



## Background

Based on the results reported in Emilia trial population, current guidelines consider TDM-1 the standard 2<sup>nd</sup> line therapy for HER2 positive metastatic breast cancer (MBC) patients. Despite that, there are no prospective studies supporting the efficacy of TDM-1 following trastuzumab (T) + pertuzumab (P) and taxane 1<sup>st</sup> line treatment. Currently, only real-world data have investigated this sequence with controversial results.

## Material and Methods

We performed a meta-analysis of the available real world data to determine the efficacy of T-DM1 after 1<sup>st</sup> line TP in HER2 positive MBC patients. We used a random-effect model to find differences in the rate of 1-year progression free survival (PFS) between TP pre-treated population and the phase III Emilia trial (T pre-treated population).

## Results

Table 1 Clinical trials included trastuzumab pertuzumab pre-treated metastatic breast cancer population. The second part of the table reported the data from the two phases III trials Emilia and Th3resa included in the analysis as comparators.

First author name (Trial)	Year	Previous treatment	T-DM1 line	PFS months	95%CI	Patients N.	1-year PFS % patients
Dzimitrovic et al.	2016	TP + CHT or ET	2nd and further	4	2,7 - 5,1	78	NA
Conte et al.	2019	TP TXT	2nd-line	6,3	4,8 - 7,7	77	28
Urruticoechea et al. (Cleopatra)	2017	TP TXT	2nd and further	7,1	0 - 44	32	NA
(Pherexa)	2017	TPC	2nd and further	4,2	0 - 22	43	NA
Fabi et al.	2017	TP TXT	2nd-line	5	4,3 - 5,7	34	48
Noda-Narita et al.	2019	TP TXT	2nd and further	2,8	1,7 - 4,8	18	12
Vici et al.	2017	TP TXT	2nd and further	4	2 - 7	47	13,2
Lupichuk et al.	2019	TP TXT	2nd and further	5,5		55	22
Battisti et al.	2020	TP TXT	2nd and further	8,7	6,6 - 11,3	37	NA
Del prete et al.	2020	TP TXT	2nd	10,5	8,6 - 12,7	135	47
Huober et al. (Pernetta)	2018	TP	2nd	7,1	4,3 - 11,9	59	30
	2018	TP TXT	2nd	5,3	4 - 10,3	42	32
<b>Comparator Phase III trial</b>							
Krop et al. (Emilia)	2012	T TXT	2nd	9,6	0,55 - 0,77	495	40

T: Trastuzumab; P: Pertuzumab; TXT: taxane, C: Capecitabine, CHT: Chemotherapy regimen

Seven studies were eligible, in three of them data were from sub-group population analysis. The meta-analysis showed a combined 1-years PFS risk difference for TDM-1 efficacy after TP in 2<sup>nd</sup> or more lines of -0.122, with lower and upper limits of -0.253 and 0.010, respectively (p=0.07), with low heterogeneity among studies (I<sup>2</sup> < 0.0001, p =0.836). Considering the four studies on TDM-1 in 2<sup>nd</sup> line setting, 1-years PFS risk was -0.034 (95% CI - 0.207 – 0,139; p=0.701) (I<sup>2</sup> < 0.0001, p =0.91).

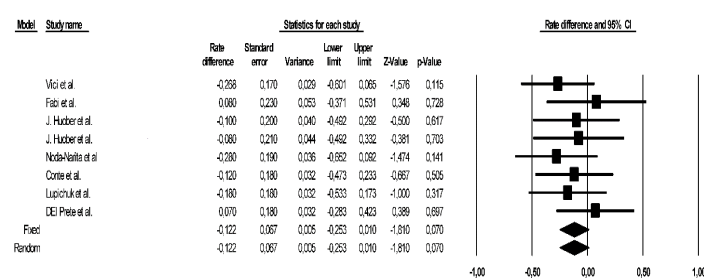


Figure 1 Comparisons of 1-year Progression Free Survival (PFS) of TDM-1 between trastuzumab pertuzumab pre-treated population and trastuzumab pre-treated one (Emilia and Th3resa trials). The left part of the figure shows the studies included in the analysis with their corresponding rate difference, standard error, lower and upper limits, z-value and p-value while the right part of the figure show a forest plot of the data. The square represents the risk difference for each study, the horizontal lines represent the values within the 95% confidence interval (8CI) of the underlying effects. The vertical line represents a risk difference of 0.

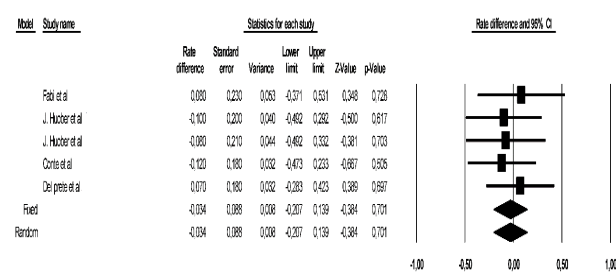


Figure 2 Comparisons of 1-year Progression Free Survival (PFS) of TDM-1 in 2<sup>nd</sup> line between trastuzumab pertuzumab pre-treated population and Emilia trial population. The left part of the figure shows the studies included in the analysis with their corresponding rate difference, standard error, lower and upper limits, z-value and p-value while the right part of the figure show a forest plot of the data. The square represents the risk difference for each study, the horizontal lines represent the values within the 95% confidence interval (8CI) of the underlying effects. The vertical line represents a risk difference of 0.

## Conclusion

Results from the meta-analysis show that the efficacy of TDM-1 after TP double-block seems to be similar to the previously reported in Emilia trial. In the second line setting, available data are not mature enough to confirm TDM-1 efficacy in TP pre-treated population. Currently, TP pretreated patients should receive T-DM1 as indicated in the guidelines

## Bibliography

Verma, S., et al., *Trastuzumab emtansine for HER2-positive advanced breast cancer*. N Engl J Med, 2012. **367**(19): p. 1783-91 - Krop, I.E., et al., *Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial*. Lancet Oncol, 2017. **18**(6): p. 743-754.