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Efficacy and safety of DP303c versus T-DM1 in HER2-positive advanced breast cancer: Interim analysis of a randomized, open-label, phase 3 trial

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Disclosure Information

Huiping Li

I have no financial relationships to disclose.

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Background

- Unresectable or metastatic HER2-positive breast cancer remains an incurable disease. Despite substantial therapeutic progress in HER2-positive breast cancer, many patients ultimately develop resistance to current anti-HER2 agents. There is still an unmet clinical needs in this population.
- DP303c is a novel antibody-drug conjugate targeting HER2, consisting of a humanized anti-HER2 monoclonal antibody conjugated to MMAE via a cleavable linker, with a DAR of ~ 2.
- In prior phase I study, DP303c demonstrated encouraging antitumor in heavily pretreated patients with HER2-positive breast, with an ORR of 51.5% in 66 efficacy evaluable patients[1,2].
- Here we report the interim analysis of a phase III study comparing DP303c to T-DM1 in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and taxanes.

Abbreviations:; ADC = antibody-drug conjugates; DAR = drug-to-antibody ratio ; HER2 = human epidermal growth factor receptor 2; MMAE = monomethyl auristatin E; ORR = objective response rate.

1.NPJ Precis. Onc. 8, 200 (2024).
2. Annals of Oncology. Volume 34, Supplement 2,S340 Oct, 2023

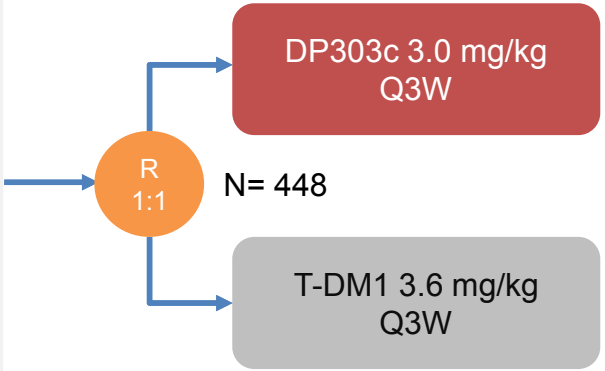
Study design

Key Eligibility Criteria

- Breast cancer
- Confirmed HER2+ status by central laboratory testing
- Prior treatment with a regimen containing trastuzumab/ inetetamab in the advanced disease setting
- Previous treatment with a taxane therapy
- Presence of measurable or non-measurable disease as per RECIST 1.1

Stratification factors:

- Line of therapy (≤1 vs. >1)
- Prior pertuzumab treatment (Yes vs. No)
- Visceral metastasis (Yes vs. No)



FPI: Mar 28, 2024
LPI: April 25, 2025

Primary endpoint：

- BIRC-assessed PFS.

Secondary endpoints：

- Investigator-assessed PFS,OS，ORR, CBR, and DOR, and safety

Planned Efficacy Analyses：

- PFS interim analyses (at~171 events)
- PFS final analysis (at ~285 events)

Abbreviations:; BIRC = blinded independ review committee; CBR =clinical benefit rate; CDK = cyclin-dependent kinase; DOR = duration of response; FPI = first patien in;HER2 = human epidermal growth factor receptor 2; LPI = last patient in; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Q3W = every three week.

Baseline Characteristics

Characteristics	DP303c (N=226)	T-DM1 (N=222)
Age, mean (SD) years	53.2 (9.11)	54.1 (9.26)
Age ≤60 years, n (%)	179 (79.2)	167 (75.2)
Female, n (%)	225 (99.6)	222 (100)
ECOG PS		
0, n (%)	105 (46.5)	104 (46.8)
1, n (%)	119 (52.7)	116 (52.3)
2, n (%)	2 (0.9)	2 (0.9)
HER2 Status		
IHC 3+, n (%)	177 (78.3)	176 (79.3)
IHC 2+ & ISH+, n (%)	49 (21.7)	46 (20.7)
Hormone receptor positive, n (%)	117 (51.8)	116 (52.3)
Presence of metastasis, n (%)	219 (96.9)	216 (97.3)
Visceral metastasis, n (%)	155 (68.6)	153 (68.9)
Prior lines of therapy, n (%)		
1	91 (40.3)	89 (40.1)
≥ 2	135 (59.7)	133 (59.9)

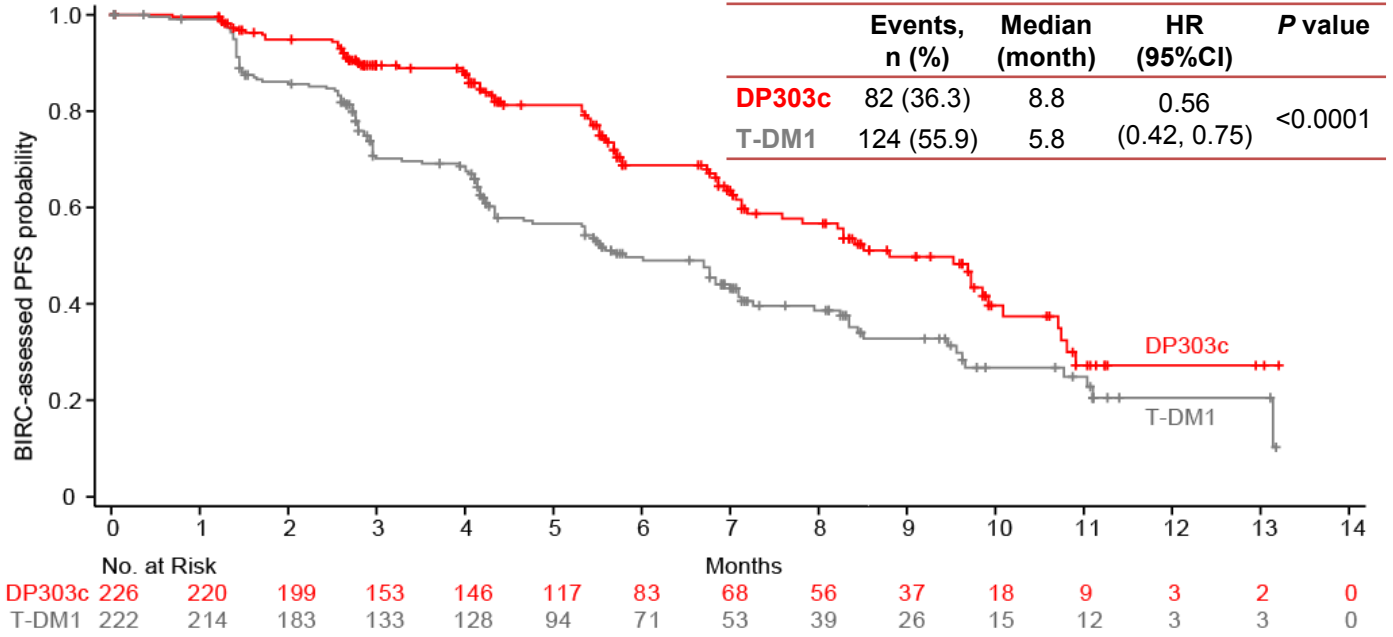
Prior Antitumor Therapies, n (%)	DP303c (N=226)	T-DM1 (N=222)
Any prior antitumor drug therapy	226 (100)	222 (100)
HER2-Targeted Therapies		
Trastuzumab	226 (100)	222(100)
Pertuzumab	115 (50.9)	114 (51.4)
HER2 tyrosine kinase inhibitor	121 (53.5)	129 (58.1)
Chemotherapies		
Taxanes	226 (100)	222 (100)
Anthracyclines and related	117 (51.8)	123 (55.4)
Platinum compounds	68 (30.1)	65 (29.3)

Cut-off date: July 8, 2025

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; SD = standard difference.

Primary endpoint: BIRC-assessed PFS

- DP303c significantly improved PFS over T-DM1 with a 44% lower risk of PD or death.

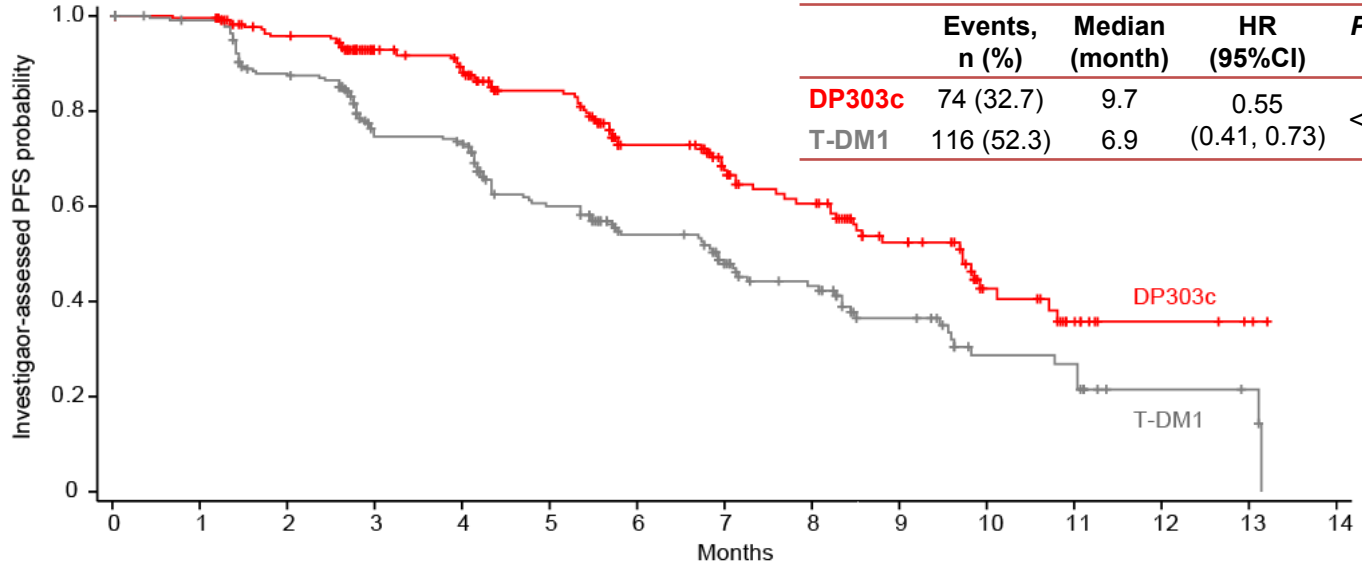


	Events, n (%)	Median (month)	HR (95%CI)	*P* value
DP303c	82 (36.3)	8.8	0.56 (0.42, 0.75)	<0.0001
T-DM1	124 (55.9)	5.8		

At interim analysis (cut-off date: July 8, 2025; median follow-up: 7.4 months)，206 BIRC-assessed PFS events occurred.
One-sided efficacy stopping boundary of 0.008

Investigator-assessed PFS

- Consistent PFS benefit was observed by Investigator assessment (HR 0.55[0.41, 0.73], P<0.0001)



	Events, n (%)	Median (month)	HR (95%CI)	*P* value
DP303c	74 (32.7)	9.7	0.55 (0.41, 0.73)	<0.0001
T-DM1	116 (52.3)	6.9		

No. at Risk

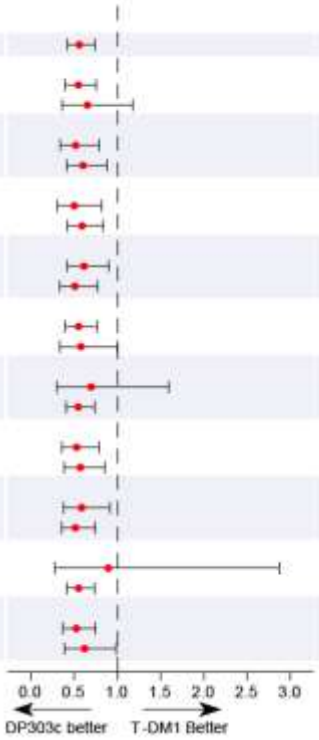
DP303c	226	220	200	160	149	124	89	72	60	40	20	10	4	2	0
T-DM1	222	214	185	137	134	97	74	56	44	28	16	15	4	3	0

At interim analysis (cut-off date: July 8, 2025; median follow-up: 7.4 months), 190 investigator-assessed PFS events occurred.

BIRC-assessed PFS : subgroup analysis

- Favorable PFS of DP303c over T-DM1 was observed across predefined subgroups.

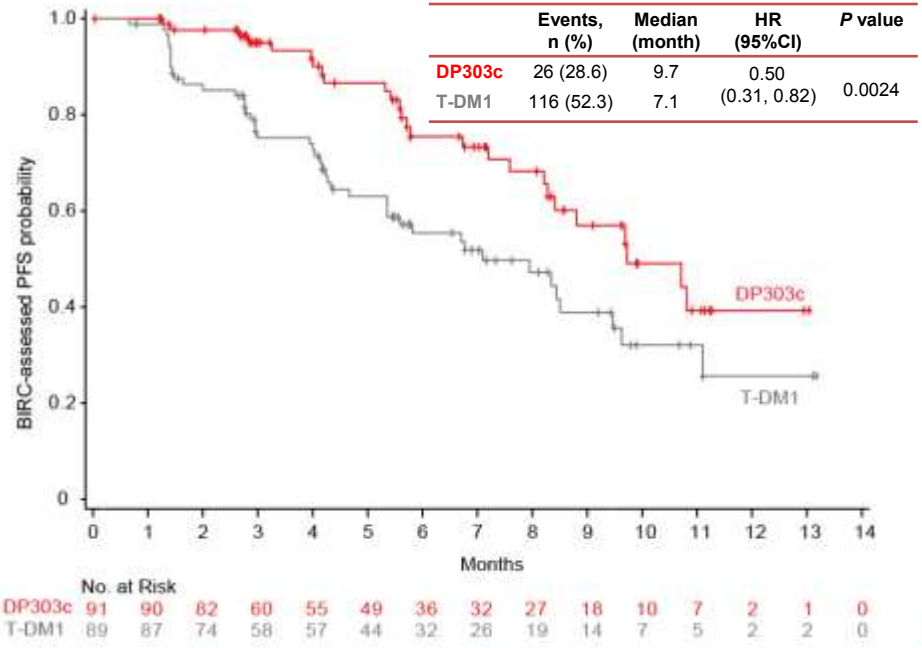
Subgroup	No. of Patients	No. of events/No. of patients		Median PFS (95%CI)		Hazard ratio for disease progression or death (95%CI)
		DP303c	T-DM1	DP303c	T-DM1	
All patients	448	82/226	124/222	8.8(7.2, 9.9)	5.8(4.7, 7.1)	0.56 (0.42 - 0.74)
Age						
≤60	346	65/179	91/167	9.7(7.6 10.7)	6.7(5.3, 7.1)	0.55 (0.40 - 0.76)
>60	102	17/47	33/55	7.8(5.6, -)	5.5(4.0, 8.3)	0.65 (0.36 - 1.18)
ECOG PS						
0	209	35/105	60/104	9.7(7.1 10.7)	5.7(4.1, 8.0)	0.52 (0.34 - 0.79)
≥1	239	47/121	64/118	8.5(7.0, 10.1)	6.7(5.4, 7.1)	0.60 (0.41 - 0.88)
Lines of previous therapy						
≤1	180	26/91	45/89	9.7(8.28 -)	7.1(5.4, 9.5)	0.50 (0.31 - 0.82)
>1	268	56/135	79/133	7.8(6.9, 9.9)	5.5(4.2, 6.8)	0.60 (0.42 - 0.84)
Previous pertuzumab						
Yes	229	46/115	64/114	8.4(6.9, 9.7)	5.6(4.2, 7.3)	0.61 (0.42 - 0.90)
No	219	36/111	60/108	9.9(7.1, -)	6.7(4.8, 8.3)	0.51 (0.38 - 0.78)
Visceral metastases						
Yes	308	60/155	92/153	7.8(6.8, 9.9)	5.7(4.2, 6.8)	0.55 (0.40 - 0.77)
No	140	22/71	32/69	9.9(8.4, -)	8.4(4.3, -)	0.58 (0.34 - 1.00)
Brain metastases						
Yes	51	9/24	15/27	7.8(4.27, -)	5.5(3.0, 8.3)	0.70 (0.30 - 1.60)
No	397	73/202	109/195	9.5(7.6, 10.7)	5.8(4.3, 7.1)	0.55 (0.41 - 0.74)
ER status						
ER+	217	44/111	59/106	9.5(7.1, 10.1)	5.8(4.2, 7.1)	0.53 (0.36 - 0.79)
ER-	231	38/115	65/116	8.8(7.0, -)	5.6(4.8, 8.4)	0.57 (0.38 - 0.86)
PR status						
PR+	144	38/76	42/68	7.8(6.8, 9.9)	4.2(3.0, 6.8)	0.56 (0.38 - 0.92)
PR-	301	44/150	80/151	9.7(7.2, -)	6.8(5.4, 8.3)	0.52 (0.36 - 0.75)
Previous anti-HER2 ADC						
Yes	18	5/9	7/9	5.8(0.7, -)	3.0(1.4, 5.7)	0.90 (0.28 - 2.87)
No	430	77/217	117/213	9.5(7.8, 10.1)	6.7(5.3, 7.1)	0.55 (0.41 - 0.74)
Previous anti-HER2 TKI						
Yes	250	51/121	80/129	7.1(6.8, 9.7)	4.3(4.1, 6.7)	0.53 (0.37 - 0.75)
No	198	31/105	44/93	10.7(8.2, -)	8.4(5.7, 11.1)	0.62 (0.39 - 0.99)



PFS by lines of previous therapy (≤1 vs >1)

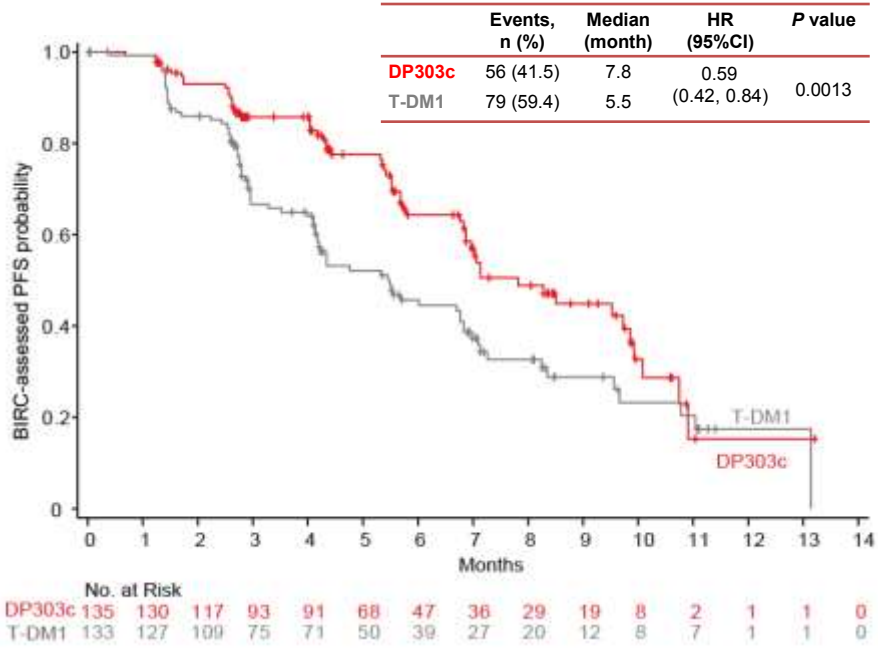
- Regardless of ≤1 or >1 lines of previous therapy, DP303c significantly improved PFS over T-DM1 .

PFS by lines of previous therapy (≤1)



	Events, n (%)	Median (month)	HR (95%CI)	*P* value
DP303c	26 (28.6)	9.7	0.50 (0.31, 0.82)	0.0024
T-DM1	116 (52.3)	7.1		

PFS by lines of previous therapy (>1)

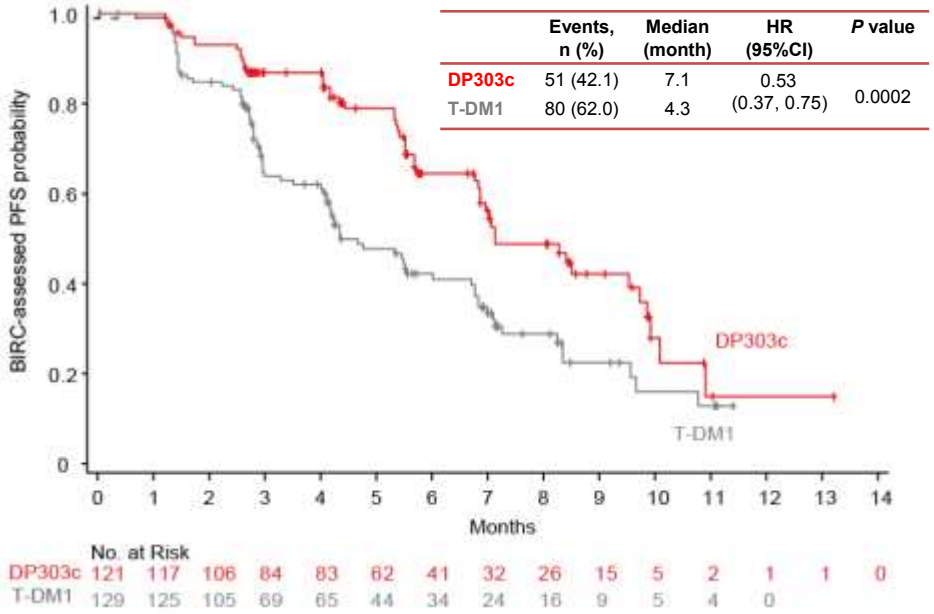


	Events, n (%)	Median (month)	HR (95%CI)	*P* value
DP303c	56 (41.5)	7.8	0.59 (0.42, 0.84)	0.0013
T-DM1	79 (59.4)	5.5		

PFS by previous anti HER2 TKI (Yes vs No)

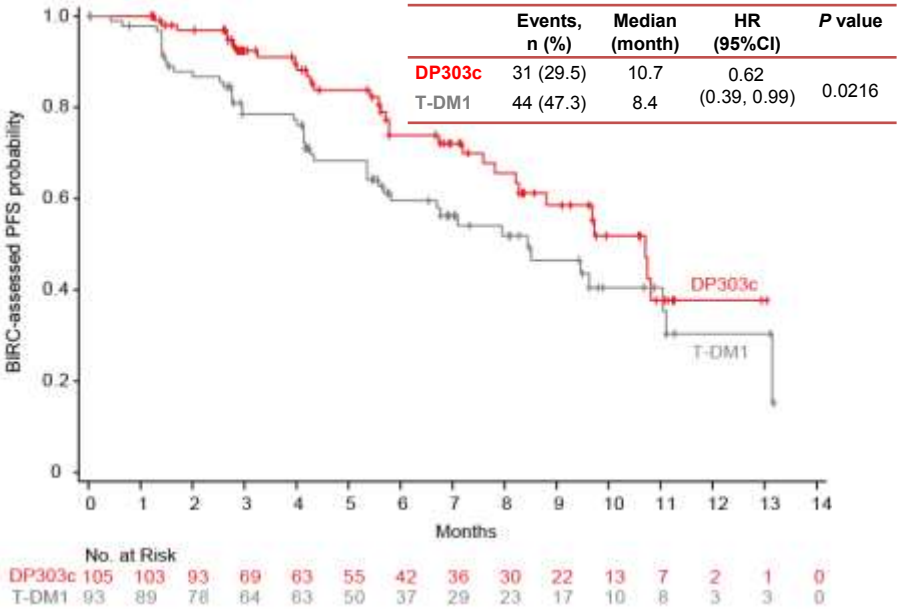
- DP303c demonstrated superior efficacy in patients previously treated or untreated with anti-HER2 TKIs over T-DM1

PFS by previous anti HER2 TKI (Yes)



	Events, n (%)	Median (month)	HR (95%CI)	*P* value
DP303c	51 (42.1)	7.1	0.53 (0.37, 0.75)	0.0002
T-DM1	80 (62.0)	4.3		

PFS by previous anti HER2 TKI (No)



	Events, n (%)	Median (month)	HR (95%CI)	*P* value
DP303c	31 (29.5)	10.7	0.62 (0.39, 0.99)	0.0216
T-DM1	44 (47.3)	8.4		

BIRC assessed tumor response

	DP303c (N=226)	T-DM1 (N=222)
Best Overall Response, n (%)		
CR	11 (4.9)	4 (1.8)
PR	131 (58.0)	91 (41.0)
SD	53 (23.5)	74 (33.3)
PD	18 (8.0)	49 (22.1)
NE	13 (5.8)	4 (1.8)
ORR, % (95% CI)	142 (62.8) (56.17, 69.15)	95 (42.8) (36.19, 49.59)
ORR difference vs. T-DM1 (95% CI)	20.0% (10.93, 29.16)	
CBR*,% (95% CI)	155 (68.6) (62.10, 74.58)	113 (50.9) (44.13, 57.65)
CBR difference vs. T-DM1 (95% CI)	17.6% (8.61, 26.57)	
DoR，months (95% CI)	8.6 (7.10, 9.33)	6.9 (5.78, 9.59)

- ORR per BIRC was 62.8% vs 42.8%, with a rate difference of 20.0% .
- CBR per BIRC was 68.6% vs 50.9%.
- DoR per BIRC was 8.6 vs 6.9 months.
- At interim analysis (cut-off date: July 8, 2025; median follow-up: 7.4 months)，only 17 OS events occurred. OS was immature at this analysis.

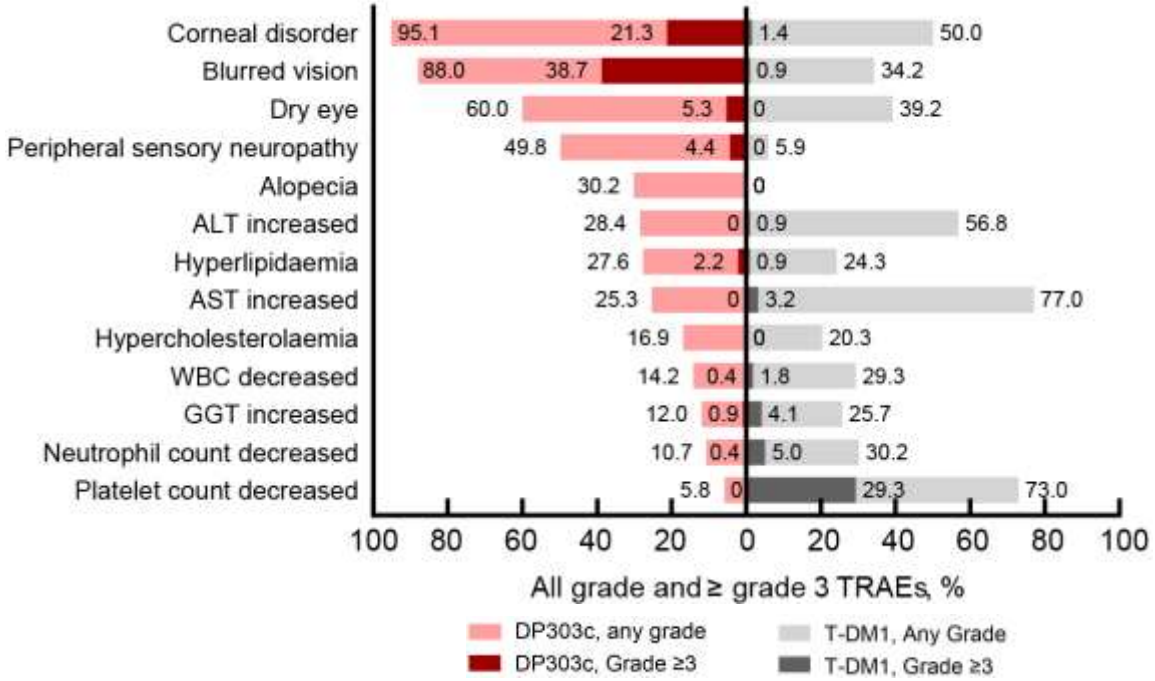
Note: The difference in ORR and CBR between groups and its 95% CI were calculated using the Cochran-Mantel-Haenszel method, adjusted for stratification factors. CBR was defined as CR+PR+SD ≥6 months; BIRC =blinded independent review committee; ; CBR = clinical benefit rate. CI = confidence Interval; DoR=duration of response ORR = objective response rate；OS = overall survival.

Safety summary

n (%)	DP303c (N=225)	T-DM1 (N=222)
Any TEAE	224 (99.6)	220 (99.1)
TEAE of grade ≥3	147 (65.3)	101 (45.5)
Serious TEAE	29 (12.9)	34 (15.3)
TEAE leading to death	1 (0.4)	1 (0.5)
TEAE leading to discontinuation	2 (0.9)	3 (1.4)
TEAE leading to interruption	195 (86.7)	57 (25.7)
TEAE leading to dose reduction	126 (56.0)	30 (13.5)
Any TRAE	224 (99.6)	217 (97.7)
TRAE of grade ≥3	145 (64.4)	93 (41.9)
Serious TRAE	21 (9.3)	25 (11.3)
TRAE leading to death	0	0
TRAE leading to discontinuation	2 (0.9)	3 (1.4)
TRAE leading to interruption	194 (86.2)	46 (20.7)
TRAE leading to dose reduction	126 (56.0)	30 (13.5)
Any AESI	222 (98.7)	204 (91.9)

Abbreviations: AESI = adverse event of special interest; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event

Most common TRAEs(incidence≥20%)



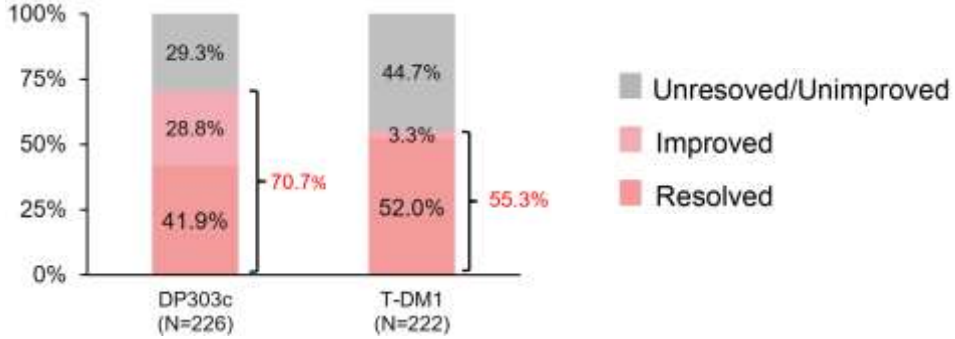
- Ocular toxicity was reversible and recoverable, primarily Grade 1-2
- Only one case of ulcerative keratitis reported，no corneal perforation or blindness.
- The neurotoxicity profile was consistent with that reported in similar products.
- Lower incidences of hematologic and hepatic toxicities.

Abbreviations: ALT=aspartate aminotransferase increased; AST= alanine aminotransferase increased; GGT = gamma-glutamyltransferase ; TRAE = treatment-related adverse event; WBC = white blood cell

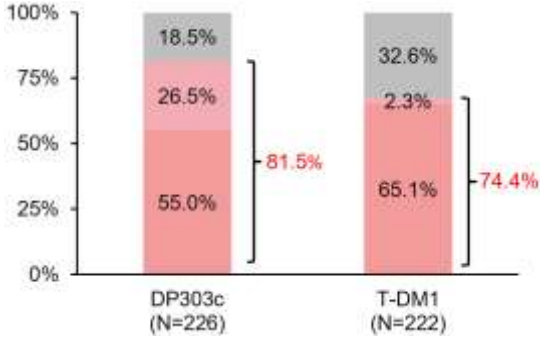
Outcome of ocular toxicity

- DP303c showed a higher rate of improved/resolved ocular toxicity compared to T-DM1.

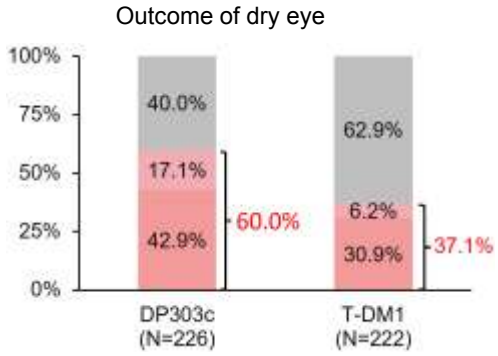
Outcome of corneal disorder



Outcome of blurred vision



Outcome of dry eye



Ocular toxicity, n (%)	DP303c (N=225)	T-DM1 (N=222)
Corneal disorder	215 (95.6)	123 (55.4)
Resolved	90 (41.9)	64(52.0)
Improved	62 (28.8)	4 (3.3)
Unresolved/unimproved	63 (29.3)	55 (44.7)
Blurred vision	200 (88.9)	86 (38.7)
Resolved	110 (55.0)	56 (65.1)
Improved	53 (26.5)	2 (2.3)
Unresolved/unimproved	37 (18.5)	28 (32.6)
Dry eye	140 (62.2)	97 (43.7)
Resolved	60 (42.9)	30 (30.9)
Improved	24 (17.1)	6 (6.2)
Unresolved/unimproved	56 (40.0)	61 (62.9)

Resolution time of ocular toxicity

- Ocular toxicity could be resolved in 0.51-1.0 months in DP30c group.

Ocular toxicity (CTCAE≥3）	DP303c (N(CTCAE=225)	T-DM1 (N=222)
Corneal disorder		
G3→G2 resolution time, n	22	1
Mean (SD), month	0.67 (0.37)	0.49 (NA)
Median (Range)	0.56 (0.26,1.48)	0.49 (0.49,0.49)
G2→G1 resolution time, n	15	1
Mean (SD), month	0.91 (0.60)	0.953 (NA)
Median (Range), month	0.72 (0.16, 2.17	0.95(0.95,0.95)
Blurred vision		
G3→G2 resolution time, n	48	1
Mean (SD), month	0.63 (0.41)	0.85 (NA)
Median (Range)	0.53 (0.03,1.84)	0.85 (0.85, 0.85)
G2→G1 resolution time, n	39	1
Mean (SD), month	0.72 (0.77)	1.45 (NA)
Median (Range), month	0.49 (0.2, 4.63)	1.45 (1.45, 1.45)
Dry eye		
G3→G2 resolution time, n	8	0
Mean (SD), month	1.0 (0.66)	NA
Median (Range)	0.95 (0.26, 1.87)	NA
G2→G1 resolution time, n	5	NA
Mean (SD), month	0.51 (0.21)	NA
Median (Range), month	0.49 (0.26, 0.72)	NA

Conclusion

- DP303c demonstrated statistically significant and clinically meaningful improvement in PFS compared with T-DM1.
  - mPFS: 8.8m vs 5.8m (HR = 0.56; 95%CI: 0.42-0.75; P< 0.0001) .
  - PFS benefit with DP303c was consistently observed across predefined subgroups.
- The safety profile of DP303c was manageable. No new safety signals
  - Ocular toxicity was reversible and recoverable, primarily grade 1-2
  - The neurotoxicity profile was consistent with that reported in similar products
  - Lower incidence of hematologic and hepatic toxicities than T-DM1
- DP303c provides a potential new treatment option for HER2 positive patients who had been previously treated with trastuzumab and taxane.

Acknowledgment

We thank the patients, their families
&
Investigators and site personnel who participated in the study