ESMO Open Cancer Horizons

In the literature: April 2019

Gema Bruxiola, Juan-Miguel Cejalvo, Valentina Gambardella, Andrés Cervantes

To cite: Bruxiola G, Cejalvo J-M, Gambardella V, *et al*. In the literature: April 2019 *ESMO Open* 2019;**4**:e000513. doi:10.1136/esmoopen-2019-000513

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

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

NEW HORIZONS IN THE TREATMENT OF GLIOBLASTOMA: THE ERA OF IMMUNOTHERAPY HAS ARRIVED

Glioblastoma (GBM) remains an unmet need in Medical Oncology considering its poor prognosis and the lack of advances in therapeutics in more than one decade.[1] Despite the initial enthusiasm, the development of immunotherapy in GBM has proved to be challenging, with a disappointing negative phase III clinical trial.[2] Some of the phenotypic hallmarks of GBM make immunotherapy difficult. Its relatively low mutational load, its immunologically 'cold' microenvironment with scarce infiltrating immune effector cells, a dominant myeloid compartment composed by microglia and myeloid-derived suppressor cells and a strong immunosuppression, both local, mediated by immunosuppressive regulatory T cells and a plethora of GBM secreted cytokines, and systemic, with severe lymphopenia related with standard first-line treatment and the use of dexamethasone.

Three publications in a recent issue of *Nature Medicine* show some steps to overcome these limitations, including a comprehensive characterisation of the immune landscape and genomics of GBM patients exposed to checkpoint inhibitors,[3] as well as neoadjuvant treatment in two small trials with a strong translational research component.[4 5]

In the first article, leaded by investigators of the Columbia University, a retrospective series of 66 recurrent GBM patients treated with checkpoint inhibitors (nivolumab or pembrolizumab) were extensively profiled, analysing 58 whole exomes and 38 transcriptomes from longitudinal tumour-matched blood normal samples for 17 patients and incorporating the results from a cancer gene panel of 39 patients. They identified 17 long-term responders, defining response by at least one of the following two criteria: (1) tissue sampled during surgery after PD-1 therapy mostly showed only an inflammatory response and very few or no tumour cells, or (2) tumour volumes by MRI were either stable or shrinking continually over at least 6 months. Response to the PD1 inhibitors was found to be significantly associated with overall survival (OS). Median OS was 14.3 months for responders compared with 10.1 months of non-responders. With regard to the genomic and transcriptomic analysis, an enrichment of MAPK pathway alterations (PTPN11, BRAF) were detected in responders, whereas in non-responders a significant enrichment of PTEN mutations associated with immunosuppressive expression signatures by RNA sequencing was observed. These results are consistent with observations in other tumours like melanoma, where PTEN loss was associated with reduced immune infiltration and resistance to PD-1 inhibition. Furthermore, responsive and non-responsive tumours exhibited a distinct pattern of evolution, with non-responding tumours following a classic linear model with higher fraction of mutations exclusively after therapy, whereas responding tumour showed a branched model with clonal alterations in the pre-anti-PD-1 determination, and absence of the dominant clone after therapy. These findings support the role of the immune system in the negative selection of clones containing immunogenic neopitopes. In addition, non-responders had a greater clonal diversity among T cells compared with responders. In summary, this retrospective study showed that a comprehensive molecular approach could help in stratifying GBM into responders and non-responders to PD-1 inhibition From this rational basis, prospective studies are required to validate their potential utility as biomarkers for precision GBM immunotherapy.

The second paper described a multi-institutional, randomised, open-label pilot trial conducted by the Ivy Consortium to evaluate immune responses and survival following neoadjuvant and/or adjuvant therapy with pembrolizumab in 35 patients with recurrent surgically resectable GBM enrolled between October 2016 and September 2017. In all, 16 patients were randomised into the neoadjuvant group and 19 into the adjuvant-only group. In all patients, authors performed T-cell receptor sequencing, gene expression profiling, mass cytometry and quantitative multiplex immunofluorescence

to explore the intratumoral immune consequences of the administration of checkpoint inhibitors and to identify potential biomarkers of response. From the perspective of clinical outcomes, it is worth noting that neoadjuvant pembrolizumab has demonstrated for the first time a significant improvement on OS, with a HR of 0.39 compared with the adjuvant-only arm with a good toxicity profile. On the other hand, from the point of view of the translational essays, neoadjuvant PD-1 inhibition was associated with upregulation of T-cell-related and interferon-γ-related gene expression, but downregulation of cell-cycle-related gene expression within the tumour, which was not observed in patients that received adjuvant therapy alone. In addition, focal induction of PDL1 in the tumour microenvironment, enhanced clonal expansion of T cells, decreased PD-1 expression on peripheral blood T cells and a decreasing monocytic population was detected more frequently in the neoadjuvant group than in patients treated only in the adjuvant setting. Taking into consideration the promising results of survival together with the elegant findings of the immune landscape modulation, we agree with authors that neoadjuvant pembrolizumab stimulates both the local and systemic antitumor immune response and may represent a more appealing approach for the development of GBM immunotherapy.

In the same way, researchers from Yale School of Medicine and the University of Navarra conducted a single-arm phase II clinical trial to explore the feasibility, safety and immunobiological effects of PD-1 inhibition in 30 patients with resectable GBM, who received a presurgical dose of nivolumab followed by adjuvant nivolumab until disease progression or unacceptable toxicity. Despite the absence of significant clinical benefit after salvage surgery, it is worth to note that two of the three patients treated with nivolumab before and after primary surgery remain alive 33 and 28 months later, with no relevant toxicity. With regard to translational studies, the availability of tumour tissue pre-nivolumab and post-nivolumab dosing allowed the assessment of immunomodulation in the tumour microenvironment by performing multiple molecular and cellular analyses. An increased expression of chemokine transcripts, higher immune cell infiltrations and enhanced TCR clonal diversity in tumour-infiltrating T lymphocytes was observed, with a local immunomodulatory effect of PD-1 blockade. Neoadjuvant nivolumab may be a promising approach in GBM, but we need to maximise the clinical benefit of this therapeutic strategy. The authors suggest exploring combinations either with other immune-checkpoints inhibitors such as anti-CTLA4 monclonal antibodies, or tumour vaccines, oncolytic viruses, adoptive T-cell therapy with CART cells, or antagonist agents for immunosuppressive myeloid cells.

Taken together, these three papers provide a strong rationale to keep working on immunotherapy for GBM patients. It has been shown that the neoadjuvant setting could be an optimal scenario to boost immune responses. In addition, clues have been given for the development of biomarkers that will improve the selection of patients and have stablished the basis for combinations to further improve clinical outcomes.

TDM1 IMPROVES OUTCOMES OVER TRASTUZUMAB IN HER2 AMPLIFIED EARLY BREAST CANCER PATIENTS RECEIVING NEOADJUVANT TREATMENT AND SHOWING PERSISTENT RESIDUAL DISEASE IN THEIR PATHOLOGICAL ASSESSMENT AFTER SURGERY

Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a microtubule inhibitor. T-DM1 has been approved for HER2-positive metastatic breast cancer patients who had progressed on a taxane and HER2-directed regimens. This new anti-HER2 drug showed in two phase III trials a significant improvement in terms of progression-free survival and OS with less toxicity as compared with capecitabine plus lapatinib or treatment of the physician's choice.[6 7] These findings leaded the approval of T-DM1 for patients with HER2 amplified metastatic breast cancer, after progression to trastuzumab plus taxane.

The role of T-DM1 in early HER2 amplified breast cancer has been recently described in an article published in the *New England Journal of Medicine*.[8] This phase III trial randomised adjuvant trastuzumab versus T-DM1 in HER2 amplified early breast cancer patients who presented residual invasive tumour in the breast or axilla at surgery after preoperative taxane-based chemotherapy with trastuzumab. This group of patients is characterised by worse prognosis and indicates partially resistant to trastuzumab. Residual disease after neoadjuvant treatment provides a valuable opportunity to explore predictive biomarkers to novel drugs.

The study showed that patients who received TDM-1 had a much lower risk of breast cancer recurrence or death than those who continued to receive trastuzumab. At 3 years, invasive disease-free survival rate was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group. Distant recurrence as the first invasive-disease event occurred in 10.5% of patients treated with T-DM1 and 15.9% in trastuzumab arm. The risk of distant recurrence was 40% lower in the T-DM1 than in the trastuzumab group. Additional follow-up will be necessary to evaluate the effect of T-DM1 on OS.

This benefit was consistent across subgroups analysis, irrespective of hormone–receptor status, the burden of residual disease at surgery, operable or inoperable disease at presentation, the pathological nodal status and single or dual HER2 blockade. However, recurrence in the central nervous system remains a persistent problem in both arms. Finally, safety profile of T-DM1 was in line with the known toxicities, with some expected increase in manageable adverse events associated with T-DM1 compared with adjuvant trastuzumab. According to the presented

results, adjuvant T-DM1 should be a new standard of care in patients with residual invasive HER2 amplified breast cancer following neoadyuvant therapy. Moreover, this clinical trial demonstrates that neoadjuvant therapy can identify patients at increased risk for recurrence based on the pathological response achieved. HER2 amplified breast cancer patients with residual disease after neoadjuvant chemotherapy plus trastuzumab can significantly benefit by switching to T-DM1 after surgery.

OVERCOMING RESISTANCE TO DUAL INNATE IMMUNE AND MEK INHIBITION DOWNSTREAM OF KRAS

KRAS is one of the most relevant driving oncogenes in solid tumours and, when constitutively activated by mutation, it confers resistance to many targeted agents. Up to now, effective treatment for oncogenic *KRAS*-driven malignancies have not been yet identified. Despite the theoretical benefit in overcoming RAS constitutive activation, the inhibition of MAPK and PI3K downstream effectors was not active in *KRAS* mutant patients with non-small-cell lung cancer (NSCLC).[9] RAS also activates RAL-GDS, which activates RALB and TBK1, inducing the secretion of interleukin 6 (IL-6) and CCL5, promoting cancer cell survival via the STAT3 and NF-kB pathways.[10] In NSCLC models, the MEK inhibitor selumetinib induces IL-6/STAT3 activation, which contributes to drug resistance,[11] whereas TBK1 inhibition rapidly induces MEK/ERK activation, confirming the relationship between the immune system and MEK providing a strong rationale for treatment combination.[12]

An article exploring the relation between MAPK signalling and the innate immune system in *KRAS*-mutated NSCLC was recently published in *Cancer Cell*.[13] Despite some initial efficacy in genetically engineered mouse models (GEMMs) with *KRAS* mutant lung cancer, momelotinib, a TBK1/JAK inhibitor, and trametinib, a MEK inhibitor, failed in achieving durable response. It was confirmed that in *KRAS*-mutated NSCLC, the presence of co-mutations of *STK11/LKB1* or *TP53* defines two different subtypes.

LKB1 loss has a relevant impact on the tumour microenvironment.[14] Proliferation and survival of LKB1-mutated and *KRAS*-mutated cells depend on innate immune cytokine inhibition, highlighting the critical role for IL-6 in GEMMs.[15] LKB1 loss impairs autophagy, which negatively regulates pTBK1, likely contributing to this effect and potentially explaining the preferential dependence of these cells on momelotinib.[16] The feedback activation of innate immune signalling following the inhibition of the MEK and/or PI3K pathway was also described. Innate immune cytokines promote drug resistance to RTK, MEK and RAF inhibitors, consistent with the relative resistance to MEK inhibitor. In this scenario, YAP1 activity, a component of the Hippo pathway, is low, and cells are particularly reliant on innate immune cytokines as an adaptive response, but, when these are suppressed together with MEK inhibition, YAP1 and the therapy-induced secretome (TIS), resistance emerges.

These data suggest the need to block several kinases simultaneously to overcome resistance, indicating a potential role for BET inhibition. Indeed, several studies have demonstrated that transcriptional reprogramming during the adaptive bypass of kinase-targeted therapies is susceptible of pharmacological targeting, preventing cancer cells from acquiring resistance. On the other hand, in the setting of both *TP53*-mutated and *KRAS*-mutated cells, this innate immune programme and secreted factors such as IGF1 remain low, but YAP1 signalling is engaged and promotes intrinsic resistance to downstream pathway therapy. Thus, in this model, it is possible that YAP1 inhibitors may reveal preferential synergy with momelotinib. In this investigation, potent and selective TBK1 and BET inhibitors were also tested. The alternating doublet strategy minimises the toxicity of inhibiting each target.

Thus, a *KRAS* pathway-targeted approach, that simultaneously inhibits innate immune cytokines, suppresses MEK signalling, and accounts for this adaptive transcriptional response, could potentially translate into effective combination therapy for these frequently refractory tumours.

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 Andrés Cervantes FIS PI18/001909. J-MC has a Rio-Hortega-SEOM contract. 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, Astelas and Fibrogen and advisory board or speaker fees from Merck Serono, Roche, Servier, Takeda and Astelas in the last five years.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987–96.
2. Reardon DA, Omuro A, Brandes AA, *et al*. *Randomized phase 3 study evaluating the efficacy and safety of nivolumab vs bevacizumab in patients with recurrent glioblastoma: Checkmate 143. 5th Quadrennial Meeting of the World Federation of Neuro-Oncology Societies (WFNOS)*. Zurich, Switzerland, 2017.
3. Zhao J, Chen AX, Gartrell RD, *et al*. Immune and genomic correlates of response to anti-PD-1 immunotherapy in glioblastoma. *Nat Med* 2019;25:462–9.
4. Cloughesy TF, Mochizuki AY, Orpilla JR, *et al*. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. *Nat Med* 2019;25:477–86.
5. Schalper KA, Rodriguez-Ruiz ME, Diez-Valle R, *et al*. Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma. *Nat Med* 2019;25:470–6.
6. Diéras V, Miles D, Verma S, *et al*. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-

positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2017;18:732–42.
7. Krop IE, Kim S-B, González-Martín A, *et al*. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:689–99.
8. von Minckwitz G, Huang C-S, Mano MS, *et al*. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 2019;380:617–28.
9. Hata AN, Yeo A, Faber AC, *et al*. Failure to induce apoptosis via Bcl-2 family proteins underlies lack of efficacy of combined MEK and PI3K inhibitors for KRAS-mutant lung cancers. *Cancer Res* 2014;74:3146–56.
10. Zhu Z, Aref AR, Cohoon TJ, *et al*. Inhibition of KRas-driven tumorigenicity by interruption of an autocrine cytokine circuit. *Cancer Discov* 2014;4:452–65.
11. Lee H-J, Zhuang G, Cao Y, *et al*. Drug resistance via feedback activation of STAT3 in oncogene-addicted cancer cells. *Cancer Cell* 2014;26:207–21.
12. Zhu Z, Golay HG, Barbie DA. Targeting pathways downstream of KRAS in lung adenocarcinoma. *Pharmacogenomics* 2014;15:1507–18.
13. Kitajima S, Asahina H, Chen T, *et al*. Overcoming resistance to dual innate immune and MEK inhibition downstream of KRAS. *Cancer Cell* 2018;34:439–52.
14. Skoulidis F, Goldberg ME, Greenawalt DM, *et al*. *STK11/LKB1* Mutations and PD-1 Inhibitor Resistance in *KRAS*-Mutant Lung Adenocarcinoma. *Cancer Discov* 2018;8:822–35.
15. Koyama S, Akbay EA, Li YY, *et al*. STK11/LKB1 deficiency promotes neutrophil recruitment and proinflammatory cytokine production to suppress T-cell activity in the lung tumor microenvironment. *Cancer Res* 2016;76:999–1008.
16. Yang S, Imamura Y, Jenkins RW, *et al*. Autophagy inhibition dysregulates TBK1 signaling and promotes pancreatic inflammation. *Cancer Immunol Res* 2016;4:520–30.