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MAY 30, 2015

Understanding the MET Gene and Receptor Tyrosine Kinase

MGCD265

POTENT MULTI-TARGETED TYROSINE KINASE INHIBITOR OF MET AND AXL

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Understanding the MET Gene and Receptor Tyrosine Kinase

A Potent Driver of Cancer in a Variety of Different Tumor Types and of Resistance to EGFR Inhibitors in Non-Small Cell Lung Cancer (NSCLC)

Extensive research has shown that driver mutations (gene amplification or mutation of the gene) that result in activation of the MET receptor tyrosine kinase (RTK) are associated with a wide range of malignancies including lung, stomach, liver, and kidney cancers.[4]

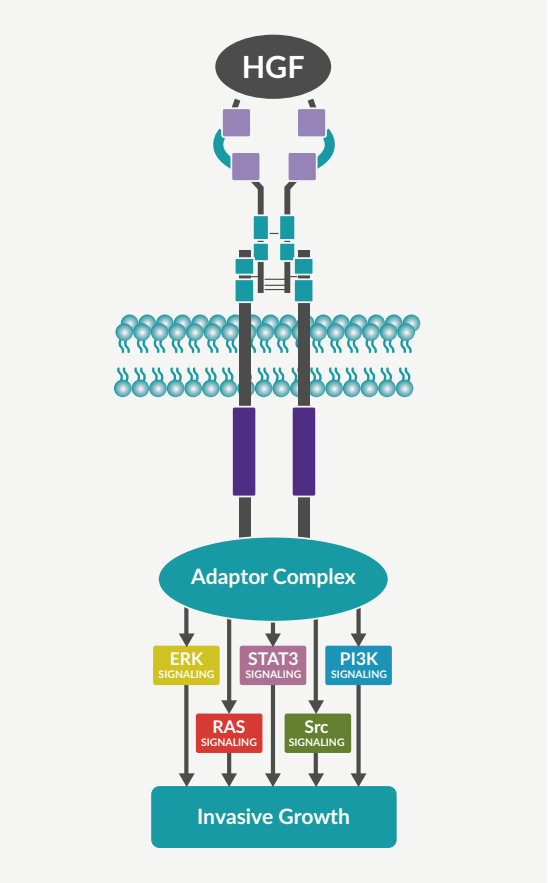
MET's Role in Cancer

The proto-oncogene c-Met (MET or mesenchymal-epithelial transition factor) has been recognized as an important mediator of uncontrolled growth of solid tumors since 1989[5]. Extensive research has shown that driver mutations (gene amplification or mutation of the gene) that result in activation of the MET receptor tyrosine kinase (RTK) are associated with a wide range of malignancies including lung, stomach, liver, and kidney cancers.[4] MET activation, due to mutation or gene amplification, fits the paradigm of "oncogene addiction." This refers to the concept that some tumors rely on one single dominant oncogene for growth and survival, despite the presence of a diverse array of genetic lesions typically present in most human cancers. Inhibition of this dominant oncogene (driver) is sufficient to reverse the neoplastic phenotype and can result in tumor regression.

MET is just one of several RTKs that, when mutated or amplified, can promote tumor growth. In recognition of the role of RTKs in the formation of solid and hematological cancers, molecularly targeted cancer therapies have been developed which inhibit these driver mutations, often resulting in tumor responses and significant clinical benefit for patients. Examples of this can be seen with the dramatic responses of NSCLC patients to Xalkori® (crizotinib) — an oncology therapy targeting ALK fusions — as well as with EGFR inhibitors in lung cancer, the bcr/abl tyrosine inhibitors in chronic myeloid leukemia, and cKit inhibition in patients with gastrointestinal stromal tumors.*

MET is a structurally distinct RTK and is the only known high-affinity cell surface receptor for hepatocyte growth factor (HGF).[4] MET can be activated through ligand-dependent or ligand-independent mechanisms.[12] Binding of HGF to the MET extracellular domain

MET RECEPTOR STRUCTURE AND SIGNALING PATHWAYS



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results in receptor multimerization, phosphorylation, and activation of MET-dependent signal transduction inside the cell.[8, 21] Activation of the MET receptor leads to the activation of downstream signals, including the mitogen-activated protein kinase (ERK/ MAPK) and phosphatidylinositol 3-kinase (PI3K/AKT) pathways, STAT3, and RAS.[8] MET and HGF are normally expressed in numerous tissues and have been shown to be important in the regulation of cell migration, invasion, cell survival, and organization of three-dimensional tubular structures during mammalian development, tissue repair, and homeostasis.[4, 12] Increased MET RTK activity can be caused by mutations of the MET receptor (constitutive activation) or gene amplification that increases receptor expression to very high levels, resulting in ligand-independent activation.[12]

The tumorigenic properties of MET are partly linked to the initiation of epithelial-mesenchymal transition (EMT), a biologic process in which an epithelial cell is transformed into a mesenchymal cell phenotype.[4] This transition is associated with loss of cell adhesion proteins, increased invasion, migration, cell proliferation, and angiogenesis.[1, 6]

MET in NSCLC

MET is highly expressed in NSCLC tumors and higher MET receptor expression rates correlate with advanced stages of tumor progression, and poor clinical outcomes.[19] The correlation of MET protein overexpression with poor prognosis generated interest in the development of MET inhibitors for the treatment of patients with NSCLC. More recent data indicates that MET is a driver of tumor growth when it is genetically altered and activated by point mutations, exon 14 deletions, and gene amplification in a significant fraction (6-7%) of NSCLC patients.[15,18] MET amplification and MET exon 14 deletion mutations were recently identified in a significant number of patients with lung adenocarcinoma in the Cancer Genome Altas consortium project (TCGA-2014a).[3] MET amplification and MET mutations, including exon 14 deletion mutations, each exhibit the key characteristics of driver oncogenes in NSCLC based on three types of data: 1) these mutations are mutually exclusive with other known oncogenic driver mutations[10], 2) nonclinical data demonstrates that tumor models exhibiting these alterations are dependent on MET overexpression for survival,[15] and 3) patients whose tumors have MET gene amplification and MET exon 14 deletion mutations have demonstrated clinical responses when treated with MET inhibitors.[9,14,18,26]

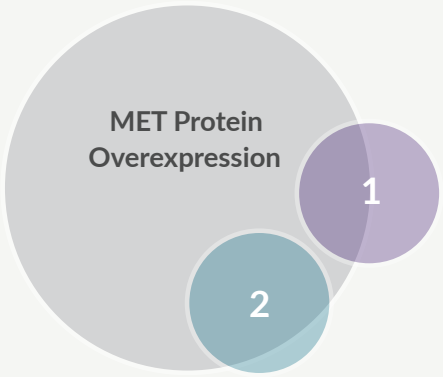
Past Studies of MET Inhibition Yielded Mixed Results

Although the scientific rationale is strong and recent studies have begun to demonstrate clinical responses to MET inhibition in patients with solid tumors, earlier studies with MET inhibitors yielded inconsistent results, likely due to the following factors:

1 SUBOPTIMAL PATIENT SELECTION CRITERIA

Initial patient selection attempts were based on high levels of MET protein expression detected by immunohistochemistry (IHC).[13,16,22] This method picks up a large percentage of patients with NSCLC, including those where MET is not genetically dysregulated, nor a driver. MET protein overexpression, by itself, has not proven to be an effective way to identify patients for treatment with MET inhibitors. In contrast, MET gene amplification is a driver, as evidenced by data in preclinical models[15] and recent clinical data in gastric cancer[11] and NSCLC.[2, 9] While patients with gene amplification also have high levels of MET protein, they make up only a small fraction of the IHC positive tumors. Therefore, a trial in patients based solely on MET protein overexpression, based on IHC, would significantly underestimate the clinical response rate to a MET inhibitor.

OVERLAP OF MET PROTEIN OVEREXPRESSION WITH MET GENE AMPLIFICATIONS & MET GENE MUTATIONS IN NSCLC*



1. MET Gene Mutations: 3.5% of NSCLC population
2. MET Gene Amplification: 3% of NSCLC population

*Diagram is illustrative. Further studies ongoing to characterize the relationship between MET gene amplification and MET protein overexpression.

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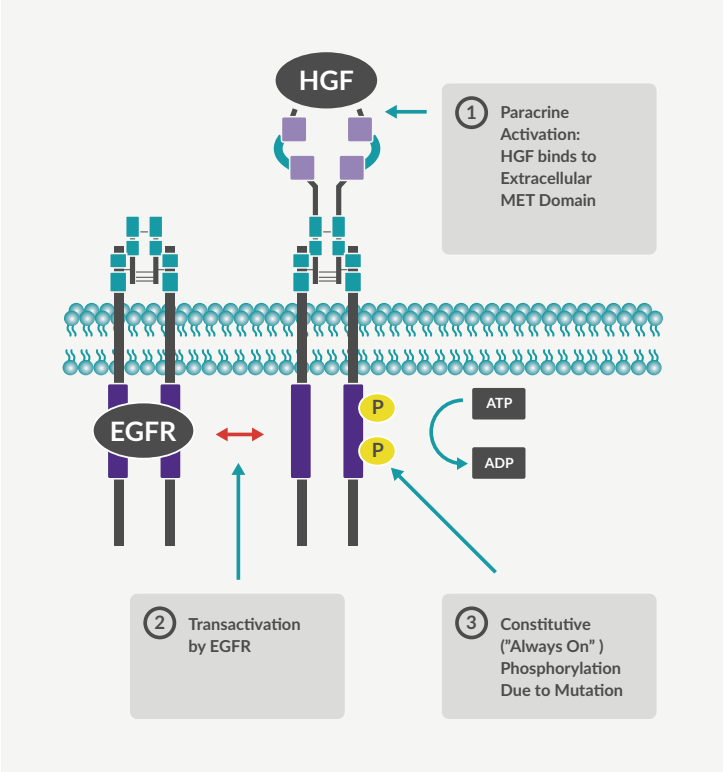
2 FAILURE TO BLOCK LIGAND-INDEPENDENT ACTIVITY

In the case of both MET gene amplification and certain MET mutations, the MET receptor can be activated independent of ligand binding. In such cases, antibody therapeutics that inhibit ligand-dependent activation of MET by blocking HGF binding are predicted to demonstrate minimal antitumor effect.

MET ACTIVATION PATHWAYS



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3 CERTAIN MET MUTATIONS ARE A POTENTIAL SOURCE OF RESISTANCE

Certain MET mutations identified in lung, kidney, and head and neck cancers (e.g., mutations involving D1246, Y1248, or Y1253 residues) are a potential source of intrinsic or acquired resistance to other small molecule inhibitors of the MET receptor tyrosine kinase (Class I; AMG337, INC280 and crizotinib).

The Mirati Development Program for MGCD265 Addresses These Issues

Inhibiting the activity of these drivers with MGCD265 could result in higher response rates, significant clinical benefit, faster clinical development and accelerated regulatory approval.

MGCD265 is the only MET inhibitor targeting MET mutations, MET gene amplification and rearrangements of the Axl tyrosine kinase gene, all of which appear to be drivers of tumor growth. Inhibiting the activity of these drivers with MGCD265 could result in higher response rates, significant clinical benefit, faster clinical development and accelerated regulatory approval.

MET mutations increase MET activity and can function as oncogenic drivers. An important class of MET mutations in NSCLC are exon 14 splice site mutations that result in expression of a MET oncogenic variant that selectively "skips" exon 14 (MET exon 14 deletion). MET exon 14 deletion mutations result in the loss of an important negative regulatory domain which results in receptor activation and tumor formation.[18] The ~3.5% of lung malignancies with these mutations do not have other known driver mutations, suggesting that MET exon 14 deletion mutations are the drivers in this defined NSCLC segment.[17]

MET gene amplification occurs when multiple copies of the gene are present. When tumors have multiple copies of the MET gene the receptors can be cross-activated leading to hyperstimulation and tumor formation. While these tumors also express high levels of the MET protein, MET IHC assays do not have a sufficient dynamic range to identify MET gene amplification-driven overexpression from a larger population of patients that have apparent high levels of MET protein expression, but not amplification of the MET gene. Thus, other assays including FISH and/or targeted Next Generation Sequencing (NGS), are required to identify the ~3% of patients with MET gene amplification.

MGCD265 is an adenosine triphosphate (ATP)-competitive inhibitor of MET and binds to the kinase active site using induced fit and key intramolecular interactions within a deep hydrophobic pocket (i.e., DFG-out conformation).[24] An important feature of the MGCD265 binding conformation is that, as demonstrated,

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it inhibits all the MET mutations tested in enzymatic and cellular screens of selected MET mutant variants.[15] In addition, the long term treatment of patients with MET driven tumors by small molecule inhibitors may select for new mutations that would be more effectively treated with MGCD265 due to its broader inhibitory activity against MET mutations.

In addition to inhibiting MET, MGCD265 also potently inhibits Axl and tumor cells driven by Axl rearrangements. This happens when the Axl gene is fused in the wrong sequence with another gene and results in activation and tumor formation.

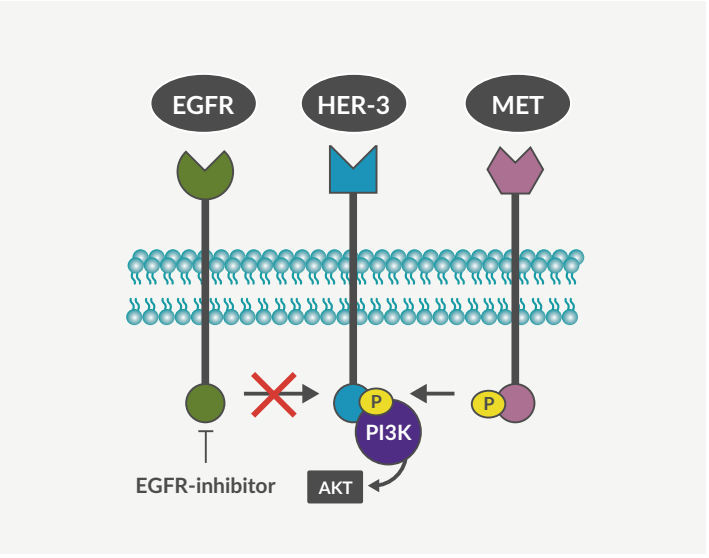
MET Signaling and Resistance to Epidermal Growth Factor Receptor (EGFR) Inhibitors

Extensive preclinical and clinical data indicate that activation of the MET pathway can result in resistance to EGFR inhibitors, such as Tarceva® (erlotinib) and Iressa® (gefitinib), as well as the third-generation EGFR inhibitors that are active against tumors with T790M mutations.[23,] * In a significant fraction of tumors, MET may substitute for, or cooperate with, EGFR to drive tumor growth and progression.[7] MET activation is believed to mediate resistance to EGFR inhibitors by bypassing EGFR dependence and activating downstream signaling.[21] In this setting, MET activation and EGFR mutations function as co-oncogenic drivers.

Research has shown that EGFR kinase inhibitor resistance can be reversed in vivo by combined EGFR and MET inhibition,[23] a finding that validates combination therapy with EGFR and MET inhibitors to address therapeutic resistance.

In addition to MET overexpression, Axl is overexpressed in patients whose tumors are becoming resistant to EGFR inhibitors.[1, 25] Both Axl and MET pathways are associated with the epithelial-to-mesenchymal transition (EMT) process. The inhibition of both pathways may be important for the successful treatment and prevention of resistance to EGFR inhibitors.[29]

MET SIGNALING IN TUMOR CELLS RESISTANT TO AN EGFR INHIBITOR[21]



ADAPTED FROM: Robinson, KW and Sandler AB. "The role of MET receptor tyrosine kinase in non-small cell lung cancer and clinical development of targeted anti-MET agents." The Oncologist 18.2 (2013): 115-122.

Unmet Need in NSCLC

Lung cancer is the most commonly diagnosed cancer worldwide, and remains the leading cause of cancer deaths:[27]

- Approximately 1.8 million people around the world are diagnosed with lung cancer each year, including approximately 220,000 patients in the U.S. annually. 85% of lung cancers are NSCLC
- In the EU, more than 300,000 people are diagnosed annually with lung cancer
- China comprises more than 1/3 of the global lung cancer incident population, with more than 650,000 people diagnosed annually
- Collectively, East Asia (China, Japan, Korea and Mongolia) accounts for the nearly 800,000 people each year who are diagnosed with lung cancer

When mutated or genetically amplified, the MET receptor tyrosine kinase is central to cancer growth, differentiation, and survival and is a "driver" of cancer progression. Mirati is targeting genetic alterations in MET and Axl that have the potential to cause cancer in up to 8% of NSCLC patients. By comparison, ALK translocations targeted by the highly successful receptor tyrosine kinase

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inhibitor, Xalkori® (crizotinib) represent ~4% of the NSCLC patient population, about half as many as MGCD265.

Combining MGCD265 with a third-generation EGFR inhibitor is a significant opportunity for an expanded indication that could potentially prevent or treat resistance to EGFR targeted therapy. Approximately 15% of NSCLC patients in the U.S. and 30% in Asia have EGFR mutations, and the majority of patients treated with EGFR inhibitors eventually become resistant.[20] The combination of MGCD265 with a third-generation EGFR inhibitor could potentially and simultaneously inhibit three targets that mediate EGFR resistance (T790M, MET and Axl) and provide an opportunity to treat a majority of these EGFR-resistant patients.

Mirati's Phase 1/1b expansion study with MGCD265 includes a "basket" cohort. That cohort is enrolling patients whose solid tumors carry MET or Axl alterations of interest, allowing us to study the effects of MGCD265 on other histologies, including head and neck squamous cell carcinoma (HNSCC), gastric, and kidney cancers.

The initial development of MGCD265 will be in patients with NSCLC. However, we are also planning for a possible trial in gastric cancer patients with MET gene amplification, where MGCD265 is expected to result in clinically meaningful responses. We have identified gastric cancer as a primary focus for expanded development because ~5% of gastric cancer patients have MET gene amplification.[8] Annually, gastric cancer strikes about one million patients worldwide and current therapy has limited clinical efficacy:[28]

- More than 20,000 people are diagnosed with gastric cancer in the U.S. annually
- In the EU, more than 80,000 patients are diagnosed with gastric cancer annually
- In Japan (where the incidence is relatively higher), more than 100,000 people are diagnosed with gastric cancer each year
- Collectively, about 550,000, or over half of the world's one million new cases of gastric cancer each year, occurs in Eastern Asia (China, Japan, North Korea, South Korea, Mongolia and Taiwan)

Results from the basket cohort study will determine which other patient populations we will pursue in the MGCD265 program.

A Proven Development Strategy for Molecularly Targeted Oncology Therapies

Mirati's development strategy is based on a regulatory approach validated by the highly successful single arm accelerated approval of Xalkori® (crizotinib), which is regarded by the U.S. Food and Drug Administration (FDA) as, "…a model of efficient drug development in this new era of molecularly targeted oncology therapy." (The Oncologist 2014;19: 1–7). In previous roles, members of the Mirati team helped pioneer development of Xalkori® and its unique regulatory approval approach. Accelerated approval can be granted by FDA on the basis of a surrogate marker (objective response rate) in cases where a treatment demonstrates significant clinical benefit for a serious disease that lacks satisfactory treatment options.

Mirati focuses on discovering and developing cancer therapies that address patient populations based on their genetic or epigenetic profile. Through our targeted oncology research, strong science, and innovative development strategies, our goal is to serve patients with these highly specific genetic profiles.

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Endnotes

1. Byers LA, et al. "An epithelial–mesenchymal transition gene signature predicts resistance to EGFR and PI3K inhibitors and identifies Axl as a therapeutic target for overcoming EGFR inhibitor resistance." Clinical Cancer Research 19.1 (2013): 279-290.
2. Camidge DR, Ou S-H I, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer (NSCLC). J Clin Oncol 32.5s (2014) (suppl; abstr 8001).
3. Cancer Genome Atlas Research Network. "Comprehensive molecular profiling of lung adenocarcinoma." Nature 511.7511 (2014): 543-550.
4. Eder JP, et al. "Novel therapeutic inhibitors of the c-Met signaling pathway in cancer." Clinical Cancer Research 15.7 (2009): 2207-2214.
5. Giordano S, et al. "Tyrosine kinase receptor indistinguishable from the c-met protein." (1989): 155-156.
6. Kalluri R. and Weinberg RA. The basics of epithelial-mesenchymal transition. 2010 J Clin Invest. 2010.
7. Karamouzis MV. "Targeting MET as a strategy to overcome crosstalk-related resistance to EGFR inhibitors." The Lancet Oncology 10.7 (2009): 709-717.
8. Kawakami H, et al. "Targeting MET Amplification as a New Oncogenic Driver." Cancers 6.3 (2014): 1540-1552.
9. Kollmannsberger CK, et al. Phase I study of receptor tyrosine kinase (RTK) inhibitor, MGCD265, in patients (pts) with advanced solid tumors. J Clin Oncol 33:5s, 2015 (suppl; abstr 2589). Full data set presented at ASCO 2015.
10. Kong-Beltran M, et al. "Somatic mutations lead to an oncogenic deletion of met in lung cancer." Cancer Research 66.1 (2006): 283-289.
11. Kwak EL, LoRusso P, et al. Clinical activity of AMG 337, an oral MET kinase inhibitor, in adult patients (pts) with MET-amplified gastroesophageal junction (GEJ), gastric (G), or esophageal (E) cancer. J Clin Oncol 33 (2015) (suppl 3; abstr 1).
12. Landi L. "MET overexpression and gene amplification in NSCLC: a clinical perspective." Lung Cancer: Targets and Therapy 30 (2013): 32. 2013.
13. Ma PC,, et al. c-Met expression/activation, functions, and mutations in non-small cell lung cancer. Proc Am Assoc Cancer Res. (2004) ;44:1875.
14. Mendenhall MA. and Goldman JW. "MET-mutated NSCLC with major response to crizotinib." [letter]. J Thoracic Oncology 10.5 (2015): e33-4.
15. Mirati data on file.
16. Nakamura Y, et al. c-Met activation in lung adenocarcinoma tissues: an immunohistochemical analysis. Cancer Sci. 2007 Jul;98(7):1006-13. Epub 2007 Apr 24.
17. Onozato R. et al. "Activation of MET by gene amplification or by splice mutations deleting the juxtamembrane domain in primary resected lung cancers." Journal of Thoracic Oncology 4.1 (2009): 5-11.
18. Paik PH., et al. "Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping." Cancer Discovery. Published online May 13, 2015. Last accessed May 14, 2015 at http://cancerdiscovery.aacrjournals.org/content/early/2015/05/13/2159-8290.CD-14-1467.abstract
19. Raghav KPH, et al., "Role of HGF/MET axis in resistance of lung cancer to contemporary management." Translational Lung Cancer Research 1.3 (2012): 179-193.
20. Rexer BN, Engelman JA, Arteaga CL. Overcoming resistance to tyrosine kinase inhibitors: Lessons learned from cancer cells treated with EGFR antagonists. Cell cycle (Georgetown, Tex). 2009;8(1):18-22.
21. Robinson KW and Sandler AB. "The role of MET receptor tyrosine kinase in non-small cell lung cancer and clinical development of targeted anti-MET agents." The oncologist 18.2 (2013): 115-122.
22. Spigel DR, et al. Randomized Phase II Trial of Onartuzumab in Combination with Erlotinib in Patients with Advanced Non–Small-Cell Lung Cancer. Journal of Clin Oncol. (2013) 31:32, 4105-4114.
23. Turke AB, et al. "Preexistence and clonal selection of MET amplification in EGFR mutant NSCLC." Cancer cell 17.1 (2010): 77-88.
24. Underiner TL. "Discovery of small molecule c-Met inhibitors: Evolution and profiles of clinical candidates." Anti-Cancer Agents in Medicinal Chemistry 10.1 (2010): 7-27.
25. Walter AO, et al. "Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC." Cancer discovery 3.12 (2013): 1404-1415.
26. Waqar SN and Sehn J. "MET mutation associated with responsiveness to crizotinib" [letter] J Thoracic Oncology 10.5 (2015): e29.
27. WHO GLOBACAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx [select lung].
28. WHO GLOBACAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp AND Rahman R, Asombang AW and Ibdah JA. Characteristics of gastric cancer in Asia. World J Gastroenterol 2014 April 28; 20(16): 4483-4490.
29. Zhang Z, et al. "Activation of the AXL kinase causes resistance to EGFR-targeted therapy in lung cancer." Nature genetics 44.8 (2012): 852-860.

Forward Looking Statements

Certain statements contained in this Backgrounder, other than statements of fact that are independently verifiable at the date hereof, contain "forward-looking" statements, within the meaning of the Private Securities Litigation Reform Act of 1995, that involve significant risks and uncertainties. For more detailed disclosures and discussions regarding such forward looking statements, please refer to Mirati's filings with the U.S. Securities and Exchange Commission ("SEC"), including without limitation Mirati's filings on Forms 10-K, 10-Q, and 8-K. Forward looking statements are based on the current expectations of management and upon what management believes to be reasonable assumptions based on information currently available to it. Such statements can usually be identified by the use of words such as "may," "would," "believe," "intend," "plan," "anticipate," "estimate," "expect," and other similar terminology, or by statements that certain actions, events or results "may" or "would" be taken, occur or be achieved. Such statements include, but are not limited to, statements regarding Mirati's development plans and timelines, potential regulatory actions, expected use of cash resources, the timing and results of clinical trials, and the potential benefits of and markets for Mirati's product candidates. Forward looking statements involve significant risks and uncertainties and are neither a prediction nor a guarantee that future events or circumstances will occur. Such risks include, but are not limited to, potential delays in development timelines or negative clinical trial results, reliance on third parties for development efforts, changes in the competitive landscape, changes in the standard of care, as well as other risks described in Mirati's filings with the SEC. We are including this cautionary note to make applicable, and to take advantage of, the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 for forward-looking statements. The information in this Backgrounder is given as of the date below and Mirati expressly disclaims any obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, unless required by law.

About Mirati Therapeutics

Mirati Therapeutics develops molecularly targeted cancer treatments that are intended to inhibit tumor growth. Mirati's approach combines the three most important factors in oncology drug development, 1) researching and developing drug candidates that target genetic and epigenetic drivers of cancer, 2) designing creative and agile clinical development strategies that select for patients whose tumors are dependent on specific driver alterations, and 3) leveraging a highly accomplished targeted oncology leadership team. The Mirati team uses a blueprint – proven by their prior work – for developing potential breakthrough cancer therapies, with accelerated development paths, in order to improve outcomes for patients. Mirati is advancing three drug candidates through clinical development for multiple oncology indications.

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