CheckMate 743 – Invited correspondence

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We thank Massimo Di Maio and Marco Tagliamento for their correspondence regarding CheckMate 743, a global, open-label, randomised, phase 3 study of first-line nivolumab plus ipilimumab versus chemotherapy in unresectable MPM.[1] We appreciate their remarks on the interaction test to investigate heterogeneity across histological subtypes.

We agree that treatment efficacy by histology is of interest and have acknowledged in the manuscript the greater magnitude of benefit observed with nivolumab plus ipilimumab compared with chemotherapy in the non-epithelioid versus epithelioid subgroup. Nivolumab plus ipilimumab performed similarly in both groups (median overall survival was 18.1 and 18.7 months for the non-epithelioid and epithelioid subgroups, respectively), while chemotherapy performed poorly in the non-epithelioid group, as reported previously.[2]

As interaction of treatment by histology was not pre-defined in the statistical analysis plan, we did not formally perform these tests. We agree that forest plots represent subgroup analyses without any correction for multiple analyses. The limitations of providing results of the interaction tests are well established: false positives due to multiple comparisons, false negatives due to inadequate power. Also, as multiple characteristics may vary simultaneously, those results have limited ability to inform individual treatment decisions. Multivariable analyses would be needed to better account for possible confounding of various demographics or disease characteristics.

While the data on novel biomarkers provided by Dr Maio are intriguing, these analyses are derived from small patient numbers and need further assessment. We agree that the tumour immune microenvironment should be further characterised; additional analyses are warranted to evaluate the predictive value of PD-L1 by histology, with sufficient patient numbers whose tumours express PD-L1 along a continuum of levels. Mesothelioma

transcriptomic studies recently suggested that, beyond PD-L1 expression or histological subgrouping, there is substantial heterogeneity based either on histo-molecular continuous gradients,[3] cytotoxic T-cell and T-helper 2 marker expression,[4] or both immune and angiogenic markers expression.[5] It will now be critical to understand the biological basis behind differing outcomes, particularly differing outcomes within the patient group with epithelioid subtype disease.

We reaffirm that this regimen provides a new therapeutic first-line treatment option for all patients with MPM, although further clinical and laboratory investigations to improve outcomes for patients with MPM remain a high priority. Further prospective studies based on biomarkers are needed to decipher optimal treatment sequencing.

Nivolumab plus ipilimumab is now approved in the United States as a first-line treatment for unresectable MPM, regardless of histology.

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2. Pasello G, Zago G, Lunardi F, et al. Malignant pleural mesothelioma immune microenvironment and checkpoint expression: correlation with clinical-pathological features and intratumor heterogeneity over time. *Ann Oncol* 2018; **29:** 1258-65.
3. Blum Y, Meiller C, Quetal L, et al. Dissecting heterogeneity in malignant pleural mesothelioma through histo-molecular gradients for clinical applications. *Nat Commun* 2019; **10**: 1333.
4. Alay A, Cordero D, Hijazo-Pechero S, et al. Integrative transcriptome analysis of malignant pleural mesothelioma reveals a clinically relevant immune-based classification. *J Immunother Cancer* 2021; **9**: e001601.
5. Alcala N, Mangiante L, Le-Stang N, et al. Redefining malignant pleural mesothelioma types as a continuum uncovers immune-vascular interactions. *EBiomedicine* 2019; **48**: 191-202.