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Increase of *MET* gene copy number confers resistance to a monovalent MET antibody and establishes drug dependence

Valentina Martin[a,b], *Simona Corso*[a,b,*], *Paolo M. Comoglio*[a,b], *Silvia Giordano*[a,b,*]

[a]*University of Torino, Department of Oncology, S.P. 142, Km 3.95, 10060 Candiolo, Torino, Italy*
[b]*Candiolo Cancer Institute–FPO, IRCCS, S.P. 142, Km 3.95, 10060 Candiolo, Torino, Italy*

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ABSTRACT

The relevant role in cancer played by the tyrosine kinase receptor encoded by the *MET* oncogene led to the development of specific inhibitors, some of which are now in advanced phases of clinical trials. Previous experience has shown that the main limit to the efficacy of most targeted treatments is the advent of resistance. Mechanisms underlying resistance to MET-specific small tyrosine kinase inhibitors (TKIs) have been already described, while nothing is known about resistance to MET monoclonal antibodies, nor about bypassing resistance to chemical TKIs by antibodies or vice-versa. EBC1 lung cancer cells are MET-addicted as a consequence of gene amplification and thus sensitive to MET inhibitors, including the monovalent form of a MET monoclonal antibody (MV-DN30). We generated cells resistant to this antibody and found that resistance was due to a further increase of gene copy number and a dramatic overexpression of the MET receptor. Such an excess of expression saturated the 'shedding' activity of MV-DN30, and prevented both the efficient down-regulation of the MET receptor from the surface and the inhibition of the ensuing constitutive activation. Notably, antibody-resistant cells remained MET-'addicted' and were still sensitive to MET TKIs. Moreover, antibody-resistant cells became 'drug-dependent', since the removal of MV-DN30 led them to death due to excess of signal. In the mirror experiment, cells made resistant to MET-specific TKIs were still sensitive to treatment with the antibody MV-DN30. These findings suggest that a discontinuous, combined treatment by antibodies and chemical kinase inhibitors may increase the clinical response and bypass resistance to anti-MET targeted therapies.