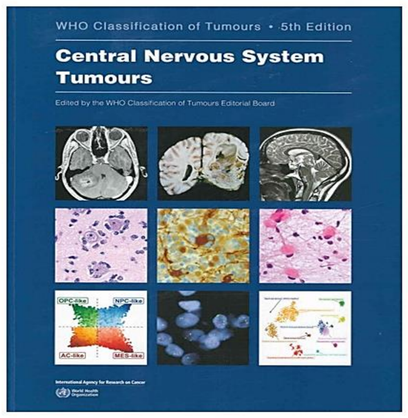
Clinical Analysis of CNS WHO Grade 4 Gliomas with IDH-mutant vs. IDH-wildtype Focused on CDKN2A Homozygous Deletion

Da Hyun Park[1], Ki Su Kim[2], Young Zoon Kim[1].
[1]Division of Neuro Oncology and Department of Neurosurgery, Samsung Changwon Hospital, Sungkyunkwan University, School of Medicine, Changwon, Korea.
[2]Department of Pathology, Samsung Changwon Hospital, Sungkyunkwan University, School of Medicine, Changwon, Korea.

THE NEW 2021 WHO CLASSIFICATION FOR CNS TUMORS



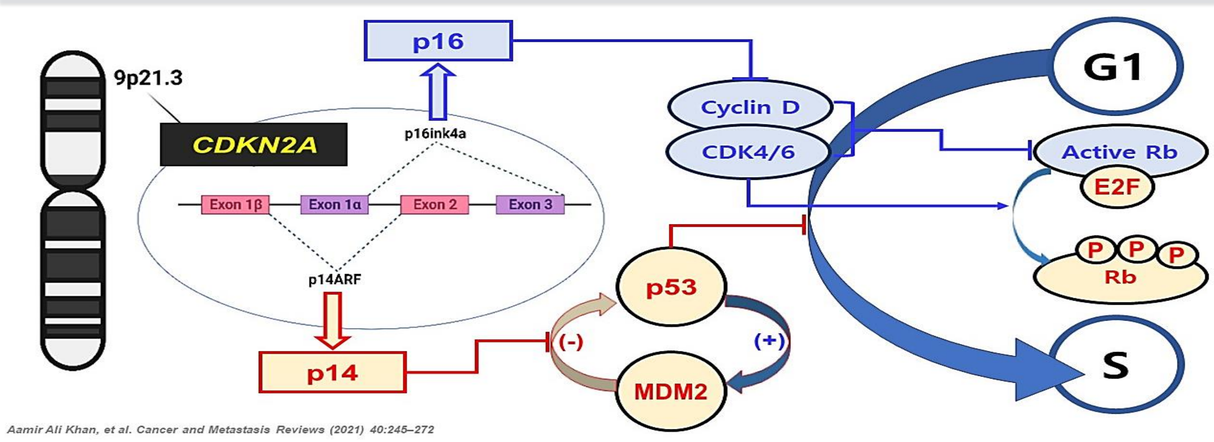
Chapter 2. Gliomas, glioneuronal tumors, and neuronal tumors. p18

Nomenclature and grading of common adult-type diffuse astrocytic gliomas

In the 2016 classification, *IDH*-mutant diffuse astrocytic tumors were assigned to three different tumor types (diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma) depending on histologic parameters. In the current classification, however, all *IDH*-mutant diffuse astrocytic tumors are considered a single type (astrocytoma, *IDH*-mutant) and are the graded as CNS WHO grade 2,3, or 4 (see Chapter 1: *Introduction to CNS tumors*).

Moreover, grading is no longer entirely histological because the finding of *CDKN2A* and/or *CDKN2B* homozygous deletion results in a CNS WHO grade of 4 even in the absence of microvascular proliferation or necrosis.

CDKN2A/B - p16INK4a/p14ARF- Rb pathway for Negative Cell Cycle Regulation



Aamir Ali Khan, et al. Cancer and Metastasis Reviews (2021) 40:245–272

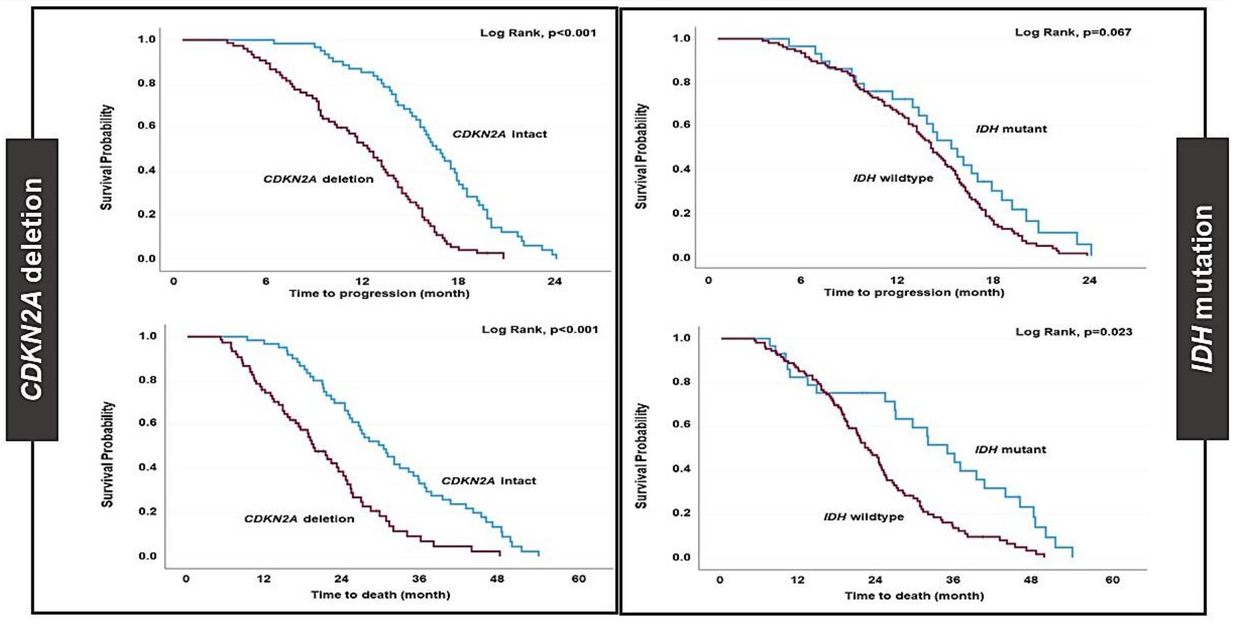
MATERIALS AND METHODS

- **Retrospective analysis of 142 GBM cohorts in SMC Changwon (2007.03 ~ 2022.12)**
- **Review of medical records in the traditional prognostic factors of literatures**
  : Age, WHO performance status, extent of resection, and MGMT promoter methylation
- **NGS analysis using ONCO accu Pannel® (Geninus Inc.)**
  : 323 genes (partial for 98 genes and entire coding sequencing for 225 gene)
  : *IDH* mutation, *TERT* promoter mutation, *CDKN2A* mutation
- **Primary endpoint**
  : *CDKN2A* deletion as prognostic factor for PFS and OS of CNS WHO grade 4 gliomas
- **Secondary endpoints**
  : validation of the role of traditional prognostic factors in CNS WHO grade 4 gliomas

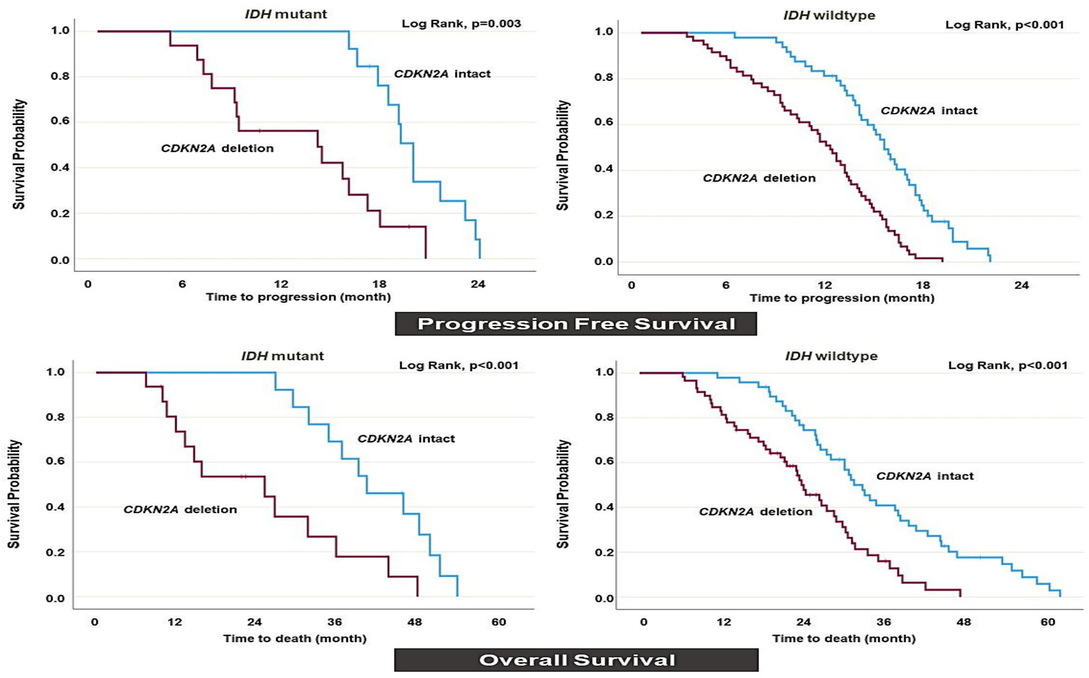
Variables		Number
Age (years)	<50	47 (34.6%)
	≥50	89 (65.4%)
Sex	Male	84 (61.8%)
	Female	52 (38.2%)
WHO performance status	0	55 (40.4%)
	1	65 (47.8%)
	2	16 (11.8%)
Extent of resection	Biopsy	17 (12.5%)
	Subtotal resection	52 (38.2%)
	Gross total resection	67 (49.3%)
RPA class	III	32 (23.5%)
	IV	79 (58.1%)
	V	25 (18.4%)
MGMT gene promoter	Methylated	86 (63.2%)
	Unmethylated	50 (36.8%)
Postoperative adjuvant therapy		
Nitrosourea-based combination CTx		35 (25.7%)
CCRT with temozolomide		101 (74.3%)

Variables		Number
EGFR amplification	Yes	95 (69.9%)
	No	41 (30.1%)
TERT promoter mutation	Yes	71 (52.2%)
	No	65 (47.8%)
CDKN2A deletion	Yes	75 (55.1%)
	No	61 (44.9%)
IDH mutation	Yes	29 (21.3%)
	No	107 (78.7%)
Salvage treatment after progression		
Second surgical resection		74 (54.4%)
Repeated irradiation		63 (46.3%)
Salvage chemotherapy		83 (61.0%)
Supportive treatment only		17 (12.5%)

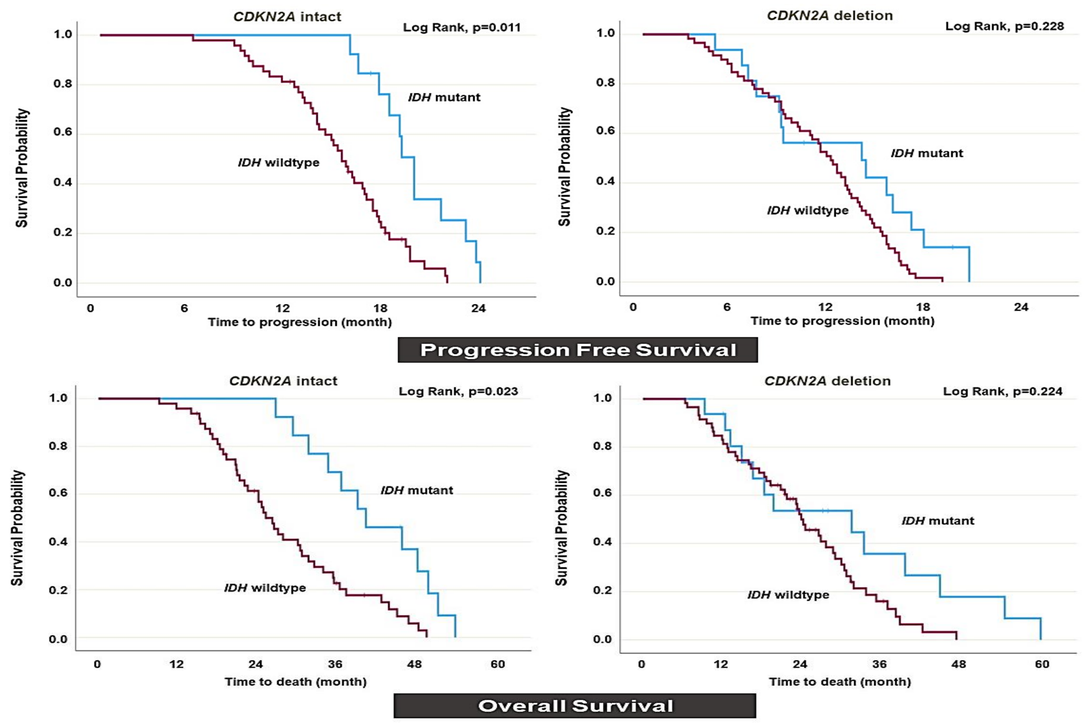
CDKN2A Deletion and IDH Mutation in WHO Grade 4 Glioma Cohorts



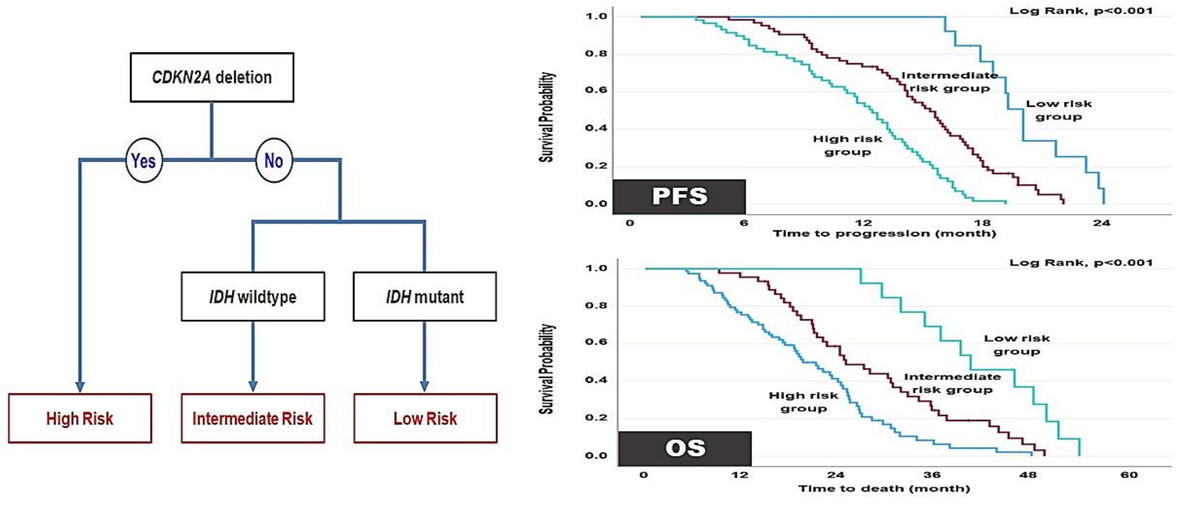
CDKN2A Deletion according to IDH Mutation in WHO Grade 4 Glioma Cohorts



IDH Mutation according to CDKN2A Deletion in WHO Grade 4 Glioma Cohorts



PFS and OS according to CDKN2A Deletion and IDH Mutation [3 Groups]



CONCLUSIONS

- *CDKN2A deletion affects the prognosis of WHO grade 4 glioma patients with IDH-mutant as well as IDH-wildtype.*
- *Statistical power of the predicting prognosis of CDKN2A deletion is stronger than IDH mutation status in WHO grade 4 glioma patients.*
- *There are several difficulties in clinical application of genetic and analytic methods to detect CDKN2A mutation in glioma research.*
- *Lack of evidence showing the biological mechanism of CDKN2A deletion in affecting prognosis of malignant gliomas makes comprehensive study be mandatory.*

● Contact : Young Zoon Kim (yzkim@skku.edu)