

# ABOUT MET ALTERATIONS IN NON-SMALL CELL LUNG CANCER (NSCLC)

## IMPLICATIONS OF MET DYSREGULATION

The mesenchymal-epithelial transition, or MET, protein is key to normal biologic processes, including embryonic and organ development, tissue repair and wound healing.<sup>1</sup> The MET pathway, however, is susceptible to dysregulation that can drive the growth, survival and spread of NSCLC.<sup>1,2</sup> MET activation is a primary oncogenic driver in lung cancer and a secondary driver that can also confer resistance to anticancer therapies targeting other pathways, such as EGFR tyrosine kinase inhibitors (TKIs).<sup>1</sup>

Types of dysregulation in the MET pathway in NSCLC include exon 14 skipping, amplification, rearrangement fusion and kinase domain mutations.<sup>3,4</sup> Exon 14 skipping and amplification are the most common and are correlated with a poor prognosis for patients.<sup>2,5</sup>

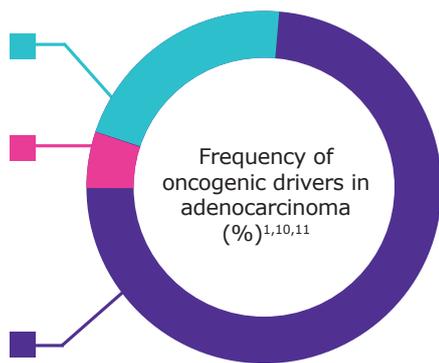
### **MET exon 14 skipping**

Loss of *MET*ex14 through exon skipping leads to increased MET stability and sustained downstream oncogenic signaling activity.<sup>1,2</sup> *MET*ex14 skipping is considered a primary oncogenic driver, as tumors with this alteration generally do not harbor other known oncogenic drivers.<sup>3,4</sup>

### **MET amplification**

Increases in the copy number of the *MET* gene result in increased synthesis of MET compared with normal cells.<sup>1,2</sup> *MET* amplification is implicated as one of the major mechanisms driving EGFR TKI resistance.<sup>1,7</sup> *MET* amplification typically co-occurs with other oncogenic drivers.<sup>1</sup>

## PREVALENCE AND DISEASE CHARACTERISTICS OF MET ALTERATIONS



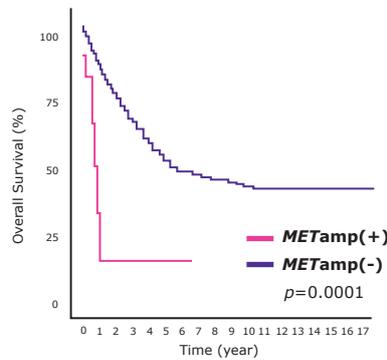
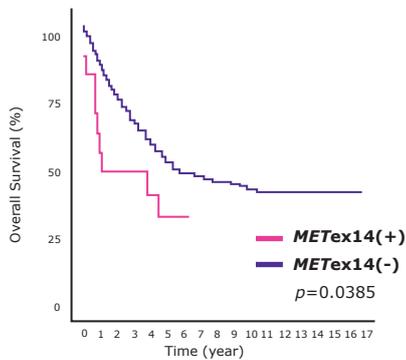
- Wild type for main oncogenic drivers **21%**
- **METex14 skipping** 3-4% mostly >65 years old, female, non-smokers
- **METamp** 1-5%, mostly male, former smokers
- All other driver alterations **73%**

Approximately 73% of patients with NSCLC adenocarcinoma may have an oncogenic driver alteration.<sup>11</sup> The remaining 21% are estimated to be wild type for the main known oncogenic drivers.<sup>11</sup>

*\*Prevalence of gene mutations varies between studies*

*MET*ex14 skipping and *MET* amplification have been identified as oncogenic drivers in 3% to 4% and 1% to 5% of patients with NSCLC, respectively.<sup>1,8</sup> These alterations in the *MET* gene cause aberrant activation of the *MET* pathway, promote tumor growth and metastasis, are associated with aggressive disease and poor prognosis and can drive resistance to other cancer therapies.<sup>1,2</sup>

Patients with *MET* amplification are commonly male, and a majority are current or former smokers.<sup>6</sup> Those with *MET*ex14 skipping are more likely to be female and non-smokers.<sup>9</sup> Patients harboring *MET*ex14 skipping tend to be older (over 65 years) than those with *MET* amplification or other NSCLC driver alterations.<sup>9</sup>



*MET* alterations are more likely to be identified in patients with advanced stage disease.<sup>10</sup>

A multivariate survival analysis assessing overall survival (OS) in patients with *MET*ex14 skipping patients (n=18) or *MET*amp (n=8) NSCLC demonstrated that those with either of these alterations had a significantly shorter OS compared with those without.<sup>6</sup>

## IMPORTANCE OF BIOMARKER TESTING AND BIOPSIES

### Biomarker Testing

Identifying the presence of biomarker alterations in patients with NSCLC, including dysregulation in *MET*, is important, as it supports the selection of appropriate targeted therapy.<sup>12</sup> EMD Serono is committed to researching additional biomarkers related to *MET* dysregulation, so more patients may benefit from targeted therapies.

### Tissue and Liquid Biopsies

Because *MET* alterations are rare and associated with a poor prognosis, biopsies are imperative to diagnosis and treatment determination.<sup>13</sup> *MET* alterations can be identified using either tissue or liquid biopsies.<sup>14</sup> Tissue biopsies are considered the gold standard approach to NSCLC diagnosis, but there is an increasing uptake of noninvasive approaches, like blood-based liquid biopsies, for biomarker testing.<sup>14</sup> Liquid biopsies also offer the opportunity for ongoing monitoring of a patient's disease progression.<sup>14</sup>



### References

1. Drlon A, et al. *J Thorac Oncol.* 2017;12(1):15-26.
2. Wu YL, et al. *Cancer Treat Rev.* 2017;61:70-81.
3. Awad M, et al. *J Clin Oncol.* 2016;34:721-730.
4. Frampton G, et al. *Cancer Discov.* 2015;5:850-859.
5. Wang Q, et al. *J Hematol Oncol.* 2019;12(63):1-11.
6. Tong J, et al. *Clin Cancer Res.* 2016;22:3048-3056.
7. Lai G, et al. *J Clin Oncol.* 2019;37:876-884.
8. Reungwetwattana T, et al. *Lung Cancer.* 2017;103:27-37.
9. Schrock A, et al. *J Thorac Oncol.* 2016;11:1493-1502.
10. Wolf J, et al. EORTC/NCI/AACR 2018. Poster 403.
11. Rosell R, Karachaliou N. *Lancet.* 2016;387:1354-1356.
12. Pruis M, et al. *Lung Cancer.* 2020;140:46-54.
13. Crowley E, et al. *Nat Rev Clin Oncol.* 2013;10:472-484.
14. Saarenheimo J, et al. *Front Oncol.* 2019;9(129):1-11.

## ABOUT EMD SERONO, INC.

**EMD Serono - the biopharmaceutical business of Merck KGaA, Darmstadt, Germany in the U.S. and Canada - is engaged in the discovery, research and development of medicines for patients with difficult to treat diseases.**

The business is committed to transforming lives by developing and delivering meaningful solutions that help address the therapeutic and support needs of individual patients. Building on a proven legacy and deep expertise in neurology, fertility and endocrinology, EMD Serono is developing potential new oncology and immuno-oncology medicines while continuing to explore potential therapeutic options for MS and other immunologic diseases. Today, the business has approximately 1,500 employees around the country with commercial, clinical and research operations based in the company's home state of Massachusetts. [www.emdserono.com](http://www.emdserono.com).

### For media information on request:

Julissa Viana: [julissa.viana@emdserono.com](mailto:julissa.viana@emdserono.com)

Kristin Mulligan: [kristin.mulligan@emdserono.com](mailto:kristin.mulligan@emdserono.com)

US-TEP-00131 © 2020 EMD Serono, Inc. All rights reserved.

**EMD  
SERONO**