

Evaluation of safety and efficacy of tivantinib in the treatment of inoperable or recurrent non-small-cell lung cancer

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Abstract: Tivantinib is a selective, oral, non-ATP-competitive, small molecule inhibitor of the c-Met receptor, tyrosine kinase, which is implicated at different levels of tumor cell migration, invasion, proliferation, and metastasis. Tivantinib has shown antitumor activity in various human tumor cell lines and in xenograft models of human cancers, including non-small-cell lung cancer. Few therapeutic options are available at present for advanced non-small-cell lung cancer, so there is a pressing need for new therapeutic strategies to improve response and survival. Amplification of *Met* has been reported in more than 20% of lung tumors that have acquired resistance to epidermal growth factor receptor inhibitors, implying that treatment of these tumors with a c-Met inhibitor should overcome resistance. Tivantinib has shown interesting and promising results in advanced non-small-cell lung cancer and appears to be well tolerated, either alone or in combination with other drugs. An interesting additional feature is the ability of the drug to delay development of new metastasis, in agreement with the proposed role of Met in this particular setting.

Keywords: non-small-cell lung cancer, Met inhibitors, tivantinib, biomarkers

Management issues in non-small-cell lung cancer

Lung cancer is the leading cause of cancer-related deaths in western countries and is one of the major health problems worldwide, with more than 1.5 million new cases per year.^{1,2} Non-small-cell lung cancer (NSCLC) accounts for more than 80% of lung tumors. The standard first-line treatment for advanced NSCLC is platinum-based doublet chemotherapy, but median survival is still less than one year.³

Increasing knowledge of the molecular pathophysiology of NSCLC has led to the development of new targeted therapies which have somewhat improved survival. The presence of the mutated epidermal growth factor receptor (EGFR) gene in NSCLC is associated with responsiveness to EGFR tyrosine kinase inhibitors (erlotinib, gefitinib) and these are now approved as first-line treatments for patients with *EGFR* mutation.⁴⁻⁷ Encouraging results have been obtained with afatinib, an irreversible EGFR tyrosine kinase inhibitor.⁸ Similarly, patients with tumors harboring anaplastic lymphoma kinase EML4 translocation are sensitive to anaplastic lymphoma kinase inhibitors such as crizotinib, which has demonstrated superiority to chemotherapy in terms of progression-free survival.⁹

However, these substantial improvements in the management of patients with NSCLC are beneficial to only a small percentage of patients (approximately 10% and 4% of total patients with NSCLC of Caucasian origin have alterations in EGFR and anaplastic lymphoma kinase, respectively). The percentage of patients with NSCLC presenting with alterations in EGFR is higher among Asians than Caucasians, and the majority of the remaining cases do not benefit, at best, from targeted therapies. In fact,

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there is recent evidence that anti-EGFR therapy may be inferior to standard chemotherapy as second line in patients with NSCLC and wild-type *EGFR*.¹⁰

In addition, it has to be pointed out that patients initially responding to targeted therapies will eventually develop resistance, hence limiting the potential effectiveness of these treatments. Mechanisms of resistance to targeted therapies include appearance of secondary mutations (both in patients with EGFR and anaplastic lymphoma kinase EML) which are no longer sensitive to selective inhibitors.^{11–14} Another mechanism of resistance is represented by amplification of the *Met* gene.^{15,16} Therefore, new therapeutic strategies are urgently needed for advanced NSCLC.

A study by the National Cancer Institute's Lung Cancer Mutation Consortium indicated that more than 60% of

patients with NSCLC harbor mutations which could affect new therapeutic modalities.¹⁷ *Met* is among the candidates, in view of the evidence discussed above that a certain percentage of resistant tumors show amplification of the *Met* gene and that *Met* is strongly implicated in metastasis.¹⁸ Preclinical evidence further indicates that *Met* is a good candidate target in NSCLC. *Met* expression is found in virtually all NSCLC samples analyzed and in approximately 90% of NSCLC cell lines. Constitutive activation of *Met* has also been observed in clinical samples and cell lines (Figure 1).^{18–22} Two compounds interfering with the *Met* signaling pathway are at present in advanced clinical studies in NSCLC, ie, a monoclonal antibody directed against *Met* (onartuzumab) and tivantinib, a small molecule which is a non-ATP-competitive inhibitor of *Met*.^{21,23}

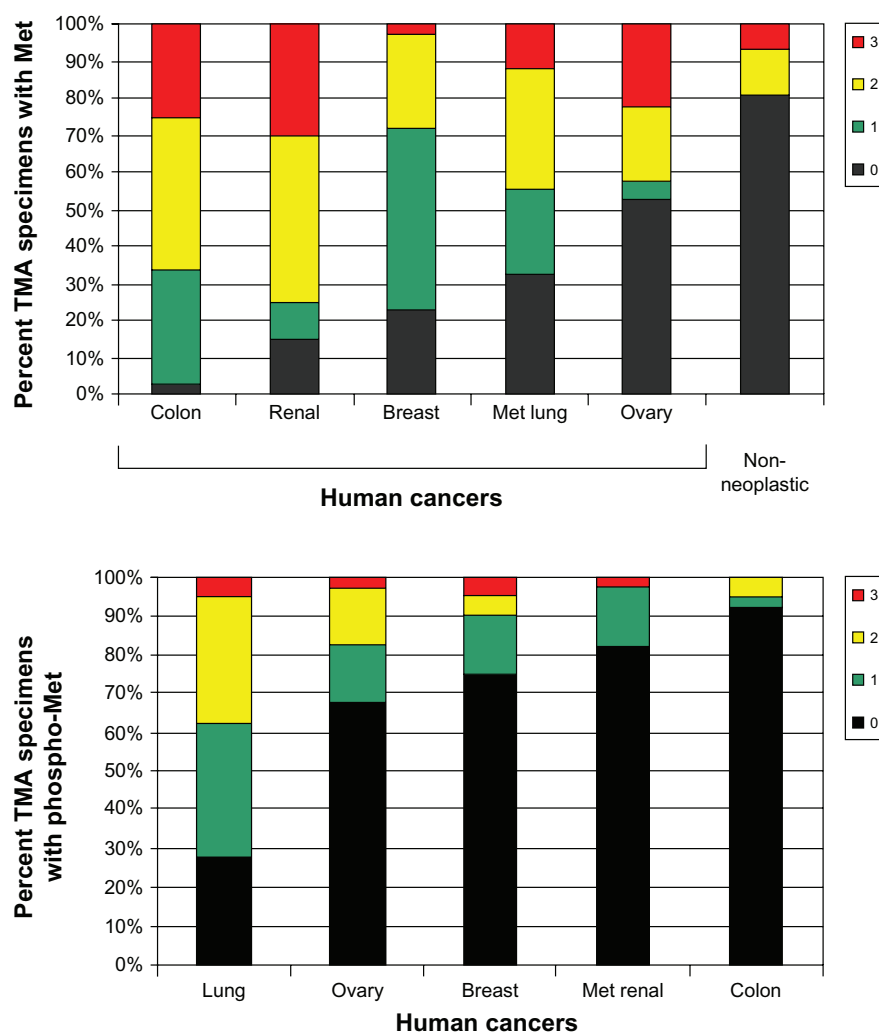


Figure 1 Expression (upper panel determined using a total anti-*Met* antibody) and activation (lower panel, determined using a phosphospecific *Met* antibody) of *Met* in non-small-cell lung cancer and other human tumors.

Notes: The different colors and the corresponding numbers refer to negative (0, black), weak (1, green), moderate (2, yellow), or strong (3, red) staining.

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Abbreviation: TMA, tissue microarray.

Pharmacology, mode of action, pharmacokinetics of tivantinib

Tivantinib is a small molecule, non-ATP-competitive inhibitor of Met (see chemical structure in Figure 2). It has relatively high specificity for Met, with no appreciable inhibition of the activity of 229 other kinases tested.²¹ Tivantinib inhibits Met autoactivation by selectively targeting the inactive form of the kinase.²⁴ This results in inhibition of Met signaling pathways downstream.

Tivantinib has shown activity in several human cancer cell lines grown in vitro. In NSCLC cells, tivantinib showed cytotoxic activity, with concentrations inhibiting cell growth by 50% (IC_{50}) below 1 μ M in cells expressing Met.²¹ In one NSCLC cell line, with confirmed lack of Met expression, the compound had no significant activity, with an $IC_{50} > 30 \mu$ M. The in vitro cytotoxic activity of tivantinib is associated with a decrease in Met phosphorylation and reduced Met signaling downstream. Tivantinib inhibited tumor growth in vivo in immunodeficient mice implanted with human tumors. Given as repeated oral doses, the compound showed antitumor activity at nontoxic doses.²¹

K-RAS mutant NSCLCs are associated with a poor response to classical chemotherapy as well as targeted therapy.^{25–27} Tivantinib showed activity independently from *K-RAS* status. In particular, isogenic NSCLC cells only differing in expression of mutant or wild-type *K-RAS* showed the same response to tivantinib in vitro²¹ (Caiola et al, manuscript in preparation). Finally, in preclinical tests, tivantinib has shown promising antimetastatic effects, inhibiting bone metastasis formation in vivo even at doses with no direct cytotoxic activity.²⁸

The compound is oxidatively metabolized by CYP2C19 and CYP3A4 isozymes of the cytochrome p450 family.²⁹ In preclinical studies, oral bioavailability was found to be higher than 20% in mice and dogs.²⁹ Pharmacokinetic

analysis in Phase I studies indicated linearity, with a half-life ranging from 3 to 6 hours, up to a dose of 400 mg twice a day, where clearance saturation might occur.³⁰ In Phase I studies where the drug was given as monotherapy to patients with NSCLC, tivantinib achieved two partial responses in 47 patients and 16 had disease stabilization.³¹ Phase I studies using the drug in combination with other chemotherapeutic agents indicated that the combinations were generally well tolerated. In a Phase I trial in solid tumors, in which tivantinib was given in combination with gemcitabine, three partial responses were observed in patients with NSCLC.³² Six of eight patients with advanced NSCLC achieved disease stabilization in a Phase I study combining tivantinib and the EGFR inhibitor, erlotinib.³³ Pharmacodynamic investigations performed in Phase I studies indicated a drop in intratumoral c-Met levels and a concomitant decrease in circulating tumor cells (>30%) and endothelial cells (up to 100%).³⁰

Efficacy studies

In a randomized Phase II trial comparing tivantinib plus erlotinib versus placebo plus erlotinib, tivantinib was given orally at a dose of 360 mg twice daily. There were 84 patients in the tivantinib plus erlotinib arm and 83 in the placebo plus erlotinib arm.³⁴ Overall and progression-free survival rates were slightly (albeit not significantly) in favor of tivantinib plus erlotinib, with a median overall survival of 8.5 months for tivantinib plus erlotinib and 6.9 for placebo plus erlotinib. All patients entering the study had, when feasible, molecular analysis including evaluation of *EGFR* and *K-RAS* mutational status and *Met* gene copy number. Subgroup analysis according to molecular and histological characteristics indicated that patients with nonsquamous histology showed a trend in favor of tivantinib plus erlotinib in both overall and progression-free survival. A benefit for tivantinib plus erlotinib was also found for patients with wild-type *EGFR*, mutated *K-RAS*, and *Met* gene copy number greater than 2³⁴ (see Figure 3). Further molecular analysis using immunohistochemistry to detect Met expression, conducted in the same samples, indicated that NSCLC with nonsquamous histology expressed higher levels of Met than squamous ones.³⁵ Progression-free and overall survival rates were better in the tivantinib plus erlotinib arm in patients with high Met expression. It is of note that tivantinib plus erlotinib and placebo plus erlotinib gave similar results for overall and progression-free survival in the Met positive population.

Interestingly, patients in the tivantinib plus erlotinib arm had a significant delay in the development of new metastases, which was again more pronounced in the nonsquamous

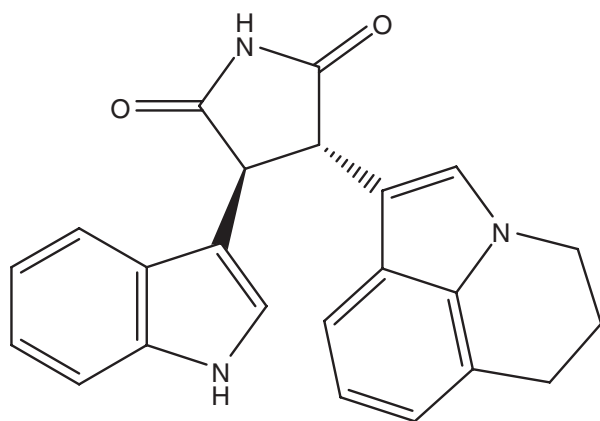


Figure 2 Chemical structure of tivantinib.

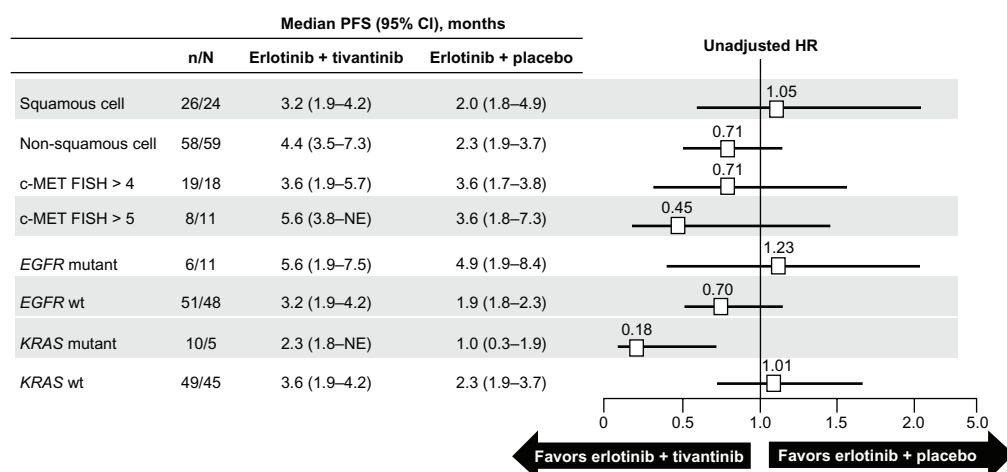


Figure 3 Cox proportional hazard ratio analysis of median progression-free survival by patient subgroup.

Reprinted from Scagliotti GV, Novello S, Schiller JH, et al. Rationale and design of MARQUEE: A Phase III, randomized, double-blind study of tivatinib plus erlotinib versus placebo plus erlotinib in previously treated patients with locally advanced or metastatic, nonsquamous, non-small-cell lung cancer. *Clin Lung Cancer*. 2012;13(5):391–395, with permission from Elsevier.³⁷

Abbreviations: CI, confidence interval; FISH, fluorescence in situ hybridization; HR, hazards ratio; PFS, progression-free survival.

population.³⁴ This clinical evidence is in line with the preclinical antimetastatic activity reported for tivatinib in human models of metastasis developing in immunodeficient mice and suggests a possible additional role for tivatinib for preventing metastasis in early-stage malignancies.^{21,28}

A randomized Phase II study is currently under way comparing erlotinib plus tivatinib versus single agent chemotherapy (gemcitabine, pemetrexed, or docetaxel) in previously treated, advanced, or metastatic patients with NSCLC and mutated *K-RAS*. The primary endpoint is progression-free survival, while secondary endpoints are overall survival, objective response rate in the entire population, and objective response rate “among subjects randomly assigned to chemotherapy who cross over following disease progression to receive erlotinib plus tivatinib and who are evaluable for a post-progression scan on crossover therapy” (clinical trial identifier NCT01395758).

Based on the encouraging Phase II results in NSCLC, a randomized, double-blind, Phase III trial (MARQUEE) is in progress in patients with advanced or metastatic non-squamous NSCLC.^{36,37} The study has overall survival as its primary endpoint, and progression-free survival and overall survival in molecularly defined subgroups as secondary endpoints. All patients entering the study are molecularly profiled and evaluated for *EGFR* and *K-RAS* mutational status and for *Met* amplification and/or expression by immunohistochemistry. Additional planned analysis includes serum circulating hepatocyte growth factor (the ligand of *Met*) levels. The study is designed to detect a 33% improvement in overall survival, requiring approximately 1000 patients

to be enrolled. This number has been reached and the final results are expected in early 2013.

However, a recent press release announced that an independent data monitoring committee recommended the trial should be stopped early following a planned interim analysis because it would not meet the primary endpoint of improved overall survival. Although the interim analysis showed a statistically significant improvement in progression-free survival, this benefit did not translate into a benefit in overall survival. No safety concerns were identified by the data monitoring committee. It will be important to identify in which subgroups the drug had any effect.

Long-term safety and tolerability issues

Cumulative data (including for those reported in patients with NSCLC) from trials incorporating tivatinib as a single agent indicate that the drug is well tolerated. The most common drug-related toxicities are myelotoxicity, including neutropenia and febrile neutropenia, leucopenia, and thrombocytopenia. Fatigue and gastrointestinal toxicities have also been reported.

The combination of tivatinib with erlotinib in patients with NSCLC did not produce any additional toxicities (compared with erlotinib alone).^{33,34} Similarly, the combination of tivatinib and gemcitabine was generally well tolerated.³² Interim analysis of the large (more than 1000 patients enrolled) controlled randomized Phase III trial comparing erlotinib versus erlotinib plus tivatinib did not bring to light any safety concerns, in agreement with the data obtained in early studies using this combination.

Patient-focused perspectives

In clinical trials, tivantinib in association with erlotinib showed superiority over erlotinib plus placebo. An interesting result from these randomized trials is that the combination of tivantinib plus erlotinib significantly delayed the development of new metastatic disease compared with erlotinib plus placebo. This delay was even more pronounced in cases with nonsquamous histology. Although this was not a classical clinical trial endpoint, it could have significant clinical implications, particularly with regard to patient quality of life.

Conclusion

Tivantinib has yielded interesting and promising results in advanced NSCLC. The encouraging results obtained with the monoclonal antibody (onartuzumab) targeting Met, in combination with erlotinib,³⁸ clearly indicate that the strategy of targeting Met in NSCLC is worth pursuing further. Tivantinib is well tolerated either as a single agent or in combination with other agents. This is an additional advantage for patients with advanced NSCLC. The Phase III trials will help to clarify whether subgroups of patients (based on histology, presence of mutations in *K-RAS* or *EGFR*) could particularly benefit from this drug. The indication that Met expression can help in defining patients more likely to respond to tivantinib is an additional advantage when biological material is available for evaluation. Nevertheless, the results obtained so far clearly indicate that tivantinib has no detrimental effects, even in the absence of Met overexpression. This, together with the evidence that tivantinib retains its activity in patients with *K-RAS* mutations (often inducing resistance to chemotherapy and targeted therapies) constitutes an additional advantage for the use of this drug in NSCLC. The sarcomatoid histotype could also be an interesting area for this drug, in considering its elevated Met expression.³⁹ Met plays an important role in metastatic progression. The initial results obtained in advanced NSCLC showing that tivantinib can delay the onset of new metastatic disease are very encouraging. Even if not yet formally proven, addition of tivantinib to other therapies, not necessarily containing erlotinib, should give similar results, thus extending its possible use in combination with other drugs. The results in other malignancies where tivantinib has been combined with other drugs support the good combinability and efficacy of this agent.

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Disclosure

The authors report no conflicts of interest in this work.

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