Our panel of experts highlights the most important research articles across the spectrum of topics relevant to the field of CNS oncology

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First draft submitted: 1 February 2017; Accepted for publication: 1 February 2017; Published online: 20 April 2017

Pagès M, Beccaria K, Boddaert N *et al.* Co-occurrence of histone H3 K27M and BRAF V600E mutations in paediatric midline grade I ganglioglioma. *Brain Pathol.* doi:10.1111/bpa.12473 (2016) (Epub ahead of print)

The new WHO classification for brain tumors [1] has introduced some new entities like midline glioma with histone 3 mutation that, as pediatric neuro-oncologists, we have to be aware of proper clarification of prognosis with patients and parents and adequate treatment comprising at least radiation therapy as for grade 4 glioma. This paper reports on the search for BRAF V600E and H3 K27M mutations in a series of 54 pediatric midline grade I gangliogliomas (midline GG) to determine the frequency of double mutations and its relevance for prognosis. While it is well known that GG is a grade I tumor characterized by alterations in the MAPK pathway, including BRAF, the occurrence of the second mutation was not reported so far. The frequency of the co-occurrence of H3F3A/BRAF mutations at diagnosis was 9.3% and the H3F3A mutation was never singularly found. Of the five patients harboring both mutations in their GG,

only one died due to progressive disease even when nobody had received adjuvant treatment after surgery. Despite the presence of H3 K27M mutation, these cases maintained the good prognosis of GG grade 1 and, the authors suggest, they should not have received any further treatment after surgery even if molecular findings were known at diagnosis. The interaction of the two different mutations could be a key of the switching off of the negative prognosis correlated to H3K27 mutation.

– Written by Maura Massimino

Brown CE, Alizadeh D, Starr R *et al.* Regression of glioblastoma after chimeric antigen receptor T-cell therapy. *N. Engl. J. Med.* 375, 2561–2569 (2016)

This paper brings to evidence the potential therapeutic benefit of adoptive T-cell therapy against glioblastoma with the use of CAR-engineered T cells targeting IL13R α 2, a glioma-associated antigen linked to a reduced rate of survival. With modified IL13R α 2-targeted CAR T cells to improve antitumor potency and T-cell persistence by incorporating 4-1BB (CD137) costimulation and a mutated IgG4-Fc linker to reduce

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off-target Fc-receptor interactions into the CAR (IL13BB ζ) and by genetically engineering enriched central memory T cells, the authors performed infusions into the resected tumor cavity followed by infusions into the ventricular system in a resistant multiple disseminated glioblastoma patient. After CAR T-cell treatment, regression of all intracranial and spinal tumors was observed, along with corresponding increases in levels of cytokines and immune cells in the cerebrospinal fluid. This experience provides initial evidence of the safety and anti-tumor activity of CAR T-cell immunotherapy in patients with malignant brain tumors, also in this not rare condition, especially in young patients, of multiple disseminated foci.

– Written by Maura Massimino

Esbenshade AJ, Kocak M, Hershon L. A Phase II feasibility study of oral etoposide given concurrently with radiotherapy followed by dose intensive adjuvant chemotherapy for children with newly diagnosed high-risk medulloblastoma (protocol POG 9631): a report from the Children's Oncology Group. *Pediatr. Blood Cancer* doi:10.1002/pbc.26373 (2016) (Epub ahead of print)

This paper concerns the report of an old study that accrued patients between 1998 and 2002 and unluckily with a follow up that stopped already in 2007. Patients with medulloblastoma residual postoperative disease and/or metastases received daily doses of oral etoposide (either 50 mg/m² or 35) during radiation therapy and thereafter adjuvant courses of chemotherapy, again containing oral etoposide, followed by eight courses of cyclophosphamide and vincristine. The results were quite the same as other concurrent strategy in North America but there are some interesting points to be highlighted.

If excluding patients with metastases, those with residual disease only had an excellent prognosis with 5-year progression-free survival and overall survival over 90%. This very favorable prognosis poses the question if these patients are really a high-risk group to be included in intensive treatment strategies, or, as the International Society of Pediatric Oncology group has recently decided, not eligible to an 'intermediate' intensive treatment.

What is really lacking in this paper is the long-term evaluation of patients, both from the neuro-cognitive outcome and the possible

hematologic consequences of the concomitant treatment with oral etoposide and radiation therapy followed by other oral etoposide. These elements could be rescued and be the object of another report.

– Written by Maura Massimino

Tirosh I, Venteicher AS, Hebert C *et al.* Single-cell RNA-seq supports a developmental hierarchy in human oligodendroglioma. *Nature* 539, 309–329 (2016)

The authors profiled 4347 cells from six 1p/19q codeleted, *IDH1* or *IDH2* mutant grade II oligodendrogliomas by RNA sequencing and reconstructed their developmental programs from their expression signatures. Tumor cells were identified by high copy number variation, 1p/19q codeletion and other features. Tumor cells could be divided into three populations. The two largest populations showed markers of astrocytic or oligodendrocytic differentiation, but a much smaller number of cells were in a third population that lacked markers of differentiation. The latter population had expression patterns of 'stemness', features shared with normal neural progenitor cells and neural stem cells. Of the 1.5–8% of cells in the six tumors with signatures of proliferating cells, nearly all were in the undifferentiated third population with stem/progenitor features. Specific subclonal mutations spanned all three cell populations. The authors conclude that grade II codeleted oligodendrogliomas with *IDH* mutation appear to have their growth driven by a small population of cancer stem cells.

– Written by Larry Junck

Ramkissoon SH, Bandopadhyay P, Hwang J *et al.* Clinical targeted exome-based sequencing in combination with genome-wide copy number profiling: precision medicine analysis of 203 pediatric brain tumors. *Neuro Oncol.* doi:10.1093/neuonc/now294 (2017) (Epub ahead of print)

The authors studied 203 pediatric brain tumor samples including profiling by high resolution array comparative genomic hybridization (aCGH) on 146 and targeted exome sequencing of 300 cancer-causing genes on 117. Arm-level copy number variations were found in 26% of the genome of embryonal tumors, 19% in high-grade gliomas and 5% in low-grade

gliomas. The copy number variation profiles fell into clusters that had a high but not complete correlation with histologic diagnosis. Exome sequencing identified 20 tumors with clinically actionable rearrangements, and an additional 44 (38%) had alterations of definite or possible clinical utility (tier 1 or 2). Important mutations identified included those in *BRAF*, *FGFR1*, *NTRK1*, *ATRX*, *TP53* and *IDH1* in glial tumors, *CTNNB1* and *PTCH1* in medulloblastomas, *KIT* in germinoma and *VHL* in hemangioblastoma. The authors conclude that such assays can identify alterations relevant to diagnosis, prognosis and treatment

of pediatric brain tumors, providing an effective precision medicine approach for these tumors.

– Written by Larry Junck

Financial & competing interests disclosure

L Junck has nonrelated NIH funding (5 POI CA085878-14). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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