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MET in ovarian cancer
Metastasis and resistance?

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Activation of the c-Met receptor promotes intracellular signaling that is often synergistic, complementary, and, at times, redundant to that of other receptor tyrosine kinases (RTKs). It is therefore not surprising that the cellular processes induced by c-Met share many common features with other RTKs, i.e., anti-apoptosis, proliferation, and angiogenesis. However, 2 important phenotypes appear to be more pronounced with activation of this receptor: metastasis and drug resistance, both of which are widely exhibited by ovarian carcinoma.[1] Our current publication investigates both phenomena through the perspective of *MET* nucleotide variations and copy number alterations.[2]

The role of c-Met in migration has long been established as important developmentally within the context of the physiologic epithelial–mesenchymal transition (EMT). An example is early muscle development, where delamination of dermomyotomes produces skeletal muscle progenitors that migrate and form the skeletal musculature. Bladt et al. demonstrated the critical role of c-Met within this process, finding that *MET* ablation results in muscle group absence.[3] Testament to the role c-Met plays in migration and metastasis is that another name for hepatocyte growth factor (HGF), the c-Met ligand, is scatter factor. In addition, not only is general metastatic phenotype promoted by c-Met activation, but also a propensity for liver metastasis has been demonstrated, a phenomenon attributed to this organ's high level of HGF expression.[4] Despite this fact, our recent analysis did not show a higher rate of metastasis sites (both site-specific or otherwise) in ovarian cancer patients exhibiting *MET* alterations. In addition, we could not detect any difference in either *MET* amplification or mutation frequency between primary and metastatic sites. Although this finding does not rule out a significant role for c-Met in the metastatic progression of this cancer type, the contributions of *MET* nucleotide variation and amplification may be overshadowed by other mechanisms, including HGF overexpression, epigenetic *MET* modification, and redundant parallel signaling pathways.

More recently, c-Met has also been established as an alternative pathway implicated in RTK inhibitor resistance. The pioneering work by Engelman et al. was one of the first to demonstrate this phenomenon, reporting the development of gefinitib-resistance in lung cancer as a result of *MET* amplification.[5] Inhibition of c-Met has therefore risen as a promising strategy to combat or prevent therapy resistance. It is therefore encouraging to report that 28% of our cohort exhibited evidence of clinical benefit (either partial response or stable disease lasting ≥6 mo) from phase I c-Met inhibition trials. Perhaps more interesting is the fact that no patients exhibiting *MET* variation or amplification derived clinical benefit. If one could remove these patients who exhibited *MET* nucleotide variation or amplification from this analysis, the rate of clinical benefit would rise to a promising 38%. However, this result should be viewed within the context of numerous caveats, not the least of which is that *MET* variations and amplifications represent a heterogeneous group of alterations with a range of different possible nucleotide changes and even more potential copy numbers. Currently under discussion is the possibility that higher *MET* amplification thresholds may derive greater benefit from c-MET inhibition. It is important to note that none of the ovarian cancer patients in our cohort had a MET/CEP7 amplification ratio above 3. As such, the fact that no patients with *MET* alteration exhibited an objective response must be viewed within this context. Furthermore, genetic variations represent only a limited number of alterations to the HGF/c-MET signaling axis.

Although the prevalence of MET amplification (3.5%) and variations (7.4%) were not high within this cohort, the implications of such alterations are potentially greater then their frequency suggests. Despite the limitation associated with the retrospective nature of these data, interesting hypotheses can be generated with regard to ovarian cancer. For example, what are the major drivers of metastatic behavior within ovarian cancer? What potential biomarkers may predict for c-MET inhibitors? Ultimately, ovarian cancer represents a devastating disease that has seen little in terms of targeted therapy and biomarker development.[1] Our data, although preliminary, suggests that *MET* variations or amplification might not be an ideal biomarker to predict benefit from c-MET inhibition. Correlation of responses with c-MET protein overexpression and, simultaneously, with *MET* amplification ratios could be a way to move forward. Future laboratory studies would do well to elucidate the mechanistic underpinnings of the HGF/c-Met axis within the specific context of

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this disease, while prospective randomized trials should be developed to test the manipulation of this multifaceted surface receptor.

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