

A model to predict progression free survival in HER2 positive progressive or recurrent locally advanced breast cancer (LABC) or previously untreated metastatic breast cancer (MBC) patients based on tumor growth inhibition metrics

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Objective

To assess the link between tumor growth inhibition (TGI) metrics and progression free survival (PFS) based HER2 positive progressive or recurrent locally advanced breast cancer (LABC) or previously untreated metastatic breast cancer (MBC) patients from the MARIANNE study [1].

Methods

- TGI data from 868 patients who received trastuzumab emtansine (T-DM1), T-DM1 plus pertuzumab or trastuzumab plus a taxane in the Phase III study Marianne [1] were fit using tumor growth inhibition models [2,3] by NONMEM version 7.3.0 [4].
- The relationship between model-based estimates of TGI metrics [5], baseline covariates and PFS were tested in a multivariate parametric distribution survival model to select the best predictors of PFS in R version 3.1.2.
- Tested TGI metrics were:
 - Growth rate (KG or its log value), shrinkage rate (KS or its log value) estimated with the empirical bi-exponential TGI model [2]

$$TS(t) = TS(0) \times (e^{-KS \times t} + e^{KG \times t} - 1)$$

- Early tumor shrinkage (ETS) at week 8 and time to growth (TTG) estimated with the simplified TGI model [3]

$$\begin{aligned} \text{if } t < 0, \quad TS(t) &= TS(0) \times e^{KL \times t} \\ \text{if } t \geq 0, \quad TS(t) &= TS(0) \times e^{KL \times t - \frac{KDE_0}{\lambda} \times (1 - e^{-\lambda \times t})} \\ t = 0, \quad &\text{time of the first dose} \\ ETS &= \frac{TS(t)}{TS(0)}, \quad TTG = \frac{\ln(KDE) - \ln(KL)}{\lambda} \end{aligned}$$

- A univariate analysis (covariate tested one by one) was performed using a Cox proportional hazards regression model (coxph function in R survival package). Statistically significant covariates in the univariate Cox analysis (p<0.05) were included in a full multivariate parametric distribution survival model (survreg function in the R survival package). Different parametric distributions of the baseline hazard were tested: logistic, loglogistic, lognormal, weibull, exponential, gaussian. A backward deletion stepwise procedure was performed (p<0.01) to retain covariates constituting the final model for PFS. T-DM1 exposure was not tested upfront in the parametric PFS model because the PK subset of Marianne comprised only 316 patients.
- PFS model performance was evaluated using posterior predictive checks (PPC) comparing the simulated distributions (1000 replicates) of PFS by quartile of TGI metric or other significant covariates with the observed distributions in the MARIANNE study.

Results: model development

- Both TGI models provided a good fit to the data based on goodness of fit plots, precision of parameters estimation (relative standard errors ≤ 10%), objective function was better (lower) with the simplified TGI model while shrinkage was lower with the empirical bi-exponential TGI model (≤ 21% versus ≤ 31%).
- Table 1 describes the results of the univariate Cox analysis. Selected covariates for the parametric PFS model are highlighted in blue color. Only the best of correlated covariates are included (e.g. predicted tumor burden better than observed). Covariates with low N are excluded. Study region was considered as not relevant.
- The log-normal distribution provided the best fit to the data. Parameters estimates of the final model are presented in Table 2. Log(KG) is the main predictor of PFS; LDH, SGOT and the number of disease sites are worsening prognostic factors.

Table 1: Univariate Cox analysis

	Score	p.LRT	N	Sign
LogKG	438.1	0	868	+
Log(TTG weeks)	219.6	0	868	-
ETS at week 8	55.1	0	868	+
Baseline tumor burden, predicted (mm)	38.9	0	897	+
LDH (U/L)	35.8	0	884	+
Screening tumor burden, observed (mm)	28.5	0	897	+
Number of disease sites >2	20.9	0	897	+
LogKS	14	2e-04	868	+
SGOT (U/L)	9.7	0.0019	890	+
Predicted T-DM1 AUC (mg.L ⁻¹ .day)	8.7	0.0032	316	-
ECOG≥1	8.4	0.0038	897	+
Brain metastasis	7.8	0.0053	897	+
Tumor type = metastatic	7.4	0.0067	897	+
Predicted T-DM1 Cmin (mg/L)	7.1	0.0077	316	-
Prior trastuzumab	7.1	0.0075	897	+
Visceral disease	6.7	0.0098	897	+
Prior anthracycline	6.2	0.0127	897	+
Month since last trastuzumab treatment	5.7	0.0167	248	-
Lung or liver metastasis	5.6	0.018	897	+
Albumin (g/L)	5.2	0.0227	878	-
Total bilirubin (μmol/L)	5	0.0248	889	-
Pertuzumab treatment	4.5	0.0333	897	+
Prior neoadjuvant/adjuvant therapy	4.3	0.0389	897	+
Prior taxane	4.3	0.0381	897	+
Asian	3.3	0.0683	897	+
TDM1 treatment	3.1	0.0775	897	-
Alkaline phosphatase (U/L)	2.6	0.1098	889	+
De-novo	2.6	0.1067	892	-
Observed T-DM1 Cmin cycle 4 (mg/L)	2.3	0.1279	268	-
HER2 mRNA expression level	1.5	0.221	821	-
Disease free interval >2 y	1.1	0.2841	892	-
Total protein (g/L)	0.8	0.3674	877	+
Baseline trastuzumab concentration (mg/L)	0.4	0.5163	317	-
Hormonal status ER-/PR-	0.2	0.6588	877	+
Observed T-DM1 Cmin cycle 1 (mg/L)	0.1	0.821	300	+
White	0	0.9563	897	-
Age	0	0.8446	897	-

p.LRT: p-value of the likelihood ratio test
Sign: + increased risk, - decreased risk

Table 2: Parameter estimates of the final model based on 861 patients

	Estimate	Std. Error	P Wald test
(Intercept)	-1.18	0.192	8.99e-10
logKG	-0.799	0.0333	4.65e-127
LDH (U/L)	-0.000481	0.000119	5.37e-05
>2 disease sites	-0.216	0.0739	0.00343
SGOT (U/L)	-0.00459	0.00151	0.00245
Log(standard deviation)	-0.193	0.0302	1.63e-10

Results: model qualification

- Table 3 shows the model qualification for median PFS. Figure 1 shows the model qualification for the entire PFS distribution. It also shows a clear separation of PFS across KG quartiles well captured by the model. The model under predicted PFS in the lowest KG quartile, in this quartile median PFS was not reached in MARIANNE and there was a lot of censored data i.e. 65% compared to 31%, 24% and 10% in upper quartiles.
- Figure 2 shows the model qualification for all prognostic factors of the model. The model is able to predict PFS in the various quartiles of T-DM1 exposure suggesting that the drug effect is fully captured by the TGI metric. The PFS model can be considered as being drug independent.

Table 3: Prediction of median PFS

KG quartiles	Median PFS (months)		
	Observed	Predicted	95% Prediction interval
Q1	not reached	35.0	[27.7; 45.1]
Q2	14.6	16.4	[13.7; 19.6]
Q3	10.4	10.9	[9.2; 13.0]
Q4	5.3	4.9	[4.1; 5.8]

Figure 1: Model predictive performance by KG quartile

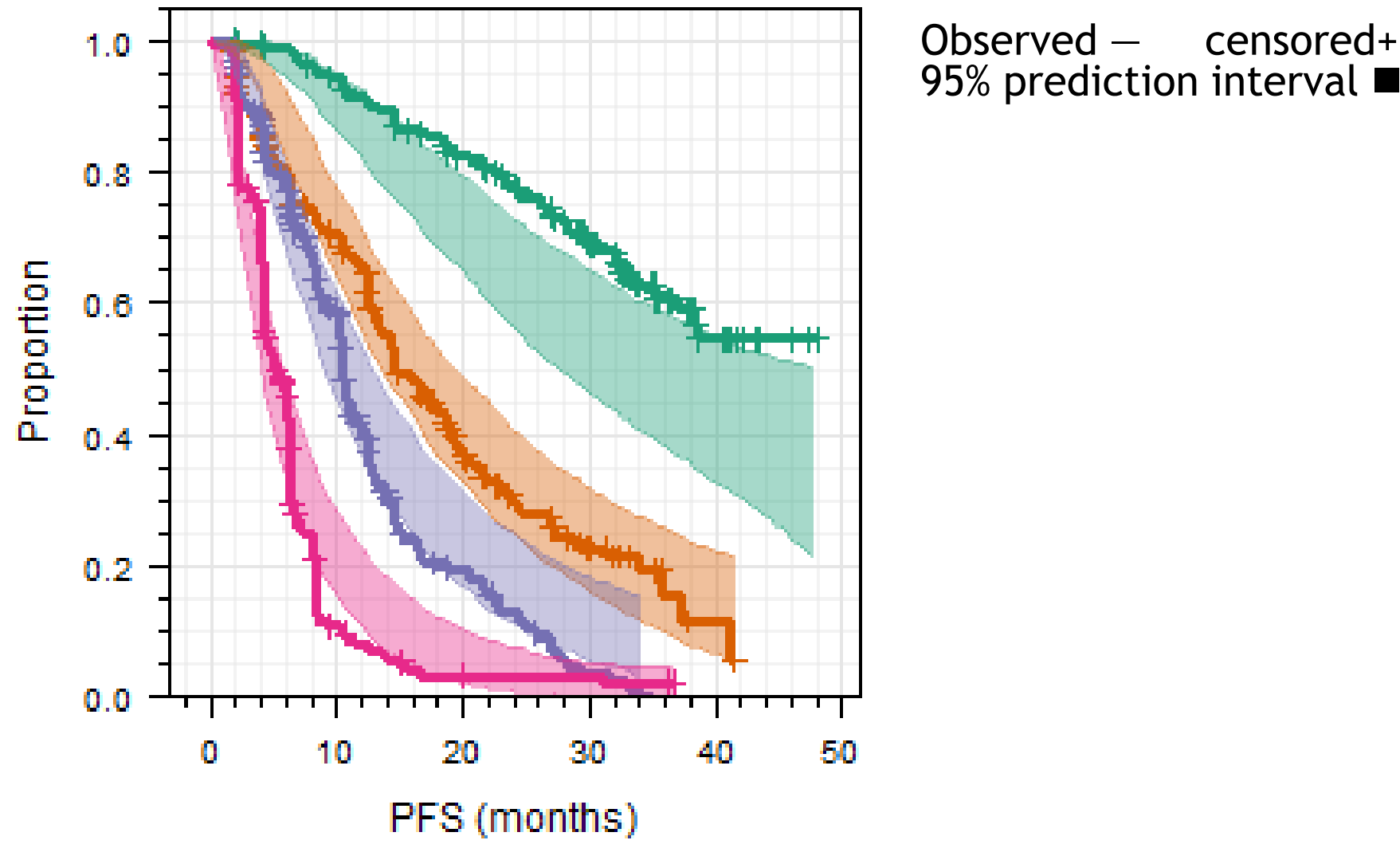
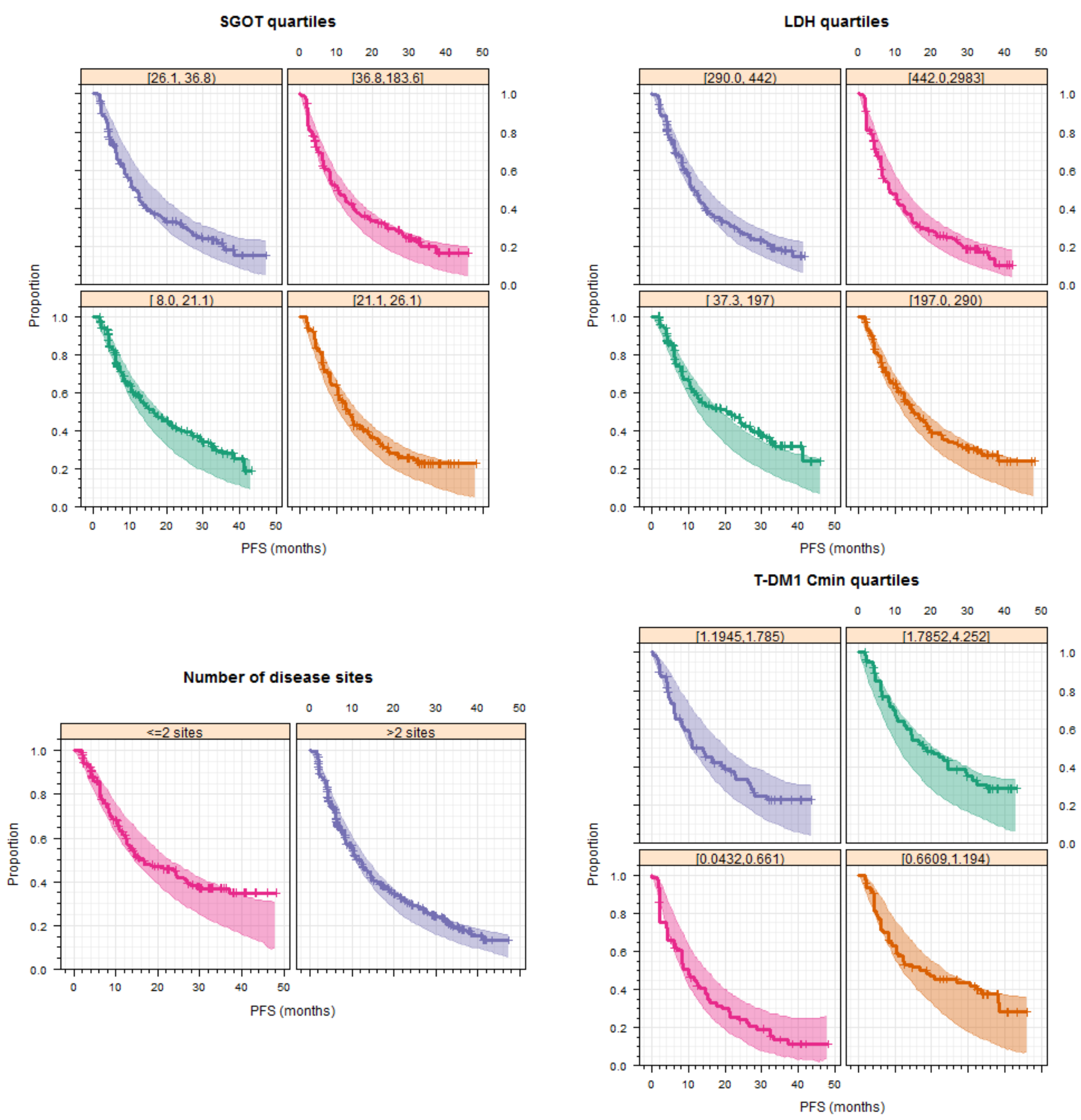


Figure 2: Model predictive performance by prognostic factors and T-DM1 exposure



Conclusions

- A drug-independent survival model that uses model-based estimates of tumor growth rate to predict PFS for previously untreated HER2-positive breast cancer has been developed and qualified.
- This model can be used to support early decision making of investigational agents in development for this indication based on this TGI metric.

References

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