ABSTRACT CITATION ID: NOAE064.311

HGG-27. IDH- AND H3-WILDTYPE HIGH-GRADE GLIOMAS OCCURRING IN TEENAGERS AND YOUNG ADULT PATIENTS COMPRISE NOVEL MOLECULAR SUBGROUPS

Rita Pereira[1], Alan Mackay[1], Yura Grabovska[1], Amelia Clarke[2], Tabitha Bloom[2], James Nicoll[2], Delphine Boche[2], John Procter[3], Andrew Moore[4], Johanna Schagen[4], Liam Walker[5], Federico Roncaroli[5], Olumide Ogunbigi[6], Thijs van Dalen[7], David Ziegler[8], Zhi-Feng Shi[9], Darren Hargrave[6], Thomas S Jacques[6], Bassel Zebian[10], Cristina Bleil[10], Joseph Yates[11], Emma Norton[11], Henry Mandeville[12], Antonia Creak[12], Liam Welsh[12], Lynley Marshall[12], Ferndando Carceller[12], Zita Reisz[10], Safa Al-Sarraj[10], Angela Mastronuzzi[13], Andrea Carai[13], Maria Vinci[13], Kathreena Kurian[14], Ho-Keung Ng[15], Sebastian Brandner[7], Chris Jones[1], Matthew Clarke[1,7]; [1]Institute of Cancer Research, London, United Kingdom, [2]BRAIN UK, University of Southampton, Southampton, United Kingdom, [3]Neuropathology and Pathology Research, Royal Preston Hospital, Preston, United Kingdom, [4]The University of Queensland Diamantina Institute, The University of Queensland, Woolloongabba, Australia, [5]Northern Care Alliance NHS Foundation Trust, Salford, United Kingdom, [6]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom, [7]National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, United Kingdom, [8]Kids Cancer Centre, Sydney Children's Hospital, Sydney, Australia, [9]Huashan Hospital, Fudan University, Shanghai, China, [10]King's College Hospital, London, United Kingdom, [11]University Hospital Southampton, Southampton, United Kingdom, [12]The Royal Marsden NHS Foundation Trust, London, United Kingdom, [13]Ospedale Pediatrico Bambino Gesù, Rome, Italy, [14]University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom, [15]Chinese University of Hong Kong, Hong Kong, China

BACKGROUND: High-grade gliomas (HGG) arise in any CNS location with a poor prognosis. HGGs in teenagers/young adults (TYA) are understudied; this project aimed to characterise these tumours and identify therapeutic targets. METHODS: HGG samples (histone/IDH-wildtype, n=207, FFPE/FF, 13-30 years) were collected from national/international collaborators. DNA methylation profiling (Illumina EPIC BeadArrays, brain tumour classifier (MNPv12.5 R package)) classified cases against reference cohorts. Calibrated scores guided workflows to characterise mutational landscapes (RNA-based ArcherDx fusion panel (n=92), whole exome sequencing (n=107), histological review). RESULTS: Of cases scoring >0.5, n=25 classified as PXA and n=8 as HGAP, differing from primary diagnoses. 53.4% (n=86) classified as paediatric-type subgroups ((pedHGG-RTK1A/B/C, 31.7%, n=51, associated with frequent *PDGFRA, CDKN2A/B, SETD2, NF1* alterations), pedHGG-*MYCN* (8.1%, n=13, *MYCN/ID2* amplifications), and pedHGG-RTK2A/B (7.5%, n=12)). 18.0% (n=29) classified as subgroups frequently seen in adults including GBM-MES (15.5%, n=25, enriched for *RB1, PTEN*, *NF1* alterations) and GBM-RTK1/2 (2.5%, n=4, *CDK4* amplifications). 16 cases were assigned to novel, poorly-characterised subgroups with distinct methylation profiles and molecular features

including paediatric-specific pedHGG-A/B (n=10 6.2%) and HGG-E (n=6 3.7%) subgroups, and HGG-B (n=2 1.0%), and GBM-CBM (n=5 3.1%, frequent cerebellar location) subgroups, associated with variable histological morphology. 8 cases showed hypermutator phenotypes, enriched in HGG-E. Age-distribution/molecular profile comparisons using publicly available methylation and sequencing data for HGG-B (n=9), GBM-CBM (n=26) and GBM-MES-ATYP (n=53), irrespective of age, shows they are TYA-specific subgroups with the latter containing fewer chr7 gains and chr10 losses, and more *CDKN2A/B* deletions and *MET* amplifications, compared with adult-specific GBM-MES-TYP. Across the cohort, other frequent copy number changes included gains in chr1q (54%, frequent in pedHGG-RTK1B/C/*MYCN*, pedHGG-A/B), chr2 (22%, pedHGG-*MYCN*), and chr13 losses (64%, pedHGG-RTK1B/C). Focal amplifications included *CDK6* (1.4%, n=3) and *EGFR* (1.0%, n=2). CONCLUSION: TYA HGG comprise well-characterised, novel methylation subgroups with distinct methylation profiles and molecular characteristics, representing opportunities to refine treatment.