Prognostic impact of immune interactions in HER2+ and triple-negative breast cancer brain metastases

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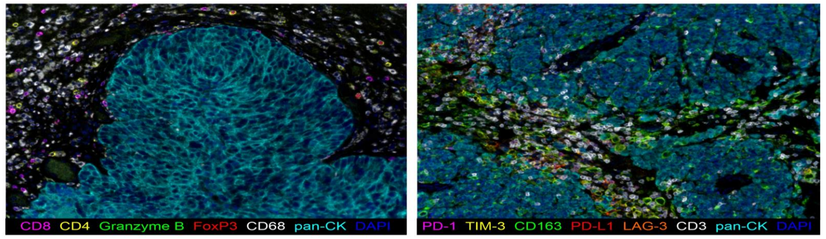
Background

- Despite clinical implications, the complexity of brain metastases (BM) immune microenvironment in breast cancer (BC) patients (pts) is still poorly understood.
- Multiplex immunofluorescence (mIF) simultaneously visualizes several IF labeled proteins while maintaining spatial information and can identify spatially interacting cells, potentially providing useful information to guide therapeutic approaches.

Patients and Methods

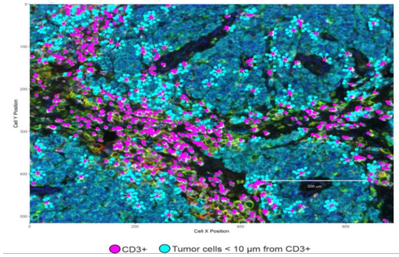
- HER2+ and triple negative (TN) archival BMs for BC pts undergoing neurosurgery (2003-2018) at 3 institutions (ICM, IOV, Montefiore) were collected.
- BCBMs were characterized using 2 custom mIF panels for immune cell subtyping and immune checkpoint and co-inhibitory markers (Fig.1).

Fig 1. Example of mIF images of BCBM using the two panels



- Considering cell dimensions, a distance up to 25 µm between two cells represents of an enhanced probability of cell-cell contact.
- Percentage of cells with reference cells within a predefined radius from a cell of different phenotype was evaluated (count within; Fig.2).

Fig 2. Cell-cell distance analysis example



- Association between spatially interacting cells and overall survival from BM diagnosis (OS) was tested in each BC subtype separately.
- All tests two-sided (significance p≤0.05).

Results

Forty-one BCBM samples were analyzed. Table 1 reports clinical characteristics.

Table 1. Patient characteristics at BM diagnosis and treatment received

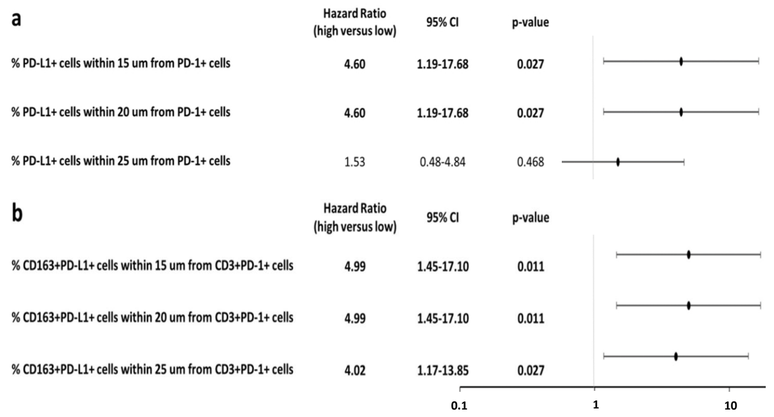
		HER2+ (N=23)		TN (N=18)	
		N	%	N	%
Number of BM	1	18	78.3%	16	88.9%
	2	2	8.7%	2	11.1%
	3 or more	3	13.0%	0	0%
Karnofsky PS	100-90	6	33.3%	5	41.7%
	80-70	11	61.1%	5	41.7%
	60 or less	1	5.6%	2	11.1%
Systemic therapy after BCBM diagnosis		21	91.3%	8	44.4%
Radiotherapy after BCBM diagnosis		20	87.0%	10	55.6%

At a median follow-up of 42.6 mos from BM diagnosis, median OS was 53.0 mos (95% CI 28.6–NR mos) and 9.4 mos (95% CI 4.7-NR mos) for HER2+ and TN BCBM pts, respectively.

Immune interactions and and Overall Survival in HER2+ BCBMs

In HER2+ BCBM, PD-1/PD-L1 interaction was significantly associated with worse prognosis (Fig.3a). This is mainly driven by interaction between PD-L1+ CD163+ macrophages and PD-1+ CD3+ lymphocytes (Fig.3b).

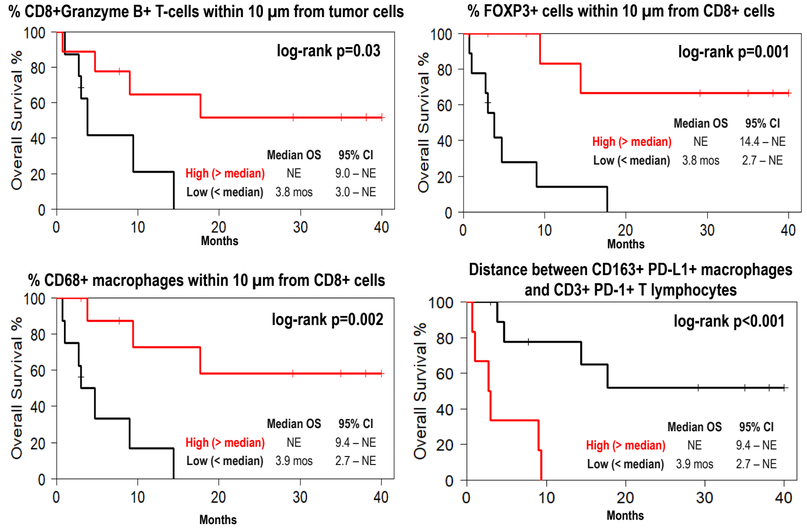
Fig 3. Association between immune interactions and OS in HER2+ BCBMs. Median value used to dichotomize each variable and Univariate Cox model HR is reported.



Immune interactions and and Overall Survival in TN BCBMs

Differently, in TN BCBM, several immune interactions were associated with better OS (Fig.4). even a shorter distance between CD163+ PD-L1+ macrophages and CD3+ PD-1+ T-cells was associated with better prognosis in TN BCBMs(Fig.4).

Figure 4. OS curves for TNBC pts according to cell-cell immune interactions



Conclusions

- In HER2+ BCBM, PD-1/PD-L1 interaction appears to negatively impact patient prognosis and might represent a potential therapeutic target.
- In TN BCBM, a general activation of the immune system is associated with better prognosis. This often involves inhibitory as well as cytotoxic immune components, potentially as a reaction to immune activation.

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