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ORIGINAL RESEARCH

Real-World Analysis of the Efficacy and Adverse Events of T-DM1 in Chinese Patients With HER2-Positive Breast Cancer

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Purpose: This study efforts to explore the association of adverse events (AEs) with efficacy in HER2-positive breast cancer patients treated with TDM1.

Methods and Materials: This retrospective study included women diagnosed with HER2+ BC treated with TDM1 from January 2012 to December 2023. Event-free survival (EFS) was the endpoint. Tumour response was assessed by disease control rate (DCR) and objective response rate (ORR). The chi-squared test, analysis of variance (ANOVA), Cox proportional hazards regression and Kaplan-Meier survival analysis was employed to evaluate the association of AEs with tumour efficacy.

Results: A total of 48 women with a median age of 52 years (median follow-up 8.4 months) were included in the study. Among them, 33 patients (68.8%) experienced adverse events, including platelet depletion and liver function abnormalities, 3 patients (6.3%) discontinued TDM1 due to severe platelet depletion. The overall objective response rate (ORR) was 25.0% and the disease control rate (DCR) was 43.8%. Using the Chi-squared test, we found a statistically significant difference in ORR and DCR between patients who developed a platelet reduction and those who did not. DCR was significantly higher in patients with liver dysfunction than in those without. ANOVA showed that exposure to hepatic dysfunction and platelet reduction, lines of therapy, and treatment course were associated with EFS. In the Kaplan-Meier survival analysis, both liver dysfunction and platelet reduction were correlated with significantly longer EFS (p=0.033 and p=0.038, respectively).

Conclusion: This retrospective study demonstrated that AEs were associated with tumour efficacy in patients with HER2+ BC treated with TDM1.

Keywords: HER2-positive breast cancer, adverse events, T-DM1, tumour efficacy

Introduction

Breast cancer is the most frequent cancer in the world, with great biological and molecular variation. HER2+ breast cancers account for roughly 15% of all breast cancers and are more typically detected in younger people and at a later stage than the more common HR+ HER2- breast cancers.[1] Nevertheless, the adoption of medicines that are directly targeted at the HER2 receptor has resulted in a significant augmentation of rates of survival for patients diagnosed with both advanced- and early-stage illness.[2]

ADCs, or antibody-drug conjugates, are a special kind of combination that combines the efficacy of cytotoxic drugs, or payloads, with the selectivity of monoclonal antibodies (mAbs).[3] Since the US Food and Drug Administration (FDA) authorized the first ADC in 2000, 14 ADCs have been licensed for sale globally,[4] with five of these approved for solid cancers.[5] The most commonly prescribed ADCs for solid tumors are those that target HER2. Research has been sparked

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by the positive outcomes of ADCs in breast cancer, with clinical researches showing promising outcomes for certain novel HER2-ADCs.[6]

The FDA initially approved trastuzumab emtansine (T-DM1) for the treatment of a solid cancer in the ADC class in 2013, when it approved its usage to treat HER2-positive metastatic breast cancer.[7] 2019 saw the addition of adjuvant therapy for patients with HER2+ early breast cancer to the list of T-DM1 indications.[8] The Phase III EMILIA trial, which showed that T-DM1 as a second-line treatment improved PFS and OS when compared to the then-standard combination of capecitabine plus lapatinib, served as the basis for these approvals.[9] According to the results of the KATHERINE trial, T-DM1 was approved for use in HER2+ patients who had not experienced a pathological complete response after receiving trastuzumab and taxane treatment as neoadjuvant therapy.[10]

The cytotoxic payload is mostly responsible for the off-target toxicities that most ADCs cause. Furthermore, on-target toxicities as well as other unidentified yet possibly fatal side effects have also been noted. Notably, 91% of patients experience treatment-related adverse events with these medicines, with 46% experiencing grade 3 occurrences,[11] with a meta-analysis of 169 clinical studies showing a 3.2% overall incidence of treatment-related dropout.[12] Generally speaking, T-DM1 is linked to controllable side effects, including neuropathy and gastrointestinal toxicity, in addition to a decrease in left ventricular ejection fraction (LVEF). The majority of these events are classified as grade 1 or 2 in severity. Thrombocytopenia, dose-limiting toxicity, and an increase in liver enzymes, including the risk of liver failure, are the most common high-grade toxicities, according to clinical trials and real-world experience.[12]

Given the paucity of studies examining the relationship between the efficacy and adverse events of T-DM1, the effectiveness and adverse event data of TDM1-based therapy for HER2-positive breast cancer were retrospectively analyzed in this study at medical facilities in China. In this retrospective study, it is expected that the association between AEs and tumour outcomes will be explored, leading to timely intervention for patients with poor prognosis who can be identified by AEs.

Materials and Methods

Participants

This retrospective study was conducted at the First Affiliated Hospital of Wenzhou Medical University on patients who received treatment between January 2012 and December 2023. The following criteria were used to determine eligibility for inclusion in the study: (1) female patients at diagnosis were over the age of 18, (2) patients were diagnosed with HER2+ breast cancer, characterized by an immunohistochemistry score of 3+ or 2+, combined with HER2 gene amplification confirmed by FISH, regardless of the hormone receptor status, (3) patients were given a targeted anti-Her2neu therapy following breast surgery, (4) patients received TDM1-based therapy after recurrence and metastasis, either as a single agent or in combination with other agents, either as a first-line treatment or back-line treatment, (5) patients exhibited hematological and hepatic functions within normal ranges, and (6) Patients' clinical and follow-up information was complete. Patients lacking complete clinical information and those who were lost to follow-up were omitted from the study.

The Wenzhou Medical University's First Affiliated Hospital Institutional Ethics Review Board authorized the study (the ethics approval number, KY2024-R322). Furthermore, informed agreement from patients is necessary before data obtained from biological samples and clinical information can be used.

Efficacy and Toxicities

TDM1 is given every 3 weeks (21-day cycle) at a dose of 3.6 mg/kg by intravenous infusion until disease progression or intolerable toxicity. Every two or three treatment cycles, tumor response evaluations were conducted in accordance with the Response Evaluation Criteria in Solid Tumors Committee.[13] Both partial and complete responses (CR and PR) were considered objective responses. The sum of the objective response (CR+PR) rate and the stable disease (SD) rate was known as the disease control rate (DCR). Event-free survival (EFS) was defined as the time between the start of TDM1 and the occurrence of any event, such as disease progression, treatment termination for any cause, or death. Adverse events were categorized in compliance with the National Cancer Institute Common Toxicity Criteria, version 5.0

(CTC5.0). According to clinical trials and real-world experience, thrombocytopenia and liver dysfunction are the most common AEs of TDM1,[12] so we further explored the relationship between them and clinical efficacy. Information on recurrence and metastasis was obtained from each patient's medical and imaging records. AEs were assessed by haematological examination and outpatient records. The data were extracted on 31 July 2024.

Statistical Analysis

For quantitative variables, a normality test was performed and variables with p-values > 0.05 were considered to have a normal distribution. For normally distributed variables, the p-value was derived from the *t*-test and for skewed variables, the p-value was derived from the rank-sum test. For categorical variables, p-values were calculated using the chi-squared test. A chi-squared test was employed to ascertain whether there were any significant differences in the objective response rate (ORR) and disease control rate (DCR) between the various patient groups. An analysis of variance (ANOVA) was employed to assess the relationship between adverse events and efficacy of treatment in patients receiving TDM1-based therapy. Cox proportional hazards regression was used to assess important factors from the univariate analysis in a multivariate model. Meanwhile, hazard ratios (HRs) and 95% confidence intervals (CIs) were computed. The EFS curves were obtained using the Kaplan-Meier technique and the Log rank test was utilized.

All statistical tests were carried out using SPSS version 26.0 software (SPSS Inc., Chicago, IL, USA). A two-tailed P value < 0.05 was considered statistically significant.

Results

Characteristics of the Patients

This study comprised 48 patients who satisfied the inclusion and exclusion criteria between January 2012 and December 2023. With a median follow-up length of 8.4 months (range: 0.8 to 29.9 months), the patients were monitored until July 31, 2024. By the conclusion of the follow-up period, 11 patients (29.9%) had succumbed to their illness.

The median age of all patients was 52 years (range, 28–67 years). A total of 33 patients (68.8%) experienced adverse events, including a reduction in blood platelet levels and abnormalities in liver function. Grade 3 or 4 platelet reduction was observed in 14 patients (29.2%), while no patients exhibited grade 3 or 4 hepatic impairment. Three patients (6.3%) discontinued TDM1 due to a severe drop in platelet count that was refractory to recovery. There were notable discrepancies in EFS between patients who had experienced adverse events and those who had not. Patients who experienced adverse events exhibited a longer EFS ($p < 0.05$) compared to patients without adverse events. Further details can be found in Table 1.

Table 1 Baseline Characteristics Between Patients With AEs and Without AEs

Variables	Without AEs		With AEs		p Value
	Normality Test (p Value)		Normality Test (p Value)		
N	15		33		
Age (years)	0.466	52.6±6.9	0.061	51.3±9.3	0.632
Menopausal status					0.907
Pre	–	7	–	16	
Post	–	8	–	17	
BMI (kg/m^2)	0.304	21.9±3.2	0.272	22.5±3.2	0.504

(*Continued*)

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Table 1 (Continued).

Variables	Without AEs		With AEs		p Value
	Normality Test (p Value)		Normality Test (p Value)		
T					0.902
1	–	3	–	7	
2	–	6	–	15	
3	–	6	–	11	
N					0.491
0	–	5	–	9	
1	–	3	–	8	
2	–	2	–	10	
3	–	5	–	6	
M					0.774
0	–	11	–	27	
1	–	4	–	6	
Ki-67 (%)	0.014	30.0 (5.0, 50.0)	0.200	37.9±23.8	0.340
The lines of therapy					0.887
1	-	2	-	7	
2	-	1	-	1	
3	-	5	-	9	
≥4	-	7	-	16	
Total course of treatment	0.020	3.0 (2.0, 10.0)	0.024	8.0 (3.5, 13.5)	0.063
EFS (months)	0.039	3.4 (1.5, 8.9)	0.022	8.8 (4.1, 14.7)	0.012

Notes: The p-values for age and BMI were calculated from t-tests; the p-values for Ki-67, total course of treatment and EFS were calculated from the rank-sum test; the p-values for menopausal status, T, N, M and the lines of therapy were calculated from the chi-squared test.

Abbreviations: AEs, adverse events; BMI, Body mass index; T, Tumor; N, Node; M, Metastasis; EFS, Event-free survival.

The ORR and DCR Difference Between Different Groups of Patients

Among the 48 patients, 12 (25%) demonstrated an objective response, comprising 2 complete responses (4.2%) and 10 partial responses (20.8%). 9 patients (18.8%) exhibited stable disease (SD) as the best response, while 27 patients (56.3%) experienced progressive disease (PD). The objective response rate (ORR) for the entire cohort was 25.0%, while the disease control rate (DCR) was 43.8%. The ORR is shown in Table 2 for patient groups with different clinicopathological and illness features.

The chi-squared test revealed a statistically significant difference in ORR (p=0.043) and DCR (p=0.027) between patients who developed platelet reduction and those who did not. Patients with lower lines of therapy exhibited a superior response to TDM1. Nevertheless, no statistically significant differences were observed in the ORR and DCR between patients with and without hepatic impairment. Further details can be found in Table 3.

Factors Influencing the EFS

The results of the ANOVA demonstrated that exposure to hepatic impairment and platelet reduction, the lines of therapy, and the course of treatment were collected with EFS (Table 4). In the Kaplan-Meier survival analysis, both liver dysfunction and platelet reduction were found to be significantly correlated with longer EFS (p=0.029 and p=0.014, Figure 1). In the Cox univariate analysis, Node, the lines of therapy, total course of treatment, platelet reduction, liver dysfunction and other AEs were discovered as important factors (Table 5). Furthermore, according to the Cox

Table 2 The ORR in Patient Groups With Different Clinicopathological and Disease Characteristics

Variables	Objective Response		ORR (%)	P Value
	Yes	No		
The lines of therapy				0.008
1	8	1	88.9	
2	1	1	50.0	
3	2	12	14.3	
4	1	22	4.3	
Whether to combine drugs				0.369
Yes	2	13	13.3	
No	10	23	30.3	
AEs				0.369
With	10	23	30.3	
Without	2	13	13.3	
Platelet reduction				0.043
With	10	18	35.7	
Without	2	18	10.0	
Liver dysfunction				0.724
With	5	11	31.3	
Without	7	25	21.9	

Notes: The p-values in Table 2 were calculated using the chi-square test.
Abbreviations: ORR, objective response rate; AEs, adverse events.

Table 3 The DCR in Patient Groups With Different Characteristics

Variables	Disease Control		DCR (%)	p Value
	Yes	No		
The lines of therapy				0.001
1	9	0	100	
2	2	0	100	
3	5	9	35.8	
4	5	18	21.7	
Whether to combine drugs				0.327
Yes	5	10	33.3	
No	16	17	48.5	
AEs				0.108
With	17	16	51.5	
Without	4	11	26.7	
Platelet reduction				0.027
With	16	12	57.1	
Without	5	15	25.0	
Liver dysfunction				1.000
With	7	9	43.8	
Without	14	18	43.8	

Notes: The p-values in Table 3 were calculated using the chi-square test.
Abbreviations: DCR, disease control rate; AEs, adverse events.

multivariate analysis results, liver dysfunction and platelet reduction were the significant independent predictors of prolonged EFS (p=0.003 and p=0.013, Table 5). Additionally, the analysis revealed that the lines of therapy and the course of treatment were statistically significant with EFS. Further details can be found in Table 5.

Table 4 Factors Influencing the EFS Analyzed by the ANOVA

MODEL: R^2=0.689		
Predictive Variables	**Regression Coefficient**	**p Value**
The lines of therapy	−0.221	0.016
Total course of treatment	0.660	0.001
Platelet reduction	0.195	0.035
Liver dysfunction	0.265	0.039
Other AEs	−0.112	0.384

Abbreviations: ANOVA, analysis of variance; EFS, Event-free survival; AEs, adverse events.

Discussion

The primary findings of the present study reveal that individuals who suffered AEs demonstrated a greater response to TDM1. The ORR of patients who exhibited a reduction in platelet levels (35.7%) was higher than that observed in patients who did not experience this reduction (10.0%), suggesting that the former group may derive greater benefit from TDM1 treatment. The results of the ANOVA demonstrated that long EFS was more prevalent in patients who exhibited platelet reduction and hepatic impairment. In terms of survival, the multivariate analysis demonstrated that both liver dysfunction and platelet reduction was the independent predictors of much prolonged EFS following TDM1 treatment. As far as we are aware, this is the first retrospective analysis that focuses exclusively on HER2+ BC in order to investigate any possible correlation between effectiveness and TDM1 adverse events.

Results in both metastatic breast cancer (mBC)[14,15] and early breast cancer (eBC)[16,17] have been linked to HER2 amplification and/or expression levels, according to exploratory biomarker analysis from earlier HER2-targeted trial studies. Markers that indicate an activated immune milieu, such as higher levels of tumor-infiltrating lymphocytes (TILs)[18] or higher expression of immune gene signatures, are related with higher pCR rates[19] and improved long-term outcomes in HER2-positive breast cancer.[20] Other indicators that may influence outcomes include the anti-apoptotic marker B-cell lymphoma-2 (bcl-2)[21] and expression of the drug efflux pump Multidrug Resistance 1/ATP Binding Cassette1 (MDR1/ABCB1), which has been linked to resistance to T-DM1 and other therapies in breast cancer.[22] Furthermore, higher HER2 heterogeneity has been linked to lower T-DM1 efficacy.[15]

Prior research examining the mechanisms of T-DM1 treatment resistance has identified a number of pre-existing and acquired changes in tumor cells, including a decrease in HER2 protein levels, as the main cause of non-reaction.[23] Downregulation of HER2 expression or its endocytosis can result in the loss of HER2 protein, which shifts reliance to other members of the ERBB family.[24,25] Resistance to T-DM1 has been linked to mutations in HER2 and elements of its

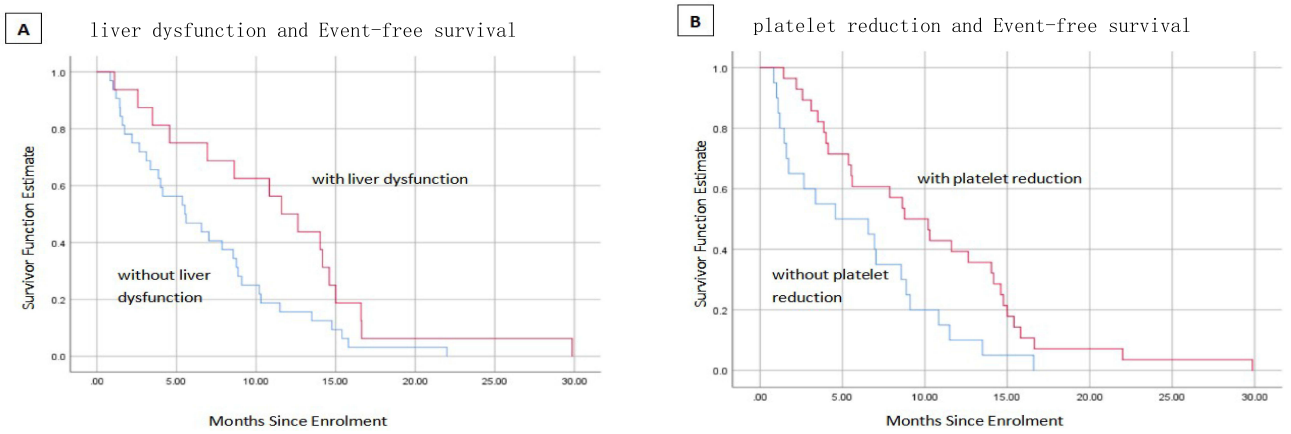

Figure 1 Kaplan-Meier curves show EFS for patients with or without liver dysfunction and platelet reduction. (**A**) liver dysfunction and Event-free survival.log-rank p=0.029 (**B**) platelet reduction and Event-free survival.log-rank p=0.014.

Table 5 Univariate and Multivariate Analysis of Factors Associated With EFS Using Cox Proportional Hazards Regression

Factors	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (years)	1.013(0.980–1.048)	0.435		
Menopausal status		0.392		
Pre	1 [Reference]			
Post	1.299(0.714–2.362)			
BMI (kg/m^2)	1.000(0.897–1.116)	0.996		
T	0.890(0.596–1.330)	0.571		
N	1.308(0.983–1.740)	0.065	1.192(0.904–1.571)	0.213
M		0.878		
0	1 [Reference]			
1	0.944(0.453–1.968)			
Ki-67 (%)	0.998(0.987–1.010)	0.767		
The lines of therapy	1.229(0.968–1.560)	0.090	1.505(1.116–2.028)	0.007
Total course of treatment	0.859(0.808–0.914)	<0.001	0.813(0.754–0.877)	<0.001
Platelet reduction		0.016		0.013
With	0.474(0.259–0.868)		0.400(0.195–0.823)	
Without	1 [Reference]		1 [Reference]	
Liver dysfunction		0.032		0.003
With	0.504(0.269–0.944)		0.274(0.116–0.648)	
Without	1 [Reference]		1 [Reference]	
Other AEs		0.058		0.508
With	0.531(0.277–1.021)		1.313(0.587–2.938)	
Without	1 [Reference]		1 [Reference]	

Abbreviations: EFS, Event-free survival; BMI, Body mass index; T, Tumor; N, Node; M, Metastasis; AEs, adverse events.

downstream signaling pathways, such as PIK3CA activating mutations, YES1 amplification, and loss of phosphatase and tensin homolog deleted on chromosome ten (PTEN).[25–27]

T-DM1 preserves trastuzumab's mechanisms of action while specifically delivering DM1 to HER2-positive tumor cells.[28] Only the proteolytic breakdown of the antibody moiety of trastuzumab emtansine in the lysosome causes active DM1 release since the non-reducible linker is stable in the bloodstream and the tumor microenvironment.[29] Therefore, T-DM1 possesses modes of action that include both trastuzumab's anti-tumor actions and those of intracellular DM1 metabolites. A certain concentration of intracellular DM1 and its metabolites must be exceeded for cell death to occur, indicating that DM1 can cause cell death in a concentration-dependent way. While low concentrations of DM1 cause mitotic catastrophe and altered intracellular trafficking, high doses cause mitotic arrest and fast apoptotic death, and the lowest amounts cause cell resistance.[30]

Uppal et al[31,32] supported the key role of FcγR in ADC drug therapy related haematological toxicity by investigating the mechanism of T-DM1 mediated thrombocytopenia. Target-dependent uptake in these cells is not anticipated because prior researchers have demonstrated that differentiated megakaryocytes (MKs) in circulating platelets and bone marrow do not exhibit HER2 expression on their surface. In addition to ruling out a direct impact of ADC on mature platelets, Uppal et al used in vitro experiments and a novel model of human bone marrow haematopoietic stem/progenitor differentiation to show that the mechanism of decreased platelet production is caused by FcγRIIa-mediated internalization of T-DM1 on the surface of megakaryocytes (in bone marrow) and the ensuing cytotoxicity (cytoskeletal disruption). T-DM1 internalisation in megakaryocytes was significantly reduced by the use of an FcγRII blocking antibody (anti-CD32 antibody) or by the use of Fcγ mutant T-DM1 that cannot bind FcγR (T-DM1-DANA carrying the D265A and N297A mutations). In addition, only T-DM1 and DM1-containing control ADCs were observed to affect megakaryocytes, whereas trastuzumab had no adverse effects despite also being internalised by megakaryocytes, suggesting that

thrombocytopenia due to megakaryocyte damage caused by T-DM1 is mediated by drug-carrying DM1, but that the Fc structural domain on the T-DM1 antibody must interact with FcγRIIa for internalisation to occur. Overall, the researchers concluded that the mechanism by which FcγRIIa contributes (at least in part) to T-DM1 binding and internalisation mediates impaired megakaryocyte differentiation and ultimately the development of thrombocytopenia. However, the data do not support co-localization of internalized trastuzumab emtansine with the lysosomal marker, LAMP1, in megakaryocytes, so it is still unclear how the ADC/FcγRIIa complex is internalized and how the effector molecule of trastuzumab emtansine, Lys-MCC-DM1, is released into the microtubules of megakaryocytes.[33]

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels might rise sharply as a result of hepatotoxicity, one of the black box warnings of T-DM1 medication.[33] Endo et al[34] developed both in vitro and in vivo models, including immortalized human hepatocytes with reduced HER2 expression in comparison to T-DM1-sensitive HER2+ breast cancer cell lines such as SKBR-3 and BT-474, in order to investigate the molecular basis of T-DM1-induced hepatotoxicity. The findings imply that T-DM1 might exploit the HER2-dependent uptake mechanism to induce hepatotoxicity. Additionally, Researchers discovered that the pro-inflammatory cytokine TNF-α can exacerbate T-DM1-mediated hepatocyte damage, which was attributed to T-DM1-induced rupture of the mitochondrial outer membrane, triggering mitochondria-dependent apoptosis.[35]

The mechanism of the association between AEs and tumour efficacy is not fully understood. In the case of TDM1, it is the drug itself that exerts its antineoplastic effect, and the higher the concentration of DM1 and its metabolites in the body, the greater the efficacy and the likelihood of adverse events. Furthermore, we suggest that patients with low HER2 expression or drug resistance may experience less toxicity and poorer efficacy due to reduced HER2 receptor binding and DM1 release.

This research has certain limitations. This study was retrospective, which may have introduced information bias. In addition, analyses according to other variables, such as the grade of AEs, were not done because of the limited number of patients in each group.

Conclusion

In conclusion, the results of this retrospective study demonstrated that AEs were associated with tumour response in patients with HER2+ BC treated with TDM1. Prospective studies are needed to further validate the predictive value of AEs and integrate it into clinical practice. In addition, the undefined underlying mechanism of AEs on tumour efficacy may require further in vivo and in vitro studies.

Ethics Approval and Informed Consent

We state that our study complies with the Declaration of Helsinki.

Ethical approval for this study was obtained from the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (the ethics approval number, KY2024-R322). Patients signed informed consent for use of data from biological samples and clinical information.

Disclosure

The authors report no conflicts of interest in this work.

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