Supplementary Online Content

Kinslow CJ, Mercurio A, Kumar P, et al. Association of *MGMT* promotor methylation with survival in low-grade and anaplastic gliomas after alkylating chemotherapy. *JAMA Oncol.* Published online May 18, 2023. doi:10.1001/jamaoncol.2023.0990

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods.

Data Sources

Jonsson et al.'s study[1] (hereafter referred to as MSK-IMPACT) was a prospective study conducted at Memorial Sloan-Kettering Cancer Center designed to integrate genomic data with clinical and treatment phenotypes to determine genetic aberrations that are associated with clinical behavior, evolution on therapy, or response to therapy. Primary and recurrent tumor samples from 923 adult patients underwent prospective genomic profiling during routine clinical care from 2013 to 2017.

EORTC 26951 was a randomized controlled trial designed by the European Organization of Research and Treatment of Cancer (EORTC) to evaluate the effectiveness of adjuvant alkylating chemotherapy in anaplastic oligodendroglial tumors.[2] Patients were eligible for this study if they were diagnosed with anaplastic oligodendroglioma or oligoastrocytoma (according to the 1993 WHO classification), age 16 – 70 years, had ECOG performance status 0 to 2, and had not received prior chemotherapy or radiotherapy. From 1996 through 2002, 368 patients were randomized to receive radiotherapy with or without procarbazine, lomustine, and vincristine (PCV). A post-hoc analysis of the trial showed that only 38% of tumors had 1p/19q codeletion and 51% had *IDH* mutation.[3] Thus, the majority of tumors in this study were not true molecular oligodendrogliomas, but rather represented a balance of all three molecular subtypes. Individualized patient data was obtained from a subsequent post-hoc analysis of the trial, designed to interrogate the prognostic and predictive value of CpG island hypermethylated phenotype and *MGMT* promoter methylation status.[4] One-hundred and fifteen patients from the original trial had samples that could be retrieved and were included in the study. A central

pathology review was conducted on all samples with available tissue according to the updated WHO 2007 classifications.

A third cohort was derived from Columbia University Irving Medical Center (CUIMC). Patients undergoing consultation in the Department of Radiation Oncology and expected to commence radiation therapy were prospectively enrolled to the Comprehensive Brain Malignancy, Brain Tumor and Brain Radiotherapy Clinical Database (IRB-AAAM2358). Clinical data was captured and entered by a research team from standard clinical sources including date of birth, gender, past medical history, clinical and pathological diagnosis, history of treatments including radiation therapy, surgery, chemotherapy, overall survival, recurrence, follow up visits, and lab results. Patients were consented from April 1st, 2013 to April 31st, 2022. Medical records were reviewed dating back to the earliest available.

Variable Selection and Coding

Clinical information obtained from MSK-IMPACT included patient age, sex, WHO 2016 integrated histological and molecular classification, tumor grade, *MGMT* promoter methylation status, date of initial diagnosis, date of patient death or last contact with hospital, surgical interventions, lines of systemic treatment and radiotherapy used, and date of first progression as determined by RANO criteria. Somatic mutations in *IDH1* or *IDH2* were determined via DNA sequencing with OncoKB annotation. 1p/19q codeletion status was determined using allele-specific or regional DNA copy number analysis inferred from DNA sequencing using MSK-IMPACT or FoundationOne, respectively. *MGMT* promoter methylation status was determined either by pyrosequencing or methylation-specific real-time PCR (MS-PCR). Borderline methylation of the promoter was deemed negative. The first line of chemotherapy was recorded

for each patient. Patients were coded as having received chemotherapy if treatment was initiated before progression and within one year of diagnosis, greater than six months before progression if within three years of diagnosis, greater than 12 months before progression if within six years of diagnosis, and greater than 24 months before progression if beyond five years of diagnosis. Receipt of radiotherapy was inferred if any of the subsequent surgical samples had received prior radiotherapy. Therefore, if no further surgeries were conducted, the patient was coded as "No Radiotherapy/Unknown".

Clinical information obtained from EORTC 26951 included patient age, sex, reviewed histological diagnosis and grade, *IDH1* mutation status, 1p/19q loss of heterozygosity (LOH), *MGMT* promoter methylation status, extent of surgical resection, initial line of treatments, overall survival (OS) status and time, and progression-free survival (PFS) status and time, according to McDonald's criteria.[5] Three samples did not have tissue available for central review and the original histological diagnosis and grade were used. Mutations in *IDH1* were determined by direct sequencing of the c.395G hotspot. 1p and 19q status were determined by fluorescent in situ hybridization (FISH). *MGMT* promoter methylation status was determined by MS-PCR using the *MGMT*-STP27 prediction model.[6] Methylation profiling was conducted using the Illumina Infinium HumanMethylation 27 or Infinium HumanMethylation 450 arrays. Two CpG sites within the *MGMT* promoter (cg12434587 and cg12981137) were used to identify the *MGMT* promoter status. Patients with 1p/19q LOH and unknown *IDH* status were assumed to be *IDH*-mutant, 1p/19q-codeleted.[7,8] *IDH2*, *ATRX*, and *TP53* status were not available in this cohort. Patients with discordant *IDH1* status and 1p19q status (ie. codeleted with *IDH1*wt) were analyzed as *IDH*-mutant/codeleted and then *IDH*-wildtype in a sensitivity analysis.[7-9]

In the CUIMC cohort, routine clinical information was obtained, as well as *IDH* status, 1p19q-codeletion, *MGMT* status, all lines of treatment, and dates of recurrence or death at follow-up. *IDH* status was determined at CUIMC via IHC staining for the IDH1 R132H hotspot mutation and/or by sequencing on the Columbia Solid Tumor Panel with the Illumina MiSeq platform, which includes *IDH1*/*2*. 1p19q-codeletion was determined via FISH probes for the 1p36 and 19q13 loci. *MGMT* promoter methylation was determined via MS-PCR. Additional markers, such as ATRX and TP53 were used to discern cases with discordant *IDH* and 1p19q-codeletion status. Radiology and clinical reports were used to determine date of progression. Patients were censored once lost to follow-up. Death was determined via the electronic medical record, the social security death index, or other communications available to the research team. Patients who were transferred to hospice and lost to follow-up were considered to have had a clinical death.

eTable 1. Review of Prospective Studies that Evaluated *MGMT* Promoter Methylation in Primary Low Grade and Anaplastic Gliomas

Study	Initial Study Design, Population, (Sample Size)	MGMT Study Design (Sample Size) Assay	Results	Conclusion(s)	Limitations
EORTC 26951[2-4,10-14]	RCT[2] RT alone vs. RT + PCV AO or AOA (n = 368)	1. Post-hoc[10] (n = 152) MS-MLPA 2. Post-hoc[11] (n = 151) MS-MLPA 3. Post-hoc[14] (n = 183 [n = 150 with *MGMT*, *IDH*, 1p/19q status]) MS-MLPA 4. Post-hoc[4] (n = 115) MS-PCR (STP27) 5. Post-hoc[3] (n = 78) MS-PCR (STP27)	1. - MVA HR of m*MGMT* for PFS and OS was 0.28 (0.13 – 0.60) and 0.24 (0.10 – 0.56), respectively. - UVA HR of m*MGMT* for PFS in RT/PCV and RT arms was 0.35 (p = .001) and 0.46 (p = .01), respectively. - In RT group, PFS and OS for u*MGMT* vs m*MGMT* was 7.8 vs 17.9 (p = .01) and 12.3 and 59.3 months (p = .002), respectively. In RT/PCV group, PFS and OS for unmethylated vs methylated was 10.5 vs 49.0 months (p = .001) and 19.0 and NR (p = .0004), respectively. 2. *MGMT* methylation not included in final MVA with stepwise selection. 3. - PFS and OS for u*MGMT* vs. m*MGMT* was 7.9 (5.7 – 9.8) vs. 33.0 (17.6 – 47.1) and 15.9 (11.6 – 19.0) vs. 59.3 (36.9 – 73.6) months, respectively. - MGMT not independently significant in MVA model with *IDH* and 1p/19q status. - UVA HR of RT/PCV for PFS was 0.52 (0.35 – 0.76) and 0.63 (0.34 – 1.16) in m*MGMT* vs. u*MGMT* groups, respectively. UVA HR of RT/PCV for OS was 0.65 (0.43 – 0.98) and 0.81 (0.44 – 1.49) in m*MGMT* vs. u*MGMT* groups, respectively. 4. - UVA HR of m*MGMT* for PFS and OS was 0.27 (p < .001) and 0.26 (p < .001), respectively. - MVA HR of m*MGMT* for PFS and OS was no longer significant (1.00 [p = .99] and 0.88 [p = .68], respectively). - UVA HR of RT/PCV for PFS was 0.30 (p < .0001) and 0.95 (p = .91) in m*MGMT* vs. u*MGMT* groups, respectively. - UVA HR of RT/PCV for OS was 0.33 (p = .0001) and 1.16 (p = .26) in m*MGMT* vs. u*MGMT* groups, respectively. Interaction was highly significant (p = .003). 5. - UVA HR of m*MGMT* for OS in *IDH*-wt was 0.57 (0.29 – 1.1). - UVA HR of RT/PCV for OS was 0.39 (0.21 – 0.74) and 1.35 (0.54 – 3.34) in m*MGMT* vs. u*MGMT* groups, respectively (p of interaction = .025).	1. *MGMT* is prognostic but not predictive of outcomes for anaplastic oligodendroglial tumors treated with PCV. 2. After accounting for *IDH* status, independent prognostic significance of *MGMT* methylation is lost. 3. Patients with m*MGMT* seemed to derive more benefit from PCV. m*MGMT* is the result of genome-wide methylation, and the prognostic impact reflects improved outcomes of *IDH*-mutated tumors. 4. MGMT promoter methylation is prognostic in AOD and predictive of response to PCV chemotherapy. Some methylation sites within the *MGMT* promoter region have less predictive power than others. 5. m*MGMT* is the single most important predictive molecular factor for benefit from chemotherapy.	1. *IDH* status not available 2. Exploratory analysis with 12 clinical and molecular features that may have been underpowered 3. MGMT unmethylated status was rare (2 cases in 71) in *IDH* mutant tumors. 4. -Cohort was relatively modest in size. - Presence of severe multicolinearity in MVA. 5. No MVA was conducted. 95% of *IDH*-mt tumors had m*MGMT.*
Brandes et al.[15]	Prospective[15] AO or AOA TMZ (n = 67)	Prospective[15] (n = 37) MS-PCR	- Response rate 54 vs. 41% in m*MGMT* vs. u*MGMT* tumors (p = .23), respectively. - PFS 12 vs. 13 months in m*MGMT* vs. u*MGMT* tumors (p = .41), respectively. - OS 41 vs. 29 months in m*MGMT* vs. u*MGMT* tumors (p = .09), respectively.	m*MGMT* not independent prognostic factor for AO/AOA on TMZ. m*MGMT* more common with 1p/19q-codeletion.	Small sample size. Prognostic implication of *MGMT* status not examined according to 1p/19q status.
Mikkelsen et al.[16]	Prospective[16] AO or AOA TMZ	Prospective[16] (n = 24) MS-PCR	12-month PFS for m*MGMT* vs. u*MGMT* tumors was 69.2 vs. 63.6% (p = 0.73).	*MGMT* methylation more common with 1p/19q-codeletion.	Small sample size. Prognostic implication of *MGMT* status not

	(n = 48)				examined according to 1p/19q status.
Gan et al.[17]	Prospective[17] AO or AOA TMZ (n = 40)	Prospective[17] (n = 21) SSE or MS-HRM	- Objective response 70 vs. 27% (p = 0.09) in MGMT m*MGMT* vs. u*MGMT* tumors. - No difference in PFS or OS with MGMT methylation: UVA HR 1.30 (0.30 – 5.58) and 1.80 (0.55-5.88), respectively.	*MGMT* methylated tumors have higher response rates to TMZ.	Small sample size. All 1p/19q-codeleted tumors were *MGMT* methylated.
NOA-04[18-20]	RCT[18] RT vs. PCV vs. TMZ AG (n = 318)	1. Prospective[18] (n = 176) MS-PCR 2. Post-hoc[19] (n = 183) MS-PCR 3. . Post-hoc[20] (n = 198) MS-PCR	1. - UVA HR of u*MGMT* for TTF and PFS was 2.4 (p < .0001) and 2.0 (p < .0001), respectively. - MVA HR of u*MGMT* for TTF and PFS was 1.9 (p = .02) and 1.7 (p = .02), respectively. - UVA HR of u*MGMT* for PFS in chemotherapy and RT arms was 2.0 (p < .03) and 2.7 (p < .003), respectively. 2. - PFS for m*MGMT* vs. u*MGMT* tumors 41.6 vs 16.9 months (p < 0.0001). - PFS for m*MGMT* vs. u*MGMT* in *IDH*-mt tumors treated with RT and chemotherapy was 36.8 (34.4 – NR) vs. 28.0 (10.9 – NR) and 44.7 (34.7 – NR) vs. 28.1 (7.4 – NR), respectively. - PFS for m*MGMT* vs. u*MGMT* in *IDH*-wt tumors treated with RT and chemotherapy was 16.3 vs. 17.2 (p = 0.33) and 27.2 vs 9.1 (p = .02), respectively. - MVA shows interaction between *MGMT* and therapy in *IDH*-wt (p = 0.001) but not *IDH*-mutant (p = .70) tumors. 3. -PFS for m*MGMT* vs. u*MGMT* in *IDH*-wt tumors that received RT and chemotherapy was 1.35 vs. 0.79 (p = 0.11) and 2.73 vs. 0.71 (p = 0.0034) years, respectively. -PFS for m*MGMT* vs. u*MGMT* in *IDH*-mutant tumors that received RT and chemotherapy was 4.22 vs. 4.84 (p = 0.67) and 3.63 vs. 1.51 (p = 0.62) years, respectively.	1. *MGMT* promoter methylation is prognostic in anaplastic gliomas but not predictive of response to chemotherapy. *MGMT* may be a prognostic marker for good outcome in patients treated with any type of genotoxic therapy or predictive for response to RT. 2. *MGMT* is prognostic in patients with anaplastic *IDH*-mt gliomas and predictive of response to alkylating chemotherapy in patients with *IDH*-wt tumors. 3. *MGMT* methylation is a predictive biomarker for benefit from alkylating chemotherapy in *IDH*-wt gliomas only.	1. Chemotherapy did not improve TTF, PFS, OS in any group. 2. *MGMT* status was not examined separately in *IDH*-mt 1p/19q-non-codeleted vs -codeleted tumors. 3. Unmethylated *MGMT* was rare in *IDH*-mt subgroup. *IDH*-mt subgroup not stratified by 1p/19q status. Mature data for prognostic implication of *MGMT* in *IDH*-mt tumors contradicts earlier report and is not addressed.
GGN[21]	Prospective[21] Data Collection Glioma/ GBM	1. Post-hoc[21] GGN/NOA-04 (n = 105) AA MS-PCR 2. Post-hoc[19] GGN/NOA-08 AG (n = 109) MS-PCR	1. OS in m*MGMT* vs. u*MGMT* AA approximately 63 vs. 33 months, respectively (no p-value provided). MVA of OS shows RR of death with u*MGMT* is 1.3 (no p-value) in AA. 2. PFS for m*MGMT* vs. u*MGMT* *IDH*-wt tumors treated with RT and chemotherapy was 5.3 vs. 9.3 (p = 0.60) and 15.8 vs 3.4 (p = .02), respectively. UVA and MVA of interaction was p = 0.04 and NS, respectively.	1. *MGMT* promoter status greater prognostic effect in GBM than AA. *MGMT* is prognostic in *IDH*-mt AA but not *IDH*-wt AA. 2. *MGMT* status is predictive of response to chemotherapy in *IDH*-wt patients.	1. *IDH* and 1p/19q status not reported in AA subgroup. 2. Few cases of *IDH*-mt *MGMT* without methylation.
RTOG BR0131[22]	Prospective[23] AO or AOA TMZ -> TMZ + RT (n = 40)	Prospective[23] (n = 21) MS-PCR	6-month PFS 100 vs. 100% for methylated vs. unmethylated tumors	N/A	Small sample size. Prognostic implication of *MGMT* status not examined according to 1p/19q status.

EORTC 22033-26033[24]	RCT RT vs. TMZ High-risk LGG (n = 477)[24]	Prospective[24] (n = 150) MS-PCR (STP27)	*MGMT* promoter methylated in almost all *IDH*-mt tumors and half of *IDH*-wt tumors. The rarity of *IDH*-wt tumors did not allow for statistical testing.	1. *MGMT* does not provide prognostic or predictive value in *IDH*-mt tumors.	Sample size prevented statistic testing from being performed.
RTOG 0424[25,26]	Prospective[25] TMZ + RT High-risk LGG (n = 129)	Prospective[26] (n = 75) MS-PCR (STP27) Prospective[27] (n = 76) MS-PCR (STP27)	1. - UVA HR of u*MGMT* was 3.52 (P < .001) and 3.06 (P < .001) for OS and PFS, respectively. - MVA HR of u*MGMT* was 2.70 (P < .05) and 2.74 (p = .02) for OS and PFS, respectively. - Median OS and PFS for m*MGMT* vs. u*MGMT* in *IDH*-wt was approximately NR vs. 27 months (no p-value) and 54 vs. 24 months (no p-value), respectively. 2. - UVA HR of m*MGMT* was 0.31 (P < .001) and 0.39 (P = .001) for OS and PFS, respectively. - MVA HR of m*MGMT* was 0.65 (P = .42) and 0.63 (p = .36) for OS and PFS, respectively, in multi-marker analysis that included *IDH* and 1p/19q status.	1. *MGMT* promoter methylation is an independent prognostic biomarker of high-risk, low-grade glioma treated with temozolomide and radiotherapy. 2. MGMT promoter methylation is a highly significant biomarker of OS and PFS but did not retain significance in multi-marker MVA.	1. 1p/19q status was not accounted for. No formal statistics conducted in *IDH*-wt subgroup. No analysis of *IDH*-mt subgroup. 2. Small sample size and/or dependency of m*MGMT* on *IDH*-mt.
RTOG 9802[28,29]	RCT[28] RT vs. RT + PCV High-risk LGG (n = 251)	Post-hoc[29] (n = 71) MS-PCR (STP27)	- UVA HR of u*MGMT* for PFS and OS was 1.65 (p = 0.09) and 1.83 (p = .06), respectively. - MVA HR of u*MGMT* for PFS and OS was 0.95 (p = 0.89) and 0.95 (p = .90), respectively.	*MGMT* status may have not held statistical significance because it is associated with histological subgroups.	1p/19q status not included in MVA. *MGMT* analysis not conducted in individual molecular subgroups. Sample size may be too small.
CATNON[30-33]	RCT[30] RT vs. RT + adj. TMZ vs. RT + conc. TMZ vs. RT + adj./conc. TMZ AG, non-codel (n = 751)	1.Prospective[30] MS-PCR (n = 550) 2. Prospective[31] MS-PCR (STP27) (n = 663) 3. Prospective[32] MS-PCR (STP27) (n = 654) 4. Post-Hoc[33] MS-PCR (STP27) (n = 152)	1. MVA HR of m*MGMT* for OS was 0.49 (p = 0.003). 2. – MVA HR of m*MGMT* for OS was 0.57 (p = 0.002) and 0.54 (p = 0.0009) when stratified by conc. and adj. TMZ, respectively (not adjusted for *IDH* status). - In *IDH*-wt, UVA HR for u*MGMT*/No conc. TMZ, u*MGMT*/conc. TMZ, m*MGMT*/No conc. TMZ, m*MGMT*/conc. TMZ was 1.00, 1.19 (0.83 – 1.71), 0.83 (0.55 - 1.26), and 0.68 (0.42 – 1.08), p = 0.08. - In *IDH*-wt, UVA HR for u*MGMT*/No adj. TMZ, u*MGMT*/adj. TMZ, m*MGMT*/No adj. TMZ, m*MGMT*/adj. TMZ was 1.00, 0.92 (0.0.64 – 1.33), 0.69 (0.45 – 1.05), and 0.66 (0.42 – 1.03), p = 0.15. - P-value of interaction between *MGMT* status and conc. TMZ, adj. TMZ, any TMZ was 0.23, 0.92, and 0.86, respectively. 3. UVA of m*MGMT* not associated with OS in *IDH*-mt non-codel patients (HR 0.92, p = 0.7) 4. - m*MGMT* associated with improved OS (HR 0.65 [0.45 – 0.92] but not PFS (0.95 [0.68 – 1.34]) in *IDH*-wt tumors. - No survival benefit of TMZ on OS in m*MGMT* (HR 1.36 [0.75 – 2.48]) or u*MGMT* tumors (0.88 [0.54 – 1.42]) in *IDH*-wt tumors. - No survival benefit of TMZ on PFS in m*MGMT* or u*MGMT* tumors (no HR given) in *IDH*-wt tumors.	1. Ongoing molecular research within this trial will reveal if *MGMT* is predictive for benefit from TMZ. 2. Unlike m*MGMT* GBM, m*MGMT IDH*-wt gliomas do not show benefit from TMZ. Further molecular analysis is required to establish the role of *MGMT* promoter methylation in *IDH*-wt tumors. 3. *MGMT* not prognostic in *IDH*-mt non-codel patients. 4. A well-powered prospective study on the effectiveness of TMZ is warranted in tumors meeting the contemporary definition of GBM, *IDH*-wt.	1. *MGMT* assay was optimized for GBM. *MGMT* analysis not stratified by *IDH* status. 2. *MGMT* analysis not conducted in *IDH*-mt tumors. *IDH*-wt tumors did not benefit for conc. or adj. TMZ. 3. *MGMT* prognostic implication not stratified by treatment. 4. Post-hoc, underpowered study.
Qui et al.[34]	RCT[34] RT vs. RT + TMZ	1. Prospective[34] Pyrosequencing (n = 37)	- Median OS 24 vs. 24 months (p = .268)	Limited sample size precluded subgroup analysis. The predictive value of m*MGMT* deserves further investigation.	Limited sample size.

	G2-3 *IDH*-wt with TERT-mt (n = 37)				

95% confidence intervals are displayed in parentheses next to the corresponding HR, where applicable.

Abbreviations:
RCT- randomized controlled trial
MS-MLPA- methylation-specific multiplex ligation-dependent probe amplification
MS-PCR- methylation-specific polymerase chain reaction
UVA- univariable analysis
MVA- multivariable analysis
HR- hazard ratio
AO- anaplastic oligodendroglioma
AOA- anaplastic oligoastrocytoma
AA- anaplastic astrocytoma
GBM- glioblastoma
LGG- low-grade glioma
AG- anaplastic glioma
TTF- time to treatment failure
PFS- progression-free survival
OS- overall survival
NR- not reached
NS- not significant
Wt- wild type
Mt- mutant
RT- radiotherapy
PCV- procarbazine, lomustine, and vincristine
TMZ- temozolomide
SSE- Sequenom Standard Epipanel
MS- HRM- methylation-sensitive high-resolution melting
Adj.- adjuvant
Conc.- Concurrent
Codel- 1p/19q-codeleted
u*MGMT*- unmethylated *MGMT*
m*MGMT*- methylated *MGMT*
GGN- German Glioma Network
EORTC- European Organization of Research and Treatment of Cancer
RTOG- Radiation Therapy Oncology Group

NOA- Neurooncology Working Group of the German Cancer Society

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eTable 2. Chemotherapy Regimens Used as First-Line Treatment

Chemotherapy	Count	%
TMZ	226	78.5%
PCV	61	21.2%
Carmustine	1	0.3%

eTable 3. Patient Demographical and Clinical Characteristics in *IDH*-Wildtype Tumors

Characteristic	Methylated, N = 56[1]	Unmethylated, N = 79[1]	p-value[2]
Age			.73
0 - 64	44 (79%)	64 (81%)	
65+	12 (21%)	15 (19%)	
Sex			.92
Male	31 (55%)	43 (54%)	
Female	25 (45%)	36 (46%)	
Grade			.14
II	6 (11%)	16 (20%)	
III	50 (89%)	63 (80%)	
Chemotherapy			**.007**
No Chemotherapy	25 (45%)	18 (23%)	
Chemotherapy	31 (55%)	61 (77%)	
Radiotherapy			**.002**
No Radiotherapy/Unknown	11 (20%)	36 (46%)	
Radiotherapy	45 (80%)	43 (54%)	

[1]n (%)

[2]Pearson's Chi-squared test

eTable 4. Patient Demographical and Clinical Characteristics in *IDH*-Mutant/Non-Codeleted Tumors

Characteristic	Methylated, N = 79[1]	Unmethylated, N = 70[1]	p-value[2]
Age			.50
0 - 64	77 (97%)	70 (100%)	
65+	2 (2.5%)	0 (0%)	
Sex			.40
Male	42 (53%)	42 (60%)	
Female	37 (47%)	28 (40%)	
Grade			**.03**
II	27 (34%)	36 (51%)	
III	52 (66%)	34 (49%)	
Chemotherapy			.51
No Chemotherapy	21 (27%)	22 (31%)	
Chemotherapy	58 (73%)	48 (69%)	
Radiotherapy			.09
No Radiotherapy/Unknown	32 (41%)	38 (54%)	
Radiotherapy	47 (59%)	32 (46%)	

[1]n (%)

[2]Fisher's exact test; Pearson's Chi-squared test

eTable 5. Patient Demographical and Clinical Characteristics in *IDH*-Mutant/Codeleted Tumors

Characteristic	Methylated, N = 94[1]	Unmethylated, N = 33[1]	p-value[2]
Age			.44
0 - 64	86 (91%)	32 (97%)	
65+	8 (8.5%)	1 (3.0%)	
Sex			.74
Male	60 (64%)	20 (61%)	
Female	34 (36%)	13 (39%)	
Grade			.21
II	45 (48%)	20 (61%)	
III	49 (52%)	13 (39%)	
Chemotherapy			.54
No Chemotherapy	26 (28%)	11 (33%)	
Chemotherapy	68 (72%)	22 (67%)	
Radiotherapy			.35
No Radiotherapy/Unknown	51 (54%)	21 (64%)	
Radiotherapy	43 (46%)	12 (36%)	

[1]n (%)

[2]Fisher's exact test; Pearson's Chi-squared test

eTable 6. Univariable and Multivariable Analysis of Progression-Free Survival in All Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	1.03	1.02, 1.04	**< .001**	1.01	1.00, 1.03	**.04**
Sex						
Male	—	—				
Female	1.04	0.75, 1.43	.83			
Grade						
II	—	—		—	—	
III	2.38	1.60, 3.54	**< .001**	1.90	1.27, 2.86	**.002**
Molecular Class						
IDH-wildtype	—	—		—	—	
IDH-mutant/non-codeleted	0.22	0.15, 0.32	**< .001**	0.30	0.19, 0.47	**< .001**
IDH-mutant/codeleted	0.15	0.10, 0.23	**< .001**	0.24	0.15, 0.38	**< .001**
Radiotherapy						
No Radiotherapy/Unknown	—	—				
Radiotherapy	1.26	0.91, 1.75	.17			
MGMT						
Methylated	—	—		—	—	

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Unmethylated	2.29	1.66, 3.17	**< .001**	1.95	1.39, 2.75	**< .001**

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 7. Univariable and Multivariable Analysis of Progression-Free Survival in *IDH*-wildtype Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	1.01	0.99, 1.03	.47			
Sex						
Male	—	—				
Female	1.05	0.65, 1.71	.84			
Grade						
II	—	—		—	—	
III	2.30	0.99, 5.34	.05	2.68	1.14, 6.26	**.02**
Radiotherapy						
No Radiotherapy/Unknown	—	—				
Radiotherapy	0.81	0.49, 1.34	.41			
MGMT						
Methylated	—	—		—	—	
Unmethylated	1.95	1.15, 3.30	**.01**	2.15	1.26, 3.66	**.005**

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 8. Univariable and Multivariable Analysis of Progression-Free Survival in *IDH*-mutant/non-codeleted Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	1.01	0.99, 1.04	.34			
Sex						
Male	—	—				
Female	0.66	0.36, 1.20	.17			
Grade						
II	—	—				
III	1.14	0.62, 2.11	.67			
Radiotherapy						
No Radiotherapy/Unknown	—	—		—	—	
Radiotherapy	1.81	0.95, 3.44	.07	1.81	0.95, 3.44	.07
MGMT						
Methylated	—	—				
Unmethylated	1.19	0.67, 2.12	.56			

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 9. Univariable and Multivariable Analysis of Progression-Free Survival in *IDH*-mutant/codeleted Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	1.00	0.97, 1.03	.97			
Sex						
Male	—	—				
Female	1.16	0.61, 2.23	.65			
Grade						
II	—	—		—	—	
III	2.82	1.32, 6.02	**.007**	3.17	1.48, 6.80	**.003**
Radiotherapy						
No Radiotherapy/Unknown	—	—				
Radiotherapy	0.78	0.40, 1.51	.46			
MGMT						
Methylated	—	—		—	—	
Unmethylated	2.54	1.24, 5.20	**.01**	2.99	1.44, 6.21	**.003**

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 10. Univariable and Multivariable Analysis of Overall Survival in All Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	1.04	1.03, 1.06	**< .001**	1.03	1.01, 1.04	**< .001**
Sex						
Male	—	—				
Female	0.96	0.66, 1.40	.83			
Grade						
II	—	—		—	—	
III	1.99	1.26, 3.13	**.003**	1.37	0.86, 2.17	.18
Molecular Class						
IDH-wildtype	—	—		—	—	
IDH-mutant/non-codeleted	0.18	0.12, 0.29	**< .001**	0.26	0.16, 0.44	**< .001**
IDH-mutant/codeleted	0.08	0.04, 0.14	**< .001**	0.11	0.06, 0.21	**< .001**
Radiotherapy						
No Radiotherapy/Unknown	—	—		—	—	
Radiotherapy	1.85	1.21, 2.81	**.004**	1.00	0.64, 1.57	.99
MGMT						

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Methylated	—	—		—	—	
Unmethylated	2.30	1.57, 3.37	**< .001**	1.65	1.11, 2.46	**.01**

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 11. Univariable and Multivariable Analysis of Overall Survival in *IDH*-wildtype Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	1.03	1.01, 1.05	**.01**	1.03	1.00, 1.05	**.02**
Sex						
Male	—	—				
Female	0.83	0.50, 1.38	.47			
Grade						
II	—	—		—	—	
III	1.77	0.83, 3.74	.14	1.92	0.90, 4.09	.09
Radiotherapy						
No Radiotherapy/Unknown	—	—				
Radiotherapy	0.65	0.36, 1.19	.16			
MGMT						
Methylated	—	—		—	—	
Unmethylated	1.83	1.06, 3.15	**.03**	1.69	0.98, 2.91	.06

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 12. Univariable and Multivariable Analysis of Overall Survival in *IDH*-mutant/non-codeleted Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	1.00	0.97, 1.03	.89			
Sex						
Male	—	—		—	—	
Female	0.49	0.24, 1.03	.06	0.49	0.24, 1.03	.06
Grade						
II	—	—				
III	0.74	0.37, 1.48	.39			
Radiotherapy						
No Radiotherapy/Unknown	—	—				
Radiotherapy	1.46	0.67, 3.18	.35			
MGMT						
Methylated	—	—				
Unmethylated	1.07	0.54, 2.12	.85			

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 13. Univariable and Multivariable Analysis of Overall Survival in *IDH*-mutant/codeleted Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	1.03	0.99, 1.08	.14	1.04	0.99, 1.08	.09
Sex						
Male	—	—				
Female	0.96	0.35, 2.65	.94			
Grade						
II	—	—		—	—	
III	5.56	1.26, 24.6	**.02**	4.87	1.07, 22.2	**.04**
Radiotherapy						
No Radiotherapy/Unknown	—	—		—	—	
Radiotherapy	2.76	0.87, 8.75	.08	2.37	0.69, 8.09	.17
MGMT						
Methylated	—	—		—	—	
Unmethylated	2.40	0.81, 7.17	.12	4.21	1.25, 14.2	**.02**

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 14. Summary of Univariable and Multivariable Subgroup Analyses in All Patients with Any First-Line Treatment

	Univariable			Multivariable		
Molecular Subgroup	HR of u*MGMT*	95% CI[1]	p-value	HR of u*MGMT*	95% CI	p-value
Progression-Free Survival						
All Cases	1.67	1.29, 2.15	**< .001**	1.36	1.04, 1.79	**.03**
IDH-wildtype	1.17	0.79, 1.73	.44	NA	NA	NA
IDH-mutant/non-codeleted	0.99	0.63, 1.57	.98	NA	NA	NA
IDH-mutant/codeleted	2.16	1.19, 3.90	**.01**	2.54	1.38, 4.67	**.003**
Overall Survival						
All Cases	1.57	1.16, 2.12	**.003**	1.17	0.86, 1.60	.31
IDH-wildtype	1.24	0.83, 1.87	.30	NA	NA	NA
IDH-mutant/non-codeleted	0.90	0.51, 1.57	.70	NA	NA	NA
IDH-mutant/codeleted	1.64	0.69, 3.92	.26	NA	NA	NA

u*MGMT* = unmethylated *MGMT* promoter, HR = Hazard Ratio, CI = Confidence Interval, NA = not applicable

Table 15. Summary of Univariable and Multivariable Subgroup Analyses in Patients that Received No Chemotherapy During First-Line Treatment

	Univariable			Multivariable		
Molecular Subgroup	HR of u*MGMT*	95% CI[1]	p-value	HR of u*MGMT*	95% CI	p-value
Progression-Free Survival						
All Cases	0.98	0.62, 1.53	.93	NA	NA	NA
IDH-wildtype	0.54	0.28, 1.05	.07	0.42	0.21, 0.85	**.02**
IDH-mutant/non-codeleted	0.76	0.35, 1.66	.50	NA	NA	NA
IDH-mutant/codeleted	1.46	0.48, 4.44	.50	NA	NA	NA
Overall Survival						
All Cases	0.79	0.46, 1.36	.40	NA	NA	NA
IDH-wildtype	0.76	0.38, 1.53	.44	NA	NA	NA
IDH-mutant/non-codeleted	0.54	0.18, 1.57	.26	NA	NA	NA
IDH-mutant/codeleted	0.73	0.15, 3.46	.69	NA	NA	NA

u*MGMT* = unmethylated *MGMT* promoter, HR = Hazard Ratio, CI = Confidence Interval, NA = not applicable

eTable 16. Summary of Sensitivity Analysis of Univariable and Multivariable Subgroup Analyses in Patients that Received Chemotherapy

	Univariable				Multivariable			
Molecular Subgroup	HR of u*MGMT*	95% CI[1]	p-value	p-value for interaction with treatment	HR of u*MGMT*	95% CI	p-value	p-value for interaction with treatment
Progression-Free Survival								
All Cases	2.29	1.66, 3.17	**< .001**	**.004**	2.05	1.46, 2.89	**< .001**	**.005**
IDH-wildtype	2.04	1.21, 3.45	**.007**	**.01**	2.26	1.33, 3.83	**.002**	**.004**
IDH-mutant/non-codeleted	1.19	0.67, 2.12	.56	.41	NA	NA	NA	.94
IDH-mutant/codeleted	2.52	1.23, 5.18	**.01**	.25	2.92	1.40, 6.07	**.004**	.37
Overall Survival								
All Cases	2.30	1.57, 3.37	**< .001**	**.003**	1.78	1.20, 2.65	**.004**	**.01**
IDH-wildtype	1.91	1.11, 3.27	**.02**	.12	1.80	1.04, 3.10	**.04**	.06
IDH-mutant/non-codeleted	1.07	0.54, 2.12	.85	.32	NA	NA	NA	.70
IDH-mutant/codeleted	2.43	0.80, 7.32	.12	.09	3.00	0.96, 9.37	.06	.08

u*MGMT* = unmethylated *MGMT* promoter, HR = Hazard Ratio, CI = Confidence Interval, NA = not applicable

eTable 17. Univariable and Multivariable Analysis of Progression-Free Survival in Age 0 – 43 *IDH*-wildtype Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Sex						
Male	—	—				
Female	0.93	0.27, 3.21	.91	-	-	-
Grade						
II	—	—				
III	1.46	0.31, 6.92	.63	-	-	-
Radiotherapy						
No Radiotherapy/Unknown	—	—				
Radiotherapy	0.55	0.15, 1.99	.36	-	-	-
MGMT						
Methylated	—	—				
Unmethylated	2	0.60, 6.75	.26	-	-	-

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 18. Univariable and Multivariable Analysis of Progression-Free Survival in Age 44+ *IDH*-wildtype Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Sex						
Male	—	—				
Female	1.13	0.67, 1.92	.64			
Grade						
II	—	—		—	—	
III	2.55	0.92, 7.08	.07	3.65	1.29, 10.4	**.02**
Radiotherapy						
No Radiotherapy/Unknown	—	—				
Radiotherapy	0.88	0.51, 1.52	.64			
MGMT Promoter Status						
Methylated	—	—		—	—	
Unmethylated	1.81	1.00, 3.30	.05	2.35	1.27, 4.35	**.007**

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 19. Univariable and Multivariable Analysis of Progression-Free Survival in Grade III* *IDH*-wildtype Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	1.01	0.99, 1.03	.33			
Sex						
Male	—	—				
Female	1.00	0.60, 1.67	.99			
Radiotherapy						
No Radiotherapy/Unknown	—	—				
Radiotherapy	0.87	0.52, 1.46	.60			
MGMT						
Methylated	—	—		—	—	
Unmethylated	2.21	1.27, 3.86	**.005**	2.21	1.27, 3.86	**.005**

[1]HR = Hazard Ratio, CI = Confidence Interval

*There were not enough grade II cases to fit a multivariable model. See Supplemental Figure S4.

eTable 20. Univariable and Multivariable Analysis of Progression-Free Survival in Grade II *IDH*-mutant/non-codeleted Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	0.98	0.94, 1.03	.49	-	-	-
Sex						
Male	—	—		—	—	
Female	0.44	0.14, 1.31	.14	0.44	0.14, 1.31	.14
Radiotherapy						
No Radiotherapy/Unknown	—	—				
Radiotherapy	0.85	0.29, 2.53	.78	-	-	-
MGMT Promoter Status						
Methylated	—	—				
Unmethylated	1.07	0.38, 2.97	.9	-	-	-

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 21. Univariable and Multivariable Analysis of Progression-Free Survival in Grade III *IDH*-mutant/non-codeleted Patients that Received Chemotherapy

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	p-value	HR[1]	95% CI[1]	p-value
Age	1.03	1.00, 1.07	.08	1.03	0.99, 1.06	.14
Sex						
Male	—	—				
Female	0.75	0.36, 1.55	.44			
Radiotherapy						
No Radiotherapy/Unknown	—	—		—	—	
Radiotherapy	2.20	0.95, 5.09	.07	2.03	0.87, 4.75	.10
MGMT Promoter Status						
Methylated	—	—				
Unmethylated	1.28	0.64, 2.59	.48			

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 22. Univariable and Multivariable Analysis of Overall Survival in IDH-mutant/codeleted Patients that Received Chemotherapy, Using *P* < .05 as Threshold for Inclusion

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	*P* value	HR[1]	95% CI[1]	*P* value
Age	1.03	0.99, 1.08	.14	—	—	—
Sex						
Male	Reference					
Female	0.96	0.35, 2.65	.94	—	—	—
Grade						
II	Reference					
III	5.56	1.26, 24.6	**.02**	5.92	1.34, 26.2	**.02**
Radiotherapy						
No Radiotherapy/Unknown	Reference					
Radiotherapy	2.76	0.87, 8.75	.08	—	—	—
MGMT						
Methylated	Reference					
Unmethylated	2.40	0.81, 7.17	.12	2.75	0.90, 8.35	.08

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 23. Patient Demographic and Clinical Characteristics of IDH-wildtype and IDH-mutant/codeleted Patients in the EORTC/CUIMC Cohorts

Characteristic	Methylated, N = 78[1]	Unmethylated, N = 46[1]	*P* value[2]
Age	48 (38 – 58)	52 (40 – 58)	.57
Sex			0.40
Male	50 (64%)	26 (57%)	
Female	28 (36%)	20 (43%)	
Molecular Class			**<0.001**
IDH-wildtype	40 (51%)	38 (83%)	
IDH-mutant/codeleted	38 (49%)	8 (17%)	
Grade			0.37
II	11 (14%)	4 (8.7%)	
III	67 (86%)	42 (91%)	
Chemotherapy			.07
Yes	43 (55%)	33 (72%)	
No	35 (45%)	13 (28%)	
Radiotherapy			.47
Yes	74 (95%)	42 (91%)	
No	4 (5.1%)	4 (8.7%)	

Characteristic	Methylated, N = 78[1]	Unmethylated, N = 46[1]	*P* value[2]
Performance Status			.87
KPS ≥ 80 or ECOG 0-1	65 (83%)	38 (84%)	
KPS < 80 or ECOG 2	13 (17%)	7 (16%)	
Extent of Resection			.33
Biopsy	5 (6.5%)	7 (15%)	
Subtotal Resection	44 (57%)	24 (52%)	
Gross-total Resection	28 (36%)	15 (33%)	

[1]n (%); Median (Interquartile Range)

[2]Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test

eTable 24. Univariable and Multivariable Analysis of Progression-Free Survival in Patients with IDH-wildtype and IDH-mutant/codeleted Tumors that Received Chemotherapy in the EORTC/CUIMC Cohorts, Including Performance Status and Extent of Resection

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	*P* value	HR[1]	95% CI[1]	*P* value
Performance Status						
KPS < 80 or ECOG 2	Reference					
KPS ≥ 80 or ECOG 0-1	0.65	0.30, 1.38	.26	—	—	—
Extent of Resection						
Biopsy	Reference					
Subtotal Resection	0.23	0.10, 0.54	**<.001**	0.29	0.13, 0.66	**.003**
Gross-total Resection	0.22	0.09, 0.53	**<.001**	0.29	0.12, 0.72	**.007**
MGMT						
Methylated	Reference					
Unmethylated	2.66	1.52, 4.67	**<.001**	2.41	1.35, 4.29	**.003**

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 25. Univariable and Multivariable Analysis of Progression-Free Survival in Patients with IDH-wildtype and IDH-mutant/codeleted Tumors that Received No Chemotherapy in the EORTC/CUIMC Cohorts, Including Performance Status and Extent of Resection

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	*P* value	HR[1]	95% CI[1]	*P* value
Performance Status						
KPS < 80 or ECOG 2	Reference					
KPS ≥ 80 or ECOG 0-1	0.63	0.31, 1.28	.20	—	—	—
Extent of Resection						
Biopsy	Reference					
Subtotal Resection	0.88	0.30, 2.60	.82	—	—	—
Gross-total Resection	0.53	0.17, 1.67	.28	—	—	—
MGMT						
Methylated	Reference					
Unmethylated	1.39	0.71, 2.72	.33	—	—	—

[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 26. Univariable and Multivariable Analysis of Overall Survival in Patients with IDH-wildtype and IDH-mutant/codeleted Tumors that Received Chemotherapy in the EORTC/CUIMC Cohorts, Including Performance Status and Extent of Resection

	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	*P* value	HR[1]	95% CI[1]	*P* value
Performance Status						
KPS < 80 or ECOG 2	Reference					
KPS ≥ 80 or ECOG 0-1	0.63	0.26, 1.52	.31	—	—	—
Extent of Resection						
Biopsy	Reference					
Subtotal Resection	0.52	0.19, 1.41	.20	—	—	—
Gross-total Resection	0.48	0.17, 1.39	.18	—	—	—
MGMT						
Methylated	Reference					
Unmethylated	2.70	1.42, 5.14	**.003**	2.70	1.42, 5.14	**.003**

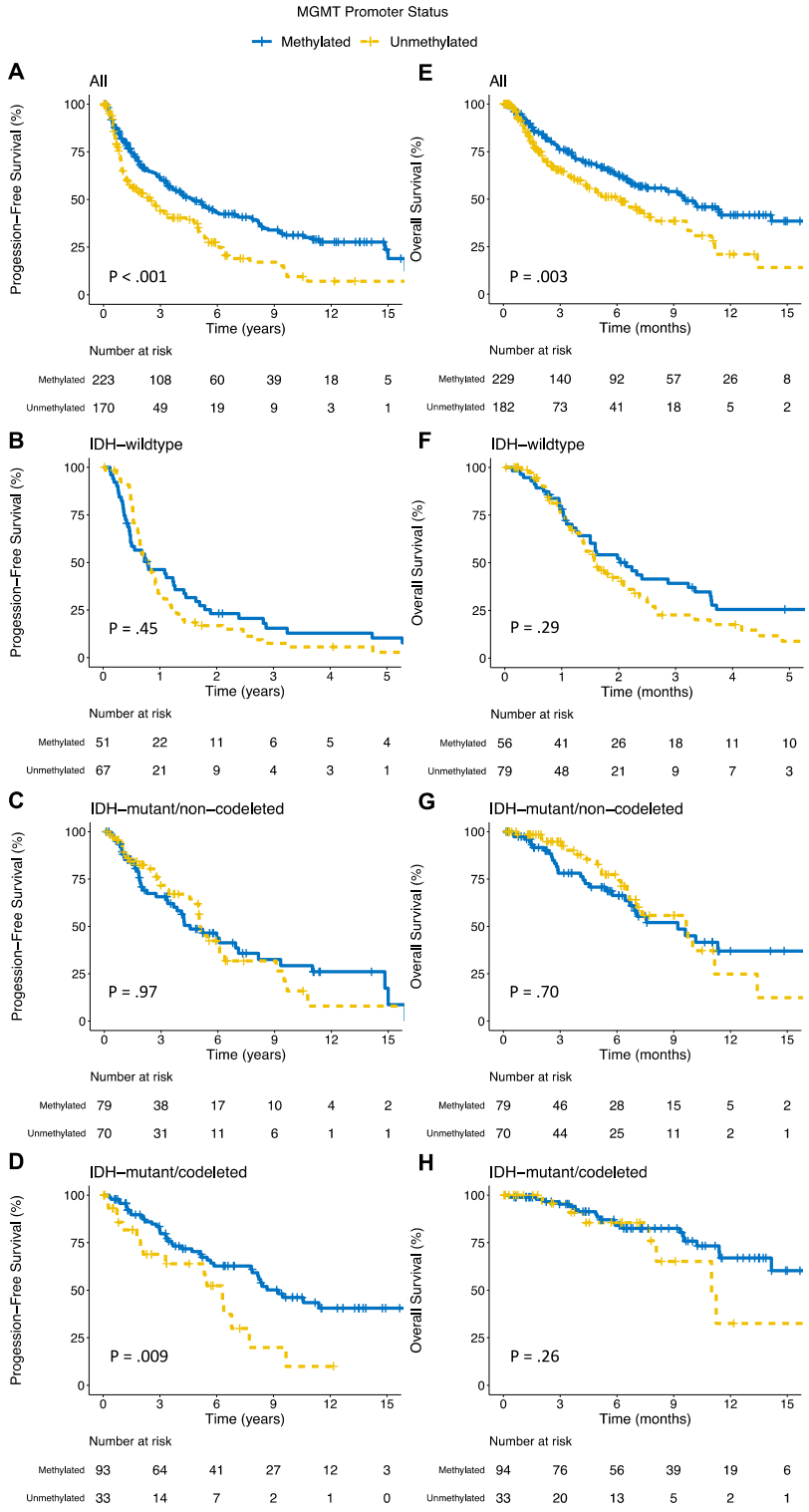
[1]HR = Hazard Ratio, CI = Confidence Interval

eTable 27. Univariable and Multivariable Analysis of Overall Survival in Patients with IDH-wildtype and IDH-mutant/codeleted Tumors that Received No Chemotherapy in the EORTC/CUIMC Cohorts, Including Performance Status and Extent of Resection

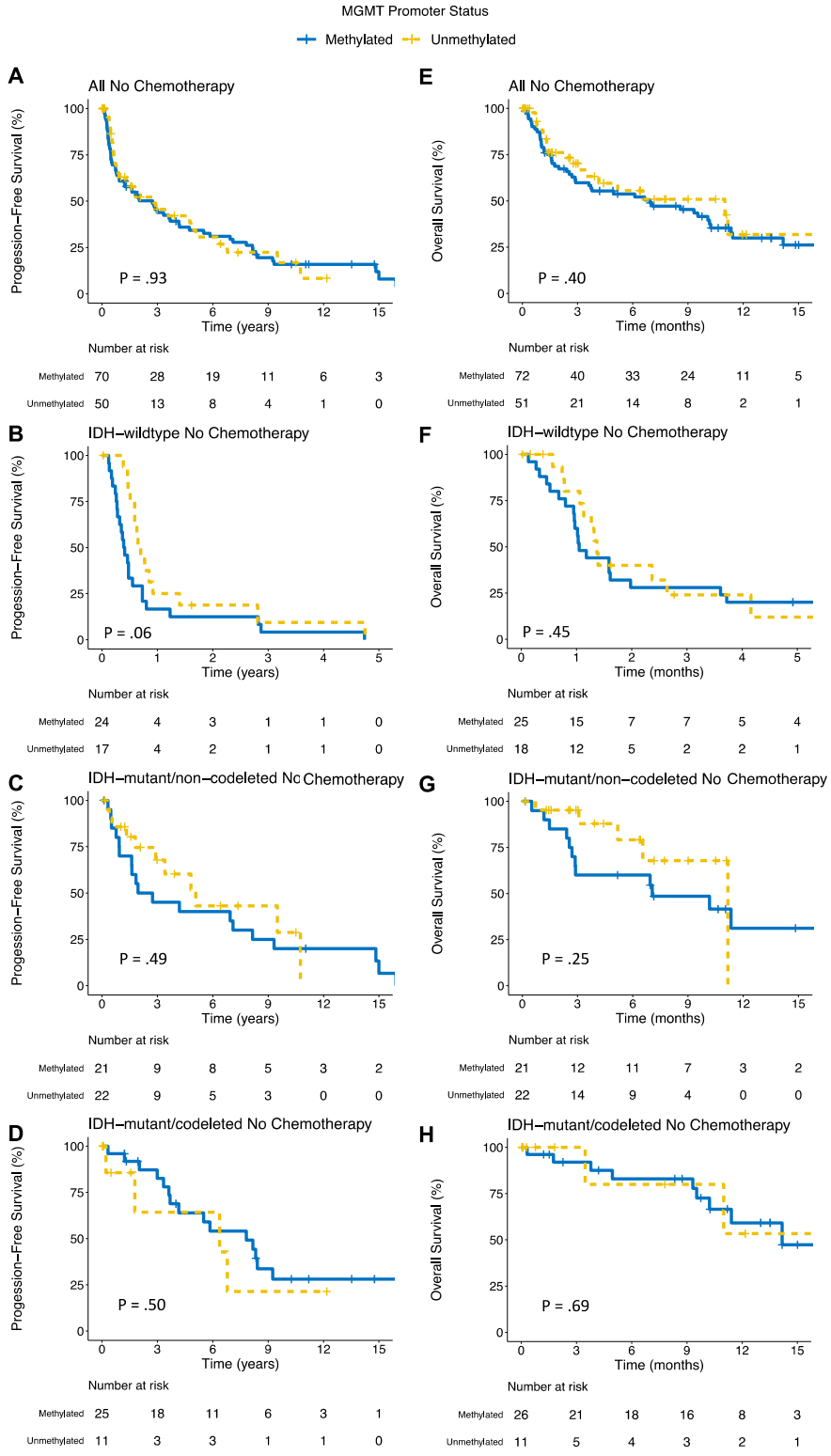
	Univariable			Multivariable		
Characteristic	HR[1]	95% CI[1]	*P* value	HR[1]	95% CI[1]	*P* value
Performance Status						
KPS < 80 or ECOG 2	Reference					
KPS ≥ 80 or ECOG 0-1	0.70	0.33, 1.46	.34	—	—	—
Extent of Resection						
Biopsy	Reference					
Subtotal Resection	0.57	0.19, 1.68	.31	0.57	0.19, 1.68	.31
Gross-total Resection	0.29	0.09, 0.93	**.04**	0.29	0.09, 0.93	**.04**
MGMT						
Methylated	Reference					
Unmethylated	1.45	0.73, 2.87	.28	—	—	—

[1]HR = Hazard Ratio, CI = Confidence Interval

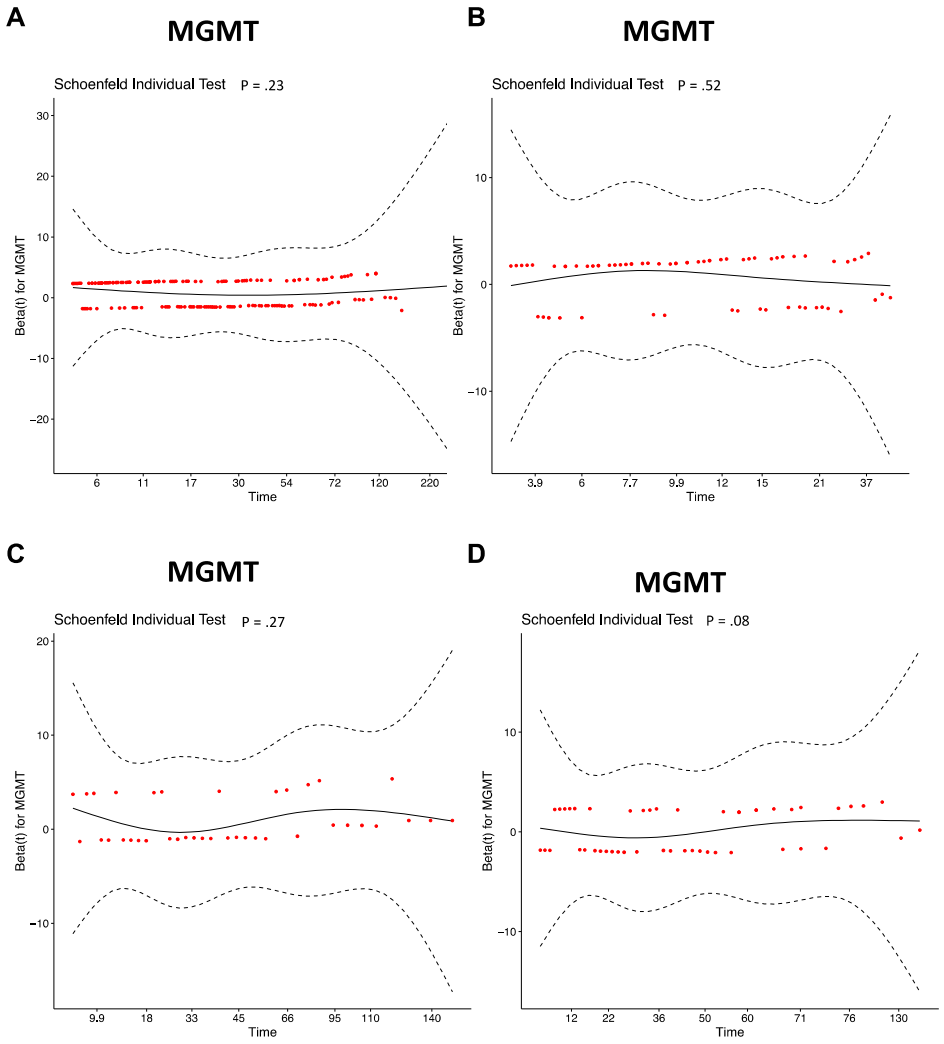
eFigure 1. Kaplan-Meier curves for progression-free (A) and overall (B) survival based on *MGMT* promoter methylation status in all patients, regardless of treatment status. Plots are stratified by molecular subgroup.



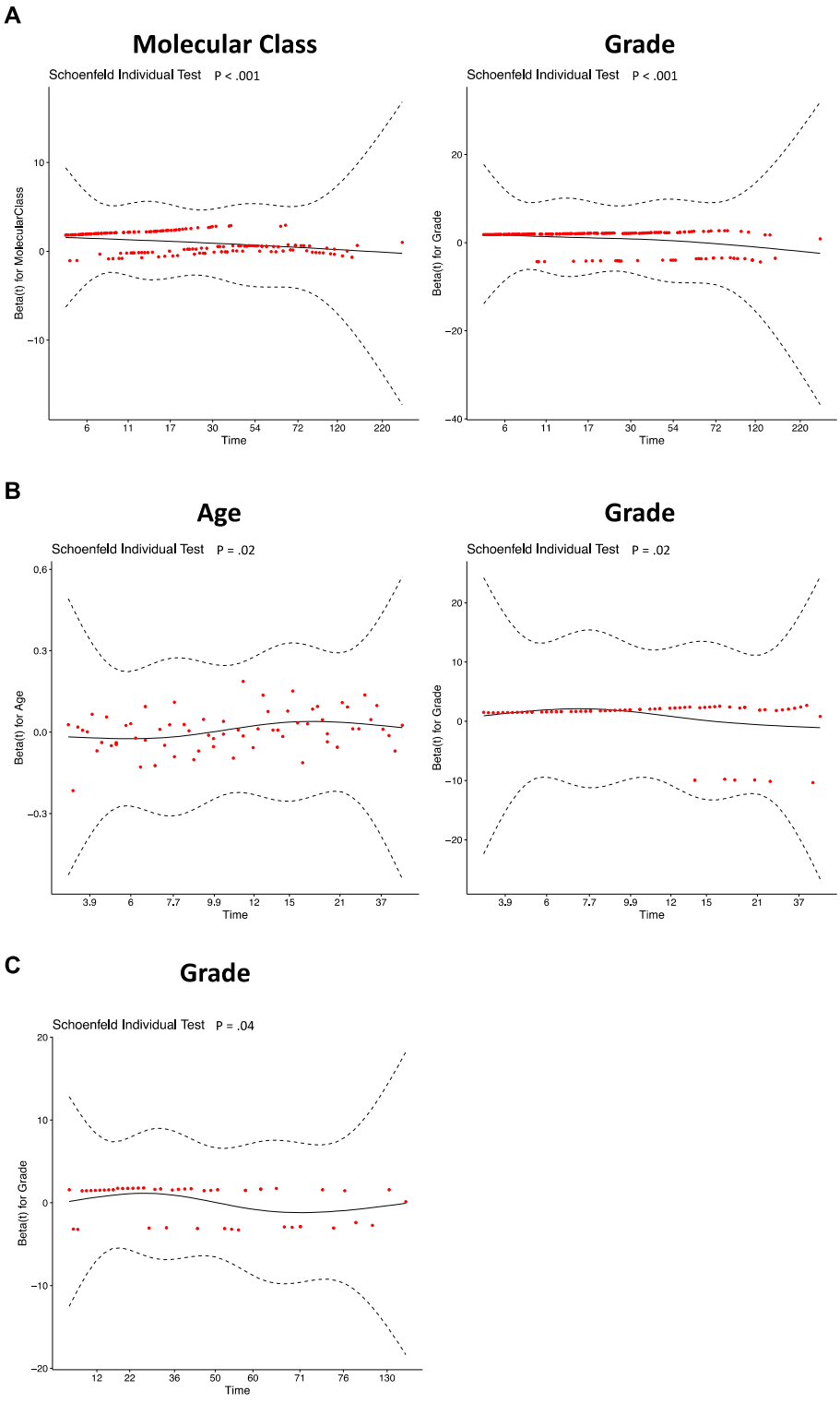
eFigure 2. Kaplan-Meier curves for (A-D) progression-free survival and (E-H) overall survival based on *MGMT* promoter methylation status in patients that did not receive chemotherapy. Plots are stratified by molecular subgroup.



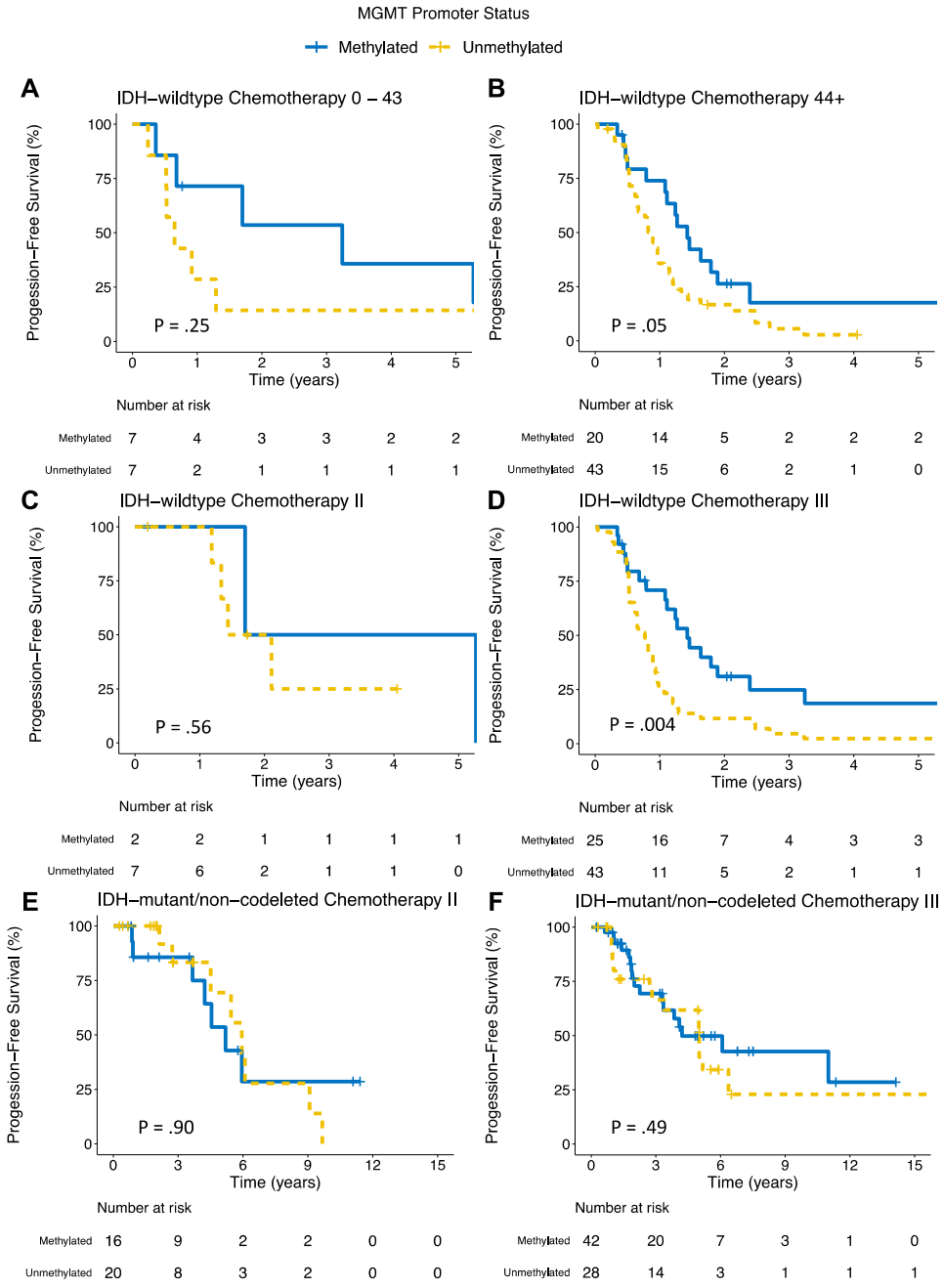
eFigure 3. Schoenfeld residual plots of PFS for *MGMT* status in all (A) *IDH*-wildtype (B), *IDH*-mutant/non-codeleted (C), and *IDH*-mutant/codeleted (D) tumors.



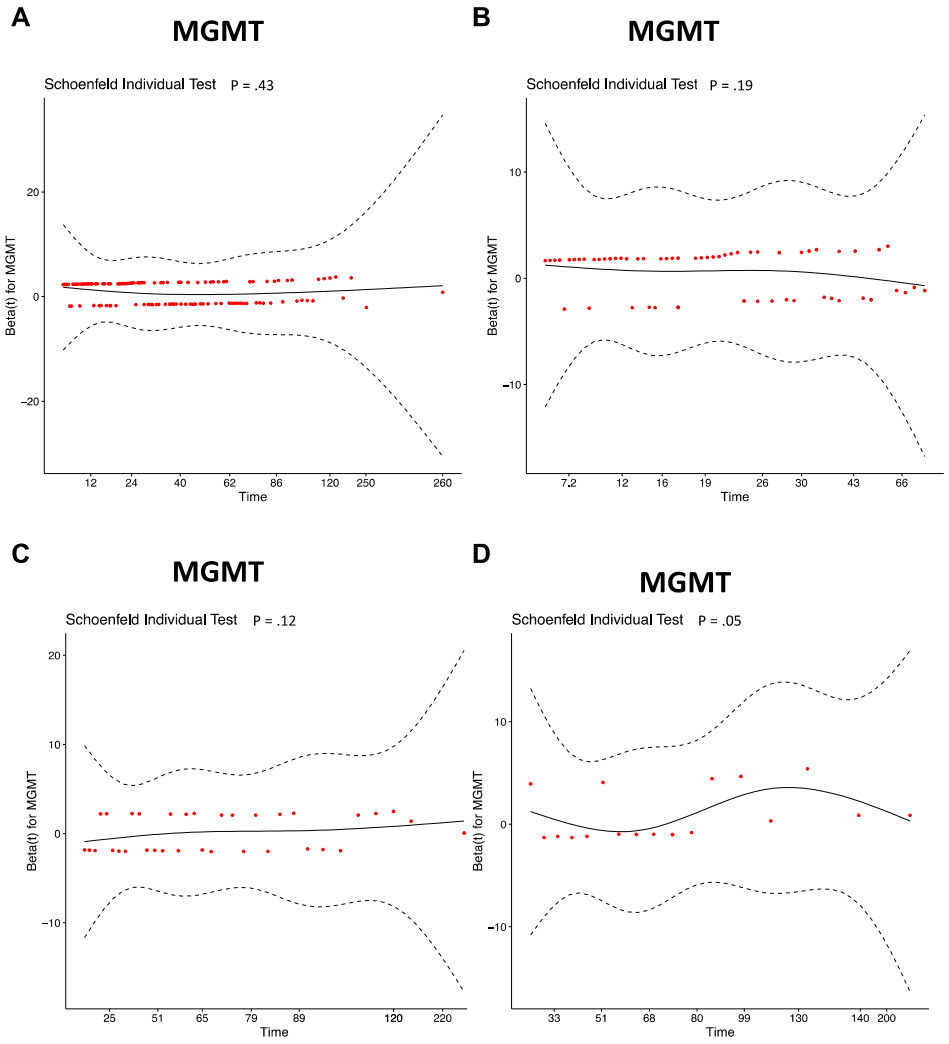
eFigure 4. Schoenfeld residual plots of PFS for variables that violated the proportional hazards assumption in all (A) *IDH*-wildtype (B), and *IDH*-mutant/non-codeleted (C) tumors.



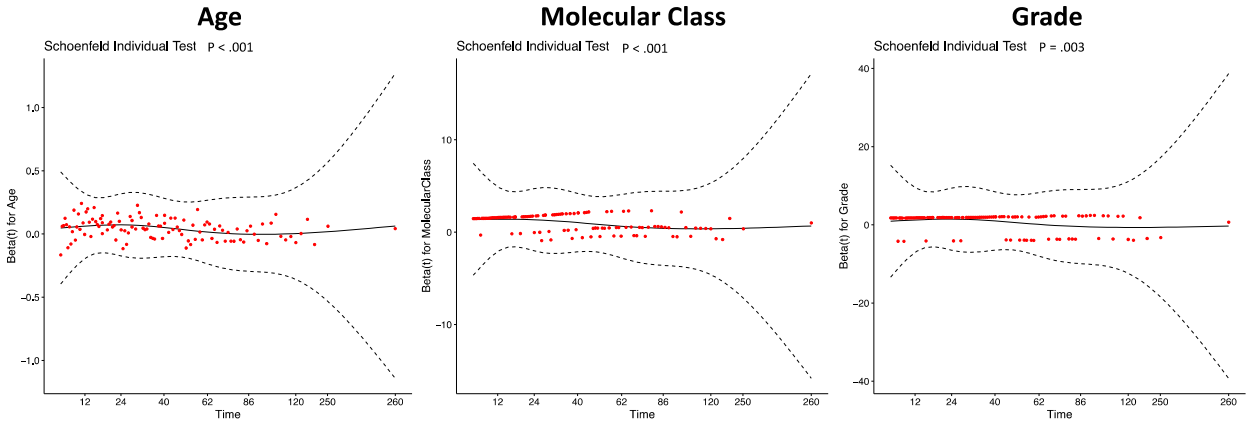
eFigure 5. Kaplan-Meier curves for progression-free survival based on *MGMT* promoter status in patients with *IDH*-wildtype tumors stratified by age and grade (A) and *IDH*-mutant/non-codeleted tumors stratified by grade (B).



eFigure 6. Schoenfeld residual plots of OS for *MGMT* status in all (A) *IDH*-wildtype (B), *IDH*-mutant/non-codeleted (C), and *IDH*-mutant/codeleted (D) tumors.



eFigure 7. Schoenfeld residual plots of OS for variables that violated the proportional hazards assumption in all tumors.



eFigure 8. Kaplan-Meier curves based on MGMT promoter status for progression-free survival (A, B) and overall survival (C, D) in patients with *IDH*-wildtype or *IDH*-mutant/codeleted tumors in the EORTC/CUIMC cohorts.