

Progression-free survival 2 (PFS2) as a surrogate for overall survival in a multicentric real-world data cohort of Glioblastoma (GBM)

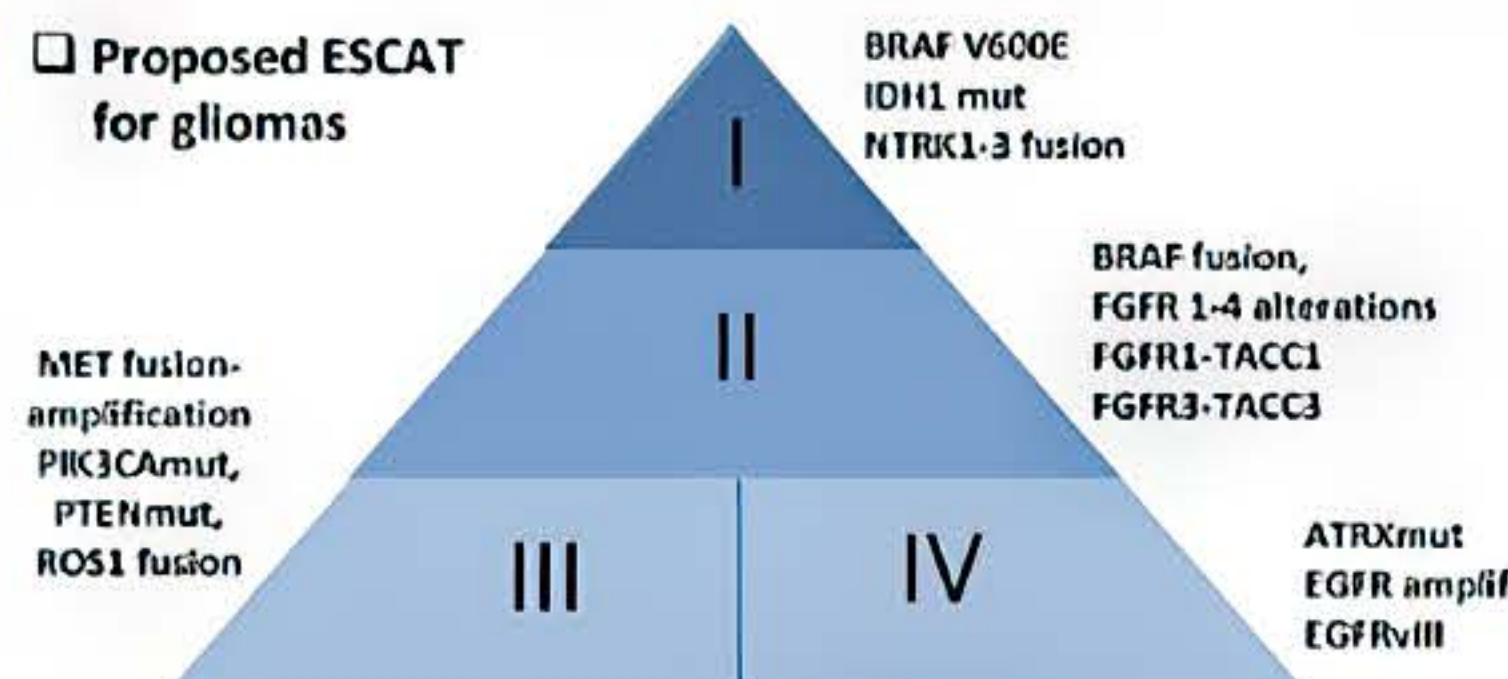
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BACKGROUND

- While OS is the default primary objective for any registrational clinical trial, other objectives such as response rate and PFS are commonly used in early clinical trials. There is however no established surrogate of OS in GBM, and assessing PFS in the first line setting, especially when the risk of pseudoprogression is not homogeneous between groups, can be difficult.
- EMA encourages the use of PFS2, defined as time from initial study randomization to second disease progression or death from any cause, to capture possible negative effects on next-line therapy and to outbalance tolerability and toxicity concerns related to maintenance therapy, although its surrogacy for OS has not been confirmed.

Proposed ESCAT for gliomas



OBJECTIVES

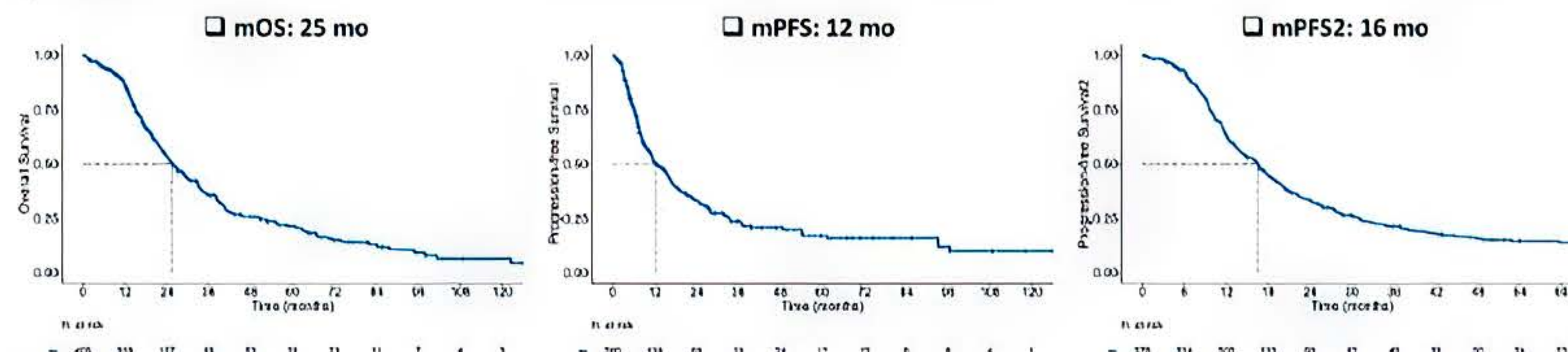
- Primary:** Our aim is to compare the association between OS, PFS and PFS2.
- Exploratory:** To analyze PFS2 on different systemic treatment options after disease progression to first-line therapy. To assess the impact of actionable mutations in survival outcomes, including PFS2.

METHODS

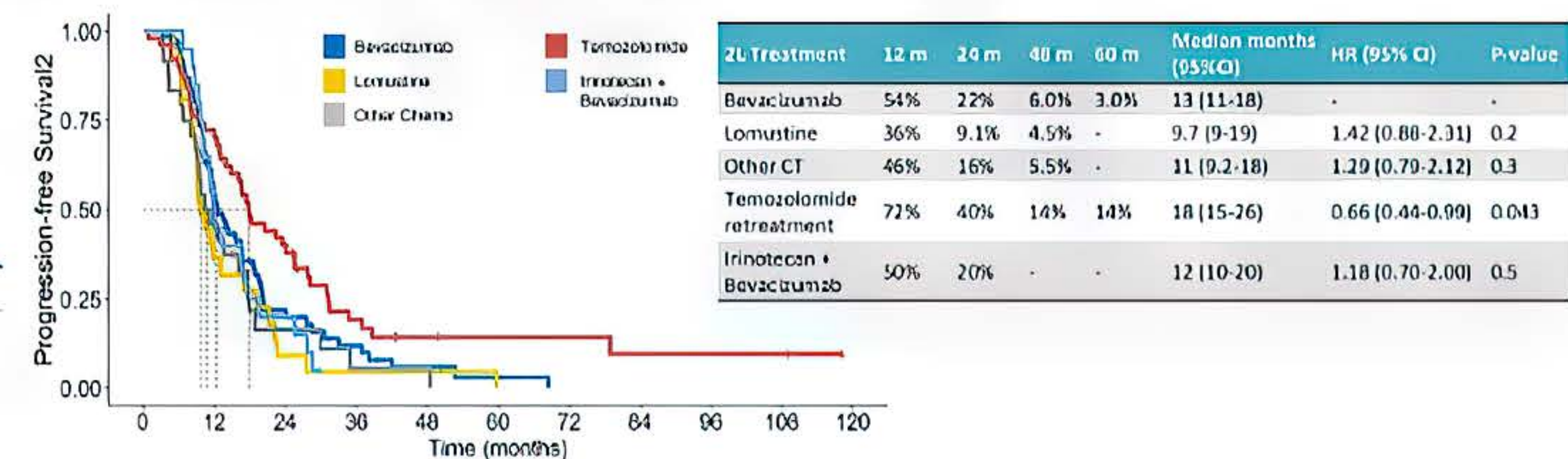
- GBM patients included in an **observational cohort** from 7 Spanish institutions with **next-generation sequencing** performed between 2018 and 2022 were analyzed.
- Correlations between OS and both PFS and PFS2 were calculated using the **iterative multiple imputation approach for estimating the rank correlation under a normal copula**, with a complementary analysis based on the proposed ESCAT classification for pBT presented by Mirallas O *et al* [ESMO 2023].

RESULTS

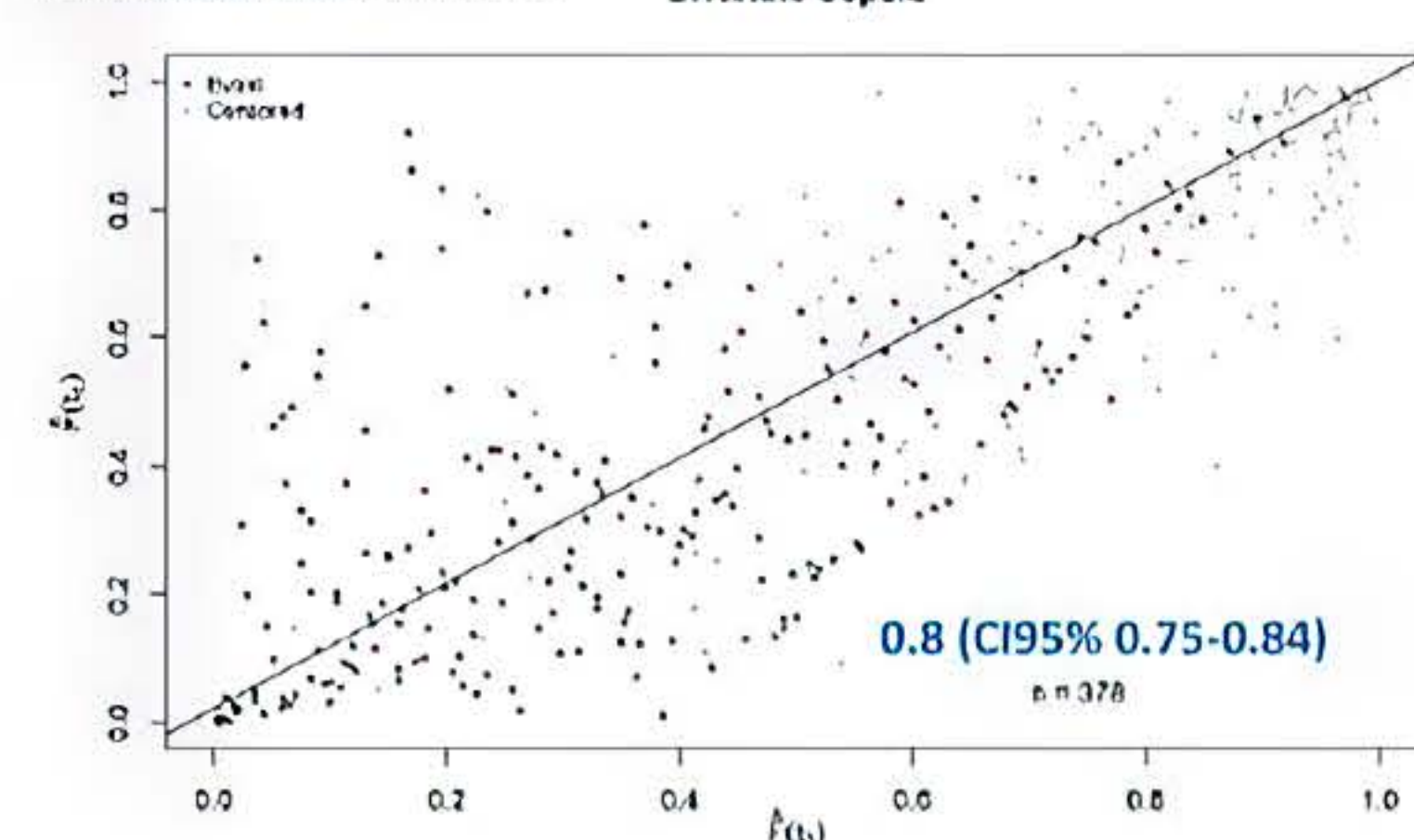
Main: We included 405 patients with GBM. Most patients were treated with conventional scheme of TMZ and RT. A second-line agent was administered to 378 patients.



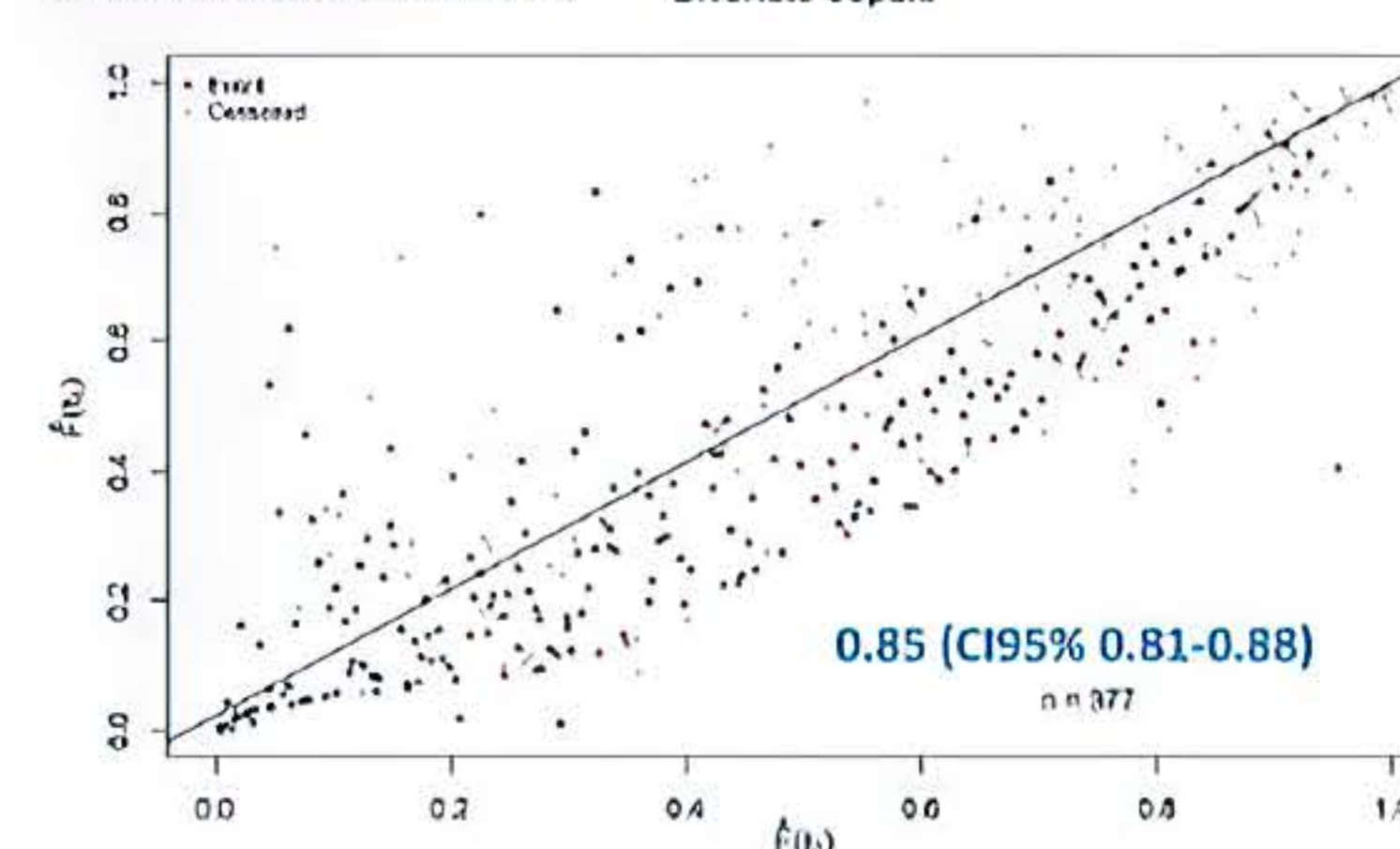
Exploratory: Between second-line options, mPFS2 was 13 months for bevacizumab, 9.7 mo for lomustine, 12 months for irinotecan plus bevacizumab, 18 months for retreatment with temozolomide (used in patients with progression free interval > 1y).



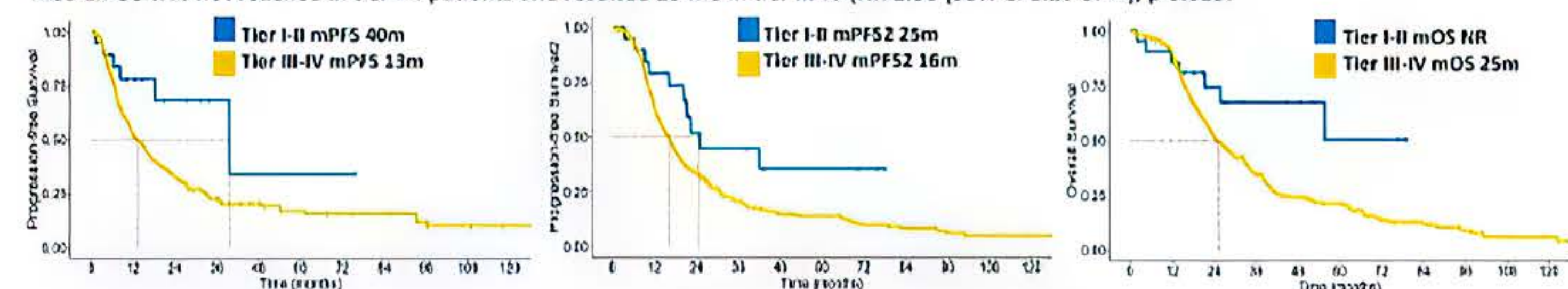
Correlation OS vs PFS



Correlation OS vs PFS2



Exploratory: In patients with actionable molecular alterations, a significant difference was found between Tier I-II and III-IV in terms of mPFS2. Median OS was not reached in tier I-II patients and resulted 25 mo in tier III-IV (HR 2.56 [95% CI 1.20-5.44], p 0.015).



CONCLUSIONS

- This is the first study reporting that PFS2 has a stronger correlation with OS than PFS in patients with GBM.
- One potential limitation for the use of PFS2 as surrogate of OS in first line trials is that the benefit of second line treatments needs to be homogeneous, which is something that does not happen in patients that harbor Tier 1-2 molecular alterations, who have access to targeted treatment at relapse.
- All second-line treatments have similar PFS2, except for patients retreated with TMZ after a long disease-free interval from the first line.
- As only patients with NGS performed were analyzed, PFS2 as surrogate for OS could find its best application in patients who are candidate for targeted therapy and/or in the context of clinical trials where the experimental treatment has a higher pseudoprogression rate than standard therapy.

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