Combined analysis of *TERT*, *EGFR*, and *IDH* status defines distinct prognostic glioblastoma classes

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ABSTRACT

Objective: To identify the prognostic significance of *TERT* promoter mutations (*TERT*p-mut) and their associations with common molecular alterations in glioblastomas (GBMs).

Methods: We sequenced the *TERT*p-mut in DNA from 395 GBMs and analyzed the results with their respective histology, genetic profile (*IDH1* mutation, *EGFR* amplification, *CDKN2A* homozygous deletion, loss of chromosome 10, *TP53* mutation), and overall survival (OS).

Results: *TERT*p-mut were found in 299 of 395 GBMs (75.7%) and were associated with an older age (median 59.6 years for *TERT*p-mut vs 53.6 years for *TERT* promoter wild type [*TERT*p-wt], $p < 0.0001$). *TERT*p-mut was an independent factor of poor prognosis (OS = 13.8 vs 18.4 months), in both *IDH*-mutated (OS = 13.8 vs 37.6 months, $p = 0.022$) and *IDH*-wt GBMs (OS = 13.7 vs 17.5 months, $p = 0.006$). *TERT*p-mut was associated with *IDH*-wt, *EGFR* amplification, *CDKN2A* deletion, and chromosome 10q loss, but not with *MGMT* promoter methylation. In the *TERT*p-wt group, OS was twice longer in *EGFR*-wt than in *EGFR* amplification GBMs (OS = 26.6 vs 13.3 months; $p = 0.005$). In the *EGFR*-wt group, patients with *TERT*p-wt had a significantly better outcome (OS = 26.3 vs 12.5 months, $p < 0.0001$), whereas in the *EGFR* amplification group, patients with *TERT*p-mut survived longer (OS = 15.8 vs 13.3 months, $p = 0.05$). Taken together, the absence of both *EGFR* amplification and *TERT*p-mut is associated with longer survival in patients with GBM (26.5 months for patients with *IDH*-wt, 36.7 months for patients with *IDH* mutation).

Conclusions: The analysis of *TERT*p-mut, in combination with *EGFR* amplification and *IDH* mutation status, refines the prognostic classification of GBMs. ***Neurology*® 2014;83:1200–1206**

GLOSSARY

CDKN2A = cyclin-dependent kinase inhibitor 2A; ***EGFR*** = epidermal growth factor receptor; **GBM** = glioblastoma; ***IDH*** = isocitrate dehydrogenase; ***MGMT*** = methylguanine methyltransferase; **OS** = overall survival; **PFS** = progression-free survival; ***TERT*** = telomerase reverse transcriptase; ***TERT*p-mut** = *TERT* promoter mutation; ***TERT*p-wt** = *TERT* promoter wild type; ***TP53*** = tumor protein p53; **wt** = wild type.

Recently, mutations affecting the promoter region of the telomerase reverse transcriptase (*TERT*) gene have been reported in numerous cancers.[1–4] Gliomas and especially glioblastomas (GBMs) were among the most frequently affected tumors.[4–7] These mutations occurred in 2 hotspot positions (chr5, 1,295,228 C>T and chr5, 1,295,250 C>T), located −124 and −146 base pairs upstream from the ATG start site (−124 G>A and −146 G>A).[7] Both mutations conferred enhanced *TERT* promoter activity, possibly by generating a consensus binding site (CCTGAA>CCGGAA) for E-twenty-six transcription factors.[2,3]

The *TERT* gene codes for a highly specialized reverse transcriptase catalyzing, with other members of the telomerase complex, the 3′ extension of chromosome ends by adding hexamers repeats.[8,9] *TERT* expression and telomerase activity are usually low in normal tissues, and the constant shortening of telomeres finally leads to cell senescence. In contrast, most human

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cancers are characterized by an increased activity of telomerase allowing the maintenance of telomere length, thus avoiding induction of senescence and conferring unrestricted growth properties to cancer cells.[10,11]

A number of genetic and genomic alterations have already been described in GBM, including epidermal growth factor receptor (*EGFR*) amplification, cyclin-dependent kinase inhibitor 2A (*CDKN2A*) homozygous deletion, methylguanine methyltransferase (*MGMT*) promoter methylation, and isocitrate dehydrogenase (*IDH*) mutation. To date, only *MGMT* promoter methylation and *IDH* mutation have been proven to be prognostic in GBMs.[12,13]

In this study, we investigated the prevalence and the prognostic impact of *TERT* promoter mutations (*TERT*p-mut), in a series of 395 patients with GBM treated in our department. We then correlated the *TERT*p-mut status with the other genetic alterations.

METHODS **Patients and tissue samples.** Selection of patients was based on the following criteria: histologic diagnosis of primary GBM according to the World Health Organization classification, and clinical data and follow-up available in the neuro-oncology database (Onconeurothèque Paris). We considered primary GBM when the first symptoms appeared less than 3 months before the patient was referred to the clinics. We excluded patients known to have a history of seizure or known low-grade gliomas.

The QIAamp DNA Mini Kit was used to extract tumor DNA from frozen tumors, as described by the manufacturer (Qiagen, Courtaboeuf, France). DNA was extracted from blood samples using a conventional saline method.

For the determination of *EGFR* amplification, *CDKN2A* homozygous deletion, and loss of chromosomes 9 and 10, genomic profiling was performed by comparative genomic hybridization array analysis or single nucleotide polymorphism array, as previously described.[14,15] Mutational status of *IDH1*, *IDH2*, and *TP53* (tumor protein p53) was determined using the Sanger technique, as previously described.[16] *MGMT* promoter methylation status was determined by 2-stage nested methylation-specific PCR after bisulfite modification.[17]

Standard protocol approvals, registrations, and patient consents. Collection of tumor and blood samples and clinicopathologic information was undertaken with informed consent and relevant ethical board approval in accordance with the tenets of the Declaration of Helsinki.

Determination of *TERT*p-mut status. The promoter region of the *TERT* gene was amplified as follows: TERT-F GGCCGATTCGACCTCTCT and TERT-R AGCACCTCGCGGTAGTGG; 3 minutes at 94°C; 35 cycles at 94°C 15 seconds, 60°C 45 seconds, 72°C 1 minute, with a final step at 72°C for 8 minutes. PCR products were then purified with the Agencourt AMPure XP PCR purification protocol (Beckman Coulter, Villepinte, France). Purified PCR products were then sequenced using the Big-Dye Terminator Cycle Sequencing Ready Reaction (PerkinElmer, Villebon sur Yvette, France). Sequences were purified with the Agencourt CleanSEQ protocol according to the manufacturer's instructions (Beckman Coulter) and analyzed on an ABI Prism 3730 DNA Analyzer (Applied Biosystems, Saint Aubin, France).

Statistical analysis. The χ^2 test was used to compare the genotypes' distribution. The association with continuous variables was calculated with a Mann–Whitney test.

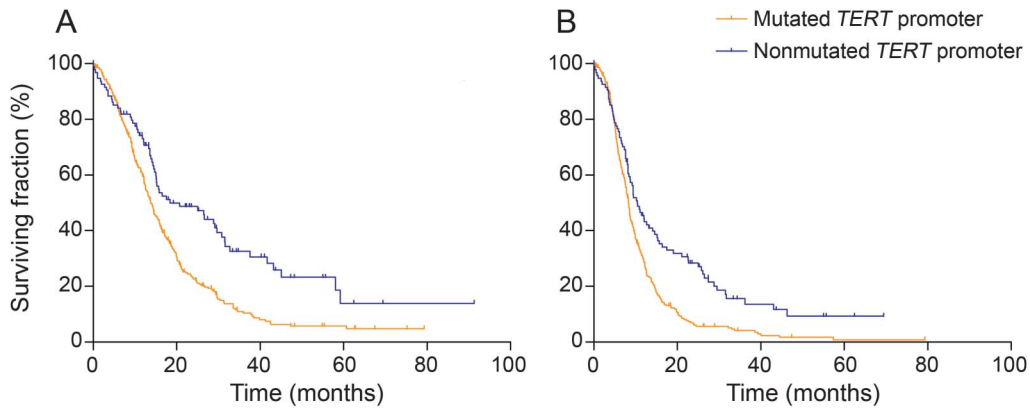
Overall survival (OS) was defined as the time between the diagnosis and death or last follow-up. Patients who were still alive at the last follow-up were considered as a censored event in analysis. Progression-free survival (PFS) was defined as the time between the diagnosis and recurrence or last follow-up. Patients who were recurrence-free at the last follow-up were considered as a censored event in the analysis. To find clinical and/or genomic factors related to OS (or PFS), survival curves were calculated according to the Kaplan–Meier method, and differences between curves were assessed using the log-rank test. Variables with a significant p value were used to build a multivariate Cox model. Two-sided p values <0.05 were considered significant.

RESULTS **Somatic and constitutional *TERT*p-mut status.** A population of 395 primary GBMs was screened for the presence of *TERT*p-mut. Median age at diagnosis was 58.5 years (range 18.2–89.1). Median Karnofsky Performance Score was 80 (range 20–100). At diagnosis, 281 patients (71.1%) underwent partial or total surgical resection and 114 (28.9%) were biopsied. One hundred seventy-four patients were treated with radiotherapy and temozolomide. One hundred forty-four patients were treated upfront with radiotherapy alone, either because they were treated before 2005 (122 patients) or because they were older than 70 years (21 patients). Twenty-seven patients received upfront chemotherapy. Fourteen patients did not receive any specific oncology treatment. The information was missing for 36 patients, who have been excluded from all PFS analyses. Median OS was 14.8 months and median PFS was 8.6 months.

We found 299 (75.7%) *TERT*p-mut, including 222 C228T (74.2%) and 77 C250T (25.8%) mutations. One tumor had both C228T and C250T mutations. This patient was considered as C228T *TERT* mutant for all subsequent analyses. Patients with *TERT*p-mut were older than patients with *TERT* promoter wild type (*TERT*p-wt) GBMs: median age at diagnosis was 59.6 vs 53.6 years, respectively ($p < 0.0001$). There was no difference of age at diagnosis between patients harboring C228T and C250T *TERT* mutations (data not shown). To confirm that such mutations were all somatic events, we investigated the presence of the *TERT*p-mut in blood DNA corresponding to 56 *TERT*p-mut GBMs. No mutation was found in blood DNA (data not shown).

***TERT*p-mut is an independent factor of poor prognosis in GBM.** In patients with GBM, patients with *TERT*p-mut had significantly shorter OS and PFS than patients with *TERT*p-wt. Median OS was 13.8

Figure 1 Prognostic impact of *TERT* promoter mutational status in glioblastomas



(A) Overall survival. (B) Progression-free survival. *TERT* = telomerase reverse transcriptase.

months in patients with *TERT*p-mut compared to 18.4 months in patients with *TERT*p-wt ($p < 0.0001$) (figure 1). Accordingly, PFS was 8.3 and 10.4 months, respectively ($p < 0.0001$). We did not find any difference in outcome between the C228T and C250T *TERT*p-mut (figure e-1 on the *Neurology*® Web site at Neurology.org).

We then input the following factors as candidate variables in the multivariate Cox proportional hazards regression model analysis: age at diagnosis, *IDH* mutation, extent of surgery, concomitant and adjuvant chemotherapy, Karnofsky Performance Score, *MGMT* promoter methylation status, and *TERT*p-mut. *TERT*p-mut appeared as an independent

Table 1 Multivariate analysis of prognostic factors for overall survival

	Univariate analysis		Multivariate analysis		
Parameters	Survival, mo	*p*	HR	95% CI for HR	*p*
KPS					
>70	17.1	<0.0001	0.801	0.569-1.127	0.2049
≤70	11.7				
IDH					
Mutated	26.6	0.005	0.603	0.332-1.094	0.0978
Nonmutated	14.5				
Extent of surgery					
Surgery	15.8	0.001	0.528	0.378-0.737	0.0002
Biopsy	10.1				
Age at diagnosis					
>60 y	10.7	<0.0001	1.720	1.272-2.325	0.0005
≤60 y	17.6				
Treatments					
Concomitant and adjuvant TMZ	19.0	<0.0001	0.478	0.351-0.651	<0.0001
Other	13.1				
MGMT promoter					
Methylated	15.8	0.022	0.684	0.515-0.908	0.0090
Nonmethylated	13.8				
TERT promoter					
Mutated	8.3	<0.0001	1.624	1.122-2.350	0.0105
Nonmutated	10.4				

Abbreviations: CI = confidence interval; HR = hazard ratio; *IDH* = isocitrate dehydrogenase; KPS = Karnofsky Performance Score; *MGMT* = methylguanine methyltransferase; *TERT* = telomerase reverse transcriptase; TMZ = temozolomide.

Table 2 Multivariate analysis of prognostic factors for progression-free survival

	Univariate analysis			Multivariate analysis	
Parameters	Survival, mo	*p*	HR	95% CI for HR	*p*
KPS					
>70	8.8	0.001	0.784	0.573–1.074	0.1321
≤70	7.4				
IDH					
Mutated	9.4	0.002	0.564	0.323–0.988	0.0439
Nonmutated	8.5				
Extent of surgery					
Surgery	8.8	0.275			
Biopsy	7.8				
Age at diagnosis					
>60 y	7.5	<0.0001	1.482	1.119–1.962	0.0063
≤60 y	9.5				
Treatments					
Concomitant and adjuvant TMZ	10.1	<0.0001	0.473	0.354–0.6733	<0.0001
Other	7.4				
MGMT promoter					
Methylated	9.2	0.012	0.660	0.504–0.865	0.0027
Nonmethylated	8.2				
TERT promoter					
Mutated	8.3	<0.0001	1.488	1.065–2.079	0.0204
Nonmutated	10.4				

Abbreviations: CI = confidence interval; HR = hazard ratio; *IDH* = isocitrate dehydrogenase; KPS = Karnofsky Performance Score; *MGMT* = methylguanine methyltransferase; *TERT* = telomerase reverse transcriptase; TMZ = temozolomide.

prognostic factor for both OS and PFS in GBM (tables 1 and 2).

***TERT* mutations are associated with specific prognostic and molecular subgroups.** The association of *TERT*p-mut with the other molecular alterations frequently found in GBMs is presented in table 3.

Table 3 Association of *TERT*p-mut with common molecular alterations found in gliomas

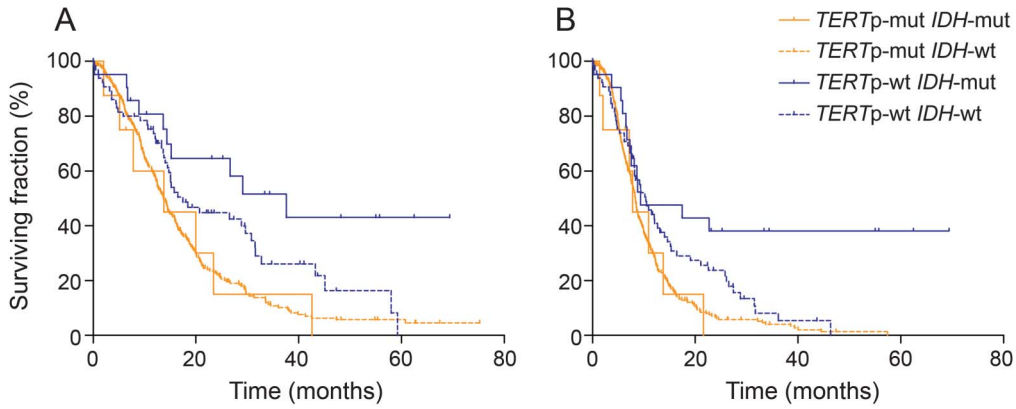
	*TERT*p-mut	*TERT*p-wt	*p*
EGFR amplification	131/299 (43.8)	13/96 (13.5)	<0.0001
Chr 10q loss	253/299 (84.6)	41/95 (43.2)	<0.0001
CDKN2A deletion	141/299 (47.2)	27/96 (28.1)	0.0013
IDH mutation	8/284 (2.8)	22/88 (25.0)	<0.0001
TP53 mutation	35/114 (30.7)	16/34 (47.1)	NS
MGMT promoter methylation	107/245 (43.7)	40/70 (50.6)	NS

Abbreviations: *CDKN2A* = cyclin-dependent kinase inhibitor 2A; Chr = chromosome; *EGFR* = epidermal growth factor receptor; *IDH* = isocitrate dehydrogenase; *MGMT* = methylguanine methyltransferase; NS = not significant; *TERT* = telomerase reverse transcriptase; *TERT*p-mut = *TERT* promotor mutation; *TERT*p-wt = *TERT* promoter wild type; *TP53* = tumor protein p53.
Data are n (%).

IDH mutation was associated with *TERT*p-wt GBM (22/88 [25%] vs 8/284 [2.8%] in *TERT*p-mut GBM). We therefore enquired whether the higher incidence of *IDH* mutation could explain the better outcome of *TERT*p-wt patients compared with *TERT*p-wt GBM. However, stratifying our population according to the *TERT*p status, we found that *TERT*p-mut was prognostic in both *IDH*-wt GBM (OS = 13.7 vs 17.5 months, $p = 0.006$) and *IDH*-mutation GBM (OS = 13.8 vs 37.6 months, $p = 0.02$). Moreover, it is particularly striking to note that *IDH* mutation was associated with a better outcome in *TERT*p-wt GBM (OS = 37.6 vs 17.5 months, $p = 0.04$) but not *TERT*p-mut GBM (OS = 13.8 vs 13.7 months, p = not significant) (figure 2).

In contrast to *IDH* mutation, *EGFR* amplification, present in 144 GBMs, was associated with *TERT*p-mut GBM (131/299 [43.8%] vs 13/96 [13.5%] in *TERT*p-wt GBM). We found that *EGFR* amplification had no prognostic impact per se (figure e-2). However, when stratifying according to *TERT*p status, we found that *EGFR* amplification was associated with shorter OS and PFS in the *TERT*p-wt group (OS = 13.3 vs

Figure 2 Prognostic impact of *TERT* promoter mutation in glioblastomas stratified according to *IDH* mutation



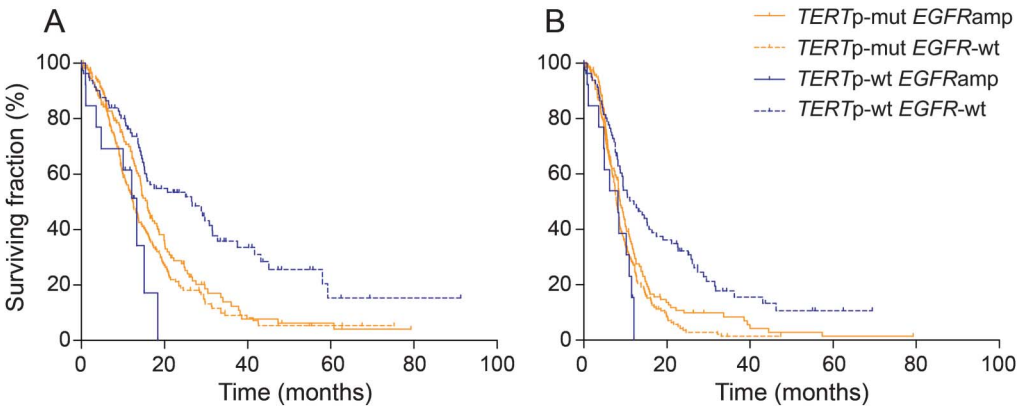
(A) Overall survival. (B) Progression-free survival. *IDH* = isocitrate dehydrogenase; *TERT* = telomerase reverse transcriptase.

26.6 months, $p = 0.005$) but not in the *TERT*p-mut group (OS = 15.8 vs 12.5 months, p = not significant) (figure 3). It is striking to note that in the *EGFR*-wt group, patients with *TERT*p-mut had a poorer outcome compared to patients with *TERT*p-wt (OS = 12.5 vs 26.6 months, $p < 0.0001$), whereas in the *EGFR* amplified group, patients with *TERT*p-mut had a better outcome than patients with *TERT*p-wt (OS = 15.8 vs 13.3 months, $p = 0.05$). To better understand this paradox, we compared the age of these different populations: there was no significant difference of age in the *EGFR* amplified group between *TERT*p-mut patients (59.1 years) and *TERT*p-wt patients (55.7 years) ($p = 0.5$), whereas *TERT*p-mut patients were significantly older than *TERT*p-wt patients (60 vs 49 years, $p < 0.0001$) in the *EGFR* nonamplified group. We therefore analyzed the impact of the *TERT*p-mut according to age in the *EGFR*-wt group. The results, reported in figure e-3, show that in each age category (<50 years; 50–65 years; >65 years), patients with *TERT*p-wt had a longer survival, but this was particularly relevant in the group of patients younger than 50 years.

We also found that *TERT*p-mut were associated with chromosome 10q loss and *CDKN2A* homozygous deletion, but these associations did not result in a prognostic stratification of our cohort.

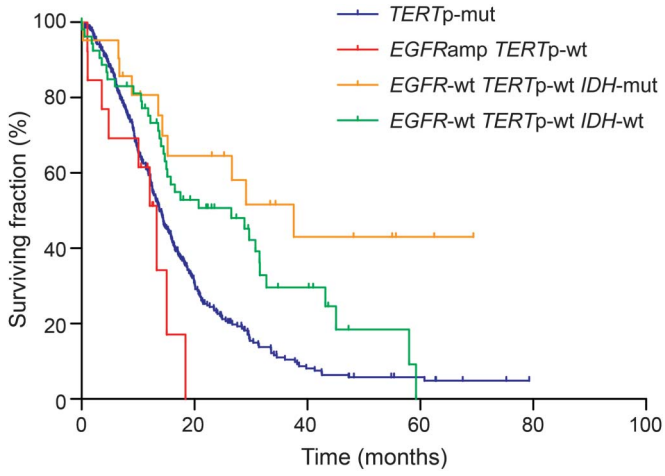
Prognostic classification of GBMs based on *TERT*p, *EGFR*, and *IDH* status. Building on these results, we propose a 4-group molecular classification of GBMs: (1) GBMs with *TERT*p-mut constituting a homogeneous group (OS = 13.8 months); (2) GBMs with *EGFR* amplification and *TERT*p-wt (OS = 13.3 months), all of which are *IDH*-wt; (3) *IDH* mutation having no prognostic impact in this group; and (4) *EGFR*-wt and *TERT*p-wt, characterized by a much better prognosis particularly in the presence of the *IDH* mutation (OS = 37.6 months), but even in the absence of the *IDH* mutation (26.5 months) (figure 4).

Figure 3 Prognostic stratification of glioblastomas according to *TERT* promoter mutation and *EGFR* amplification status



(A) Overall survival. (B) Progression-free survival. amp = amplification; *EGFR* = epidermal growth factor receptor; *TERT* = telomerase reverse transcriptase.

Figure 4 Survival curves corresponding to the 4 prognostic groups



*TERT*p-mut (OS = 13.8 months); *EGFR* amp with *TERT*p-wt (OS = 13.3 months); *EGFR*-wt with *TERT*p-wt and *IDH*-wt (OS = 26.5 months); *EGFR*-wt with *TERT*p-wt *IDH* mutation (OS = 37.6 months). amp = amplification; *EGFR* = epidermal growth factor receptor; *IDH* = isocitrate dehydrogenase; mut = mutation; OS = overall survival; *TERT* = telomerase reverse transcriptase; *TERT*p-mut = *TERT* promoter mutation; *TERT*p-wt = *TERT* promoter wild type; wt = wild type.

DISCUSSION *TERT* is the most frequently mutated gene in GBMs,[4,6,7] suggesting that it may be an early event in the development of these tumors. These mutations create a putative binding site for the E-twenty-six/ternary complex factor transcription factors and increase 2- to 4-fold transcriptional activity of the promoter.[3,18] Increasing telomerase activity confers a selective advantage and promotes immortalization of cells by preventing the senescence induced by telomere shortening.

In our series, *TERT*p-mut were associated with an older age at diagnosis, as previously reported in medulloblastomas,[7] conjunctival melanomas,[1] and recently in gliomas.[19] Telomeres are shorter in the GBMs of older patients,[20] and preventing telomere shortening may therefore be more critical in older patients. Accordingly, the polymorphism rs2736100, which maps to the *TERT* locus, has also been associated with the *IDH*-wt and older age gliomas.[21]

In this work, we show that *TERT*p-mut is an independent factor of poor outcome in GBMs. Indeed, we clearly show here that this effect is not due to the association of *IDH* mutation with *TERT*p-wt status as previously believed.[22] Moreover, the impact of *TERT*p-mut is even stronger in patients with *IDH* mutation than in patients with *IDH*-wt, with a median OS decreasing from 37.6 months in *TERT*p-wt to 13.8 months in *TERT*p-mut. In other words, our data suggest that the favorable prognostic impact of the *IDH* mutation in GBMs is lost in the presence of an associated *TERT* mutation, because the survival in *IDH* mutation *TERT*p-mut GBMs is identical to standard (i.e., *IDH*-wt) GBMs.

We further dissected the prognostic impact of the *TERT*p-mut in the context of different genetic backgrounds. *EGFR* amplification is a hallmark of GBM. It affects 40% of GBMs and is mutually exclusive with *IDH* mutation. In line with previous reports, we show here that *EGFR* amplification has no prognostic impact in the whole GBM population.[23,24] However, determination of the *TERT*p-mut status revealed that in the *TERT*p-wt group, patients with *EGFR*-wt had a median survival twice superior to that of patients with *EGFR* amplification. Consequently, we show a very sharp and opposite effect of the *TERT*p-mut on survival according to *EGFR* status. Similar results have been obtained in medulloblastomas, also showing an opposite prognostic effect of *TERT*p-mut according to different genetic subtypes.[25] Our study also makes it clear that the difference of age—a well-known prognostic factor in GBM—is not a valid explanation, because in the *EGFR* amplified subgroup, patients with *TERT*p-mut were older but still had a better outcome (OS = 15.8 vs 13.3 months, $p = 0.05$).

Finally, we propose a 4-group molecular classification that summarizes our results: when either *EGFR* amplification or *TERT*p-mut is present, the prognosis is poor with median survival ranging from 12 to 16 months. Median survival is much better when none of these 2 alterations is present, ranging from more than 2 years for patients with *IDH*-wt, to more than 3 years for patients with *IDH* mutation.

In this study, we found that the *TERT*p-mut is a strong and independent prognostic marker in GBM, and is not related to *IDH* status. We also show an opposite prognostic effect of *TERT*p-mut in *EGFR*-wt GBM. Finally, we propose a refined prognostic classification of GBMs based on the joint analyses of *TERT*, *EGFR*, and *IDH*.

AUTHOR CONTRIBUTIONS

M.L. and M.S. designed the study and wrote the manuscript. M.L., B.B., A.R., A.-L.D.S., M.R., P.C., O.S., R.P., and G.F. performed genes analysis. K.M. performed the histologic analysis. Clinical data were collected and analyzed by Y.M., M.R., and M.S. All contributed to the data analysis and interpretation. All read and approved the manuscript.

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DISCLOSURE

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