The clinical landscape of central nervous system (CNS) involvement in triple-negative breast cancer (TNBC)

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Background
- Triple-negative breast cancer (TNBC), i.e., oestrogen receptor (ER)/progesterone receptor (PR)/HER2-negative at immunohistochemistry, is an aggressive disease entity with a particular tropism for the central nervous system (CNS).
- Patients with TNBC are living more and thereby their life-time risk of developing brain metastases is a growing concern.
- Therefore, we retrospectively reviewed medical charts of TNBC patients treated in a high-volume cancer centre in Belgium to provide a through picture of the clinical landscape of CNS involvement.

Methods & Objectives
- Retrospective analysis of a cohort of 432 patients with stage IV TNBC diagnosed and treated at Institut Jules Bordet, Belgium, from 02/2000 to 12/2014, after approval of the institutional ethics committee.
- Electronic patient charts were reviewed, with a cut-off date for survival analysis on 02/2015.
- Primary endpoint: brain metastases-free survival (BMFS), defined as the time from diagnosis of TNBC to the development of a CNS event (detection of parenchymal or leptomeningeal metastases, or computed tomography scan or magnetic resonance imaging of the brain, according to the radiology report).
- Secondary endpoints: to identify risk factors(s) for developing a CNS event, to determine overall survival (OS) according to the development of a CNS event; and to the time to second neurologic failure (TTF-2), i.e. time between the diagnosis of a CNS event and the diagnosis of a 2nd CNS event.
- Frequency tables were assembled by baseline characteristics and development of a 2nd CNS event, and were compared with Fisher’s exact test or Chi-square test, with the Chi-squared proportional hazards model used to determine risk factors for the development of a 1st CNS event.
- Comparisons of survival between subgroups were assembled through log-rank tests and hazard ratios (HRs), with survival curves plotted with the Kaplan-Meier method.
- All tests were 2-sided and a p-value < 0.05 was considered statistically significant.

Results
- With a median follow-up of 7 years (IQR: 2.3–10.5), patients who developed a 1st CNS event were younger, presented higher clinical tumour staging (cT4), higher clinical nodal staging (cN3), or more metastatic disease, affected lymph nodes at surgery (pN2), and more commonly were not exposed to trastuzumab chemotherapy (Table 2).
- The median BMFS for the overall population was not reached (90% CI, 18.0 months to non-estimable), 1st–2nd CNS-free event rate was 97.2%, which decreases to 88.2% at 10 years (Figure 1).
- A numerically lower OS for the 55 patients with metastatic disease (recurrent or de novo) with a 1st CNS event was seen, compared to the 367 patients without an event (Figure 2).
- After multivariate analysis, cT4 stage, cN2 and cN3 stage, and having de novo metastatic disease persisted as risk factors for developing a 1st CNS event (Table 2), with lower BMFS rates (Figure 3).
- 35 patients had a 2nd CNS event (TTF-2~4.1 months; 95% CI, 2.3–6.8).

Conclusion
- We have described a better OS for patients with TNBC that developed CNS metastases, as compared to previous literature (progression less than 6 months), possibly because the overall management of CNS metastases may be improved, especially in selected patient populations from academic cancer centres.
- Patients presenting with locally-advanced or de novo metastatic TNBC, due to their higher risk of brain metastases, should be considered for screening strategies with CNS imaging, aiming at early detection and possibly the delivery of optimal CNS-directed therapies (e.g. intrathecal therapies).
- Unsurprisingly, TTF-2 is short, thus trials focusing on new treatments with CNS activity are warranted.

References

Table 1: Baseline clinicopathological characteristics of patients with TNBC according to treatment strategy.

Table 2: Multivariate analysis for the correlation of baseline clinicopathological characteristics and the development of a 1st CNS event.

Table 3: BMFS according to identified risk factors.

Figure 1: Kaplan-Meier curve of BMFS for the whole cohort.

Figure 2: Kaplan-Meier curves according to T2 (cT2, cN0, cN1, and cN2) and T3 (cT3, cN0, cN1, and cN2), from left to right and up to bottom, respectively.