Poor prognosis associated with TERT gene alterations in meningioma is independent of the WHO classification: an individual patient data meta-analysis

Poor prognosis associated with TERT gene alterations in meningioma is independent of the WHO classification: a meta-analysis of individual patient data

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ABSTRACT

TERT gene alterations (*TERT*-alt) have been previously linked to increased risk of recurrence in meningiomas. The association between *TERT*-alt and mortality has been incompletely investigated in the majority of previous studies. As incongruence between clinical course and WHO grade exists, reliable biomarkers have been sought.

We applied the PRISMA-IPD Statement. We compiled data from all published cases and allocated patients to *TERT*-alt or their *TERT*p-wt (*TERT* promoter wild-type) counterpart. We compared subgroups of *TERT*-alt patients versus *TERT*p-wt patients stratified for WHO grades as: incidence rates, survival probabilities and cumulative recurrences. Moreover, we estimated the effects of WHO grade, age at diagnosis and sex as hazard ratios.

We included eight studies (n=677, *TERT*-alt n=59) in our meta-analysis. The median recurrence-free survival was 14 months (95% CI: 10 – 24) for all *TERT*-alt patients versus 101 months (95% CI: 90 - 124) for all *TERT*p-wt patients. The hazard ratio for *TERT*-alt was 3.74 (95% CI: 2.65 – 5.30) in reference to *TERT*p-wt. For all *TERT*-alt patients versus all *TERT*p-wt patients, the median overall survival was 58 months (95% CI: 33 – 77) and 160 months (95% CI: 131 – 336) months, respectively. The hazard ratio for *TERT*-alt was 2.77 (95% CI: 1.86 – 4.11) compared to *TERT*p-wt. *TERT*-alt affected prognosis independent of WHO grades. Particularly, the recurrence rate was 4.8 (95% CI: 3.3 – 6.9) times higher in WHO-I & -II *TERT*-alt patients compared to WHO-III *TERT*p-wt patients. The mortality rate was 2.7 (95% CI: 1.8 – 6.9) times higher in the WHO-I & -II *TERT*-alt patients compared to WHO-III *TERT*p-wt patients.

TERT-alt is an important biomarker for significantly higher risk of recurrence and death in meningiomas. *TERT*-alt patients should be managed aggressively and equally across WHO grades. We propose that *TERT*-alt analysis should be implemented as a routine diagnostic test in meningioma and integrated into the WHO classification.

INTRODUCTION

Cell immortalization and senescence escape, which is mainly caused by telomere maintenance, are hallmarks of cancer. The enzyme telomerase, a specialized DNA polymerase that adds telomere repeat segments to the ends of telomeric DNA, actively counteracts the telomere shortening [1]. The telomerase enzymatic subunit *TERT* (telomerase reverse transcriptase) is transcriptionally inactive in most non-neoplastic cells, whereas reactivation may induce cell immortalization. It has been proposed that 90% of cancers express functionally significant levels of telomerase and that 73% of cancers demonstrate *TERT* gene alterations (*TERT*-alt) – including promoter mutations, gene translocations and DNA amplifications [2].

The WHO grading system classifies meningiomas based on histopathological morphology [3]. The main parameters are the number of mitoses per 10 high power field along with other more subjective criteria [3,4], which yields a risk of inter-observer bias [5]. There are examples of incongruence between the WHO grade and clinical course, in which low grade meningiomas rendered a poorer prognosis than higher grades of meningiomas in terms of recurrence-free survival [6]. As the current WHO grading system is not sufficient to predict the clinical course, reliable biomarkers have been sought. A particularly interesting target are *TERT*-alt including promoter mutations [5,7–11] and gene translocations [12].
TERT mutations occur in specific "hotspots" of the promoter (*TERT*p) region known as C228T and C250T (chromosomal positions 1,295,228 and 1,295,250). These C>T transition mutations result in new binding sites for a specific transcription factor family known as ETS (E-twenty-six), which leads to maintenance of the telomere length as binding of ETS-transcription factors are involved in the upregulation of *TERT* expression [5,11,13]. Similarly, genomic rearrangements that have led to *LPCAT1-TERT* and *RETREG1-TERT* fusions, also upregulate TERT expression [8,12]. Genomic rearrangements that associate with increased *TERT* expression and telomerase activity are seen in solid cancers, such as melanoma [14], follicular-derived thyroid and bladder cancer [15], other CNS malignancies [16,17], and thus represent a major biological hallmark of cancer [1].

The incidence of *TERT*-alt has not yet been studied in consecutively collected meningioma tumor samples, but ranges from 6.3% to 9.8% in the largest cohorts hitherto investigated [5,7,10,11]. Interestingly, all previous studies consistently show a higher risk of recurrence in patients with *TERT*-alt meningiomas compared to their wild-type (*TERT*p-wt) counterpart, but the majority of

these studies have incompletely discussed other clinically important differences, such as survival effects and patient characteristics – primarily due to small study cohorts.
When considering that meningioma is the most common intracranial neoplasm with an annual incidence of 7.8 per 100,000 inhabitants [18], *TERT*-alt may affect a large population. While up to 80% of meningiomas can be cured through surgery, more than 20% of the patients experience a recurrence and progressive tumor behavior [5,19–23]. Focusing on this subgroup, it is of high priority to unfold the prognostic implications of *TERT*-alt comprehensively.

Our primary objectives were to: first, report recurrence and mortality rates; and second, investigate risk of recurrence and death in *TERT*-alt versus *TERT*p-wt meningioma patients in general and in subgroups of WHO grades ranging from I to III. Our secondary objectives were to report characteristics of *TERT*-alt patients, and to investigate effect modification of *TERT*-alt by the patients' age, sex and WHO grade.

MATERIAL AND METHODS

This study was a meta-analysis using individual patient data (IPD) from a set of relevant studies. The approach adhered to the PRISMA-IPD (Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data) Statement [24].

Literature search & Study selection

We performed a search that consisted of the keywords "TERT" or "telomerase reverse transcriptase" in combination with "meningioma". We searched PubMed (n=70), Embase (n=97) and Cochrane (n=0). Two authors duplicated and performed the search independently (CM and AM). There was consensus on the identified papers and the extracted data.
We performed the initial search September 1st, 2018 and was reperformed the 25th June, 2019. This was because we invested considerable amount time in data synthesis and extraction since the initial search. We identified one additional paper published in between the two searches, which we consequently included **(Figure** 1 depicts the search diagram).

Inclusion criteria comprised: first, a specific laboratory test of *TERT*-alt; second, histopathological confirmation of WHO grade; third, reporting of *both* recurrence status (yes/no/lost to follow-up) *and* recurrence-free survival time; *and*/*or* fourth, reporting of *both* survival status (alive/dead/lost to follow-up) *and* survival time.
Exclusion criteria comprised: first, evaluation of *TERT* in other contexts than genomic alterations; second, non-meningioma tumors; third, animal studies; and fourth, conference abstracts.

In total, eight studies were eligible [5,7–12,25]. We applied the 'one-stage' approach in the PRISMA-IPD Statement and contacted the corresponding authors of all eight studies requesting raw IPD. The process was successful and we obtained IPD from all eight studies.
We registered this study on PROSPERO and was published in its approved form on the 16th of October, 2018, following submission in September 2018. The registration number is: CRD42018110566.

Outcomes & Data Extraction

We allocated patients into either *TERT*-alt or *TERT*p-wt. We chose the WHO grade at time of diagnosis as baseline, in case of multiple samples were collected. We excluded ineligible patients,

which comprised: first, five patients in the Peyre et al. study as the baseline-WHO grade was unknown [9]; and second, 21 patients from the Spiegl-Kreinecker et al. study and 30 patients from the Bertero et al. study due to missing recurrence-free and/or overall survival time [11,25]. In addition, it was not possible to retrieve age on *TERT*p-wt patients in one study [12].

The IPD from each study did not necessarily contain all data needed to evaluate both recurrence *and* overall survival. Consequently, some patients were eligible for the analysis of both recurrence-free and overall survival, whereas others were included for only *one* of the analyses.

Data Synthesis & Statistical Analysis

We estimated recurrence and mortality rates per 100 persons-years for different subgroups of WHO grades. The subgroups comprised: first, *TERT*-alt (all), i.e. all WHO grades were combined in the *TERT*-alt group, *TERT*-alt (WHO-I & -II) and *TERT*-alt (WHO-III): and second, *TERT*p-wt (all), i.e. all WHO grades combined in the *TERT*p-wt group, and *TERT*p-wt (WHO-III). Subsequently, we compared the incidence rates as ratios corresponding to the different subgroups mentioned above.

We estimated and plotted the survival probabilities for *TERT*-alt patients versus *TERT*p-wt patients in the subgroups described above. We applied The Kaplan-Meier method and the log-rank test for significance.

In the analyses of recurrence, we estimated the cumulative risk of recurrence while considering death *without* recurrence as a competing risk. Furthermore, we applied the Aalen-Johansen method to estimate the cumulative incidence and Gray's test to compare the curves [26,27].

In addition, we applied a Cox regression model to investigate the association between the risk of either recurrence or death and age at diagnosis, sex, WHO grade and *TERT* gene alteration status. We reported the beforementioned covariates as: first, unadjusted estimates. The unadjusted estimates were (only) adjusted for the effect from each individual center ('center effect'), to account for differences among the eight studies; and second, as adjusted estimates, which were adjusted to listed covariates and the center effect. We tested non-linear effects for the continuous covariate *age at diagnosis* with restricted cubic splines, and found that continuous covariate effect was linear. Thus, we included age at diagnosis as a linear continuous covariate.

We used time since diagnosis as underlying time scale. End of follow-up was either date of death, the date of lost to follow-up or the date of study termination in each individual study, whichever came first.
We evaluated the assumption of proportionality for all models with visual inspection of Schoenfeld residuals. We found that all covariate effects were proportional, except for sex in relation to both recurrence-free and overall survival. To accommodate this, we divided the time scale into two separate time periods: first, from zero to 36 months; and second, from 36 months and onwards (in which the assumption was valid).

We applied a likelihood ratio test (Chi-squared) to evaluate potential effect modification. We investigated interactions between the effect of *TERT*-alt and age at diagnosis, sex and WHO grade, respectively.

We considered p-values equal to or below 0.05 significant

We performed all analyses in R version 3.6.0 [28] with the packages “rms”, “survival”, “cmprsk” and “etm” [29–32]. We visualized data using ggplot2 and metafor [33,34].

RESULTS

Patients

In total, we included data on 677 patients in our study. Of these, 667 and 527 patients were eligible for recurrence-free and overall survival analysis, respectively.

The pooled cohort of 677 patients comprised: 59 *TERT*-alt (all) patients and 618 *TERT*p-wt (all) patients; 169 WHO-I patients, 365 WHO-II patients and 143 WHO-III patients; the female (n=373) to male (n=304)-ratio was 1.23. It was not possible to retrieve age from one of the studies [12], but the mean age was 58 yrs. based on the remaining seven studies (standard deviation (SD): 15.0, range: 6 yrs. to 89 yrs.) (**Table 1A**).

TERT-alt patient characteristics

TERT-alt (all) comprised 60 *TERT* gene alterations in 59 *TERT*-alt patients, as one patient had synchronous mutations in C228T and C250T: comprising, 27 C228T, 11 C250T, one C228A, 18 not reported, two *RETREG1-TERT* fusions and one *LPCAT1-TERT* fusion. There were eight, 29 and 22 *TERT*-alt patients diagnosed with WHO-I, -II and –III meningioma, respectively. Hence, *TERT*-alt occurred in 4.7% of WHO-I meningiomas, 7.9% of WHO-II meningiomas and 15.4% of WHO-III meningiomas. In contrast to the entire pooled cohort, the female to male-ratio had shifted to 0.74. *TERT*-alt was associated with patients' sex (Chi squared test, p=0.05); in total, 7% of females and 11% of males had *TERT* gene alterations in the entire pooled cohort. The mean age was 60.8 yrs. (SD: 12.5, range: 25 yrs. to 84 yrs.), which was not significantly different from the mean age of 57.7 yrs. (SD: 15.2, range: 6 yrs. to 89 yrs.) among *TERT*p-wt patients in a two sample t-test (p=0.08) (**Table 1B**).

Recurrence-free survival

The recurrence rate was 5.4 (95% CI: 4.0 – 7.3) times higher in *TERT*-alt (all, n=59) patients compared to *TERT*p-wt (all, n=608) patients (**Figure 2**). Including all WHO grades, the median recurrence-free survival was 14 months (95% CI: 10 – 24) for *TERT*-alt (all) patients compared to 101 months (95% CI: 90 – 124) for *TERT*p-wt (all) patients (log-rank test p< 0.0001, **Figure 3A** and **Table 1B**).

By analyzing data from patients with WHO grade III meningioma exclusively (n=140), the recurrence rate was 5.8 (95% CI: 3.6 – 9.5) times higher for *TERT*-alt (WHO-III, n=22) patients than in their *TERT*p-wt (WHO-III, n=118) counterparts (**Figure 2**). The median recurrence-free

survival was 11 months (95% CI: 9 – 28) for *TERT*-alt (WHO-III) patients versus 29 months (95% CI: 23 – 60) for *TERT*p-wt (WHO-III) patients (log-rank test p=0.0015, **Figure 3B**). In comparison between *TERT*-alt (WHO-I & -II, n=37) patients and *TERT*p-wt (WHO-III, n=118) patients, we found that *TERT*-alt (WHO-I & -II) patients rendered a 4.8 (95% CI: 3.3 – 6.9) times higher recurrence rate (**Figure 2**). Further, the median recurrence-free survival was 16 months (95% CI: 12 – 31) for *TERT*-alt (WHO-I & -II) patients and 29 months (95% CI: 23 – 60) for *TERT*p-wt (WHO-III) patients as mentioned above (log-rank test p=0.00096, **Figure 3C**).

The effect of *TERT*-alt on recurrence-free survival was not modified by age at diagnosis (Chi sq. p=0.09), sex (Chi sq. p=0.7) or WHO grade (Chi sq. p=0.2).

Cumulative incidence of recurrence

The 1- and 2-yr cumulative incidence of recurrence for *TERT*-alt (all) patients was 40.7% (95% CI: 20.4% - 54.2%) and 63.4% (95% CI: 51.2% – 75.6%), respectively, when considering death *without* recurrence a competing risk (**Figure 4A)**.

The cumulative incidence of recurrence for *TERT*p-wt (WHO-III, n=118) patients was 23.7 (95% CI: 16.8% - 32.9%) after one yr., and 43.0% (95% CI: 34.1% - 53.2%) after two yrs. In contrast, the *TERT*-alt (WHO-III, n=22) patients had a cumulative incidence of recurrence with a 1- and 2-yrs rate of 52.5% (95% CI: 34.6% - 74.6%) and 70.4% (95% CI: 50.1% - 87.8%), respectively (Gray's test p=0.01, **Figure 4B**). In further comparison to *TERT*p-wt (WHO-III) patients, *TERT*-alt (WHO-I & -II, n=37) patients had a significantly poorer prognosis: the 1-yr cumulative incidence of recurrence was 35.1% (95% CI: 22.1% - 52.7%) whereas the 2-yrs cumulative incidence of recurrence was 60.1% (95% CI: 45.2% - 75.7%) (Gray's test p=0.002, **Figure 4C**).

Cox regression analysis

In the unadjusted model, females (n=369) had a lower risk of recurrence after the initial 36 months compared to men (n=298) with a hazard ratio of 0.50 (95% CI: 0.33 – 0.75). We found that a 10-yrs increase in age at diagnosis increased the risk of recurrence with a hazard ratio of 1.14 (95% CI: 1.04 – 1.25). As expected, the risk of recurrence increased gradually with higher WHO grade. With WHO-I meningiomas (n=169) as reference, the hazard ratio was 1.60 (95% CI: 1.15 – 2.22) and 2.38 (95% CI: 1.67 – 3.39) for WHO-II (n=358) and WHO-III (n=140), respectively. The hazard

ratio for *TERT*-alt (n=59) was 3.82 (95% CI: 2.76– 5.28) compared to *TERT*p-wt (n=608) (**Table 2**).

In the adjusted model, there was no difference between sexes during the initial 36 months, but the hazard ratio was 0.43 (95% CI: 0.28 – 0.67) for women from 36 months and onwards compared to men. A 10-yrs increase in age at diagnosis was found to increase the risk of recurrence with a hazard ratio 1.10 (95% CI: 1.00 – 1.20). WHO-II and -III meningiomas had a hazard ratio of 1.38 (95% CI: 0.98 – 1.93) and 2.27 (95% CI: 1.58 – 3.25) compared to WHO-I, respectively. The hazard ratio for *TERT*-alt was 3.74 (95% CI: 2.65 – 5.30) with *TERT*p-wt as reference group (**Table 2**).

Overall survival

The mortality rate was 3.6 (95% CI: 2.5 – 5.2) times higher in *TERT*-alt (n=49) patients compared to *TERT*p-wt (n=478) patients (**Figure 2**). *TERT*-alt (all) patients had a median survival of 58 months (95% CI: 33 – 77) compared to 160 months (95% CI: 131 – 336) in *TERT*p-wt (all) patients (log-rank test p<0.0001, **Figure 5A** and **Table 1B**). Moreover, *TERT*-alt (WHO-III, n=16) patients had a 6.8 (95% CI: 4.1 – 11.4) times higher mortality rate than *TERT*p-wt (WHO-III, n=113) patients (**Figure 2**). Similarly, a log-rank test indicated a significant difference in survival probability (p=0.0015) (**Figure 5B**): the median survival was 25 months (95% CI: 13 – not reached) and 79 months (95% CI: 61 – not reached) in *TERT*-alt (WHO-III) patients and in *TERT*p-wt (WHO-III) patients, respectively. Similar trends were observed when evaluating *TERT*-alt (WHO-I & -II, n=33) patients versus *TERT*p-wt (WHO-III) patients. The mortality rate was 2.7 times higher (95% CI: 1.8 – 4.1) in *TERT*-alt (WHO-I & -II) patients compared to *TERT*p-wt (WHO-III) patients. The median survival of *TERT*-alt (WHO-I & -II) patients was 72 months (95% CI: 54 – 113) and, as mentioned, 79 months (95% CI: 61 – not reached) for *TERT*p-wt (WHO III) patients (log-rank test p=0.05, **Figure 5C**).

From the likelihood ratio test, we found that the effect of *TERT*-alt on overall survival was not modified by sex (Chi.sq. p=0.9) or WHO grade (Chi sq. p=0.2). However, for age at diagnosis, we found a significant effect modification (Chi.sq. p=0.04). The effect of *TERT* on age at diagnosis was more profound in younger patients compared to older patients.

Cox regression analysis

In the unadjusted model, females (n=270) and males (n=257) had a higher risk of death the initial 36 months with a hazard ratio of 2.90 (95% CI: 1.86 - 4.54). However, females had a lower risk of death after the initial 36 months with a hazard ratio of 0.64 (95% CI: 0.44 – 0.93) (**Table 2**). A 10-yrs increase in age at diagnosis increased the risk of death with a hazard ratio of 1.61 (95% CI: 1.41 – 1.83). As expected, increasing WHO grades were gradually associated with a higher hazard ratio. With WHO-I meningiomas (n=78) as reference, the hazard ratio was 1.89 (95% CI: 1.17 – 3.05) and 3.61 (95% CI: 2.21– 5.91) for WHO-II (n=320) and WHO-III (n=129), respectively. *TERT*-alt (n=49) had a hazard ratio of 2.84 (95% CI: 1.96 – 4.13) with *TERT*p-wt (n=478) as reference (**Table 2**).

In the adjusted model, females had a higher risk of death the initial 36 months with a hazard ratio of 2.86 (95% CI: 1.80 - 4.54), however, females had a lower risk of death after the initial 36 months with a hazard ratio of 0.56 (95% CI: 0.39 – 0.82). A 10-yrs increase in age at diagnosis was associated to death with a hazard ratio 1.52 (95% CI: 1.33 – 1.74). The hazard ratio increased for increasing WHO grades: WHO-II and -III meningiomas had a hazard ratio of 1.45 (95% CI: 0.89 – 2.37) and 2.65 (95% CI: 1.60 – 4.39) compared to WHO-I, respectively. *TERT*-alt had a hazard ratio of 2.77 (95% CI: 1.86 – 4.11) with *TERT*p-wt as reference. (**Table 2**).

DISCUSSION

Here, we present a meta-analysis of individual meningioma patient data harboring *TERT* gene alterations. To our knowledge, our meta-analysis includes the largest number of meningioma patients with *TERT* alterations published to date. This include all published cases with analyses of recurrence-free and overall survival until 25th of June, 2019. Our meta-analysis confirms previous findings that *TERT*-alt meningioma patients had significantly higher risk of recurrence than *TERT*p-wt patients. Furthermore, we have evidently confirmed that *TERT*-alt patients also render a poorer overall survival compared to *TERT*p-wt meningioma patients.
We show that *TERT*-alt (WHO-III) patients and even *TERT*-alt (WHO-I & -II) patients had a significantly higher recurrence rate as well as higher mortality rate than *TERT*p-wt (WHO-III) patients. We saw an increased risk of recurrence and death in the *TERT*-alt meningioma group, compared to their *TERT*p-wt counterpart in the adjusted Cox regression analysis that included multiple factors (age at diagnosis, sex, WHO grade and center effect).

We detected differences in the clinical characteristics of *TERT*-alt patients when compared with their *TERT*p-wt counterparts. Namely, male patients were over-represented among *TERT*-alt patients and *TERT*-alt patients were slightly older than *TERT*p-wt patients. Notably, *TERT*-alt occurred in meningioma of all WHO grades, however, the effect of *TERT*-alt on the recurrence and mortality rate was not modified by WHO grade. Thus, the poor prognosis associated with *TERT*-alt was independent of WHO grade.

Most importantly, our findings highlight the incongruence that is implied within the current WHO classification for meningioma, and evidently demonstrate the dismal prognosis associated with acquiring *TERT* gene alterations in meningioma.
The WHO classification describes 15 different histological subtypes, and does not, however utilize molecular markers. The grading is based on visual assessment of histology that includes an element of subjectivity and is prone to inter-observer bias [6]. Furthermore, the WHO grading does not correlate with clinical course in all cases. While WHO grade I meningiomas are considered benign with few cases that have aggressive phenotypes, a substantial fraction of WHO grade II and WHO grade III meningiomas tumors have a less-favorable natural history [35–37].
Molecular profiling has been introduced to improve WHO classification for other CNS tumors. For instance, distinct epigenetic subgroups of medulloblastoma [38–40] as well as isocitrate

dehydrogenase 1/2 status and 1p/19q status in diffuse gliomas provide prognostic information which can serve to tailor management of the patient [41–43].

Molecular data that correlates with clinical phenotypes is becoming available for meningiomas [44,45]. Sahm et al., as an example, generated genome-wide methylation profiles, which revealed two major epigenetic groups; group A and group B [45]. Group A comprises four subgroups, three benign and one intermediate, whereas group B comprises two subgroups, one intermediate and one malignant. Interestingly, the methylation-based classification showed a better correlation with the clinical behavior than the WHO-classification. Notably, four of the five meningiomas with *TERT*-alt in their cohort were mapped to group B [45].

Strength and limitation

The major strength of this IPD meta-analysis is the inclusion rate of 100% of all published articles on *TERT* gene alterations in meningioma. The strength of IPD meta-analyses is the simultaneous analysis of raw data from included studies, which allows for a better statistical adjustment and exploration of data compared to traditional meta-analyses of aggregated data.

However, our meta-analysis had some limitations. It was not possible to include or adjust for the extent of surgical resection, which is recognized as prognostically important [46–49]. Moreover, it was not known whether the included patients received other treatment than surgery that might have affected the prognosis. In addition, we only had limited access to information whether the included high-grade meningiomas were *de novo* or secondary, which also may affect prognosis [7,9]. Furthermore, the majority of patients in the included studies has been classified according to WHO 2007 and not the WHO 2016 classification [3]. However, evidence of microscopic brain invasion (as stand-alone grading criterion for atypical meningiomas) was the only change, which would not be expected to impact the presented results in this study. Finally, it was not possible to adjust for important comorbidities, such as other cancer diagnoses, cardiovascular disease and other major risk factors that might affect the prognosis.

Comparison to literature

Notwithstanding, we acknowledge that the population in our IPD meta-analysis differed from what would be expected from a large meningioma cohort. Our sex-ratio for females to males was 5:4, which was in alignment with higher incidences of meningioma in females, but lower than the 2:1 distribution in population based epidemiological reports [22,50]. However, the higher proportion of

males might be explained by the high number of WHO-II & -III meningioma aggregated in this study, which have higher male frequency [51,52]. Given that we are searching for biomarkers of aggressive behavior, a skewed population with more aggressive phenotypes would not affect the external validity.

Noteworthy, a meta-analysis of published data on *TERT* promoter mutations was previously published in December 2018 [53]. However, that study had not accessed and analyzed original data as was done in this study and included fewer studies.

Clinical implications

Our analysis confirmed that *TERT*-alt is a reliable prognostic biomarker in meningioma, which, when present, rendered a remarkable poorer outcome independent of WHO grade.

The incidence of *TERT*-alt has not been established in consecutively collected meningiomas, but our analysis supports the generally reported rate of 6% to 8% in all meningiomas. Given that meningiomas are the most common intracranial neoplasm, a large patient cohort may be affected by *TERT*-alt. *TERT*-alt is an important and reliable prognostic biomarker. Independent of WHO grade, we found that *TERT*-alt patients did consistently worse compared to *TERT*p-wt patients - even *TERT*-alt (WHO-I & -II) rendered a poorer recurrence-free and overall survival compared to *TERT*p-wt (WHO-III) patients. Hence, WHO-I and -II patients with *TERT*-alt might allocated to treatment and follow-up algorithms that is not currently balanced by the aggressive behavior in this meningioma genotype. The prognosis of these patients may be improved by more aggressive treatment management and planning. We therefore propose that 1) analysis of *TERT*-alt should be integrated as a standard laboratory test in the histopathological diagnosis of meningiomas and 2) that should be implemented into the WHO classification of meningioma.

Specifically, one might consider whether a fourth WHO-grade of malignancy should be introduced to accommodate the most aggressive genotypes. Further, it is possible that *TERT*-alt could define such a group of meningiomas.

Regardless of changes in classification, our findings have a clear impact on management of patients with *TERT*-alt meningiomas: *TERT*-alt patients should probably be treated equally and aggressively independent of WHO grades. There is an urgent need for prospective trials to produce scientific warrant. As for now, we suggest that WHO-I and -II meningiomas with confirmed *TERT*-alt should be allocated to the same observational and therapeutic algorithm as WHO-III.

Conclusion

Our meta-analysis analyzed original data from 677 patients provided by the authors of all hitherto published studies on *TERT*-alt in meningiomas.

TERT-alt occur in all WHO grades of meningioma. The effect of *TERT*-alt was not modified by WHO grade. This study indicates that *TERT*-alt is a biomarker yielding significantly higher recurrence and mortality rate in meningiomas. This is an important finding, given that meningiomas are the most common intracranial neoplasms. Thus, *TERT*-alt potentially affect a large population in which prognosis can be improved by better treatment management and planning.

Prospective trials should determine the ideal management of *TERT*-alt patients. Awaiting these, *TERT*-alt patients should probably be managed aggressively regarding surgical planning, radiotherapy and follow-up independent of WHO grade. This include that *TERT*-alt in WHO-I and WHO-II meningiomas should be allocated to the same treatment algorithm as WHO-III. We propose that *TERT*-alt detection should be implemented as a routine diagnostic test in meningioma and integrated into the next WHO classification. However, it is still premature to implement an additional WHO grade, WHO-IV, for meningiomas based on the presented results.

Table 1A. Study characteristics.

Abbreviations: **SD**, standard deviation. **Recur**, total recurrences. **P-yrs**, total person-yrs. **RR**, recurrence rate per 100 person-yrs. **MR**, mortality rate per 100 person-yrs.

	Goutagny et al. [7] *2014, n=61*	Sahm et al. [5] *2016, n=255*	Juratli et al. [8] *2017, n=26*	Peyre et al. [9] *2018, n=52*	Biczok et al. [10] *2018, n=88*	Spiegl-Kreinecker et al. [11] *2018, n=89*	Juratli et al. [12] *2018, n=42*	Bertero et al. [25] *2019, n=64*	All combined *n=677*
					TERT gene alterations				
C228A *or* C228T	5	NA	3	8	2	6***	NA	4	28
C250T	1	NA	3	1	4	1	NA	1	11
Sum of patients with a mutation (% in cohort)	6 (9.8%)	16 (6.3%)	6 (23.1%)	8** (15.4%)	6 (6.8%)	7 (7.9%)	2 (4.8%)	5 (7.8%)	56 (8.3%)
TERT promoter fusion	0	0	1*	0	0	0	2****	0	3
Laboratory test	PCR amplification	Sanger	Sanger	PCR amplification	PCR amplification	PCR amplification	Sanger	Sanger	
					For the entire cohort				
Age, mean (SD)	49.7 yrs (SD: 17.0)	56.8 yrs (SD: 14.2)	55.7 yrs (SD: 16.6)	61.5 yrs (SD: 13.9)	62.7 yrs (SD: 15.0)	60.4 yrs (SD: 14.7)	NA	59.1 yrs (SD: 13.5)	57.9 yrs (SD: 15.0)
Sex (female/male)	34 / 27	163 / 92	12 / 14	25 / 27	38 / 50	51 / 38	18 / 24	32 / 32	373 / 304 (=1.23)
WHO-I	15	119	3	9	0	23	0	0	169
WHO-II	38	88	13	14	73	54	29	56	365
WHO-III	8	48	10	29	15	12	13	8	143
Recur / p-yrs (RR)	23 / 319.2 (7.2)	99 / 1458.3 (6.8)	19 / 8.7 (219.2)	46 / 164.0 (28.1)	51 / 236.5 (21.6)	17 / 547.0 (3.1)	36 / 152.8 (23.6)	22 / 166.8 (13.2)	313 / 3053.2 (10.3)
Deaths / p-yrs (MR)	10 / 382.3 (2.6)	28 / 857.2 (3.3)	14 / 16.5 (85.0)	44 / 313.7 (14.0)	25 / 294.2 (8.5)	38 / 598.3 (6.4)	13 / 330.8 (3.9)	20 / 311.7 (6.4)	192 / 3104.7 (6.2)

* LPCAT1-TERT fusion, ** One patient harbored both the TERTp-C228T and -C250T mutation, *** One case was C228A, **** RETREG1-TERT fusion

Table 1B. Patient characteristics stratified on TERT gene alterations

* N=521, age at diagnosis could not be retrieved from one study (n=38) [12].

	***TERT*-alt** *n=59*	***TERT*p-wt** *n=618*
Age, mean (SD)	60.8 yrs (SD: 12.5)	57.7 yrs (SD: 15.2) *
Sex (female / male)	25 / 34 = 0.74	319 / 240 = 1.29
WHO-I	8	161
WHO-II	29	336
WHO-III	22	121
Recurrences / person-yrs.	49 / 101.9	264 / 2951.3
Recurrence rate per 100 persons-yrs.	48.1 (95% CI: 35.6 – 63.6)	8.9 (95% CI: 7.9 – 10.1)
Median recurrence-free survival	14.0 months (95% CI: 10 - 24)	101.9 months (95% CI: 90 - 123)
Dead / person-yrs.	37 / 193.2	155 / 2911.5
Mortality rate per 100 persons-yrs.	19.2 (95% CI: 13.5 – 26.4)	5.3 (95% CI: 4.5 – 6.2)
Median overall survival rate	58 months (95% CI: 33 - 77)	160 months (95% CI: 131- 336)

Table 2. Hazard ratios and 95% confidence intervals from Cox regression models. The unadjusted estimates were adjusted to center effect, exclusively. The adjusted models included center effect, WHO age at diagnosis, sex and *TERT* gene alterations. Sex was evaluated in the two different time periods to accommodate the assumption of proportionality: first, from zero to 36 months; and second, after 36 months.

Abbreviations: NA, not applicable

	Recurrence		**Death**	
	Unadjusted Hazard ratio (95% CI)	**Adjusted** Hazard ratio (95% CI)	**Unadjusted** Hazard ratio (95% CI)	**Adjusted** Hazard ratio (95% CI)
Male (≤ 36 months)	Ref.	Ref.	Ref.	Ref.
Female (≤ 36 months)	0.83 (0.63 – 1.09)	0.90 (0.67 – 1.19)	2.90 (1.86 – 4.54)	2.86 (1.80 – 4.54)
Male (> 36 months)	Ref.	Ref.	Ref.	Ref.
Female (> 36 months)	0.50 (0.33 – 0.75)	0.43 (0.28 – 0.67)	0.64 (0.44 – 0.93)	0.56 (0.39 – 0.82)
Age at diagnosis, per 1-yr increase	1.01 (1.00 – 1.02)	1.01 (1.00 – 1.02)	1.05 (1.04 – 1.06)	1.04 (1.03 – 1.06)
Age at diagnosis, per 10-yrs increase	1.14 (1.04 – 1.25)	1.10 (1.00 – 1.20)	1.61 (1.41 – 1.83)	1.52 (1.33 – 1.74)
WHO-I	Ref.	Ref.	Ref.	Ref.
WHO-II	1.60 (1.15 – 2.22)	1.38 (0.98 – 1.93)	1.89 (1.17 – 3.05)	1.45 (0.89 – 2.37)
WHO-III	2.38 (1.67 – 3.39)	2.27 (1.58 – 3.25)	3.61 (2.21 – 5.91)	2.65 (1.60 – 4.39)
*TERT*p-wt	Ref.	Ref.	Ref.	Ref.
TERT-alt	3.82 (2.76 – 5.28)	3.74 (2.65 – 5.30)	2.84 (1.96 – 4.13)	2.77 (1.86 – 4.11)

Figure 1. Search diagram.

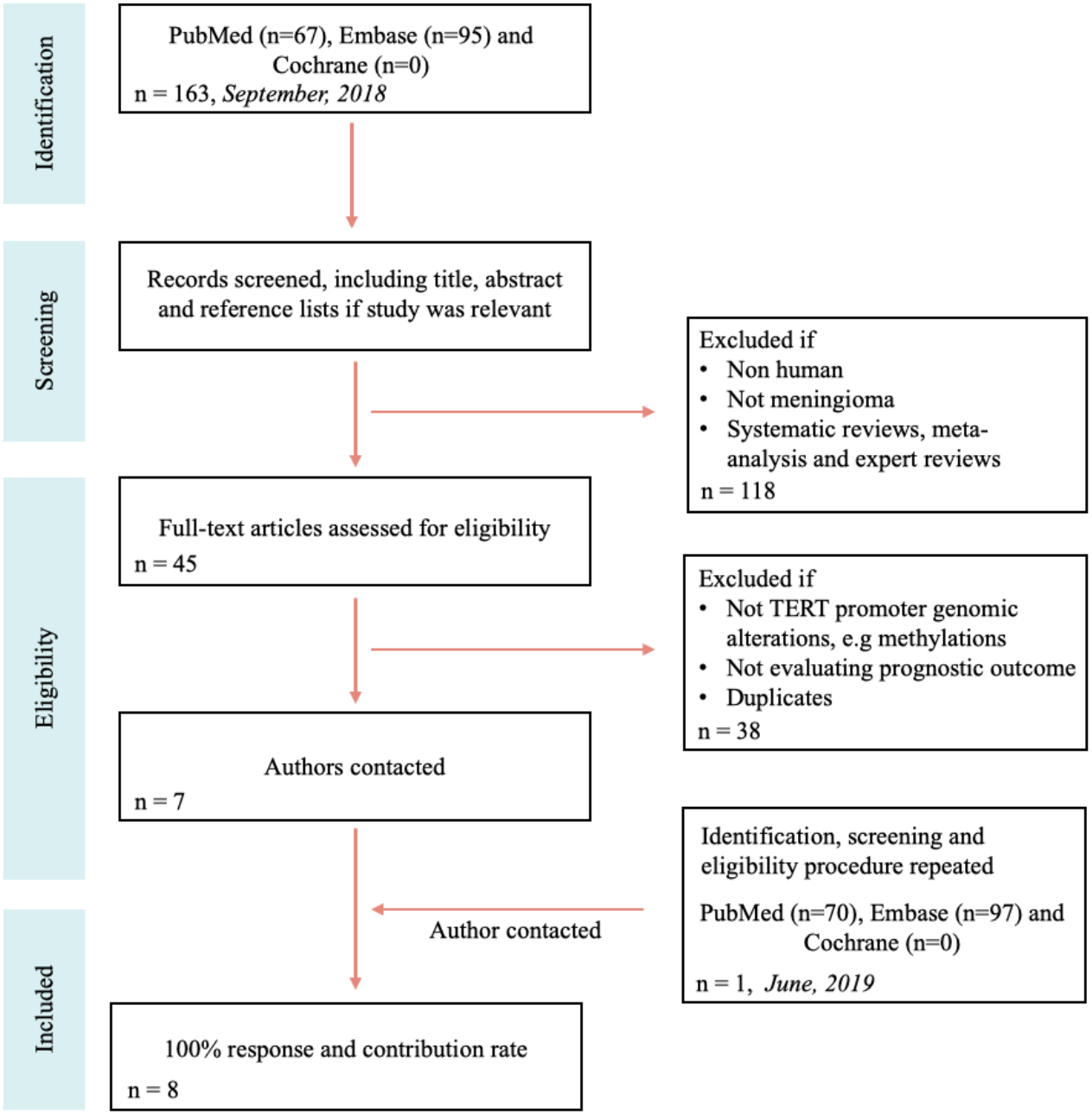


Figure 2. Incidence rates (events/100 person-years) and rate ratios for recurrence and death for different subgroups of *TERT* gene alterations (*TERT*-alt) and TERT promotor wild-type (*TERT*p-wt).

Abbreviations: P-yrs, person-years. IR, incidence rate per 100 persons-years.

	TERT-alt			TERTp-wt				Incidence rate ratio [95% CI]
Recurrence rate ratios	**Events**	**P-yrs**	**IR**	**Events**	**P-yrs**	**IR**		
TERT-alt (all) versus TERTp-wt (all)	49	102	48	264	2951	8.9	Figure 3A	5.4 [4.0, 7.3] *p<0.0001*
TERT-alt (WHO-III) versus TERTp-wt (WHO-III)	17	31	54.8	281	2983	9.4	Figure 3B	5.8 [3.6, 9.5] *p<0.0001*
TERT-alt (WHO-I & -II) versus TERTp-wt (WHO-III)	32	71	45.1	281	2983	9.4	Figure 3C	4.8 [3.3, 6.9] *p<0.0001*
Mortality rate ratios	**Events**	**P-yrs**	**IR**	**Events**	**P-yrs**	**IR**		
TERT-alt (all) versus TERTp-wt (all)	37	193	19.2	155	2911	5.32	Figure 5A	3.6 [2.5, 5.2] *p<0.0001*
TERT-alt (WHO-III) versus TERTp-wt (WHO-III)	16	40	39.5	179	3064	5.84	Figure 5B	6.8 [4.1, 11.4] *p<0.0001*
TERT-alt (WHO-I & -II) versus TERTp-wt (WHO-III)	24	153	15.7	179	3064	5.84	Figure 5C	2.7 [1.8, 4.1] *p<0.0001*

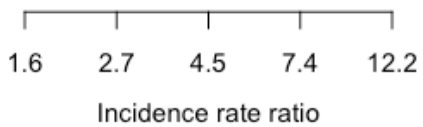


Figure 3A. Recurrence-free survival of all grades *TERT*p-wt (all) versus all grades *TERT*-alt (all).

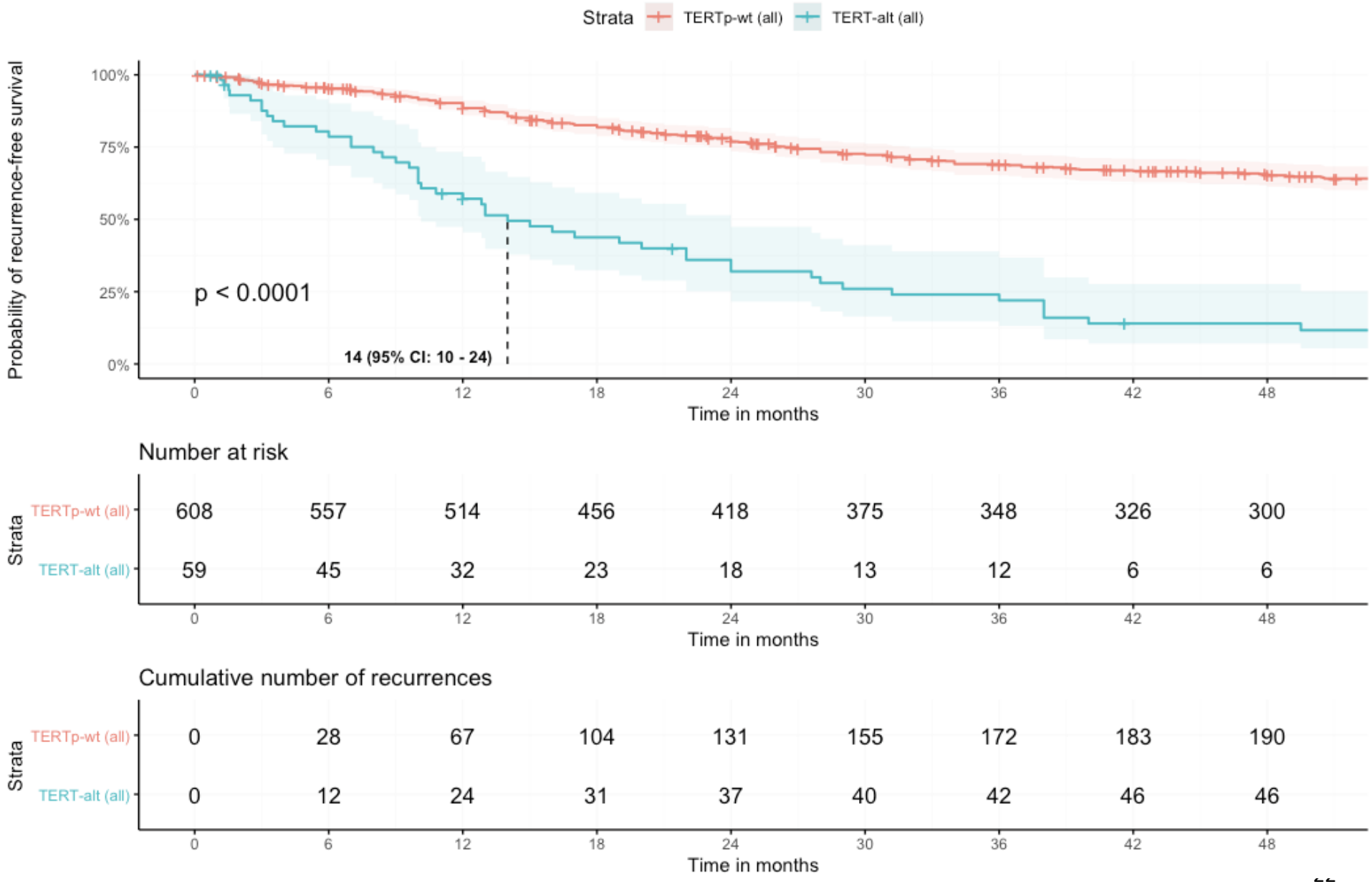


Figure 3B. Recurrence-free survival of WHO-III: *TERT*p-wt (WHO-III) versus all grades *TERT*-alt (WHO-III).

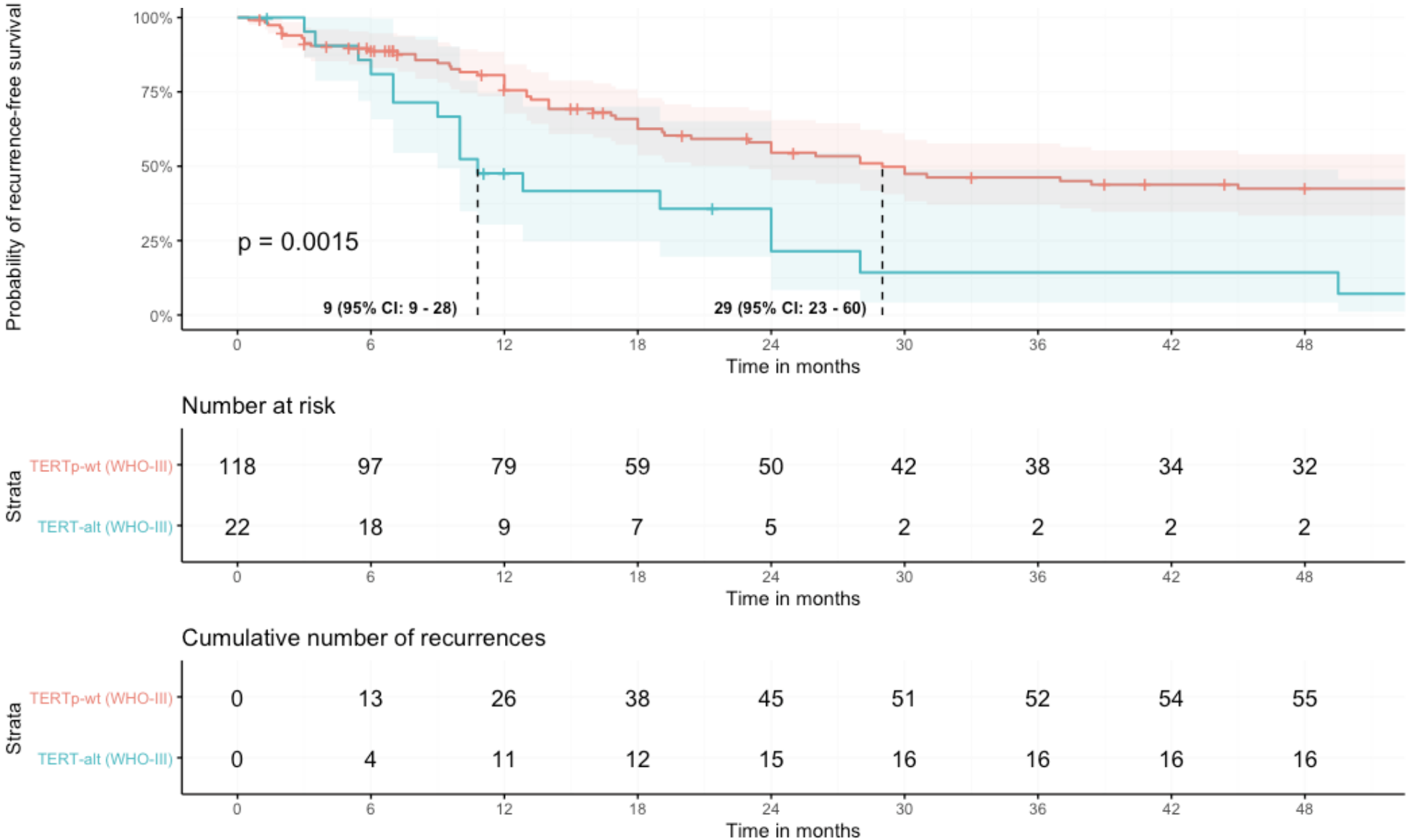


Figure 3C. Recurrence-free survival of WHO-III wild-type, *TERT*p-wt (WHO-III), versus WHO-I & -II combined of TERT gene alterations, *TERT*-alt (WHO-I & -II).

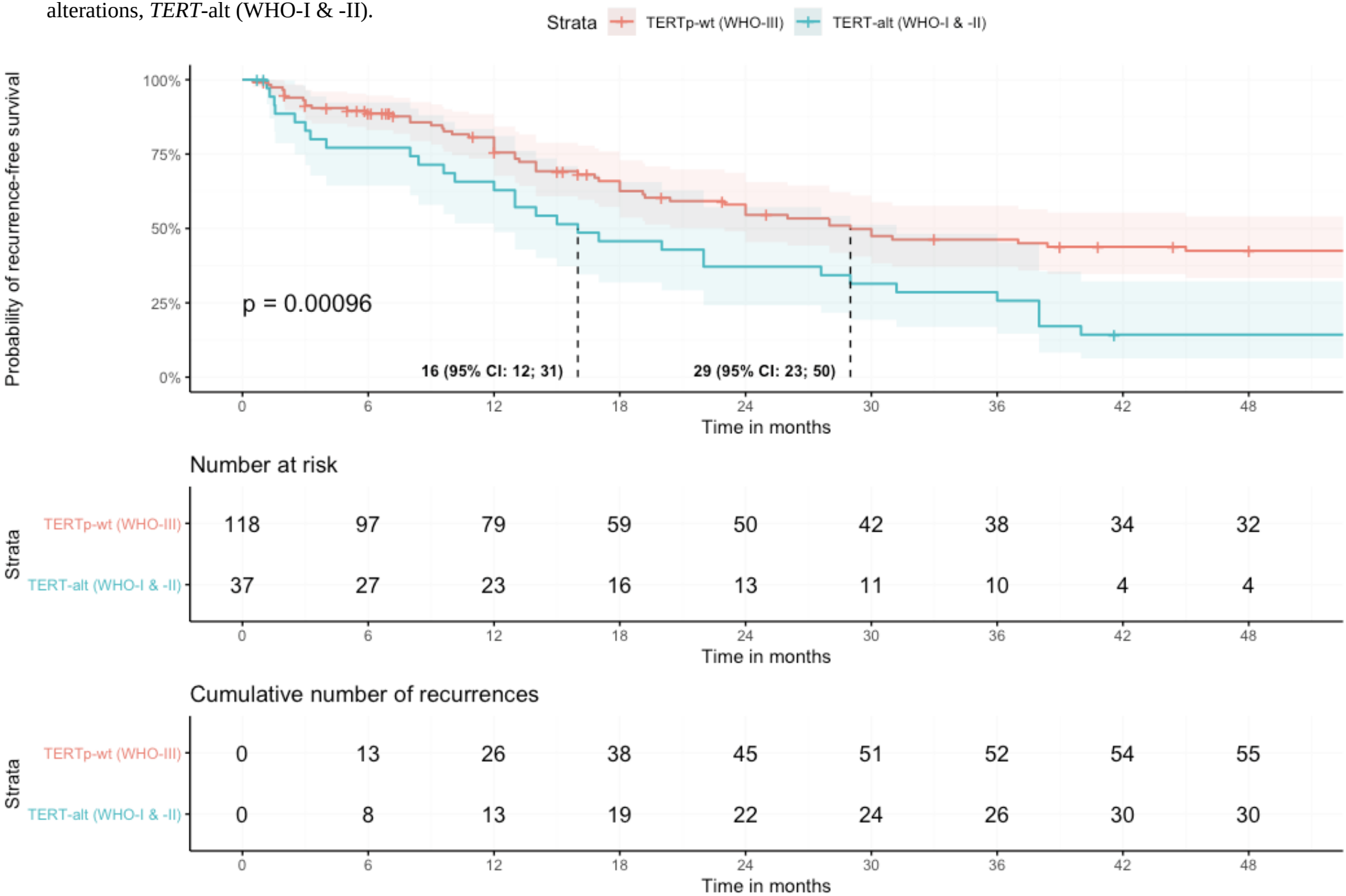


Figure 4A: Cumulative incidence of recurrence in *TERT*-alt, when considering death *without* recurrence as competing risk

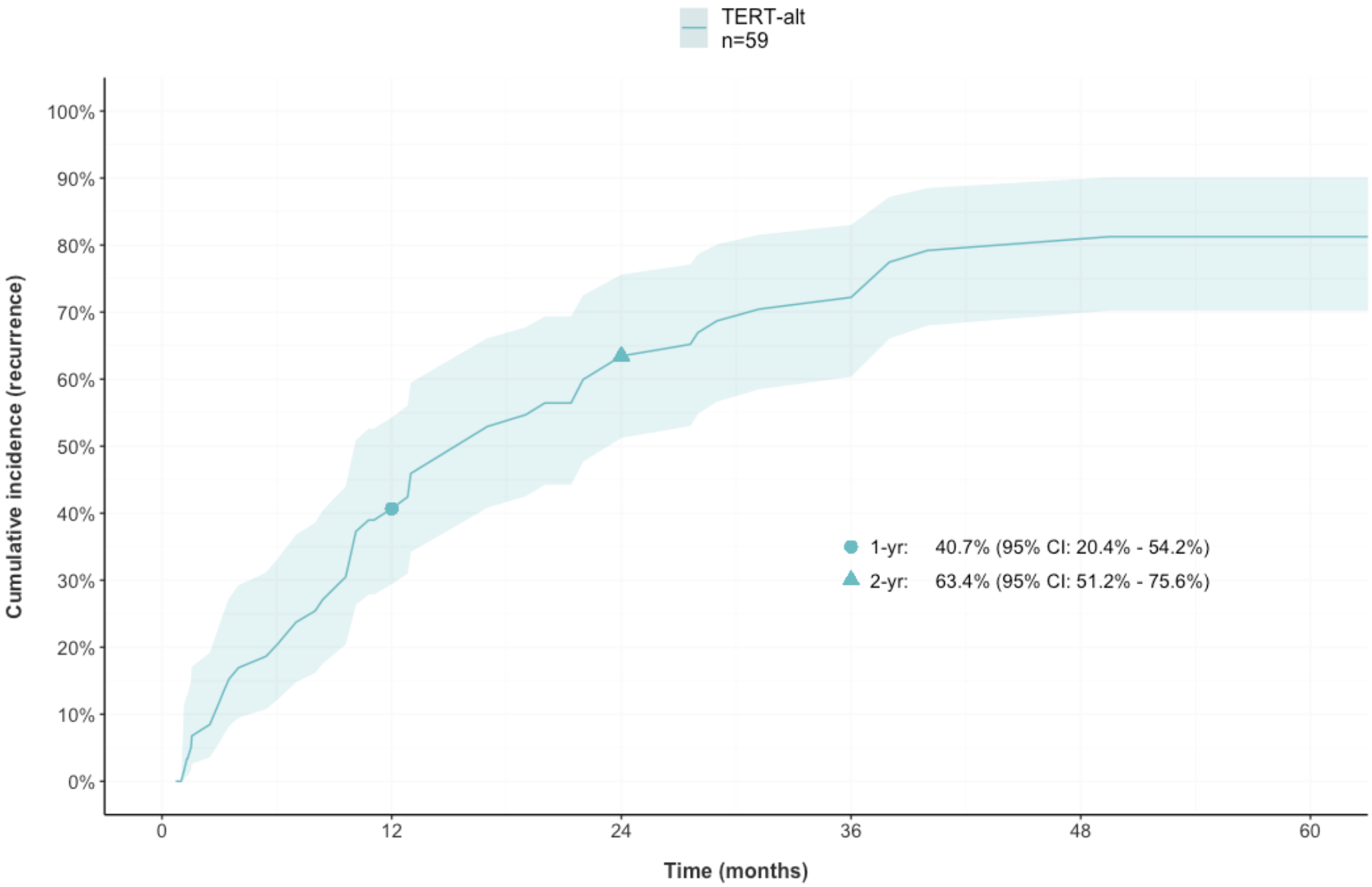


Figure 4B: Cumulative incidence of recurrence in *TERT*p-wt (WHO-III) versus *TERT*-alt (WHO-III) when considering death *without* recurrence as competing risk.

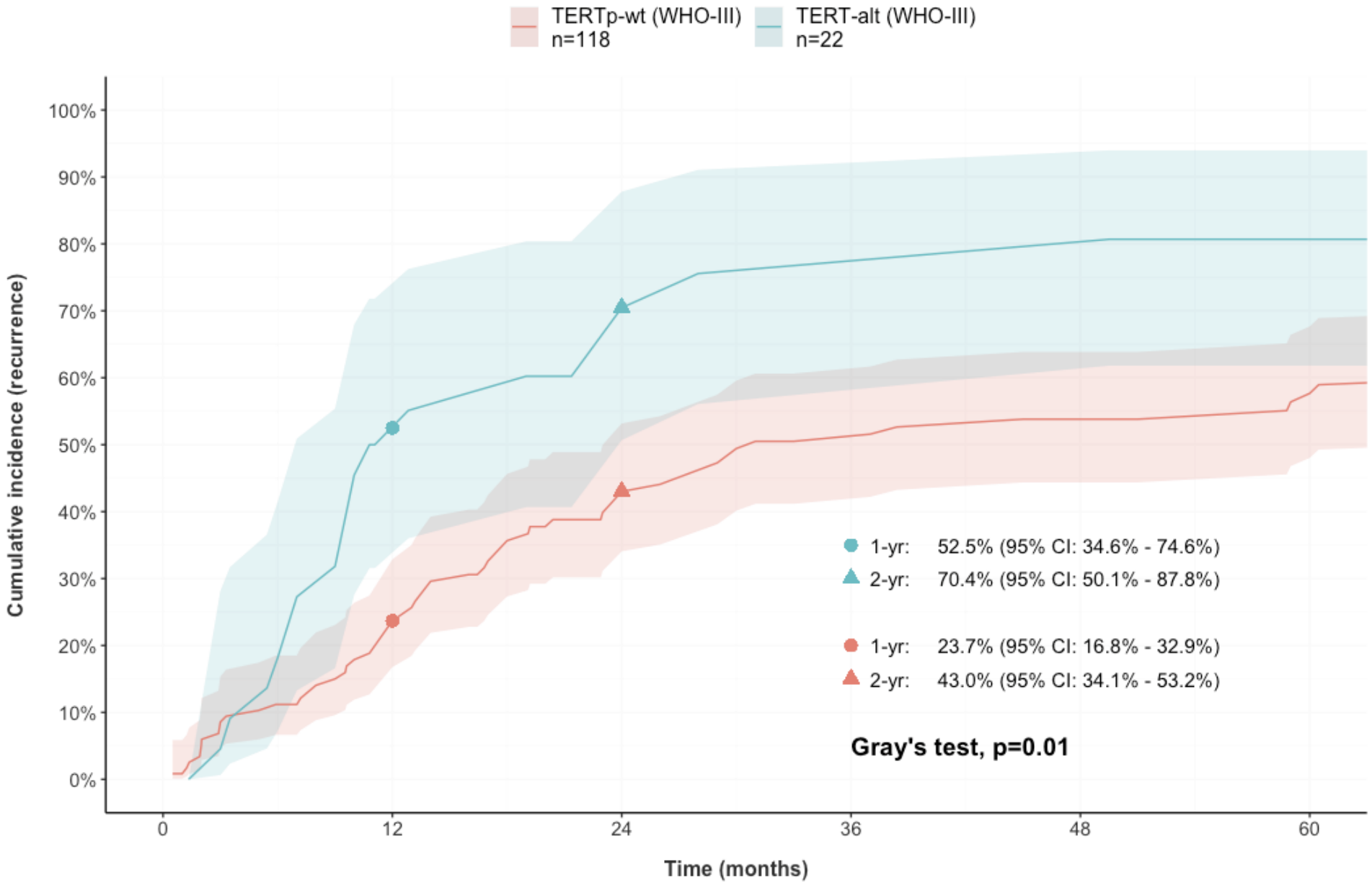


Figure 4C: Cumulative incidence of recurrence in *TERT*p-wt (WHO-III) versus *TERT*-alt (WHO-I & -II) when considering death *without* recurrence as a competing risk.

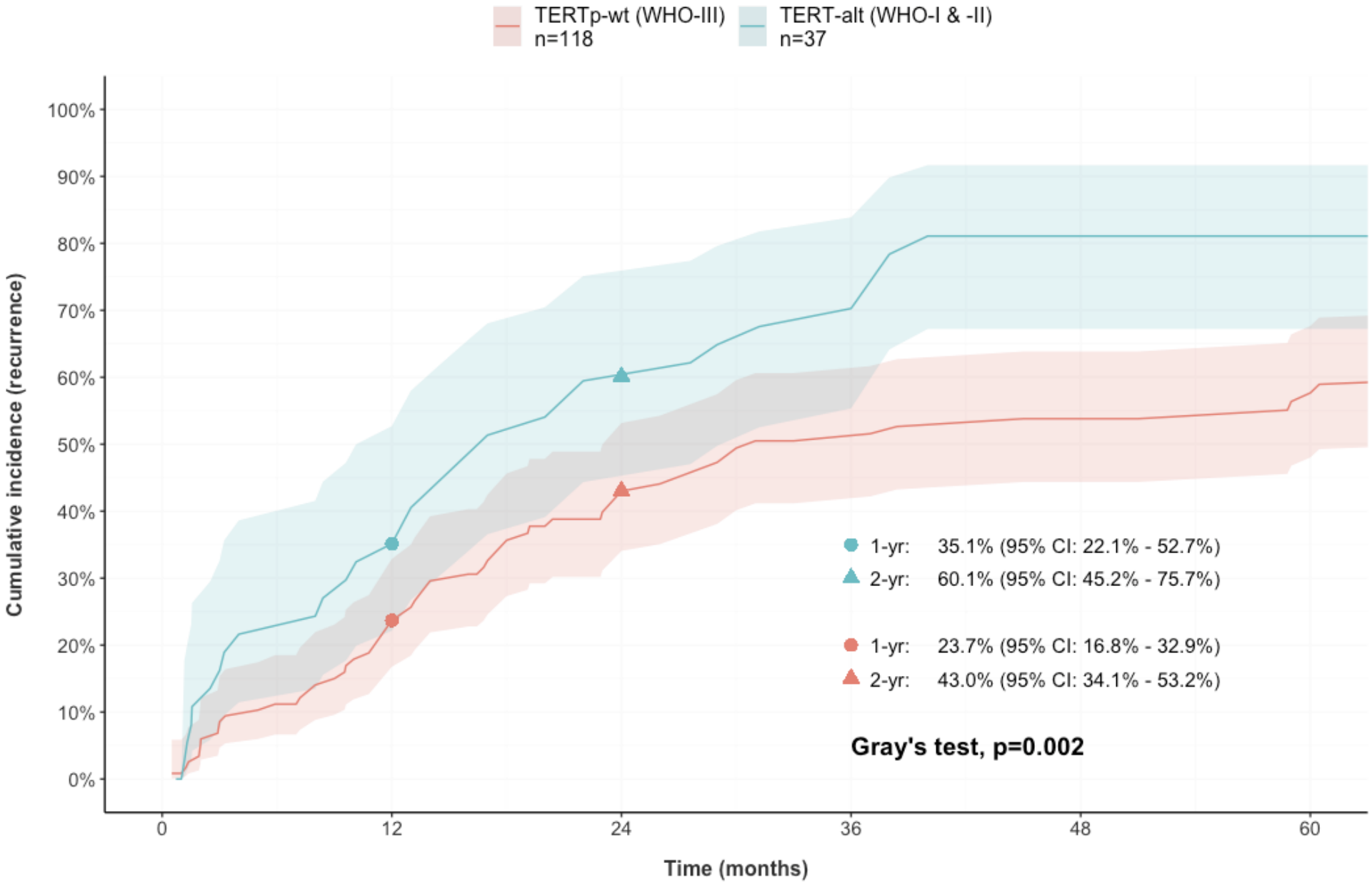


Figure 5A. Overall survival of all grades *TERT*p-wt (all) versus all grades *TERT*-alt (all).

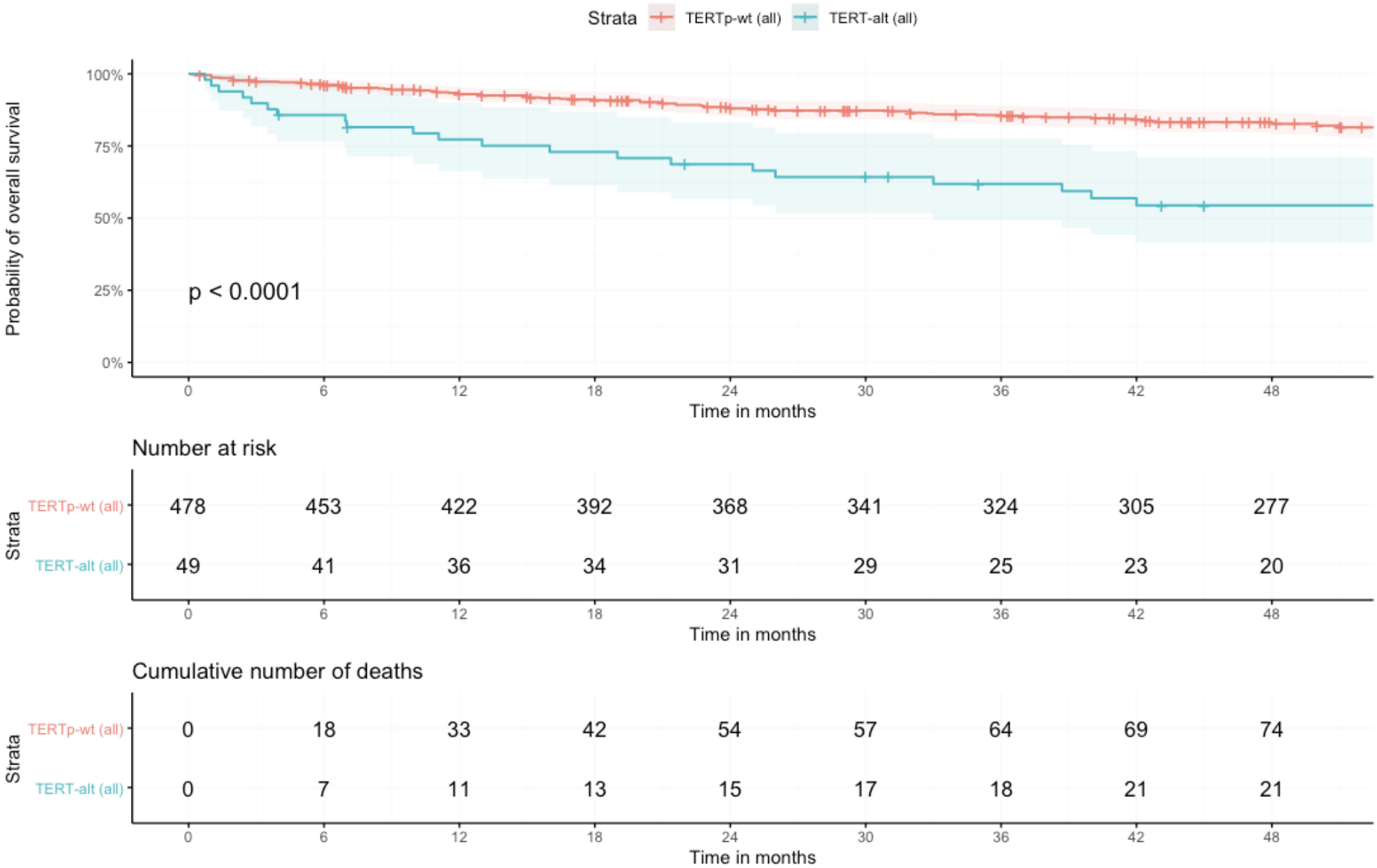


Figure 5B. Overall survival of WHO-III: *TERT*p-wt (WHO-III) versus all grades *TERT*-alt (WHO-III).

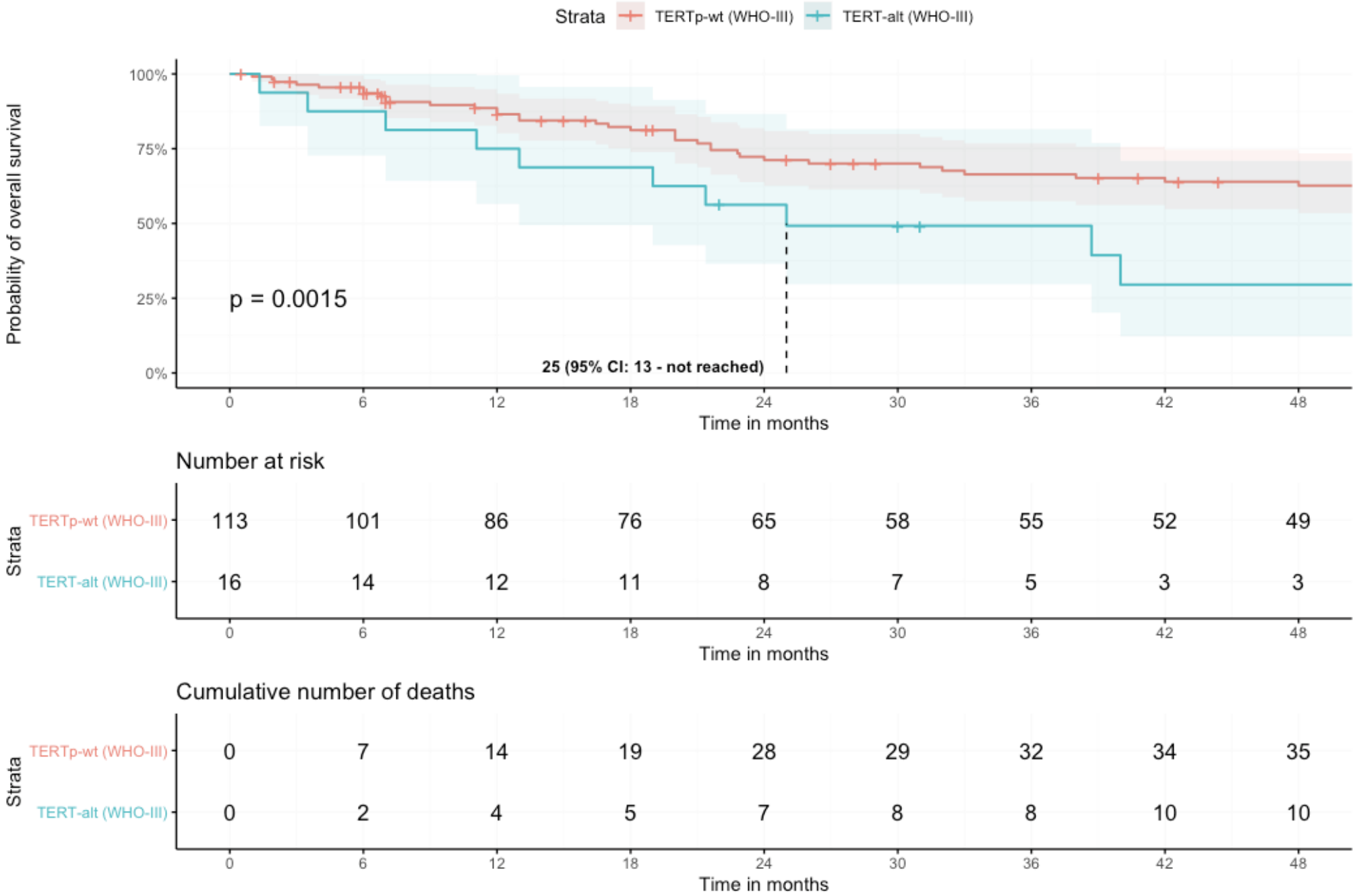
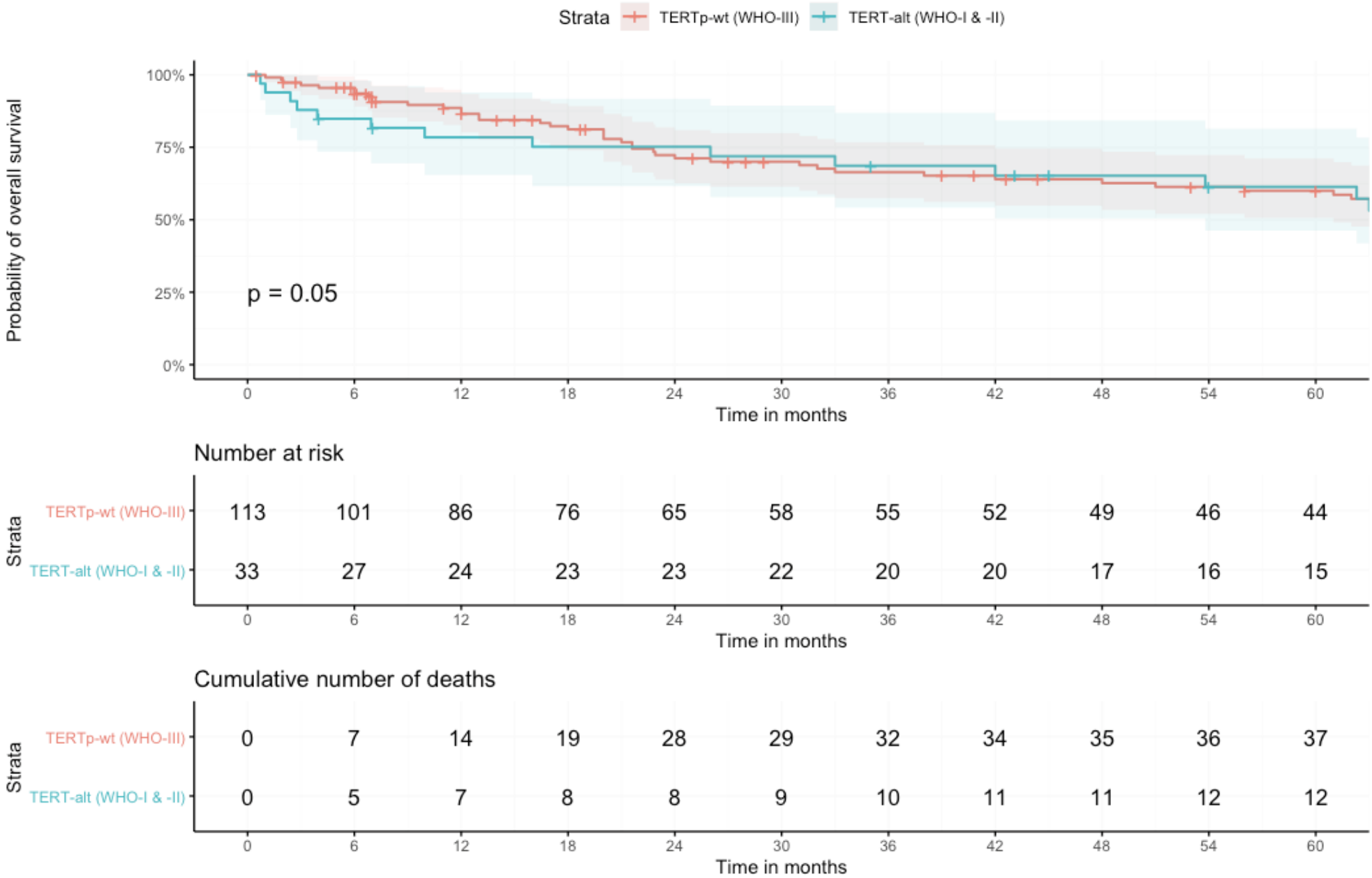


Figure 5C. Overall survival of WHO-III wild-type, *TERT*p-wt (WHO-III), versus WHO-I & -II combined of TERT gene alterations, *TERT*-alt (WHO-I & -II).



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