Monotherapy
TAK701	Phase I	HGF IgG1 Mab	Solid tumours Monotherapy
Onartuzumab (MetMAb)	Phase II/III	MET IgG1 Mab	NSCLC/Solid tumours
Sym015 (mAb Mixture)	Pre-clinical / Phase I	MET	Multiple solid tumors

Drug name	Stage of development	Drug target	Comments
Tyrosine kinase inhibitors			
Tivantinib (ARQ 197)	Phase II/III	Selective MET TKI	NSCLC/HCC/Gastric Cancer/Solid tumours Combination
AMG337	Phase I/II	Selective MET TKI	GI cancers/Solid tumours
Tepotinib (EMD1214063/ MSC 2156119)	Phase I/II	Selective MET TKI	NSCLC/HCC
Capmatinib (INCB28060)	Phase I/II	Selective MET TKI	HCC/NSCLC/Solid tumours
Savolitinib (HMP504/ AZD2094)	Phase I/II	Selective MET TKI	Solid tumours
Cabozantinib (XL184)	Phase II/III	MET, VEGFR2, Ret, Kit, Flt3, Tie-2 inhibitor	Multiple solid tumours/approved by FDA for Metastatic Thyroid cancer in 2012 Combination
Foretinib (GSK1363089)	Phase I/II	MET, VEGFR2, Axl, PDGFR, Kit, Flt3, Tie-2 inhibitor	Multiple solid tumours Monotherapy/Combination
Crizotinib (PF02341066)	Phase I/II/III	MET, Alk, Ron Axl, Tie-2 inhibitor	NSCLC/Lymphoma/Solid tumours Approved by FDA in 2011 Mainly targeting ALK
MGCD265	Phase I/II	MET, VEGFR, RON, Tie-2, FLT3 inhibitor	Solid tumours Monotherapy/combination
Golvatinib (E7050)	Phase I/II	MET, VEGFR inhibitor	Solid tumours Monotherapy/combination

The promise of cMet inhibitors is likely to be seen in combination therapies, with patients selected by predictive biomarkers, all of which are currently under investigation.

C. A clinical perspective

The cMet signaling pathway is involved in all of the key processes of cancer growth and dissemination, and has been implicated in resistance of cancer cells to cytotoxic chemotherapy, as well as targeted agents such as EGFR inhibitors and VEGFR inhibitors. cMet inhibitors have therefore been seen as exciting drugs for cancer therapy. The promise of these compounds is likely to be seen in combination therapies, with patients selected by predictive biomarkers, all of which are currently under investigation. Unlike the highly selective cMet inhibitors, some of the multitargeted cMet inhibitors may possess single-agent activity.

Inhibition of cMet is a promising therapeutic strategy in HCC and NSCLC. Given the heterogeneous mechanisms underlying cMet dysregulation, there is an urgent and unmet need for the development of predictive biomarkers to identify which subsets of cMet-dependent tumors are most likely to benefit from specific classes of inhibitors.

Section 2: Operational aspects

Trials targeting the cMet pathway have to face a number of different operational challenges as they are essentially looking for a rare patient population which is also difficult to identify due to the fact that the biomarker is not routinely assessed at the site level.

- cMet testing is not routinely performed as a part of the standard clinical practice as there is no drug yet approved requiring testing for cMet gene amplification or other alterations.

- Where sites are performing this test, a high level of variability in testing and scoring across the local labs shall be expected.

- Niche patient populations (average 5% incidence) in a competitive environment, with several new investigational drugs under clinical development, create patient recruitment challenges.

A. Feasibility data on cMet local testing

The extent of local cMet testing was assessed by Quintiles team in February 2015. Fifty sites in 15 countries from three regions were asked about cMet local testing capability. Table 2 summarizes the finding at the local level. Key findings from this exercise are:

1. cMet is rarely routinely tested (12 of a total 51 sites performs the test routinely);

2. Testing is performed on selected indications which vary from site to site and is linked to specific areas of interest;

3. Most of the sites are able to implement local testing mainly through the FISH technique for cMet amplification but they raised the need for test reimbursement;

4. Some of the sites do have experience in testing mainly related to ongoing clinical trials

Table 2: Sites feedback on a country level – data collected from Quintiles (February 2015)

Country	Feedback
Australia	Two sites responded out of four contacted. None assesses cMet routinely; one site would have the capability to assess it at the local level (with FISH, IHC or possibly NSG). Two sites didn't respond because of participation in a competing trial. One site mentioned, "PI is already involved in a directly competing study. There is a low prevalence of amplification, so recruitment is already challenging. We will therefore decline progressing discussions any further." Another site commented, "We do not routinely test cMet here since there is no validated target/therapy and I don't think our pathologist have the capacity to test for it even if we were to request it. Hence any study involving this patient group would require central (sponsor arranged) testing."
Belgium	Three responding sites. None of them is routinely testing cMet but all of them would have the capability to implement cMet testing at the local level. FISH would be used, one site commented, "IHC preferable because it is easier." Interesting comments received: 1. "No, cMet is not done at our hospital because for now there is not enough demand for this test (No medication available (MNP, EAP or else) for treating this patient)." 2. "No, cMet is not available at site and is not reimbursed." 3. "I have major doubt that the pathology department is interested in collaboration by implementing this test, I expect that the number of eligible patients will be very low I prefer not to open our center even if a trial comes to Belgium. Testing could be implemented if reimbursed but it will lead to a discussion with labs and Physician. For Method, we don't know as it is not done till now (I would say FISH but IHC preferred if reproducible because it is easier)." 4. "Local testing could be implemented if reimbursed/paid by sponsor."
Canada	One site responded out of two contacted. They are not routinely testing cMet at the local level and also commented the following: "Unfortunately we cannot implement cMet at the moment. Perhaps after our Molecular Lab is up and running but that would be a more long term initiative. We would be happy to send off tumour samples for central testing though."
Denmark	One site commented they are testing cMet for "All solid tumours referred for Phase 1 studies (+100 annually)" This is done through FISH (Routine Met expression by RNA sequencing, and supplementary amplification when over expressed). In a 15 month period they could provide" 6-12 cMet amplified patients across different indication depending on whether also high-grade gliomas are accepted." The second site commented they could implement local testing through FISH.
France	Six sites were contacted for a feasibility earlier in 2014. Three of them reported they were routinely assessing cMet at the local level but only in very defined indications (2 Gastric Cancer, 1 in Colorectal Cancer). In addition to the sites performing Gastric Cancer and Renal Cell Carcinoma (which do have a database) another site reported they have a database for NSCLC even if they are not routinely pre-screening (the situation at this site is therefore unclear). All sites reported they could implement local testing through FISH.

Country	Feedback
Germany	Two sites contacted. One reported that they are routinely assessing cMet through FISH for NSCLC and adenocarcinoma. Number of pool of available patients would "depend on level of amplification." Another site reported they could implement local testing "as needed for the trial."
Hong Kong	The two contacted sites reported they are not routinely assessing cMet and they can implement it at the local level (FISH and also ICH at one site).
Italy	The four contacted sites reported they are not routinely assessing cMet and they can implement it at the local level (FISH at three sites and IHC at four sites). Comments received: 1) IHC yet implemented for other clinical trials; 2) No testing except for some external patients.
Netherlands	Of the four contacted sites, one reported they are routinely performing cMet on patients with NSCLC, with progression on first line treatment. They would have a pool of 3 to 4 patients in a 15 month period. Local testing could be implemented at the other sites: FISH (3), IHC (2), NGS (1). Comments received: 1. "We are not testing cMet routinely, but our pathology lab has a validated test (IHC but also FISH). We use it for pre-selection for certain Phase I trials (Phase 1 trials in which lung SCC, gastric tumours are included)." 2. "We work with pre-selection at our Phase I unit, but not on a routinely basis in regular care. So if a patient is a potential candidate for a cMet, we will perform this test. Turnaround time of this test is short. For Phase I in general, we use NGS analysis as a routinely pre-selection tool." 3. "We are currently performing these tests in a clinical trial setting for a pharmaceutical company (the trial is not running in our hospital, however)."
Poland	Four contacted sites, none is testing cMet at the local level. One could implement IHC or "maybe" FISH local testing. Comments received: Local testing "could probably be done, but it depends what method would be used – IHC, most likely yes; FISH, maybe, however not sure; other methods, rather not."
Singapore	One site is routinely assessing cMet at the local level for NSCLC (FISH/IHC). Comments received: Site not performing the test could do it locally "Only if the test can be easily done by the study coordinators. Local lab not able to."
South Korea	Two contacted sites are routinely screening for cMet at the local level. Comments received: 1. "We routinely use IHC for cMet in NSCLC and gastric cancer and we use FISH for selected cases. We just started to assess cMet CNV using NGS. It would be a routine procedure for all types of cancer soon. We would find 20-30 patients with cMet amplified tumours across different indication over 15 months" 2. "cMet testing is performed for Colorectal, gastric, biliary, HCC, and other rare tumours. We screen met by ICH first (Ventana's IHC), then confirm by FISH. We would have a pool of 15 patients in a 15 months in GC, CRC, HCC, Biliary Sarcoma and other rare tumours." 3. "Gastric Cancer team is screening by qPCR. However, FISH which is standard, isn't routinely used due to high cost and non-reimbursement. We could implement FISH at the local level. If its cost is reimbursed by sponsor, we can identify more potential subjects."

Country	Feedback
Spain	One site reported they are routinely screening lung cancer patients for cMet amplification through FISH and in a 15-month recruitment period they could provide 8 to 10 amplified patients. Other 6 sites could implement local testing: FISH (5), IHC (1), DNA sequencing (1) and beaming (1). Comments received: 1. "We don't assess cMet protein expression or gene amplification as part of our routine clinical practice, but we've got some experience in cMet testing in the context of clinical trials or research projects (We are using an IHC assay with the monoclonal antibody SP44 (Ventana Medical Systems)/MET4 (Dako)." 2. "We're currently testing cMet locally in the context of clinical trials or research projects." 3. "We have local cMet testing already in place for clinical trials."
Taiwan	One contacted site reported that they are not routinely performing cMet and that they prefer to send samples to a central lab.
U.S.	Five sites contacted. Two are routinely assessing for cMet, one "fairly often." Indication tested "NSCLC, HCC, gastric, GE junction." Methods used: IHC (Ventana, SP44 Ab) (1), NGS (1), FISH (1). Reported available patients in 15 months: 1. "10 to 12." 2. "We would be able to identify these patients as needed. We do not currently have a database to pull patients with specific mutations. In 2014 there were 21 patients that were positive for amplification (out of 164 tested), again mostly lung cancers." 3. "Not too many, no database of this info / patients. Maybe 6 to 10." The other two sites reported they can perform testing at the local level through FISH and IHC.

B. Risk assessment – local cMet testing

Table 3 summarizes the risks connected with the implementation of a cMet trial based on a cMet local testing.

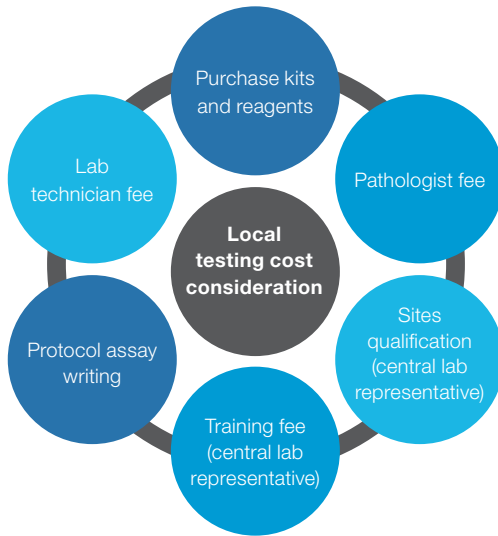## Table 3: Risk and contingency plan – local cMet testing

Risk	Contingency Plan
Finding an adequate number of sites assessing cMet amplification as a part of their routine practice	As there is no drug yet approved requiring testing for cMet gene amplification, the corresponding test is not performed on a routine basis. Quintiles recommends that at the study start-up a thorough site identification exercise is conducted with an unblinded protocol version to identify the sites performing cMet analysis for the relevant indications targeted in the protocol.
Sites routinely performing cMet at the local level but already involved in the development of other drugs in the same indication	As a part of the site identification, site interest in taking part in the trial and their willingness to dedicate their cMet amplified patients to that particular trial and that particular company shall be assessed.

Risk	Contingency Plan
The number of patients to be pre-screened at the local level for sites not routinely assessing cMet is high	As a part of the site identification, sites shall be assessed for their screening capability based on the number of patients with the protocol targeted tumour they visit per month.
	Sites shall also agree to take part in a trial where a high screening failure rate is expected.
	Provide adequate compensation to the site for screening high volumes of patients.
Testing done at the local level:	The below contingency plans are recommended when testing is conducted at the local level:
• High level of variability in testing and scoring across the local labs	• A central lab shall be involved in writing an assay protocol to standardize the scoring to be used by the individual laboratories preforming the assay
• FISH assessment will utilize an innovative kit that is new to sites, training and education would be needed as well as the sites would have to have the appropriate lab capable to perform and validate the test to the required quality standards in time for the study and provide the results back in the necessary time for enrollment	• Representatives from central lab could provide training on the assay to the sites
	• As a part of the site identification process to investigate the assay turnaround time and how frequently the assay could be run (as needed when suitable patients are visited, in batches, etc.)
	• As a part of the site identification process to investigate the cost of the provision of the kits at the local level and include this cost in the sites contracts
	• Lab kit accountability to be put in place as a part of the monitoring process
• Different turnaround time	• At the Site Selection Visits and Site Initiation Visits to assess the qualification of the lab personnel performing the assay and the quality control they would be using
• Unknown qualification of the lab personnel performing the FISH assays, and the quality control they would be using	• Upfront discussion with the FDA/EMA to obtain feedback with regards to acceptance of test results from the local lab for enrollment of patients
• Reimbursement to be provided	• Retrospective central analysis for cMet amplification to be set-up to analyse how many of the enrolled patients were confirmed to be cMet amplified
• Patients assessed with kits provided for a given trial but then enrolled in other trials	• Protocol to clearly indicate that enrolled patients will be retrospectively analysed at the central laboratory and based on this assessment it can be expected that a certain percentage of enrolled patients will not be confirmed as cMet amplified
• Retrospective central lab analysis will reveal a pool of patients not confirmed as amplified	• Consider the use of Circulating Tumour DNA to determine cMet status to increase the potential number of patients participating in the trial and to reduce the "screening fatigue"
Sites likely to do cMet testing locally are often slower in clinical trial start-up timelines	As a part of the study plan the time required to activate the sites able to perform cMet testing shall be included in the study timelines in order to build a realistic plan.
Inadequate sample amount and quality	Provide alternate plan for patients to have re-biopsy; for patients undergoing the non-standard of care screening biopsy, consider testing the sample with an NGS targeted panel in addition to FISH / IHC to provide value to patients in undergoing the more invasive screening procedure where they will likely be a screen failure.

C. Cost considerations

In addition to the operational aspects, there are several cost drivers which should be taken into account when planning local testing. Figure 1 summarizes the main aspects to be budgeted for. They include the need to purchase the lab kits/reagents and to reimburse the local lab (as this is not a test considered to be standard of care), plus the need to put measures in place to make sure the trial quality is kept under control.

Figure 1: Cost considerations for local cMet testing

Purchase kits and reagents

Lab technician fee

Pathologist fee

Local testing cost consideration

Protocol assay writing

Sites qualification (central lab representative)

Training fee (central lab representative)

D. Solutions

Given the challenges above described, key aspects to be addressed from the operational prospective are summarized in Figure 2 and proposed solutions are explained in the subsequent paragraphs.

Figure 2: cMet trials – Key operational aspects

Analysis of patient pathway

Countries and sites selection

Sites support and engagement

cMet trial delivery

Central lab testing

Innovative approach: Disease focused networks

Operational key aspects
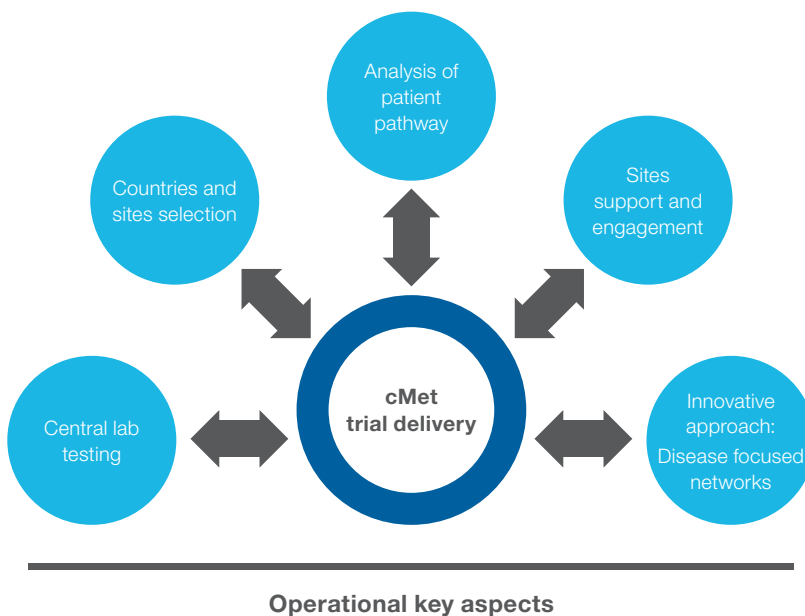
E. Considerations for central lab testing

Lab strategy is of primary importance when planning a cMet trial. The optimal solution to ensure quality of the data and homogeneity across the recruited patients is central lab testing. Use of a central laboratory testing strategy requires strict adherence to sample transport, management and rapid cycle time to not delay patient treatment. A prospective sample management plan is required to ensure high quality and fast sample testing. This may require a central laboratory presence in multiple regions.

In case consideration is given to the use of the local labs, it is important to both put in place the contingency planning described above and to ensure a retrospective patients analysis in batches so that the number of amplified patients is cross-checked at the central level and results are taken into account for the final study analysis. A prospective decision needs to be made regarding how to handle patients where were positive with local testing and negative at the central testing: will data be reporting back to the Investigator? Will the patient continue participation on the trial?

F. Data Integration to inform country / site selection

Careful country/site identification represents the major mechanism by which patient recruitment can be facilitated. Initial country/site recommendations for a given trial should be based on a data-driven process which includes a country algorithm and site tiering based on weighted variables tailored to the success of the specific studies. The first factor to be considered is the indication targeted by that specific trial. Using a variety of data sources, it is possible to develop a preliminary country ranking algorithm for the trial that includes the characteristics and key success factors summarized in Table 4.

Given the specificities of a trial targeting a personalized medicine approach, special consideration shall be given to target those oncology academic centres which do have interest and experience in running these trials, including also their local lab capabilities and interest in patients molecular profiling.

Another important aspect to consider is the competitive landscape; the presence of competing trials can affect the availability of both patients and sites for clinical trial participation. Given the rare incidence of cMet alterations, this is even more important to assess given that ongoing trials are targeting small subset of oncology patients.

For each new protocol being started, it is extremely important to conduct a specific assessment of the competitive landscape through publically available data, taking into account the patient population being targeted. However, it is also important to have a full knowledge of the competitive environment at a given site, so that the site can ensure that it has enough staff and resources to manage all clinical and administrative tasks.

Table 4: Country ranking algorithm data points and source

Data points	Source
Quintiles historical start-up timeline	Quintiles regulatory database
Incidence, mortality and prevalence	GLOBOCAN 2012
Past enrollment rates in similar studies	Quintiles investigator database
Number of experienced investigators	Quintiles investigator database
Quintiles indication experience (overall studies)	Quintiles investigator database
Global indication experience	Biopharm clinical
Number of competing studies	Biopharm clinical
Number of patients targeted by studies recruiting	Biopharm clinical
Impact of competing trials	Biopharm clinical

As indicated in Figure 3, a layered approach is recommended to reduce patient screening costs and recruitment timelines. Quintiles combines the hard data with local knowledge of the site gained from our global team of dedicated Site Network Managers (SNM). Our SNMs are able to provide important information such as investigator excitement with the trial, changes to local staff that may affect recruitment or start-up timelines and local patient treatment pathways to support effective recruitment strategies.

Figure 3: Layered approach to select countries and sites

Data integration to inform country / site selection

Country level incidence of the targeted indication/s

Competitive trial landscape: cMet targeting molecules in the protocol indication/s

Site performance: Recruitment and start-up timelines

On the ground knowledge of site / capabilities

Country level SOC testing

Enrich with known sites cMet / NGS testing

Data driven value add feasibility

Feasibility planning → Assessment of initial interest → Sites in consideration → Final site list

3 month timeline

G. Pre-screening visits and patients pathway

Time and budget impact of the screening process can be minimized by introducing in the protocol a pre-screening process. Patients should be asked to provide their consent to have their available FFPE tissue tested for the cMet amplification or expression, and only the positive patients will undergo the full screening process for the other protocol criteria. As a part of this process, patients that have already been tested and are positive for the cMet can start the protocol screening process. Study budget shall foresee the allocation of a fee to be paid to the sites for this pre-screening visit.

Figure 4: Patient pathway in a cMet clinical trial

cMet Patient Pathway

Targeted tumors

sites non routinely screening for cMet

Oncologist

sites routinely screening for cMet

Pool of identified cMet patients

Subject Identification

Pre-screen consent

Local FISH testing or central lab testing

FFPE tissue

Amplified for cMet 5% patients

Not amplified for cMet 95% patients

Study specific consent

Pre-screen fail

Study screening

Enrolled pats

Screen fail pats

H. Finding the patients

The rare incidence of the cMet amplification needs to be accounted for when planning a cMet trial. Included sites need to be interested in taking part in a trial where a high screening failure is predicted and there must be evidence that they are be able to support the high level of screening required to complete the enrollment. A balance needs to be in place to include a sufficient number of sites and to allocate to each site a sufficient number of patients to motivate them to take part in the trial.

Site Recruitment Action Plans need to be discussed with the sites to understand how they are going to support the high screening rate that is required. Depending on the indication and the stage of the disease being targeted by a protocol, patient options might include:

• Currently on approved treatment for disease

• Currently on another clinical trial for disease

• Newly diagnosed

• Not receiving treatment (recovering from previous therapies, needed/requested treatment interruptions, exhausted all available treatment options)

Depending in which class the patient falls into, investigators can start to pre-screen/pre-identify patients who will then be considered for inclusion in the study, and also start to look at availability of their tumor issue.

I. Engaging and supporting the sites throughout the study

Given all the challenges around the trial targeting the cMet pathway, it is important to provide an ongoing support to the investigators, and to keep them engaged.

As illustrated in Figure 5, patients and sites enrollment strategies should be focused on the following:

- Engaging sites and keeping the study top of mind, through **study branding and site toolkits** that include protocol reference tools for the site staff

- Increasing awareness of the study among the **multidisciplinary care team** (oncologists, pathologists, local laboratories, site staff coordinators) and promoting referrals through **site and "bridging" tools**

- Enhancing and streamlining interaction between the study team and investigators throughout the study duration via a **branded investigator portal**

- **Providing adequate compensation to Investigators** to cover the costs of high volume patient screening

- **Removing barriers for patients participating in protocol screening**; consider providing testing beyond a single biomarker so even screen failure patients will have value from spending limited time and tissue in participation within the screening processes

- **Providing direct to patient study materials** explaining the sample screening process to streamline site staff time during the consent process

Figure 5: Suggested recruitment strategies
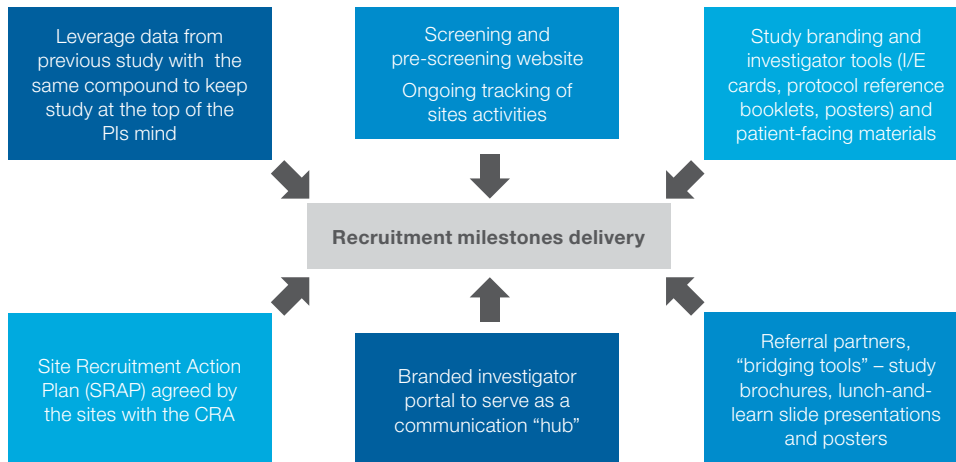
J. Innovative approach: Disease Focused Networks – Pre-profiling

A potential innovative approach that Quintiles has been building over the past 3 years is called Disease Focused Networks – Pre-profiling. This approach sets up a minimal registry for biomarker screening at a large number of sites within a defined disease focused site footprint and then opens the study sites at those locations that actually have a biomarker qualified patient. In this way, the length and risks of recruitment may be significantly decreased. We define Pre-profiling as genomic testing, in the context of a registry protocol, followed by a 14 calendar day start-up, placing the treatment protocol only at sites where biomarker positive patients have been identified. Pre-profiling with rapid start-up of sites enables screening at a large number of sites without the set up costs, risk of non-enrolling sites and long study duration. Quintiles currently uses pre-profiling only in the U.S. There are plans for future geographic expansion. Pre-profiling may be combined with other strategies for use within a global clinical trial.

Quintiles early data and modelling suggest that using pre-profiling for a portion of the U.S. sites on average global trial may result in recruitment timeline savings of 6-20 months depending on the particular indication, prevalence of the biomarker and number of sites opened within the Disease Focused Network. The costs and timelines may be modulated on any given trial to allow for an appropriate balance to be achieved. Pre-profiling is designed to be fully customizable to meet the needs of sponsors, the CDx strategy and drug development strategy.
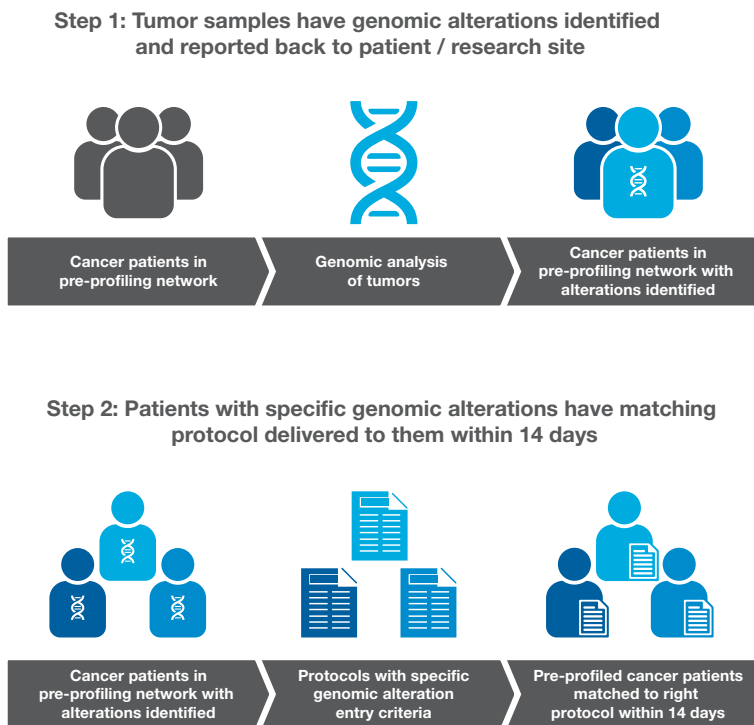
Figure 6: Pre-profiling explanation

Step 1: Tumor samples have genomic alterations identified and reported back to patient / research site

| Cancer patients in pre-profiling network | Genomic analysis of tumors | Cancer patients in pre-profiling network with alterations identified |

Step 2: Patients with specific genomic alterations have matching protocol delivered to them within 14 days

| Cancer patients in pre-profiling network with alterations identified | Protocols with specific genomic alteration entry criteria | Pre-profiled cancer patients matched to right protocol within 14 days |

Figure 7: How pre-profiling works

Genomic testing registry

Patient presents - ICF, patient enrollment sample collection

Genomic testing

Bio informatic analysis

Clinical annotation and reporting

Clinical report

Physician - patient discuss options

Site request start-up within 14 days, ICF signed, patient enrolled in treatment study

Site staff activities of treatment decisions and study initiation

Genomic testing
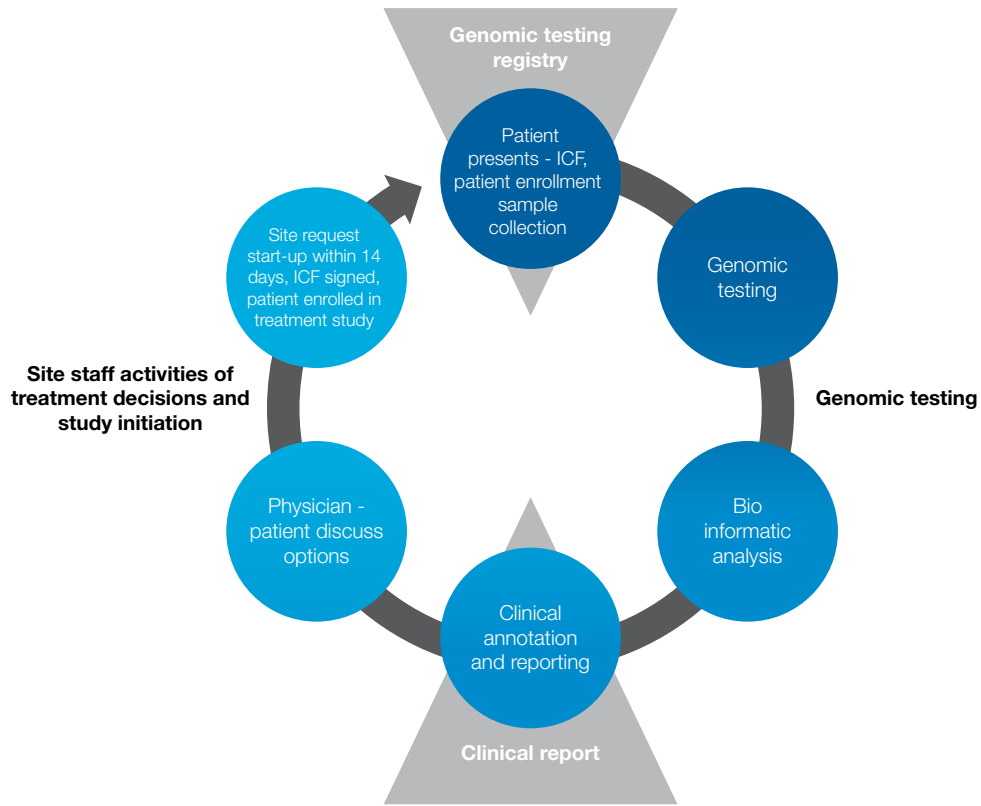
Conclusion

cMet signaling pathway in cancer is an increasingly interesting target in the era of personalized medicine. Additional studies are required and are being planned to determine the clinical efficacy of cMet targeting.

Given the heterogeneous mechanisms underlying cMet dysregulation, there is an urgent and unmet need for the development of predictive biomarkers to identify which subsets of cMet-dependent tumors are most likely to benefit from specific classes of inhibitors. It is therefore important that trials be designed to enable robust retrospective biomarker analysis from both a sample access, banking and consent perspective and a statistical perspective. It is also likely that retrospective subgroup analysis will be crucial for advancing cMet biomarker strategies in the future.

Studies targeting cMet Pathway have to face several challenges which have to be managed for the trials to be successful. Identifying and engaging patients in an appropriate way and enabling research sites to run these studies more efficiently is a real challenge.

Based on the experience in running similar trials, Quintiles' team of Oncology Therapeutic Medical Advisors and Project Lead experts in Oncology can support the sponsor team to make sure the final study design is feasible, can be operationalized efficiently and in line with desired objectives. Quintiles' Translational Medicine team within Quintiles Advisory Services can provide recommendations and support for the clinical, laboratory and biomarker strategies for drug development as well as the development of innovative tools for targeted drugs and companion diagnostics.

In addition to the traditional best practice in planning and managing oncology clinical trials, innovative strategies are being developed and are being implemented which takes into account the specific aspects of the cMet trials. Quintiles Site & Patient Networks Team specific focus is on helping to find niche patient populations. They are challenging the conventional definition of a clinical trial site to enable researchers to operate in a more patient centric approach effectively "taking the study" to the targeted patient.

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10. Adis R&D Insight: Development Status Chart

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