QUESITO GRUPPO A:

Nelle pazienti con carcinoma mammario metastatico HER2 positivo è opportuno considerare un trattamento di 1° linea contenente TDM1 (+/- pertuzumab) rispetto a trastuzumab+taxano?

QUESITO GRUPPO A:

Nelle pazienti con carcinoma mammario metastatico HER2 positivo è opportuno considerare un trattamento di 1° linea contenente TDM1 (+/- pertuzumab) rispetto a trastuzumab+taxano?

LE PROBLEMATICHE

QUESITO GRUPPO A:

P: - pazienti con carcinoma mammario metastatico HER2 positivo
- 1° linea di terapia

I: TDM1 (+/- pertuzumab)

C: trastuzumab+taxano?

VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

***MULTEPLICITY*/ANALISI DI SOTTOGRUPPO**

IMPRECISIONE DELLE STIME

VALUTAZIONE DI TRASFERIBILITA’

ADERENZA AL QUESITO CLINICO

VALUTAZIONE DI RILEVANZA

ADEGUATEZZA DEL RISULTATO

VALUTAZIONE DI AFFIDABILITA’

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***MULTEPLICITY*/ANALISI DI SOTTOGRUPPO**

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ADEGUATEZZA DEL RISULTATO

VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

	PFS (primary)	**OS**	**SAFETY***	**QoL**
SELECTION				
PERFORMANCE				
ATTRITION				
DETECTION				
REPORTING				

*** Alopecia, mielotossicità, neurotossicità**

Perez et al. J Clin Oncol. 2017

VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

	PFS (primary)	**OS**	**SAFETY***	**QoL**
SELECTION				
PERFORMANCE				
ATTRITION				
DETECTION				
REPORTING				

*** Alopecia, mielotossicità, neurotossicità**

Perez et al. J Clin Oncol. 2017

VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

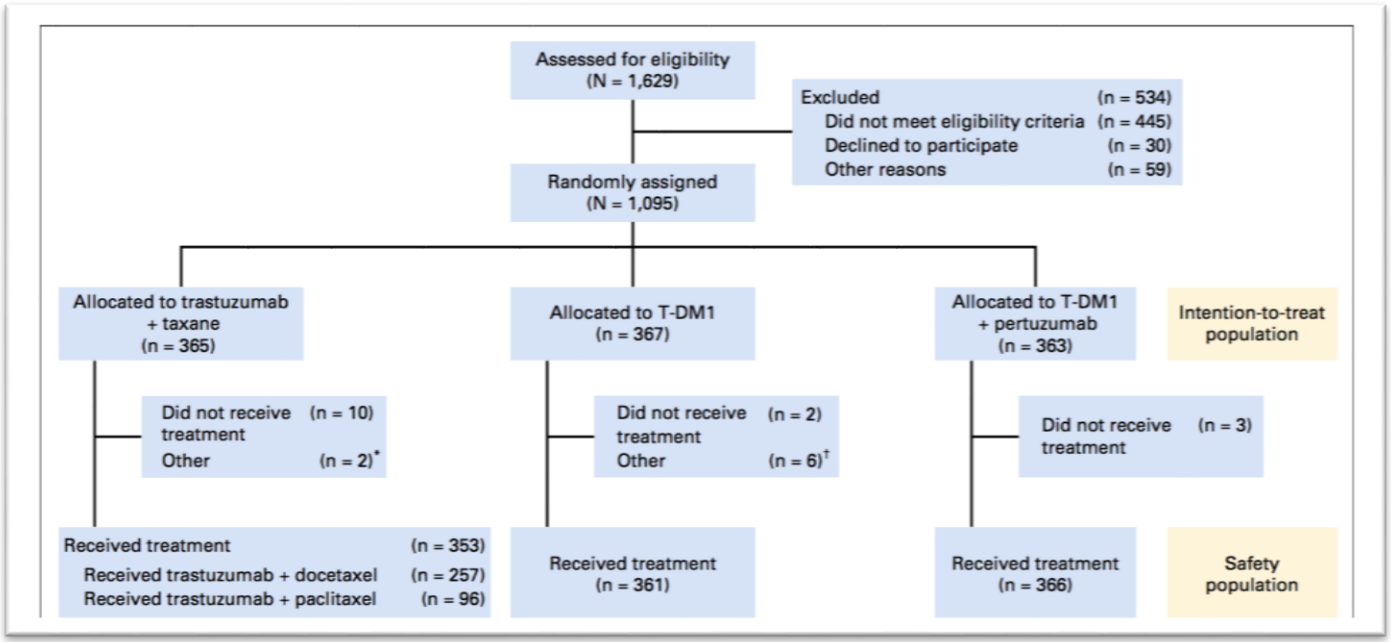
	PFS (primary)	OS	SAFETY*	QoL
SELECTION				
PERFORMANCE				
ATTRITION				
DETECTION				
REPORTING				

*** Alopecia, mielotossicità, neurotossicità**

Perez et al. J Clin Oncol. 2017

VALUTAZIONE DI AFFIDABILITA’

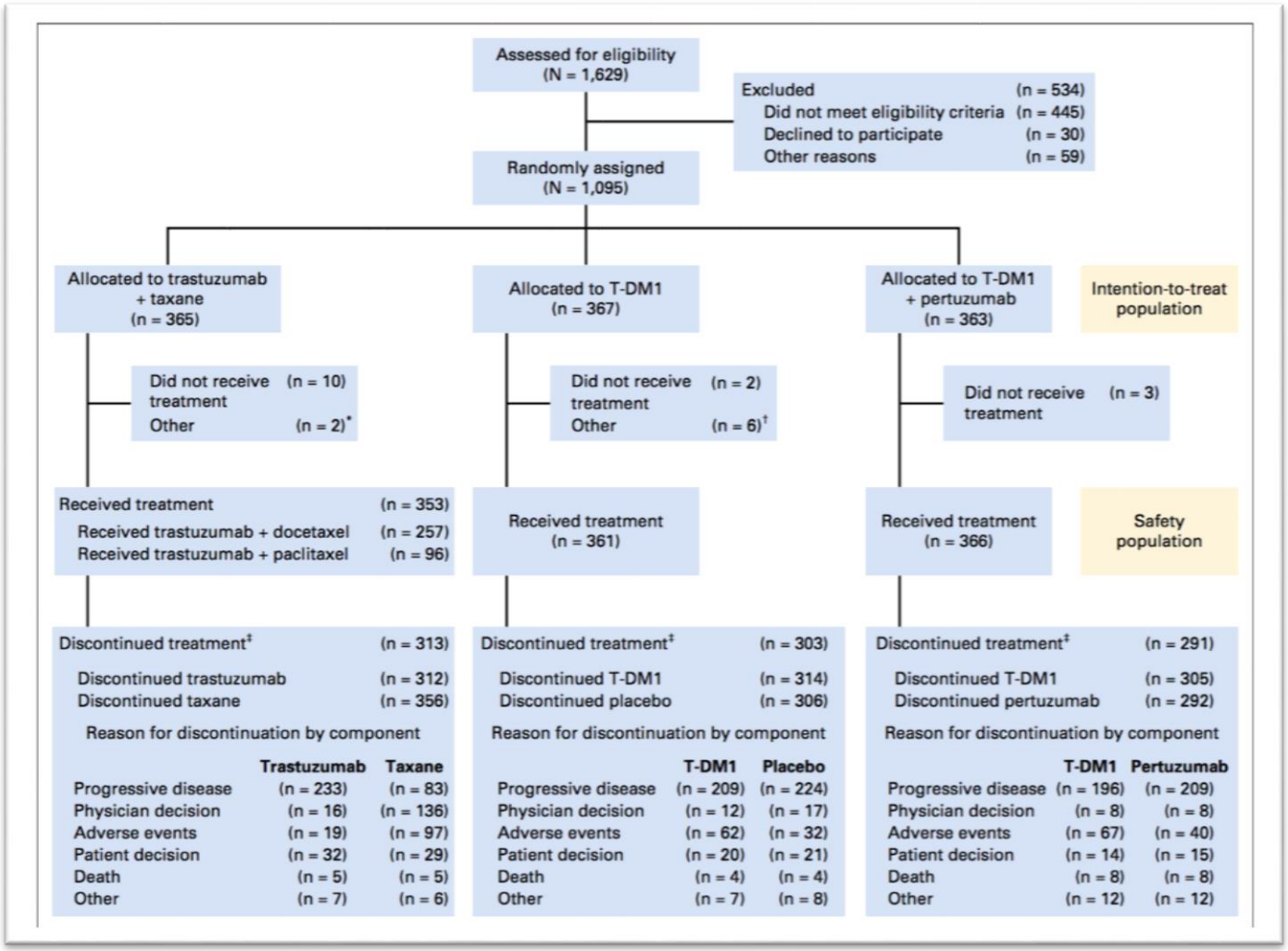
RISCHIO DI BIAS



Perez et al. J Clin Oncol. 2017

VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS



Perez et al. J Clin Oncol. 2017

VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

	PFS (primary)	OS	SAFETY*	QoL
SELECTION				
PERFORMANCE				
ATTRITION				
DETECTION				
REPORTING				

*** Alopecia, mielotossicità, neurotossicità**

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VALUTAZIONE DI AFFIDABILITA'

RISCHIO DI BIAS

Table A3. Sensitivity Analysis of the Time to Clinically Meaningful Decrease in Health-Related Quality of Life

Time to Event*	Trastuzumab + Taxane (n = 173)	T-DM1 (n = 171)	T-DM1 + Pertuzumab (n = 154)
Median, months	3.4	8.0	11.8
Stratified hazard ratio 95% CI (*v* trastuzumab plus taxane)	—	0.69 (0.51 to 0.94)	0.66 (0.48 to 0.92)

NOTE. Health-related quality of life was measured by the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) of the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire.[21] This sensitivity analysis is based on the subset of patients who were randomly assigned after implementation of a protocol amendment (March 7, 2011) that increased the assessment frequency (Appendix Table A2). Sensitivity analysis included all female patients from the intention-to-treat population who were randomly assigned after the signature date for the protocol amendment (March 7, 2011) and who also completed the FACT-B at baseline and at least once postbaseline.

Abbreviation: T-DM1, trastuzumab emtansine.

*An event was defined as a clinically meaningful decrease in health-related quality of life, which is a ≥ 5-point decrease from the baseline in FACT-B TOI-PFB score.[22]

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VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

	PFS (primary)	OS	SAFETY*	QoL
SELECTION				
PERFORMANCE				
ATTRITION				
DETECTION				
REPORTING				

*** Alopecia, mielotossicità, neurotossicità**

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VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

	PFS (primary)	OS	SAFETY*	QoL
SELECTION				
PERFORMANCE				
ATTRITION				
DETECTION				
REPORTING				

*** Alopecia, mielotossicità, neurotossicità**

Perez et al. J Clin Oncol. 2017

VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

MODERATA

	PFS (primary)	OS	SAFETY*	QoL
SELECTION				
PERFORMANCE				
ATTRITION				
DETECTION				
REPORTING				

*** Alopecia, mielotossicità, neurotossicità**

Perez et al. J Clin Oncol. 2017

VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

***MULTEPLICITY*/ANALISI DI SOTTOGRUPPO**

IMPRECISIONE DELLE STIME

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ADERENZA AL QUESITO CLINICO

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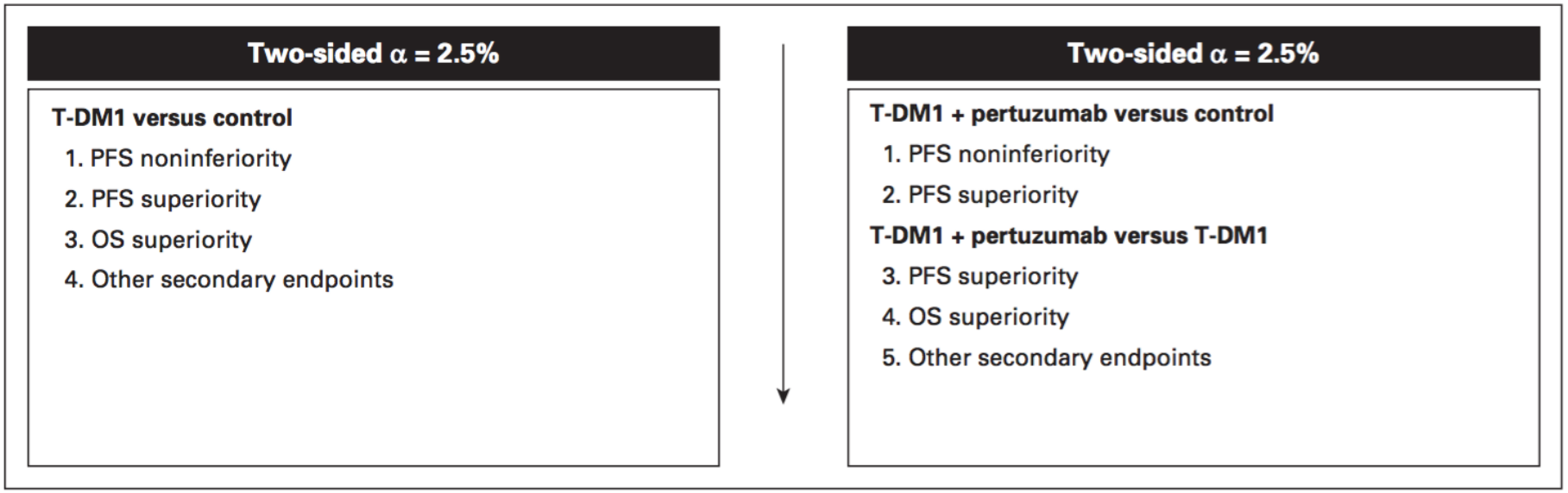
ADEGUATEZZA DEL RISULTATO

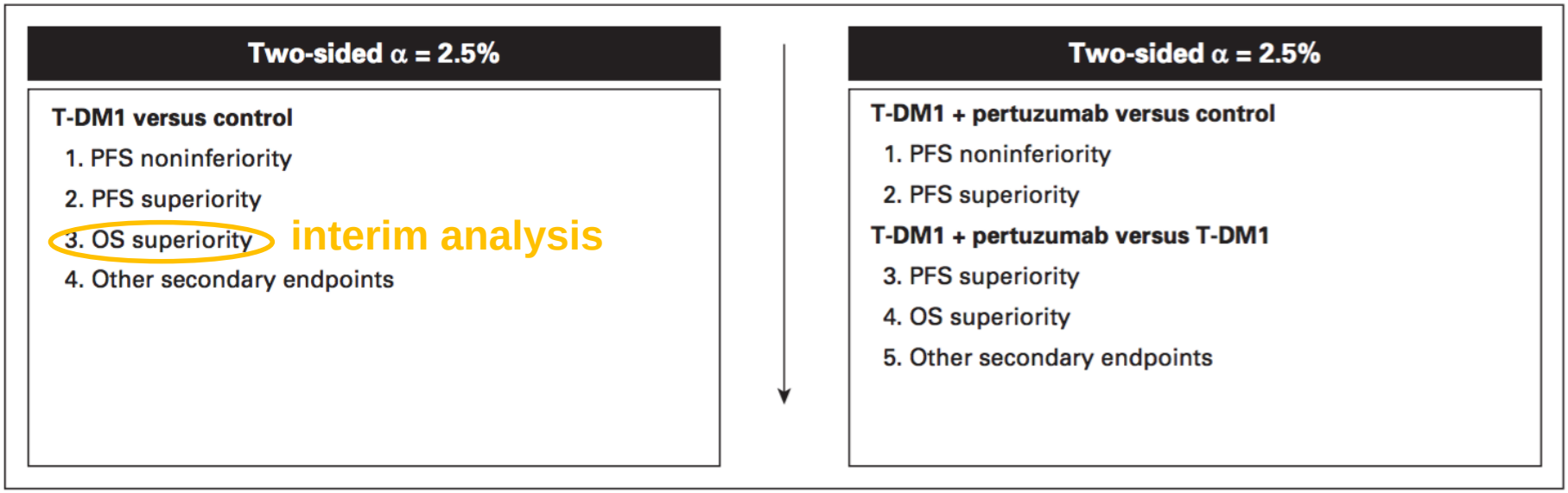
VALUTAZIONE DI AFFIDABILITA’

MULTEPLICITY



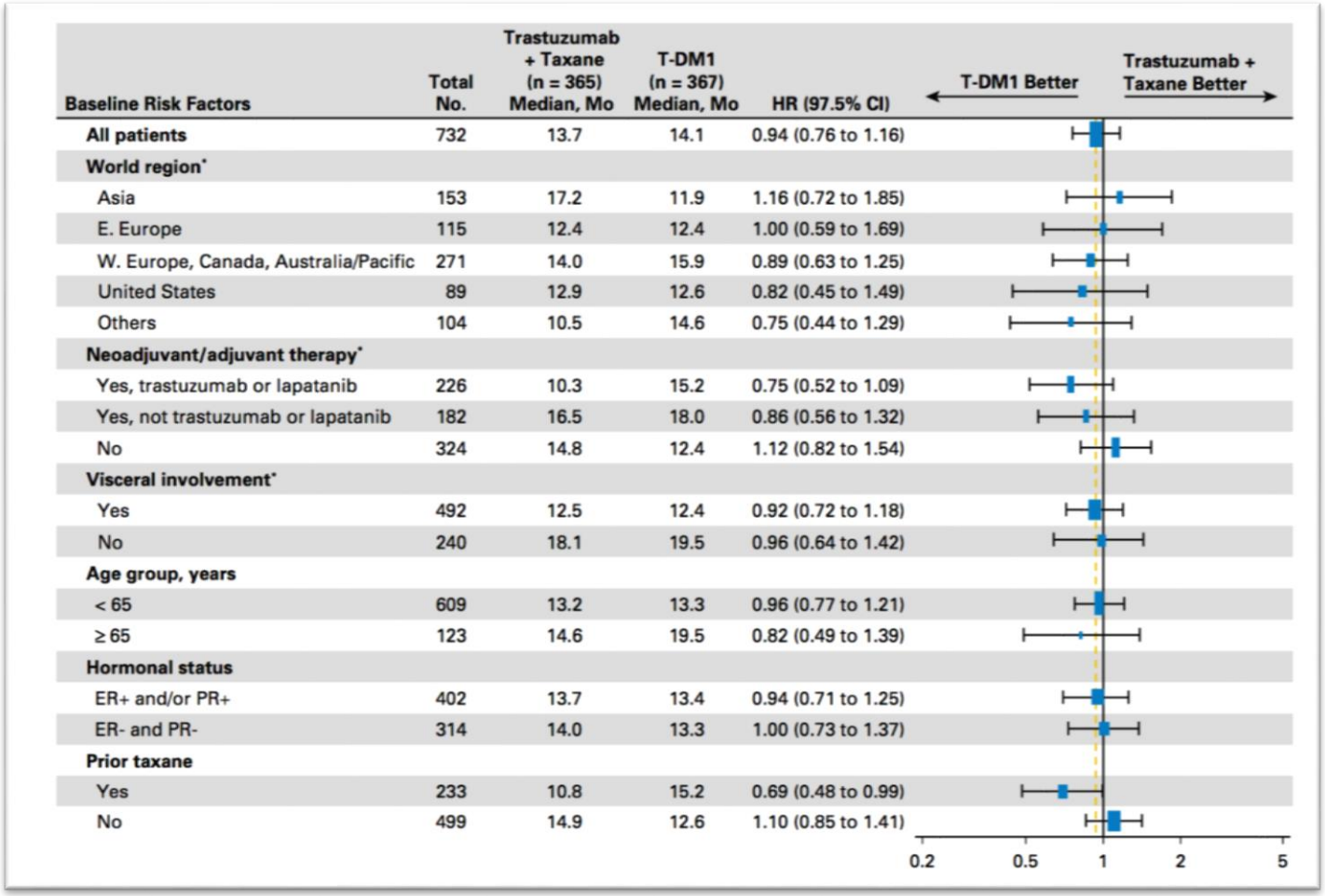
VALUTAZIONE DI AFFIDABILITA’

MULTEPLICITY



VALUTAZIONE DI AFFIDABILITA’

ANALISI DI SOTTOGRUPPO – *pre-specified*



Baseline Risk Factors	Total No.	Trastuzumab + Taxane (n = 365) Median, Mo	T-DM1 (n = 367) Median, Mo	HR (97.5% CI)
All patients	732	13.7	14.1	0.94 (0.76 to 1.16)
World region*				
Asia	153	17.2	11.9	1.16 (0.72 to 1.85)
E. Europe	115	12.4	12.4	1.00 (0.59 to 1.69)
W. Europe, Canada, Australia/Pacific	271	14.0	15.9	0.89 (0.63 to 1.25)
United States	89	12.9	12.6	0.82 (0.45 to 1.49)
Others	104	10.5	14.6	0.75 (0.44 to 1.29)
Neoadjuvant/adjuvant therapy*				
Yes, trastuzumab or lapatanib	226	10.3	15.2	0.75 (0.52 to 1.09)
Yes, not trastuzumab or lapatanib	182	16.5	18.0	0.86 (0.56 to 1.32)
No	324	14.8	12.4	1.12 (0.82 to 1.54)
Visceral involvement*				
Yes	492	12.5	12.4	0.92 (0.72 to 1.18)
No	240	18.1	19.5	0.96 (0.64 to 1.42)
Age group, years				
< 65	609	13.2	13.3	0.96 (0.77 to 1.21)
≥ 65	123	14.6	19.5	0.82 (0.49 to 1.39)
Hormonal status				
ER+ and/or PR+	402	13.7	13.4	0.94 (0.71 to 1.25)
ER- and PR-	314	14.0	13.3	1.00 (0.73 to 1.37)
Prior taxane				
Yes	233	10.8	15.2	0.69 (0.48 to 0.99)
No	499	14.9	12.6	1.10 (0.85 to 1.41)

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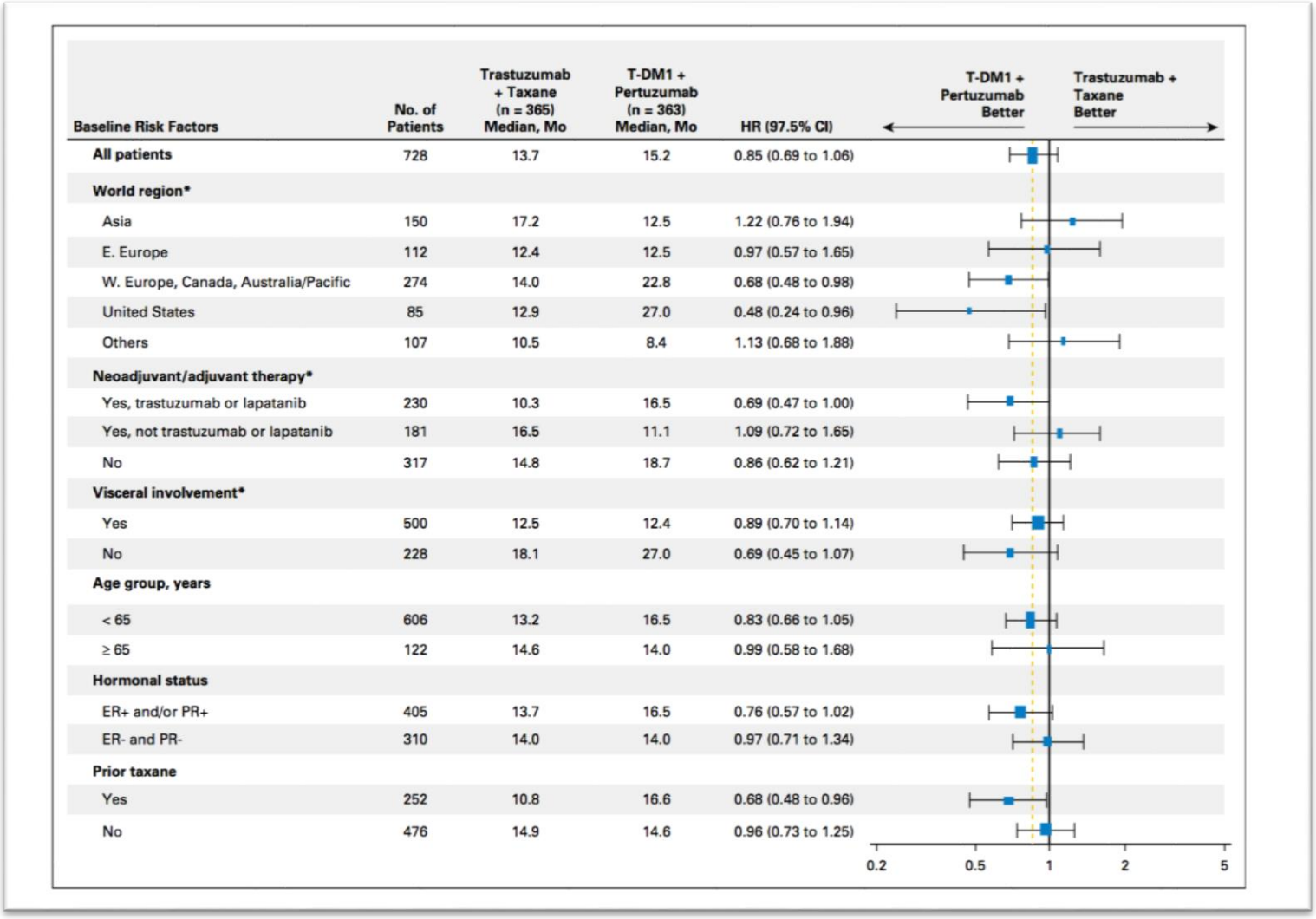
VALUTAZIONE DI AFFIDABILITA’

ANALISI DI SOTTOGRUPPO – *pre-specified*



Baseline Risk Factors	No. of Patients	Trastuzumab + Taxane (n = 365) Median, Mo	T-DM1 + Pertuzumab (n = 363) Median, Mo	HR (97.5% CI)
All patients	728	13.7	15.2	0.85 (0.69 to 1.06)
World region*				
Asia	150	17.2	12.5	1.22 (0.76 to 1.94)
E. Europe	112	12.4	12.5	0.97 (0.57 to 1.65)
W. Europe, Canada, Australia/Pacific	274	14.0	22.8	0.68 (0.48 to 0.98)
United States	85	12.9	27.0	0.48 (0.24 to 0.96)
Others	107	10.5	8.4	1.13 (0.68 to 1.88)
Neoadjuvant/adjuvant therapy*				
Yes, trastuzumab or lapatanib	230	10.3	16.5	0.69 (0.47 to 1.00)
Yes, not trastuzumab or lapatanib	181	16.5	11.1	1.09 (0.72 to 1.65)
No	317	14.8	18.7	0.86 (0.62 to 1.21)
Visceral involvement*				
Yes	500	12.5	12.4	0.89 (0.70 to 1.14)
No	228	18.1	27.0	0.69 (0.45 to 1.07)
Age group, years				
< 65	606	13.2	16.5	0.83 (0.66 to 1.05)
≥ 65	122	14.6	14.0	0.99 (0.58 to 1.68)
Hormonal status				
ER+ and/or PR+	405	13.7	16.5	0.76 (0.57 to 1.02)
ER- and PR-	310	14.0	14.0	0.97 (0.71 to 1.34)
Prior taxane				
Yes	252	10.8	16.6	0.68 (0.48 to 0.96)
No	476	14.9	14.6	0.96 (0.73 to 1.25)

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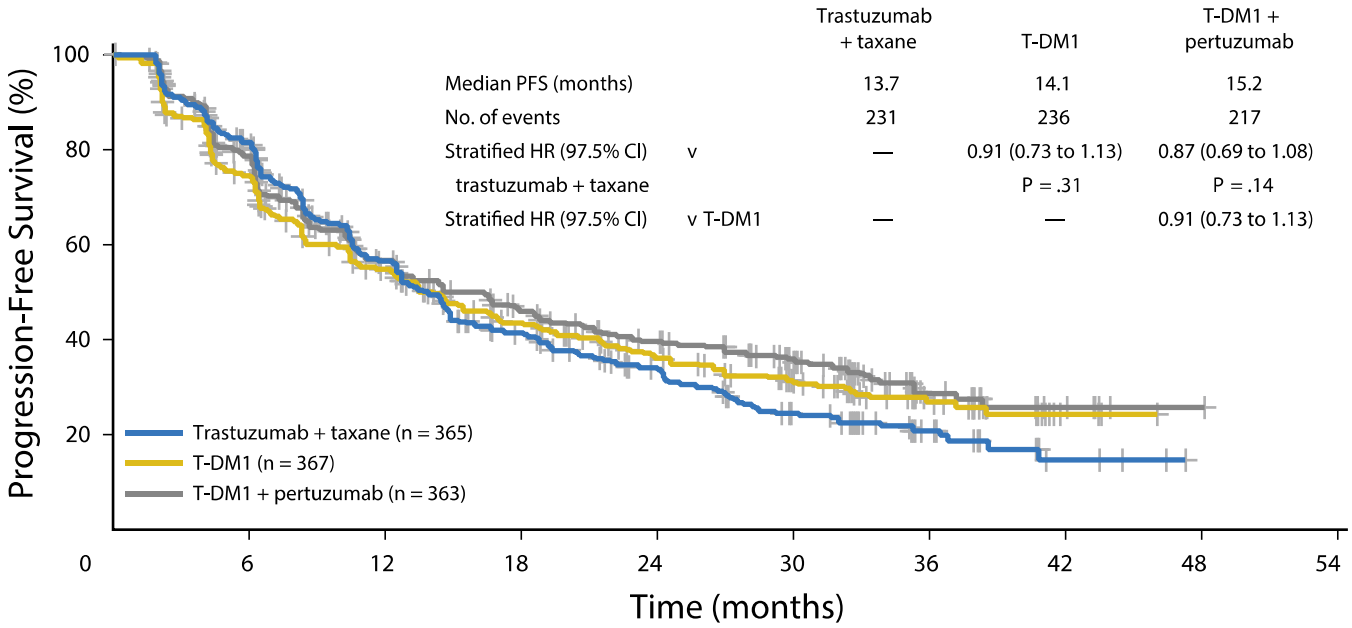
VALUTAZIONE DI AFFIDABILITA’



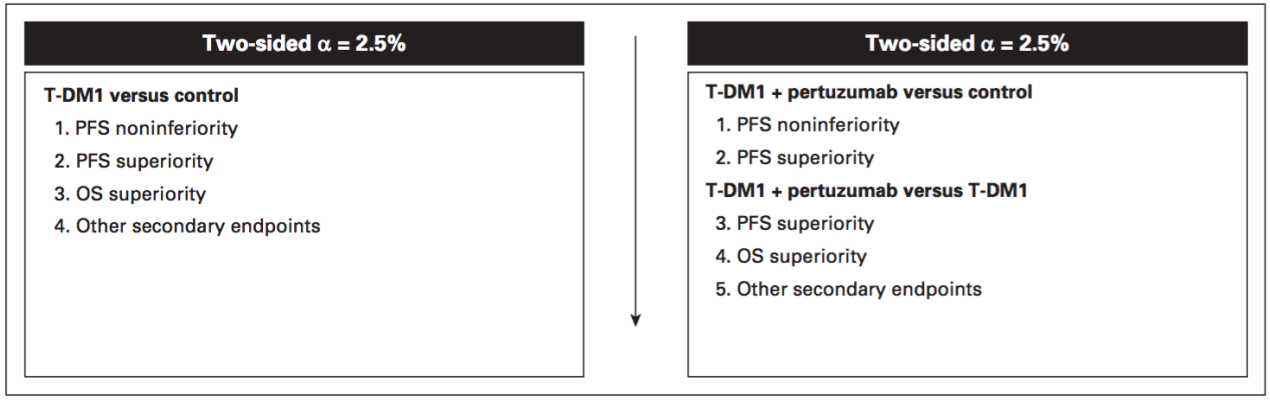
		Trastuzumab + taxane	T-DM1	T-DM1 + pertuzumab
Median PFS (months)		13.7	14.1	15.2
No. of events		231	236	217
Stratified HR (97.5% CI)	v	—	0.91 (0.73 to 1.13)	0.87 (0.69 to 1.08)
trastuzumab + taxane			P = .31	P = .14
Stratified HR (97.5% CI)	v T-DM1	—	—	0.91 (0.73 to 1.13)

No. at risk:									
Trastuzumab + taxane	365	265	163	107	75	50	21	5	
T-DM1	367	257	176	133	104	67	28	3	
T-DM1 + pertuzumab	363	261	177	135	109	75	25	5	1

Perez et al. J Clin Oncol. 2017

VALUTAZIONE DI AFFIDABILITA’

IMPRECISIONE DELLE STIME



Baseline Risk Factors	Total No.	Trastuzumab + Taxane (n = 365) Median, Mo	T-DM1 (n = 367) Median, Mo	HR (97.5% CI)
All patients	732	13.7	14.1	0.94 (0.76 to 1.16)

VALUTAZIONE DI AFFIDABILITA’

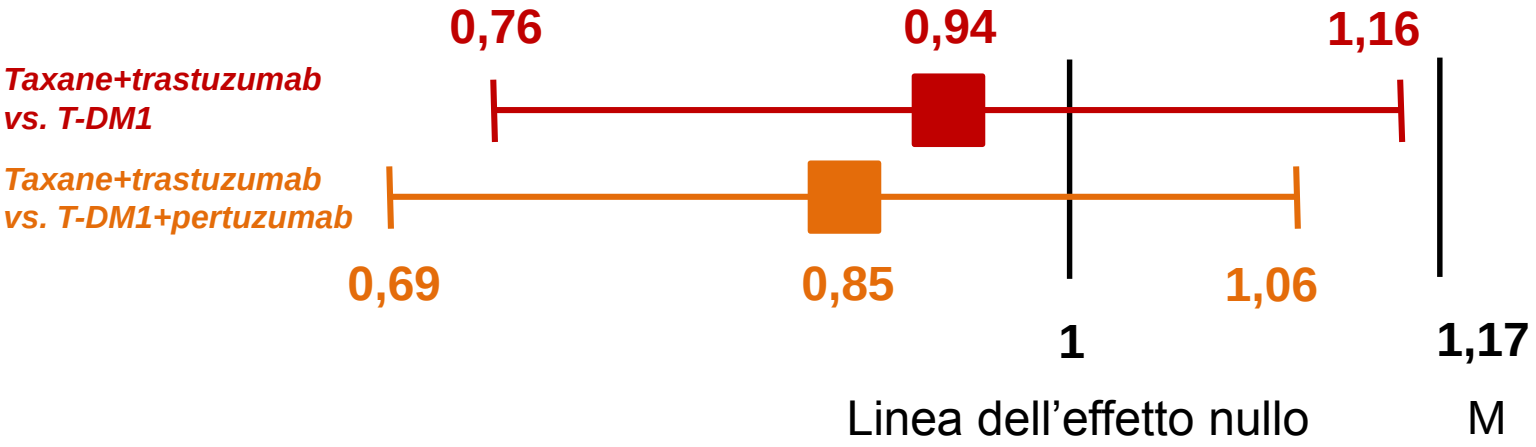
IMPRECISIONE DELLE STIME - *noninferiority*

Two-sided α = 2.5%	Two-sided α = 2.5%
T-DM1 versus control 1. PFS noninferiority 2. PFS superiority 3. OS superiority 4. Other secondary endpoints	**T-DM1 + pertuzumab versus control** 1. PFS noninferiority 2. PFS superiority **T-DM1 + pertuzumab versus T-DM1** 3. PFS superiority 4. OS superiority 5. Other secondary endpoints

VALUTAZIONE DI AFFIDABILITA’

IMPRECISIONE DELLE STIME - *noninferiority*

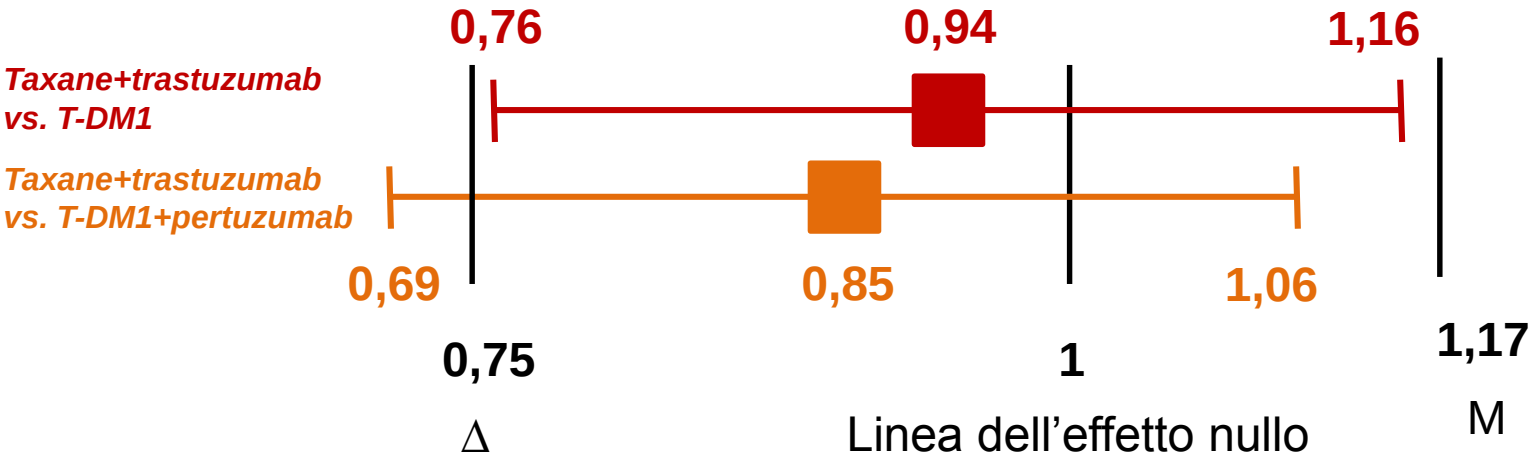
Two-sided α = 2.5%	Two-sided α = 2.5%
T-DM1 versus control	**T-DM1 + pertuzumab versus control**
1. PFS noninferiority	1. PFS noninferiority
2. PFS superiority	2. PFS superiority
3. OS superiority	**T-DM1 + pertuzumab versus T-DM1**
4. Other secondary endpoints	3. PFS superiority
	4. OS superiority
	5. Other secondary endpoints



VALUTAZIONE DI AFFIDABILITA’

IMPRECISIONE DELLE STIME - *superiority*

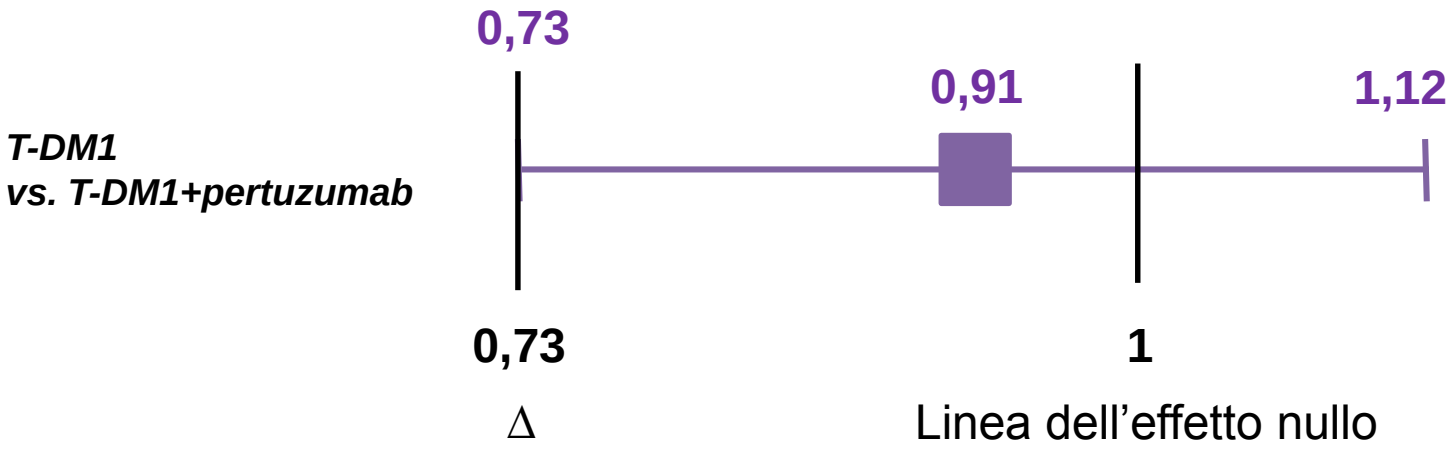
Two-sided α = 2.5%	Two-sided α = 2.5%
T-DM1 versus control	**T-DM1 + pertuzumab versus control**
1. PFS noninferiority	1. PFS noninferiority
2. PFS superiority	2. PFS superiority
3. OS superiority	**T-DM1 + pertuzumab versus T-DM1**
4. Other secondary endpoints	3. PFS superiority
	4. OS superiority
	5. Other secondary endpoints



VALUTAZIONE DI AFFIDABILITA’

IMPRECISIONE DELLE STIME - *superiority*

Two-sided α = 2.5%	Two-sided α = 2.5%
T-DM1 versus control	**T-DM1 + pertuzumab versus control**
1. PFS noninferiority	1. PFS noninferiority
2. PFS superiority	2. PFS superiority
3. OS superiority	**T-DM1 + pertuzumab versus T-DM1**
4. Other secondary endpoints	3. PFS superiority
	4. OS superiority
	5. Other secondary endpoints



VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

ANALISI DI SOTTOGRUPPO

IMPRECISIONE DELLE STIME

VALUTAZIONE DI TRASFERIBILITA’

ADERENZA AL QUESITO CLINICO

VALUTAZIONE DI RILEVANZA

ADEGUATEZZA DEL RISULTATO

QUESITO GRUPPO A:

P: - pazienti con carcinoma mammario metastatico HER2 positivo
- 1° linea di terapia

I: TDM1 (+/- pertuzumab)

C: trastuzumab+taxano?

O: PFS, OS, ORR, HRQOL, safety

Table 1. Demographic and Baseline Characteristics

Characteristic	Trastuzumab + Taxane (n = 365), No. (%)	T-DM1 (n = 367), No. (%)	T-DM1 + Pertuzumab (n = 363), No. (%)
Age, year			
Median	55	52	52
Range	(22-88)	(27-82)	(27-86)
Race			
White	232 (63.6)	239 (65.1)	233 (64.2)
Black	23 (6.3)	11 (3.0)	10 (2.8)
Asian	89 (24.4)	84 (22.9)	83 (22.9)
Other	21 (5.8)	33 (9.0)	37 (10.2)
World region			
Western Europe, Canada, Australia/Pacific	137 (37.5)	134 (36.5)	137 (37.7)
Asia	76 (20.8)	77 (21.0)	74 (20.4)
Eastern Europe	56 (15.3)	59 (16.1)	56 (15.4)
United States	43 (11.8)	46 (12.5)	42 (11.6)
Other	53 (14.5)	51 (13.9)	54 (14.9)
ECOG PS*			
0	245 (67.1)	239 (65.1)	235 (64.7)
1	119 (32.6)	128 (34.9)	127 (35.0)
ER/PR status†			
ER and/or PR positive	207 (56.7)	195 (53.1)	198 (54.5)
ER and PR negative	154 (42.2)	160 (43.6)	156 (43.0)
Visceral involvement			
Yes	241 (66.0)	251 (68.4)	259 (71.3)
No	124 (34.0)	116 (31.6)	104 (28.7)
Measurable disease			
Yes	287 (78.6)	303 (82.6)	299 (82.4)
No	78 (21.4)	64 (17.4)	64 (17.6)
Prior neoadjuvant/adjuvant therapy			
None	159 (43.6)	165 (45.0)	158 (43.5)
HER2-directed (trastuzumab/lapatinib)	113 (31.0)	113 (30.8)	117 (32.2)
Taxane	120 (32.9)	108 (29.4)	129 (35.5)
Anthracycline	152 (41.6)	162 (44.1)	168 (46.3)
Hormonal	86 (23.6)	85 (23.2)	90 (24.8)
Prior LABC/MBC therapy			
Hormonal	26 (7.1)	21 (5.7)	20 (5.5)
HER2 directed	8 (2.2)	9 (2.5)	8 (2.2)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; PR, progesterone receptor; T-DM1, trastuzumab emtansine.

*ECOG PS = 2 was an exclusion criterion (n = 2).

†Twenty-five patients had unknown ER/PR status.

Table 1. Demographic and Baseline Characteristics

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Age, year			
Median	55	52	52
Range	(22-88)	(27-82)	(27-86)
Race			
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Black	23 (6.3)	11 (3.0)	10 (2.8)
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World region			
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Hormonal	26 (7.1)	21 (5.7)	20 (5.5)
HER2 directed	8 (2.2)	9 (2.5)	8 (2.2)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; PR, progesterone receptor; T-DM1, trastuzumab emtansine.

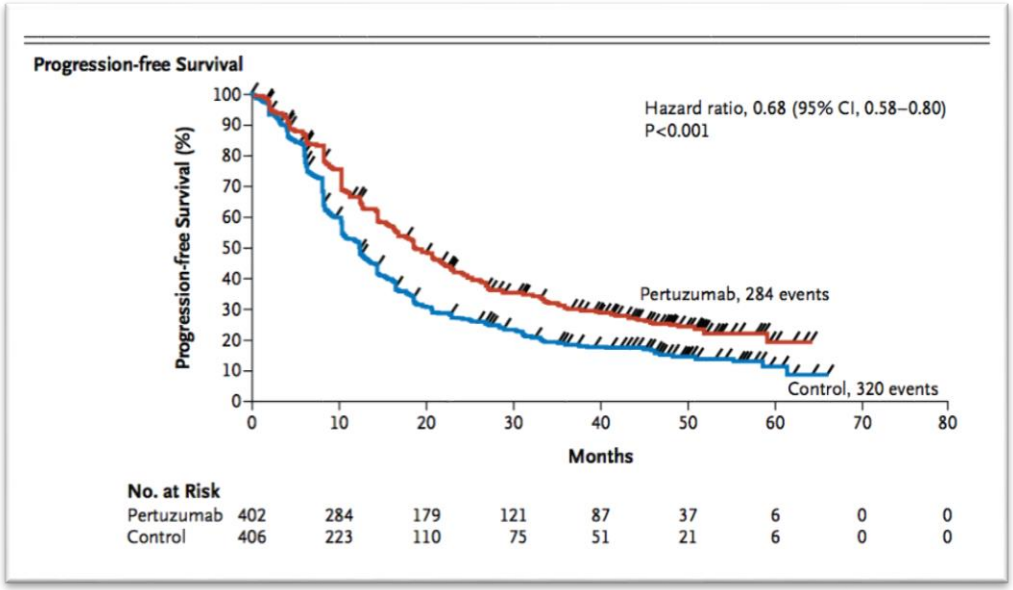
*ECOG PS = 2 was an exclusion criterion (n = 2).

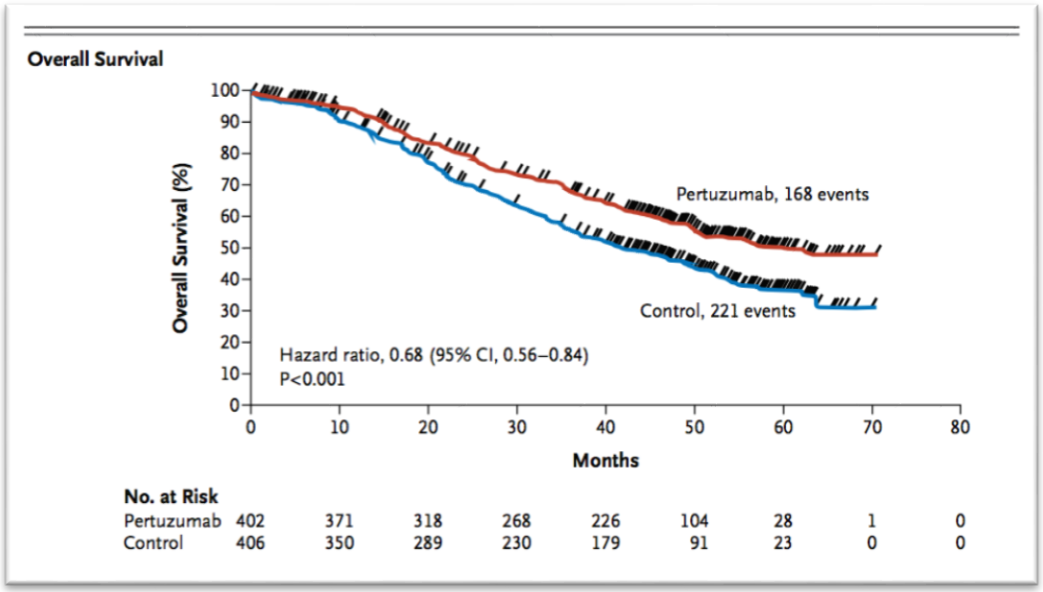
†Twenty-five patients had unknown ER/PR status.

ORIGINAL ARTICLE

Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer

Sandra M. Swain, M.D., José Baselga, M.D., Sung-Bae Kim, M.D., Jungsil Ro, M.D., Vladimir Semiglazov, M.D., Mario Campone, M.D., Eva Ciruelos, M.D., Jean-Marc Ferrero, M.D., Andreas Schneeweiss, M.D., Sarah Heeson, B.Sc., Emma Clark, M.Sc., Graham Ross, F.F.P.M., Mark C. Benyunes, M.D., and Javier Cortés, M.D., for the CLEOPATRA Study Group*





VALUTAZIONE DI AFFIDABILITA’

RISCHIO DI BIAS

ANALISI DI SOTTOGRUPPO

IMPRECISIONE DELLE STIME

VALUTAZIONE DI TRASFERIBILITA’

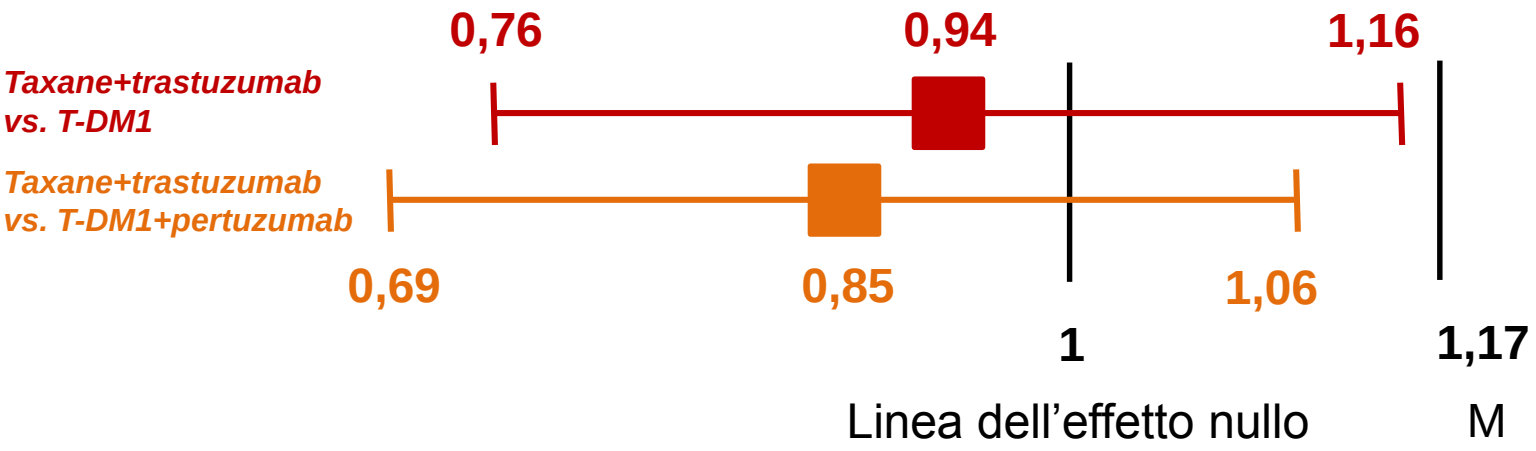
ADERENZA AL QUESITO CLINICO

VALUTAZIONE DI RILEVANZA

ADEGUATEZZA DEL RISULTATO

VALUTAZIONE DI RILEVANZA

ADEGUATEZZA DEL RISULTATO *- noninferiority*



VALUTAZIONE DI AFFIDABILITA'

ADEGUATEZZA DEL RISULTATO – *noninferiority*

Table 2. Time to Clinically Meaningful Decrease in Health-Related Quality of Life

Time to Event*	Trastuzumab + Taxane (n = 327)	T-DM1 (n = 352)	T-DM1 + Pertuzumab (n = 338)
Median, months	3.6	7.7	9.0
Stratified hazard ratio 95% CI (vs. trastuzumab plus taxane)	—	0.70 (0.57 to 0.86)	0.68 (0.55 to 0.84)

NOTE. Health-Related Quality of Life was measured by the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) of the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire.[21] The analysis included all female patients from the intention-to-treat population who completed the baseline and at least one postbaseline FACT-B assessment.

Abbreviation: T-DM1, trastuzumab emtansine.

*An event was defined as a clinically meaningful decrease in health-related quality of life, which is a ≥ 5-point decrease from baseline in FACT-B TOI-PFB score.[22]

Perez et al. J Clin Oncol. 2017

VALUTAZIONE DI RILEVANZA

ADEGUATEZZA DEL RISULTATO – *noninferiority*

Table 3. Adverse Events in the Safety Population

Adverse Event	Trastuzumab + Taxane (n = 353)	T-DM1 (n = 361)	T-DM1 + Pertuzumab (n = 366)
Grade ≥ 3 adverse events	191 (54.1)	164 (45.4)	169 (46.2)
Grade ≥ 3 adverse events reported in ≥ 3% of patients in any treatment arm			
Neutropenia	70 (19.8)	16 (4.4)	10 (2.7)
Febrile neutropenia	23 (6.5)	0 (0)	0 (0)
Diarrhea	15 (4.2)	1 (0.3)	9 (2.5)
Hypertension	11 (3.1)	16 (4.4)	18 (4.9)
Anemia	10 (2.8)	17 (4.7)	22 (6.0)
ALT increased	3 (0.8)	16 (4.4)	19 (5.2)
AST increased	1 (0.3)	24 (6.6)	11 (3.0)
Thrombocytopenia	0 (0)	23 (6.4)	29 (7.9)
Any adverse event	348 (98.6)	357 (98.9)	361 (98.6)
All-grade adverse events in > 20% of patients in any treatment arm with a > 5-percentage-point difference between trastuzumab + taxane and T-DM1 arms			
Alopecia	211 (59.8)	24 (6.6)	33 (9.0)
Diarrhea	172 (48.7)	91 (25.2)	176 (48.1)
Nausea	131 (37.1)	170 (47.1)	191 (52.2)
Peripheral neuropathy	99 (28.0)	48 (13.3)	65 (17.8)
Peripheral edema	98 (27.8)	34 (9.4)	31 (8.5)
Arthralgia	87 (24.6)	80 (22.2)	69 (18.9)
Rash	86 (24.4)	63 (17.5)	86 (23.5)
Myalgia	82 (23.2)	64 (17.7)	62 (16.9)
Neutropenia	80 (22.7)	41 (11.4)	32 (8.7)
Headache	78 (22.1)	116 (32.1)	118 (32.2)
Peripheral sensory neuropathy	71 (20.1)	47 (13.0)	44 (12.0)
Vomiting	67 (19.0)	78 (21.6)	110 (30.1)
Pyrexia	58 (16.4)	100 (27.7)	118 (32.2)
Epistaxis	52 (14.7)	112 (31.0)	127 (34.7)
Chills	14 (4.0)	56 (15.5)	98 (26.8)