MET Immunohistochemistry Should Be Avoided in Selecting Non–small-cell Lung Cancers Requiring *MET* Exon 14 Skipping Mutation Analysis

Laetitia Lambros,[1] Arnaud Uguen[1,2]

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To the Editor

Because *MET* exon 14 skipping mutations have been reported as biomarkers predicting response to tyrosine kinase inhibitors, searching for *MET* mutations has become mandatory for treatment choices in patients with non–small-cell lung cancer (NSCLC).[1] *MET* exon 14 skipping mutations occur typically in tumors lacking other molecular alterations in *EGFR*, *KRAS*, *BRAFV600*, *ALK*, and *ROS1* genes.[2] Beyond multiplex testing, using next generation sequencing methods analyzing *MET* with other oncogenes, a multistep diagnostic strategy combining individual gene testing may be chosen by some laboratories, notably for turnaround times and cost-related reasons. In their article, Kim et al have concluded that quantitative real time-polymerase chain reaction can also be appropriate for screening *MET* exon 14 as a single gene testing and can be used to analyze preselected *EGFR*-/*KRAS*-/*BRAFV600*-/*ALK*-/*ROS1*-wild type NSCLC samples.[3] To maximize the detection of *MET* exon 14 skipping mutations in a multistep diagnostic strategy, the place of MET immunohistochemistry (IHC) remains uncertain. In this letter, we report about a study evaluating the interest of adding MET IHC to *EGFR*, *KRAS*, *BRAFV600*, *ALK*, and *ROS1* molecular status in the prescreening of NSCLC samples requiring *MET* mutation analysis.

We led a retrospective study on 1484 NSCLC cases analyzed for *EGFR*, *KRAS*, *BRAF*, *ALK*, *ROS1*, and *MET* molecular testing as well as MET IHC at the Brest Molecular Genetics Platform of Cancer located in the Brest University Hospital from January 2015 to October 2018. Molecular analyses were performed as part of the diagnostic workup using next generation sequencing (*EGFR*, *KRAS*, *BRAF*, and *MET*), IHC, and fluorescence in situ hybridization (*ALK*, *ROS1*) methods. Also integrated in our diagnostic panel, MET IHC (clone SP44) was interpreted as negative (ie, score 0 or 1+ staining) or positive (ie, score 2+ or 3+ staining as the presence of moderate and/or strong staining intensity in at least 50% of tumor cells) using the scoring system used in the MetMAB (onartuzumab) phase II trial (NCT00854308).[4] Comparisons of areas under the receiver operating characteristic curves were used to reflect the ability of different prescreening criteria to select NSCLC samples with *MET* exon 14 skipping mutations. Statistical analyses were performed using MedCalc Statistical Software version 13.2.2 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014). The level of significance was set at $P < .05$.

Among the 1484 NSCLC cases, 174 (11.7%) cases were *EGFR*-mutated, 470 (31.7%) *KRAS*-mutated, 26 (1.8%) *BRAFV600E*-mutated, 39 (2.6%) *ALK*-rearranged, 5 (0.3%) *ROS1*-rearranged, and 21 (1.4%) contained a *MET* exon 14 skipping mutation. About MET IHC, 506 (34.1%) cases were diagnosed MET-IHC negative and 978 (65.9%) were diagnosed MET-IHC positive. Trying to best predict the existence of *MET* exon 14 skipping mutations among NSCLC samples, we have tested the following criteria: MET IHC positive/negative result (criterion #1), the presence/absence of any identified targetable molecular alteration (ie, *EGFR* or *BRAFV600E* mutation or *ALK* or *ROS1* rearrangement, criterion #2), the presence/absence of any identified molecular alteration (ie, *EGFR*, *BRAFV600E*, *ALK*, *ROS1* ones or also *KRAS* mutation, criterion #3), and the combinations of MET IHC result with *EGFR*, *BRAV600*, *KRAS*, *ALK*, and *ROS1* status (criteria #1 + #2 and #1 + #3) (see Table 1 for details). The more performing criteria was the presence/absence of any identified molecular alteration without taking into account the result of MET

[1]Department of Pathology, CHRU Brest, Brest, France
[2]Inserm U1053 BaRITOn, Bordeaux, France

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Table 1 Summary of the Performances and Comparisons of Different Criteria in Predicting *MET* Exon 14 Skipping Mutation Among Non–small-cell Lung Cancer Samples

Criteria	AUROC (95% confidence interval)	Comparisons of AUROC With Criteria, *P*				
		#1	#2	#3	#1 + #2	#1 + #3
Criterion #1: MET IHC positive/negative	0.576 (0.551; 0.602) $P = .0852$	–	.8986	.0179[a]	< .0001[a]	.7939
Criterion #2: *ALK/EGFR/BRAFV600E/ROS1* mutated/wild-type status	0.582 (0.556; 0.607) $P < .0001$[a]	.8986	–	.0010[a]	.0577	.6939
Criterion #3: *ALK/EGFR/BRAFV600E/ROS1/KRAS* mutated/wild-type status	0.691 (0.667; 0.715) $P < .0001$[a]	.0179[a]	.0010[a]	–	≤ .0001[a]	.0038[a]
Criteria #1 + #2	0.595 (0.570; 0.620) $P = .0046$[a]	< .0001[a]	.0577	≤ .0001[a]	–	.1864
Criteria #1 + #3	0.506 (0.481; 0.532) $P = .8710$	.7939	.6939	0038[a]	.1864	–

Abbreviations: AUROC = areas under the receiver operating characteristic curves; IHC = immunohistochemistry.
[a]Indicates results with $P < .05$.

IHC (criterion #3, areas under the receiver operating characteristic of 0.691). Interestingly, to add the result of MET IHC to the presence/absence of any identified molecular alteration statistically diminished the performances of the prescreening strategy (see Table 1 and Figure 1 for details and receiver operating characteristic curves). The sensitivity and the specificity of the prescreening strategy based on the presence/absence of any identified molecular alteration permitted to select samples with *MET* exon 14 skipping mutations with a sensitivity of 90.48% (range, 69.6%-98.8%) and a specificity of 47.64% (range, 45.1%-50.2%) (2 cases had concurrent *KRAS* and *MET* mutations).

To conclude, beyond a typical *EGFR-/KRAS-/BRAFV600-/ALK-/ROS1*-wild type molecular status, MET IHC has no interest in preselecting NSCLC samples that require *MET* exon 14 skipping mutations analysis. Given the limited performances of prescreening methods and potent albeit rare concurrent *MET* mutation and other driver/targetable molecular alteration in one sample, integrating *MET* analysis in a first-line multiplex gene panel analysis could be, as proposed by Kim et al, the most appropriate diagnostic strategy.

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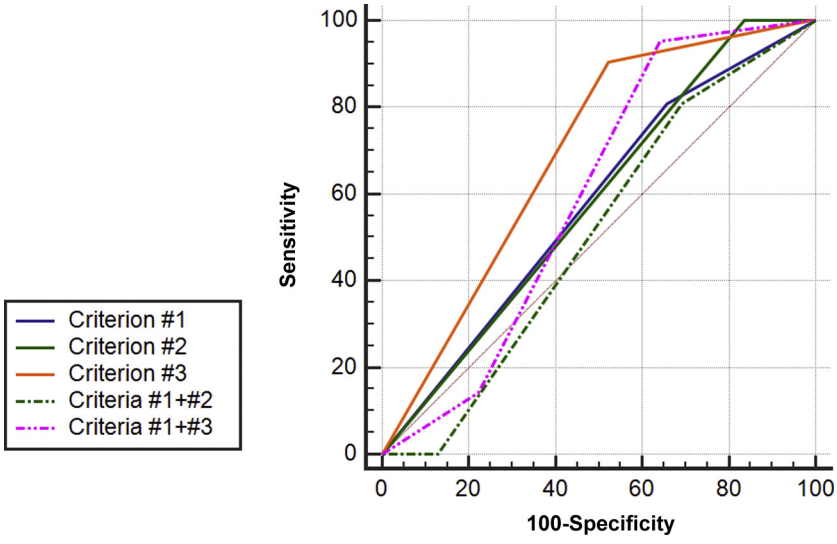
Figure 1 Comparison of the Receiver Operating Characteristic Curves Predicting *MET* Exon 14 Skipping Mutations in Non–small-cell Lung Cancer Samples



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