ESMO Open Cancer Horizons

In the literature: February 2019

Amelia Insa, Valentina Gambardella, Andrés Cervantes

To cite: Insa A, Gambardella V, Cervantes A. In the literature: February 2019 *ESMO Open* 2019;**4**:e000490. doi:10.1136/esmoopen-2019-000490

Department of Medical Oncology, Biomedical Research Institute INCLIVA, University of Valencia, CIBERONC, Valencia, Spain

Correspondence to
Professor Andrés Cervantes; andres.cervantes@uv.es

INTEGRATIVE MOLECULAR CHARACTERISATION OF MALIGNANT PLEURAL MESOTHELIOMA

Malignant pleural mesothelioma (MPM) is a rare and lethal cancer associated to asbestos exposure. Currently, the pemetrexed and cisplatin combination chemotherapy remains the only approved treatment. In the last 5 years, a growing knowledge on mesothelioma pathobiology has translated into the development of multiple novel therapeutic strategies.[1] One of the largest reports of comprehensive genomic profiling of MPM was conducted by Bueno and colleagues. Using RNA-seq data, they identified four distinct molecular subtypes, and through exome analysis, they found that *BAP1*, *NF2*, *TP53*, *SETD2*, *DDX3X*, *ULK2*, *RYR2*, *CFAP45*, *SETDB1* and *DDX51* were significantly mutated.[2] In an article recently published in *Cancer Discovery*, Hmeljak and colleagues[3] report on a genomic study of 74 MPM samples as part of The Cancer Genome Atlas where they performed a comprehensive molecular profiling, including whole-exome sequencing (WES), copy-number arrays, mRNA sequencing, non-coding RNA expression, DNA methylation and proteomic data.

Some interesting observations derive from their work. Using WES, the authors report a low tumour mutational burden (TMB) with <2 non-synonymous mutations per megabase in all but one sample which places mesothelioma at the low bottom of TMB among cancers. A low TMB may represent a negative predictive biomarker for immunotherapy. However, TMB may have been underestimated as recent studies have revealed that minute deletions are frequent in mesothelioma and are often missed by the approaches used in this study.[4] Moreover, an interesting finding of this work is a strong expression of the immune-checkpoint gen VISTA in epitheloid MPM, on the tumour cells themselves. It remains to be seen if this finding will translate into a valuable clinical target for emerging anti-VISTA therapy.

The authors confirm that, from a genomic standpoint, mesothelioma is characterised by a preponderance of tumour suppressor alterations. Indeed, they find a high frequency of BAP1 inactivation (57%) by mutation and copy number loss, as well as recurrent inactivation alterations in CDKN2A, NF2, TP53, LATS2 and SETD2. Mutations in these five genes did not show association with asbestos exposure or smoking and could be validated in an independent cohort using a different algorithm to define significantly mutated genes. No fusions involving EWSR1 were identified and a low rate of targetable driver mutations in receptor tyrosine kinases (RTKs), MAPK or PI3K signalling pathway genes was observed. In addition to these known loss-of-function events, this study characterises a novel molecular subtype of MPM accounting for 3% of MPM, defined by evidence of genomic near-haploidisation and recurrent TP53 and SETDB1 mutations, with a different clinical phenotype showing female predominance and younger age at diagnosis. No deletions or point mutations in BAP1, PBRM1 or SETD2 were found in this molecular subset.

Although MPM are broadly divided into three histological subtypes (epitheloid, sarcomatoid and biphasic) and this current classification is prognostically useful, there remains variability in patient's outcomes within the histological subtypes. To find out whether molecular profiling may provide additional information to define prognostic subsets, the authors perform integrative clustering across multiple assay platforms using two algorithms: iCluster and PARADIGM. Four different subtypes of MPM were identified. Cluster 1 was found to have the best prognosis and this group was enriched for epitheloid tumours, low rate of mutations and copy-number alterations, relatively few CDKN2A alterations and a high level of methylation and BAP1 alterations. The poor prognostic cluster 4 had a high score for epithelial–mesenchymal transition based on gene expression, low expression of mesothelin, enrichment for LATS2 mutations, upregulation of the PI3K and mTOR signalling pathways, and a high rate of CDKN2A homozygous deletions and AURKA mRNA expression. These results were reproducible in samples from other cohorts and they were highly similar when the analysis was restricted to the epitheloid-only subset. This

work provides a deeper analysis of histology-independent molecular prognostic subsets of MPM. A rationale for potentially novel therapies including immune-checkpoint anti-VISTA or inhibition of PARP, aurora kinase or EZH2 among other agents is suggested by the authors and by an accompanying editorial.[5]

LINK BETWEEN THE MULTIVERSE OF IMMUNE MICROENVIRONMENTS IN METASTASES AND SURVIVAL OF PATIENTS WITH COLORECTAL CANCER

During the last years, a significant improvement of clinical outcomes has been observed in patients with advanced colorectal cancer. Nevertheless, their medical treatment is still based on the assumption that metastases are homogeneous within a patient, which is certainly not the case. In an elegant article published in *Cancer Cell*, van den Eynde *et al*[6] analysed the differences in immune infiltration between primary tumours and their metastasis in 222 patients diagnosed with advanced colorectal cancer, stressing the need of properly assessing tumour immune microenvironment to predict risk of relapse. The fundamental role of cytotoxic and memory T lymphocytes in predicting survival was already demonstrated in localised disease by the same authors in previous articles.[7 8]

To better clarify that point, both primary tumours and metastatic lesions were studied, observing that primary lesions, and synchronous and metachronous metastases, had a heterogeneous immune infiltrate and mutational diversity. Notably, the study identified the association between elevated T-cell infiltration and lower number of metastases, most likely reflecting sustained adaptive immune pressure on tumour development and spreading.[9] Possibly due to the same phenomenon, T-cell cold metastases are more numerous and associated with worse prognosis. A mutational analysis was also performed. Mutations were found in 13 out of 50 cancer genes including PIK3CA, APC, TP53 and KRAS, and differed between primary tumours and metastases. RAS mutated patients had significantly less intrametastatic immune infiltrates than wild-type lesions.

The unsupervised clustering of mutational data revealed two main groups of metastatic lesions and primary tumours that had a different immune infiltrate and immunoscore, in particular the presence of germline variant of KDR (Q472H) and PIK3CA mutation (I391M) and had a higher $CD8^+$ lymphocyte infiltrate and immunoscore. The role of different treatments in changing immune infiltrates and microenviroment was also evaluated. It was possible to observe that anti-epidermal growth factor receptor (EGFR) antibodies modified immune gene expression by a larger extent and significantly increased CD8 infiltrates in the metastasis core. This effect was not observed with chemotherapy alone or anti-vascular endothelial growth factor antibodies. The authors suggest that the proinflammatory side effects, such as skin rash and increased EGFR-specific cytotoxic T-lymphocyte frequency, during anti-EGFR treatment, implies that EGFR may function as an immunogenic protein. The prognostic value of $CD8^+$ T-cell infiltration regarding progression-free survival and overall survival in metastases, although lower than in primary tumours, is still significant.

In conclusion, it was possible to observe that the predictive accuracy of the immunoscore from a single biopsy was superior to the PD-L1 evaluation. Cytotoxic T lymphocytes infiltrating metastases are positively associated with long-term survival of advanced patients. The immune phenotype of the least-infiltrated metastasis had a stronger association with better patient outcome than other metastases with higher lymphocyte infiltration. Therefore, metastasis with the lowest immune infiltration represented the worse prognostic indicator for patient tumour relapse, survival and progression-free survival (HR >2, $p<0.05$).

AURORA KINASE A IS RESPONSIBLE OF RESISTANCE TO THIRD-GENERATION ANTI-EGFR INHIBITORS IN LUNG CANCER

The use of EGFR tyrosine kinase inhibitors in EGFR mutant non-small cell lung cancer has been one of the major advances derived from precision oncology. The development of third-generation compounds such as osimertinib is able to induce prolonged responses even in tumours bearing the T790M mutation, which made tumours resistant to first-generation inhibitors. However, despite a deep initial effect, drug resistance emerges as the main limitation for the use of these drugs.

A group of investigators of the University of California San Francisco have modelled on how resistance to third-generation anti-EGFR tyrosine kinase agents may develop. In an extensive set of experiments with cell lines, xenografts and patient samples, they try to decipher how those complex mechanisms can be better understood.[10] Their main finding is a synthetic lethal interaction between these drugs and Aurora kinase inhibitors in acquired resistant cells. This observation may imply a role for the development of new treatment strategies aimed at preventing rather than overcoming acquired resistance.

TPX2 emerges during chronic EGFR inhibition where it mitigates drug-induced apoptosis. Aurora kinase inhibitors suppress this adaptive survival programme, increasing the magnitude and duration of EGFR inhibitor response in preclinical models. On the other hand, their findings also suggest that TPX2 overexpression could be used as a biomarker to select patients for combination therapy with an EGFR TKI and an Aurora kinase inhibitor in EGFR-mutant lung adenocarcinoma. In fact, a combination of osimertinib with an Aurora kinase inhibitor (MLN8237, alisertib) induces apoptosis and acts synergistically in suppressing the growth of acquired resistant cells in vitro and in vivo.

These data suggest that the combination of anti-EGFR tyrosine kinase inhibitors and Aurora kinase inhibitors administered simultaneously or sequentially at the time of residual disease may be an effective way to enhance the

initial response and prevent acquired resistance. Aurora kinase A activation might co-occur with other factors driving resistance or could even provide a mechanism on which such resistance causing mutations could appear, giving rise to multiple genetically distinct clones. Moreover, it appears that this activation is also associated with a number of apparently disparate mechanisms of acquired resistance, deserving further investigation. These results need to be confirmed in properly designed clinical trials testing the combination of Aurora kinase and EGFR inhibitors in EGFR-mutant lung adenocarcinoma, up front, at the point of residual disease and after acquired resistance in tumours harbouring high levels of TPX2.

Contributors All authors contributed equally.

Funding This work has been supported by the Ministerio de Economía y Competitividad. Instituto de Salud Carlos III with a grant to AC FIS PI18/001909. VG has a Rio-Hortega contract CM18 and was a recipient of an ESMO translational research fellowship.

Competing interests AC declares institutional research funding from Genentech, Merck Serono, BMS, MSD, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astellas and Fibrogen and advisory board or speaker fees from Merck Serono, Roche, Servier, Takeda and Astellas in the last 5 years. AI and VG declare no conflict of interest.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

1. Yap TA, Aerts JG, Popat S, *et al*. Novel insights into mesothelioma biology and implications for therapy. *Nat Rev Cancer* 2017;17:475–88.
2. Bueno R, Stawiski EW, Goldstein LD, *et al*. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet* 2016;48:407–16.
3. Hmeljak J, Sanchez-Vega F, Hoadley KA, *et al*. Integrative molecular characterization of malignant pleural mesothelioma. *Cancer Discov* 2018;8:1548–65.
4. Tsao AS, Lindwasser OW, Adjei AA, *et al*. Current and future management of malignant mesothelioma: a consensus report from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. *J Thorac Oncol* 2018;13:1655–67.
5. Aggarwal C, Albelda SM. Molecular characterization of malignant mesothelioma: time for new targets? *Cancer Discov* 2018;8:1508–10.
6. Van den Eynde M, Mlecnik B, Bindea G, *et al*. The link between the multiverse of immune microenvironments in metastases and the survival of colorectal cancer patients. *Cancer Cell* 2018;34:1012–26.
7. Galon J, Mlecnik B, Bindea G, *et al*. Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. *J Pathol* 2014;232:199–209.
8. Galon J, Pagès F, Marincola FM, *et al*. The immune score as a new possible approach for the classification of cancer. *J Transl Med* 2012;10.
9. de Andrea CE, Schalper KA, Sanmamed MF, *et al*. Immunodivergence in metastatic colorectal cancer. *Cancer Cell* 2018;34:876–8.
10. Shah KN, Bhatt R, Rotow J, *et al*. Aurora kinase A drives the evolution of resistance to third-generation EGFR inhibitors in lung cancer. *Nat Med* 2019;25:111–8.