HER2-overexpressing circulating tumor cells in patients treated by trastuzumab deruxtecan for metastatic HER2+ breast cancer: clinical and prognostic implications.

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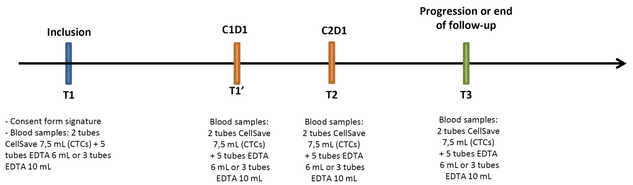
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BACKGROUND

Trastuzumab deruxtecan (T-DXd) has become the standard second-line treatment of HER2-overexpressing metastatic breast cancer (HER2$^+$ MBC). However, to date, no reliable circulating biomarker has been identified to anticipate the resistance or sensitivity to this compound, and to better understand the underlying mechanisms of resistance / sensitivity. We evaluated in a prospective cohort the respective value of circulating tumor cell (CTC) levels, as well as CTC HER2 immunostaining and its heterogeneity, before and early during therapy as a tool to evaluate the prognosis of HER2$^+$ MBC patients.

METHODS

We prospectively enrolled patients with HER2$^+$ MBC receiving T-DXd across three French clinical centers (NCT04025541). Peripheral blood samples were collected at three timepoints: prior to treatment initiation (T_1+$T_{1'}$, pooled [positivity defined as at least one of the 2 samples positive] in order to maximize the statistical power, referred in the results as T_1), before the second treatment cycle (T_2), and at the time of confirmed disease progression (T_3). CTCs were detected using the CellSearch® system. For each detected CTC, both enumeration and quantitative assessment of HER2 expression by immunofluorescence were performed. HER2 staining intensity and intra-patient heterogeneity were evaluated using the ACCEPT image analysis algorithm, enabling characterization of HER2-positive CTCs (HER2$^+$ CTCs). Progression-free survival (PFS) was modeled based on longitudinal trajectories of HER2$^+$ CTC levels using shared random effects joint models.



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RESULTS

Table 1. Patient and tumor characteristics

	Overall N = 60	HER2+ CTC- N = 53	HER2+ CTC+ N = 7	p-value
Age				0.8
Median (Q1 - Q3)	58 (52 - 65.5)	58 (52 - 66)	59 (52 - 65)	
PS ECOG, n (%)				0.027
0	28 (50.9%)	27 (56.3%)	1 (14.3%)	
1	16 (29.1%)	11 (22.9%)	5 (71.4%)	
2	7 (12.7%)	7 (14.6%)	0 (0.0%)	
3	4 (7.3%)	3 (6.3%)	1 (14.3%)	
Missing	5	5	0	
Histology, n (%)				0.070
NST	49 (81.7%)	44 (83.0%)	5 (71.4%)	
Lobular	3 (5.0%)	3 (5.7%)	0 (0.0%)	
Mixed	2 (3.3%)	2 (3.8%)	0 (0.0%)	
Other	6 (10.0%)	4 (7.5%)	2 (28.6%)	
ER expression, n (%)				0.7
Negative	20 (33.3%)	17 (32.1%)	3 (42.9%)	
Positive	40 (66.7%)	36 (67.9%)	4 (57.1%)	
PR expression, n (%)				0.2
Negative	35 (59.3%)	29 (55.8%)	6 (85.7%)	
Positive	24 (40.7%)	23 (44.2%)	1 (14.3%)	
HER2 Status, n (%)				0.2
2+ (amplified)	14 (25.0%)	14 (28.6%)	0 (0.0%)	
3+	42 (75.0%)	35 (71.4%)	7 (100.0%)	
Metastatic CT[1] lines, n (%)				0.015
0	2 (3.3%)	2 (3.8%)	0 (0.0%)	
1	35 (58.3%)	33 (62.3%)	2 (28.6%)	
2	12 (20.0%)	11 (20.8%)	1 (14.3%)	
3	7 (11.7%)	6 (11.3%)	1 (14.3%)	
4	3 (5.0%)	1 (1.9%)	2 (28.6%)	
5	1 (1.7%)	0 (0.0%)	1 (14.3%)	
Metastatic Trastuzumab lines, n (%)				0.2
0	2 (3.3%)	2 (3.8%)	0 (0.0%)	
1	40 (66.7%)	36 (67.9%)	4 (57.1%)	
2	11 (18.3%)	10 (18.9%)	1 (14.3%)	
3	6 (10.0%)	5 (9.4%)	1 (14.3%)	
4	1 (1.7%)	0 (0.0%)	1 (14.3%)	
Prior Pertuzumab, n (%)				0.6
No	12 (20.0%)	10 (18.9%)	2 (28.6%)	
Yes	48 (80.0%)	43 (81.1%)	5 (71.4%)	
Prior T-DM1, n (%)				0.012
No	44 (73.3%)	42 (79.2%)	2 (28.6%)	
Yes	16 (26.7%)	11 (20.8%)	5 (71.4%)	
Prior Lapatinib, n (%)				0.2
No	58 (96.7%)	52 (98.1%)	6 (85.7%)	
Yes	2 (3.3%)	1 (1.9%)	1 (14.3%)	
Prior Tucatinib, n (%)				0.6
No	52 (86.7%)	45 (84.9%)	7 (100.0%)	
Yes	8 (13.3%)	8 (15.1%)	0 (0.0%)	

[1]CT: Chemotherapy

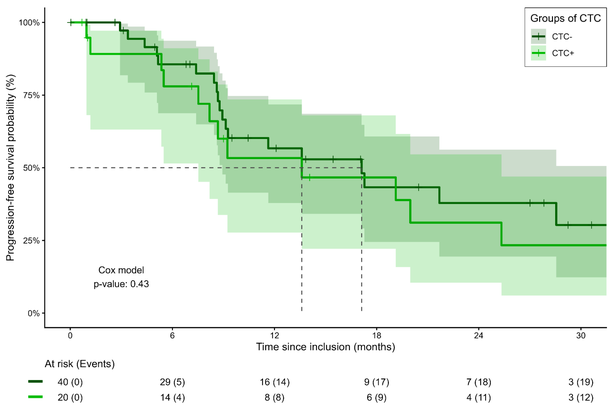


Figure 1. Progression-Free Survival by CTCs

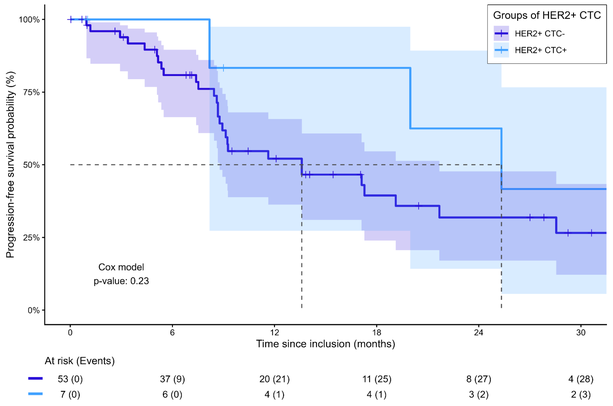


Figure 2. Progression-Free Survival by HER2+ CTCs

A total of 60 evaluable patients were enrolled between June 2021 and February 2025. As of the data cutoff date (July 1, 2025), with a median follow-up of 17.2 months (95% CI: 11.6-21.7 months), disease progression had occurred in 28 patients. CTCs were detectable at baseline (T_1) in 20 patients (33.3%) and at the second timepoint (T_2) in 4 patients (6.6%). No baseline clinical or pathological variables were found to be significantly associated with CTC positivity at T_1. Neither the baseline presence of CTCs (with a median PFS of 13.6 months [7.5 - 25.4] *vs*. 17.1 [8.9 - NA], p=0.4, for the CTC+ (≥1 detected cell) and CTC- populations, respectively) nor the longitudinal evolution model were associated with PFS. HER2$^+$ CTCs were detected in 7 patients (11.6%). Among CTC-positive cases, no statistically significant correlation was observed between the number of CTCs and the presence of HER2$^+$ CTCs. Notably, HER2$^+$ CTCs were exclusively identified in patients whose tumor tissue exhibited HER2 3+ expression. While not significant (p=0.2), the HER2$^+$ CTC population presented a PFS twice longer compared to the HER2$^+$ CTC-negative population (25.3 [8.1 - NA] *vs.* 13.6 months [8.7 - 21.7], respectively, HR=0.48), even if the HER2$^+$ CTC population was more heavily pretreated (median of 3 previous cytotoxic treatments in the MBC setting compared to 1 for the HER2$^+$ CTC-negative group, p=0.01). The longitudinal evolution model was not associated with PFS.

CONCLUSION

Detection of HER2$^+$ CTCs appears to be a rare event in HER2$^+$ MBC. This low detection rate could be linked to the targeted therapy treatment, as previously published (Bidard FC *et al*., Lancet Oncology 2014). However, their presence may help identify a subset of patients who derive greater benefit from T-DXd treatment. Larger studies and evaluation of additional circulating biomarkers, such as ctDNA, are warranted.

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