Editorial Commentary

The combination of osimertinib and savolitinib as molecular inhibition of EGFR and MET receptors may be selected to provide maximum effectiveness and acceptable toxicity

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Lung cancer is the leading cause of cancer-related deaths worldwide (1). Almost 50% of patients receive their initial diagnosis of lung cancer when the disease is already in the advanced stage, with adenocarcinoma being its most common histological subtype. In the case of adenocarcinoma, in approximately 10–20% of patients of Caucasian origin and approximately 50% of patients of Asian origin, genetic tests detect the presence of an activating mutation in the epidermal growth factor receptor (*EGFR*) gene (the most common are Del in ex 19 and the *L858R* substitution in ex 21) (2). In these patients, the use of *EGFR* receptor tyrosine kinase inhibitors (TKIs) is standard.

Currently, most patients in the first line of treatment receive osimertinib (3rd generation of TKI). In the FLAURA study, osimertinib showed superiority over 1st generation *EGFR* TKIs by prolonging both progression-free survival (PFS) and overall survival (OS) (3). Tolerance of treatment was acceptable. However, in almost all patients treated with osimertinib, after various durations of therapy, the disease progresses and the so-called secondary drug resistance both in the on-target mechanism (secondary mutations in the *EGFR* gene) and in the off-target mechanism [activation of alternative signaling pathways or transformation into another tissue, e.g., small cell lung cancer (SCLC)]. Many mechanisms of secondary resistance to *EGFR* TKIs have been described. The most common is amplification/overexpression of the mesenchymal epithelial transition (*MET*) gene, which occurs in approximately 25% of patients treated with 3rd generation TKIs (4).

Currently, ongoing clinical trials focus on overcoming resistance to *EGFR* TKIs in patients after progression, as well as preventing resistance by using combination therapy from the beginning. The idea is to use a drug that blocks the *MET* receptor. Attempts are being made to use blocking antibodies or small molecule inhibitors.

Amivantamab is a bispecific antibody that blocks both the *EGFR* and *MET* receptors. The drug showed effectiveness in the MARIPOSA 2 trial in patients with an activating mutation in the *EGFR* gene previously treated with Osimertinib (5). All patients were eligible regardless of the mechanism of secondary resistance. However, in the MARIPOSA study, amivantamab was evaluated as a first-line therapy (6). The PALOMA trial is currently ongoing,

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enrolling patients after progression while receiving osimertinib and chemotherapy, in whom amivantamab is used in combination with the 3rd generation *EGFR* TKI lazertinib. FDA approved amivantamab for treatment of patients suffering from non-small cell lung cancer (NSCLC) and positive for *EGFR* exon 20 insertion mutation provided that such patients have shown disease progression or have undergone platinum-based chemotherapy.

The second option to overcome secondary resistance to *EGFR* TKIs is the use of small-molecule *MET* receptor TKIs. Currently, we have positive results of mainly phase 1 and 2 trials for three drugs: tepotinib, capmatinib and savolitinib.

Savolitinib is a small molecule, potent and highly selective *MET* tyrosine kinase (*c-MET*) inhibitor (7). Jones *et al.* strived for developing a pharmacokinetic and pharmacodynamic model with a view to linking the inhibition of phosphorylated MET (pMET) with the antitumor activity of savolitinib (8). pMET changes in tumor cells and tumor growth inhibition (TGI) were assessed after 28 days of treatment. Up to a dose of 30 mg/kg, a linear increase in drug activity was observed, but at higher doses, drug activity was higher than proportional and the drug elimination time was prolonged. Savolitinib showed rapid (pMET inhibition was observed practically without delay) high dose-dependent anticancer activity and dosing regimen—administration of lower doses daily was more effective than less effective intermittent regimens, where the drug was administered in a higher dose for 2 days with a 5-day break or for 4 days with a 3-day break. It was also shown that long-term pMET suppression >90% was necessary to achieve TGI and subsequent regression.

The discussed work by Jones *et al.* (9) is a valuable addition to the existing preclinical data on animal models, as it concerns the use of combined treatment with both drugs, osimertinib and savolitinib, in mice transplanted with lung cancer cells with the presence of the *L858R* activating mutation in the *EGFR* gene and amplification of the *MET* gene. The cells were obtained from patients previously treated with erlotinib.

Combining drugs in clinical trials raises difficulties in that it is necessary to select a dose and administration regimen that will have optimal effectiveness along with the best possible tolerability. In order to narrow down the selection options, preclinical experiments can be conducted to help determine the appropriate doses and method of drug administration. The work discussed here links drug exposure with changes in biomarkers that may reflect TGI. The study analyzed how inhibition of pMET and phosphorylated EGFR (pEGFR) translates into antitumor activity in mice with NSCLC with an *EGFR* mutation, with *MET* amplification, which were administered osimertinib in combination with several savolitinib administration regimens. The goal, not unexpectedly, was to ascertain whether a course of savolitinib would show activity against resistance to osimertinib. Additionally, dose ascertainment for savolitinib was performed to obtain maximum benefit. Importantly, in the animal model performed, administration of 0 to 15 mg/kg of savolitinib corresponded to a dose of 0 to 600 mg in humans, while osimertinib administration in the dose of 10 mg/kg corresponded to a dose of 80 mg once daily in humans.

In the main experiment: savolitinib at a dose of 15 mg/kg once daily produced significant antitumor activity (84% TGI), osimertinib at a dose of 10 mg/kg once daily did not demonstrate significant antitumor activity (34% TGI), confirming resistance in the model inhibiting only *EGFR*. The antitumor activity of savolitinib-osimertinib depended to a significant degree on dose selection, with tumor regression reaching 84% and TGI standing at 96%.

Osimertinib administered alone did not inhibit pMET and savolitinib did not inhibit pEGFR. The administration of savolitinib at a dose of 1 or 15 mg/kg resulted in a pMET dose-dependent inhibition. When used alone at a dose of 10 mg/kg, a dose-dependent inhibition of pEGFR was achieved with a maximum inhibition level of 50%. When savolitinib was added to osimertinib the inhibition of pEGFR in a dose-dependent manner was increased with respect to the extent and duration thereof. The administration of a 15 mg/kg dose resulted in an increase of the level of maximal pEGFR inhibition from 50% to ≥90%.

It was verified whether increasing the maximum pEGFR inhibition from 50% without savolitinib to 90% with savolitinib dosage at 15 mg/kg would be equivalent to a nearly complete inhibition of pMET over the entire dose range. A previous *in vitro* study using an osimertinib-resistant lung cancer cell line showed a minimal inhibition of *ErbB3* phosphorylation by osimertinib. However, a complete phosphorylation of *ErbB3* was achieved in combination with the *MET* inhibitor (10). *ErbB3*, likely due to activation of *ErbB3/PI3K* signaling by *MET* amplification, plays a role of a key mediator of *MET*-dependent resistance to *EGFR* inhibitors. *EGFR* and *MET* alike may require dimerization for phosphorylation and activation of receptors; moreover, *EGFR* is capable of

forming homodimers and heterodimers not only with its family members, i.e., *ErbB2* and *ErbB4*, but also with more distant receptor tyrosine kinases, including *MET*, insulin-like growth factor receptor 1, and *Axl* (11). Research has demonstrated that *MET* and *EGFR* interplay may mediate changes in growth control in tumorigenesis (12).

Lastly, the correlation between pEGFR and pMET and antitumor activity was tested using the same model. The suppression of pMET below 80% has minimal effect on pEGFR; however, pMET suppression ≥80% showed a significant effect on pEGFR EC50. In this regard the maximum effect was observed at suppression ≥95%.

What significance do these preclinical study results have for current clinical management? The assumptions of simulations performed using pharmacokinetic models of savolitinib and osimertinib were as follows: a fixed dose of 80 mg of osimertinib in combination with savolitinib at doses from 0 to 600 mg once daily and from 0 to 300 mg twice daily. The level of pMET inhibition over the dosing interval was ≥95% with respect to all doses, whereas the level of pEGFR inhibition grew from 65% without savolitinib to 85% and 90% when administered with savolitinib 50 and 300 mg, respectively.

The goal was for the patient to achieve the criteria of >95% pMET inhibition and >80% pEGFR inhibition during the specified dosage.

- For savolitinib 50 mg once daily, the probability stood at only 25% for pMET and 35% for pEGFR.
- For savolitinib 600 mg once daily, this probability increased to 80% for both pMET and pEGFR.
- For savolitinib at a dose of 50 mg twice daily, the pMET and pEGFR inhibition criteria were achieved in 75% and 85%.
- For savolitinib 300 mg twice daily, the pMET and pEGFR inhibition grew to 95% and 100%, respectively.

When analysing the tested clinical doses, i.e., 300 mg once daily/twice daily or 600 mg once daily, one can be expected that a dose of 300 mg twice daily should provide the best exposure profile necessary to maximize anticancer activity.

The combination of savolitinib and osimertinib is a promising therapy for patients with advanced NSCLC with *EGFRm* and *MET* amplification/overexpression, with disease progression after prior EGFR-TKI treatment. Mechanisms of acquired resistance to this combination include *MET*, *EGFR* and *KRAS*-related mechanisms and ctDNA dynamics during treatment may predict prognosis and aid in earlier clinical decision-making (13).

The key TATTON study is a multi-arm, multi-center, open-label phase Ib study assessing the effectiveness of, among others, osimertinib in combination with savolitinib in patients with NSCLC with an activating mutation in the *EGFR* gene, after disease progression on previous *EGFR* TKI therapy. The study has several phases:

- Part A—osimertinib in a standard dose of 80 mg in combination with savolitinib administered in 2 doses—initially 600, then 800 mg once a day (14);
- Part B/D = expansion phase—due to a better safety profile and comparable effectiveness, it was decided that a dose of savolitinib 600 mg would be administered in this phase (15);
- Due to reported cases of drug hypersensitivity (anaphylactic reactions, anaphylactic shock, fever), it was decided that the dose of savolitinb would depend on body weight: 300 mg for weight <55 kg and 600 mg for others.

Finally, in this study, comparing cohort B with D, it was found that with a lower dose of savolitinib used in combination with osimertinib, the tolerability of the treatment slightly improved while maintaining the activity of the drug. Therefore, it was determined that the recommended dose for savolitinib in combination with osimertinib should be 300 mg administered orally once daily.

In the TATTON study, *MET* amplification was determined using 3 different methods performed in parallel: next generation sequencing (NGS), fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). Unfortunately, there was not full consistency in the detection of *MET* disorders. We do not have data that could clearly indicate the preferred method of assessing *MET* disorders (16). A certain solution is the idea of using at least two methods of assessing the presence of MET amplification in subsequent prospective studies to increase the accuracy and efficiency of diagnostics.

SAVANNAH (17) is a single-arm phase II study in which patients with *EGFRm* NSCLC who had *MET* overexpression and/or amplification following disease progression after osimertinib treatment received oral savolitinib at a dose of 300/600 mg once daily or 300 mg twice daily, in combination with oral osimertinib 80 mg once daily. In the central laboratory, *MET* overexpression was assessed by IHC and *MET* amplification by FISH. Efficacy in the IHC90+ and/or FISH10+ subgroup compared to subgroups without such status was favorable:

objective response ratio (ORR) was 49% *vs.* 9%, median duration of response (DoR) was 9.3 *vs.* 6.9 months, median PFS was 7.1 *vs.* 2.8 months. Therefore, the study confirms the need for appropriate patient selection based on *MET* biomarkers.

SAFFRON (18) is a multicenter, open-label, phase 3, randomized study in patients with locally advanced or metastatic NSCLC, with *EGFRm* (*Ex19del/L858R*) and/or *T790M* and *MET* overexpression and/or amplification confirmed by a central laboratory using IHC or FISH. Patients with disease progression during first or second-line treatment with osimertinib. Randomization will be 1:1 to the following groups:

- Savolitinib at a dose of 300 mg twice a day (i.e., as suggested in the discussed article) + osimertinib 80 mg once a day.
- Intravenously pemetrexed 500 mg/m^2 plus carboplatin or cisplatin (four cycles), then pemetrexed at a maintenance dose of 500 mg/m^2 every three weeks.

The collected material will be used in exploratory analysis to understand the mechanisms of response and resistance to treatment.

Several other studies are currently underway assessing the effectiveness of the combination of osimertinib and savolitinib, both in patients who have progressed while taking osimertinib and in treatment-naive patients. e.g., flowers (19). Also, two other *MET* TKIs showed effectiveness in the discussed indication in combination with osimertinib: tepotinib—INSIGHT 2 study (20) or capmatinib (21).

In conclusion an absolute condition for starting lung cancer treatment is to establish a pathological diagnosis based on the examination of tissue or cellular material, which should be supplemented by the results of immunohistochemical and genetic tests (22,23). In patients with advanced lung cancer, it is recommended to perform multigene profiling based on next generation sequencing due to possible available treatment with new targeted therapies. not only *EGFR*, *ALK* and *ROS1* but also many others (like *BRAF*, *MET*, *RET*, *NTRK*, *HER2*, *KRAS* etc.).

Identification of genes with predictive significance determines the choice of targeted therapy and redefines both the first and also subsequent line of cancer therapy. Combining targeted therapies is important in overcoming primary resistance and preventing secondary resistance to therapies, which translates into improved patients' survival. It is difficult to simultaneous use of targeted therapies due to the high risk of interactions and cumulative toxicity. Preclinical models help to select an appropriate dose that guarantees optimal control of cancer disease while minimizing a risk of side effects.

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