Studio EMBRACE

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Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study

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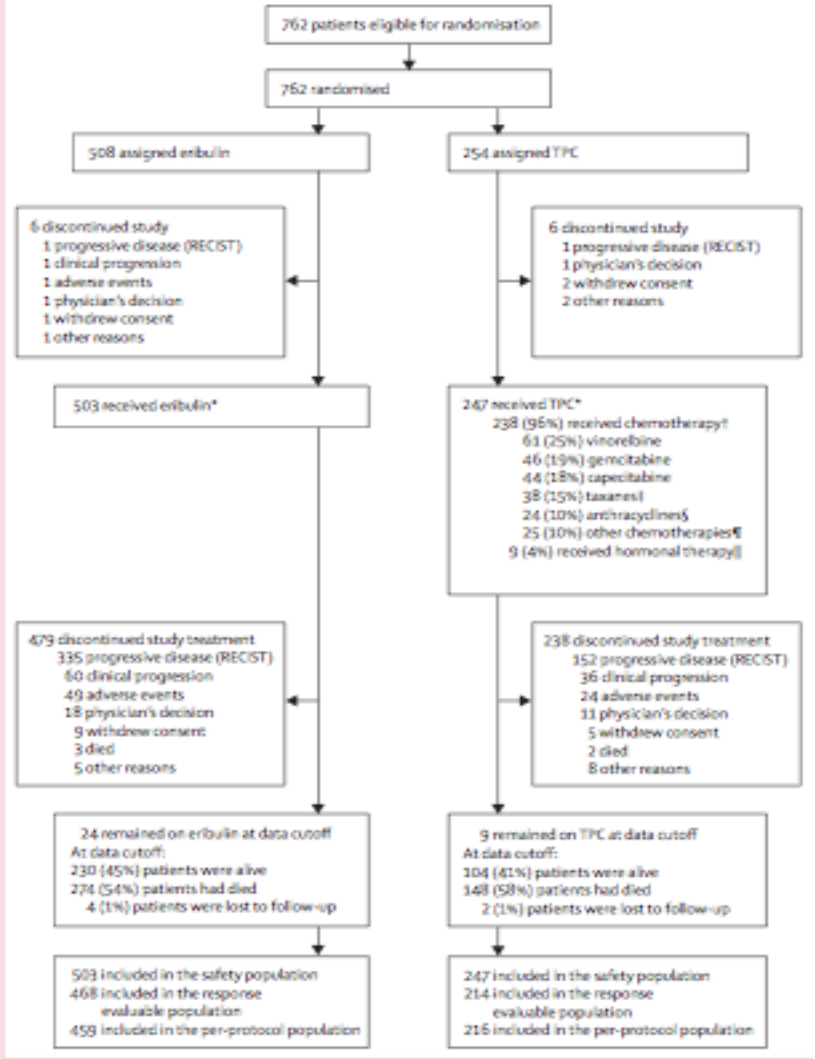

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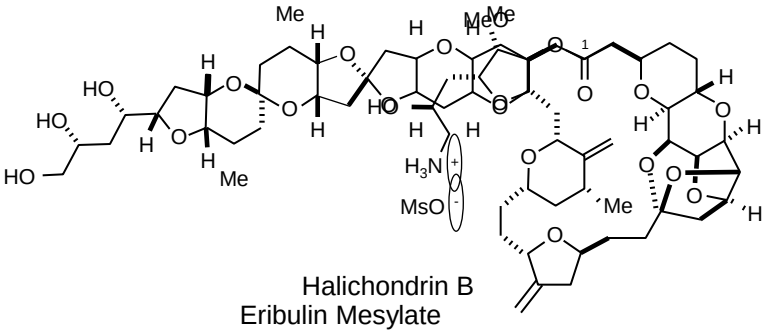
ERIBULINA

- Inibitore non taxano della dinamica dei microtubuli, [1-5]
- Appartiene alla nuova classe di agenti antineoplastici delle alicondrine[2]
- E' un'analogo sintetico strutturalmente semplificato dell'alicondrina B, un prodotto naturale isolato dalla spugna marina Halichondria okadai[2]
- Meccanismo d'azione diverso da quello degli altri agenti che agiscono a livello della tubulina[1-5]
- Studi preclinici dimostrano che eribulina ha attività contro diverse linee cellulari tumorali tassani-resistanti [6,7]

Halichondria okadai[4]

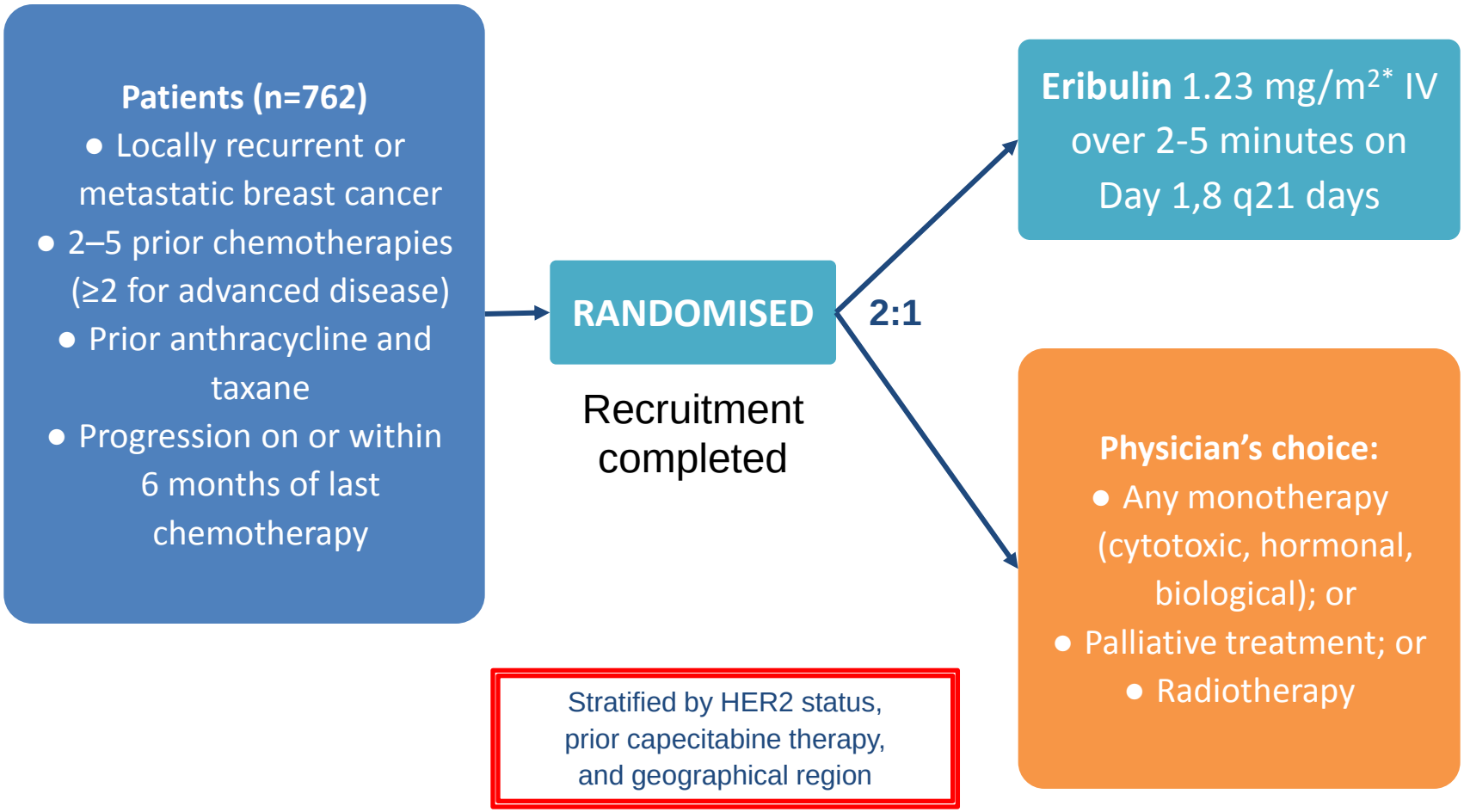


Halichondrin B
Eribulin Mesylate

1. Towle M, *et al*. *Cancer Res.* 2001; **61**:1013-21.
2. Jordan M, *et al*. *Mol Cancer Ther.* 2005; **4**:1086-95.
3. Kuznetsov G, *et al*. *Cancer Res.* 2004; **64**:5760-6.
4. Okouneva T, *et al*. *Mol Cancer Ther.* 2008; **7**:2003-11.
5. Smith J, *et al*. *Biochemistry.* 2010; **49**:1331-7.
6. Kuznetsov G, *et al*. *Cancer Res.* 2004; **64**:5760-6.
7. Okouneva T, *et al*. *Mol Cancer Ther.* 2008; **7**:2003-11.

Progetto CANOA

Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study



Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study

End points

- Primary endpoint:
  - Overall survival
- Key secondary endpoints:
  - Progression-free survival
  - Objective response rate by RECIST
  - Safety
- All subset analyses were pre-defined

Patient Characteristics by Stratification Factors

	Eribulina n=508	TPC n=254	Totale N=762
Regione Geografica (%)			
Regione 1: Nord America, Europa Occidentale, Australia	64	64	64
Regione 2: Europa Orientale, Russia	25	25	25
Regione 3: America Latina, Sud Africa	11	11	11
HER2 status (%)			
Negativo	73	76	74
Positivo	16	16	16
Sconosciuto/non determinato	10	9	10
Precedente capecitabina (%)			
Si	73	74	73
No	27	26	27

Disease and Tumour Characteristics

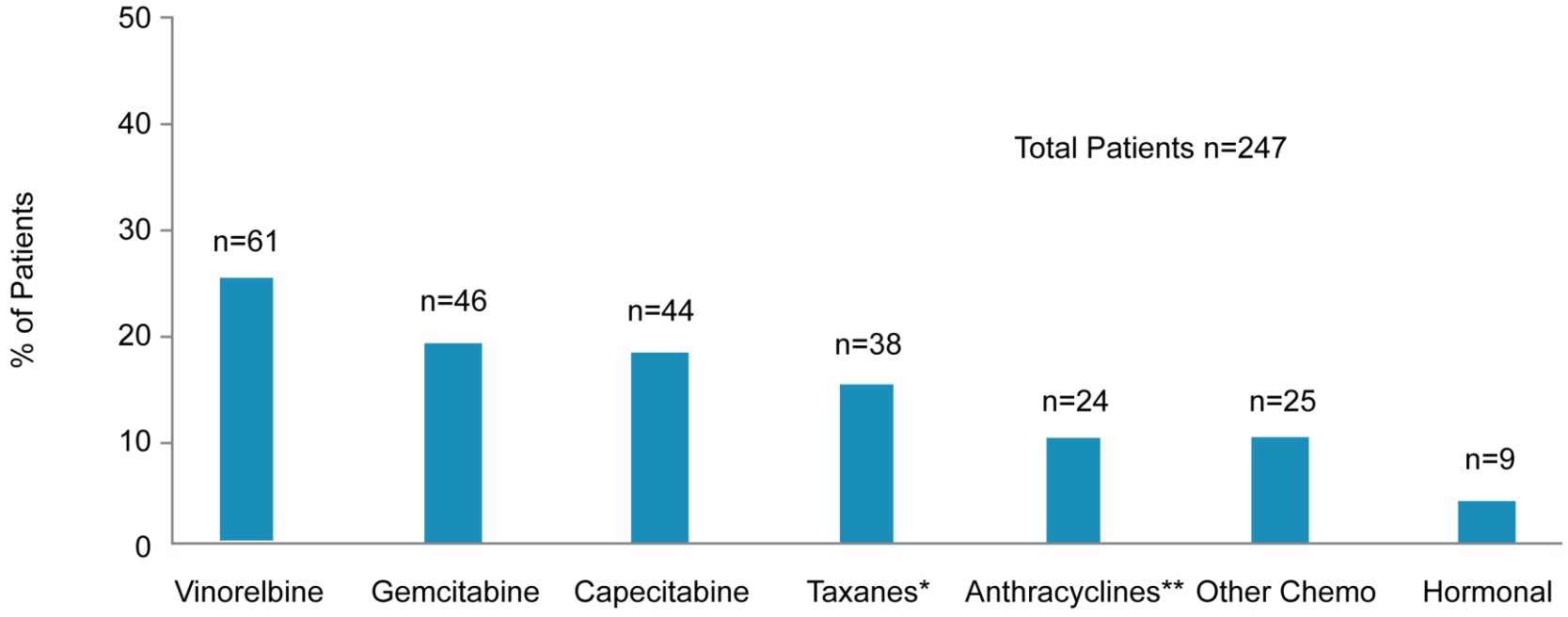
	Eribulin n=508	TPC n=254	Total N=762
ER/PR status (%)			
ER and/or PR+	64	64	64
ER and/or PR-	24	25	25
Unknown	11	11	11
ER/PR/HER2 negative (%)	18	20	19
Number of disease sites (%)			
1	17	14	16
2	34	32	33
3	29	30	29
4	20	24	22
Sites of disease (%)			
Liver	58	63	60
Lung	39	37	38
Bone	60	62	61

Prior chemotherapies (ITT)

	Eribulin, % n=508	TPC, % n=254	Total, % N=762
Number of prior chemotherapy regimens for metastatic disease [1]			
2	43	36	41
3	32	33	32
4	18	22	19
Number of prior chemotherapy regimens* [2]			
1	<1	0	<1
2	13	12	13
3	35	33	34
4 (median)	33	31	32
5	17	20	18
≥6	3	4	3

Treatment of Physician's Choice (TPC)

96% of patients treated with chemotherapy



No patient received best supportive care or "biological" therapies only

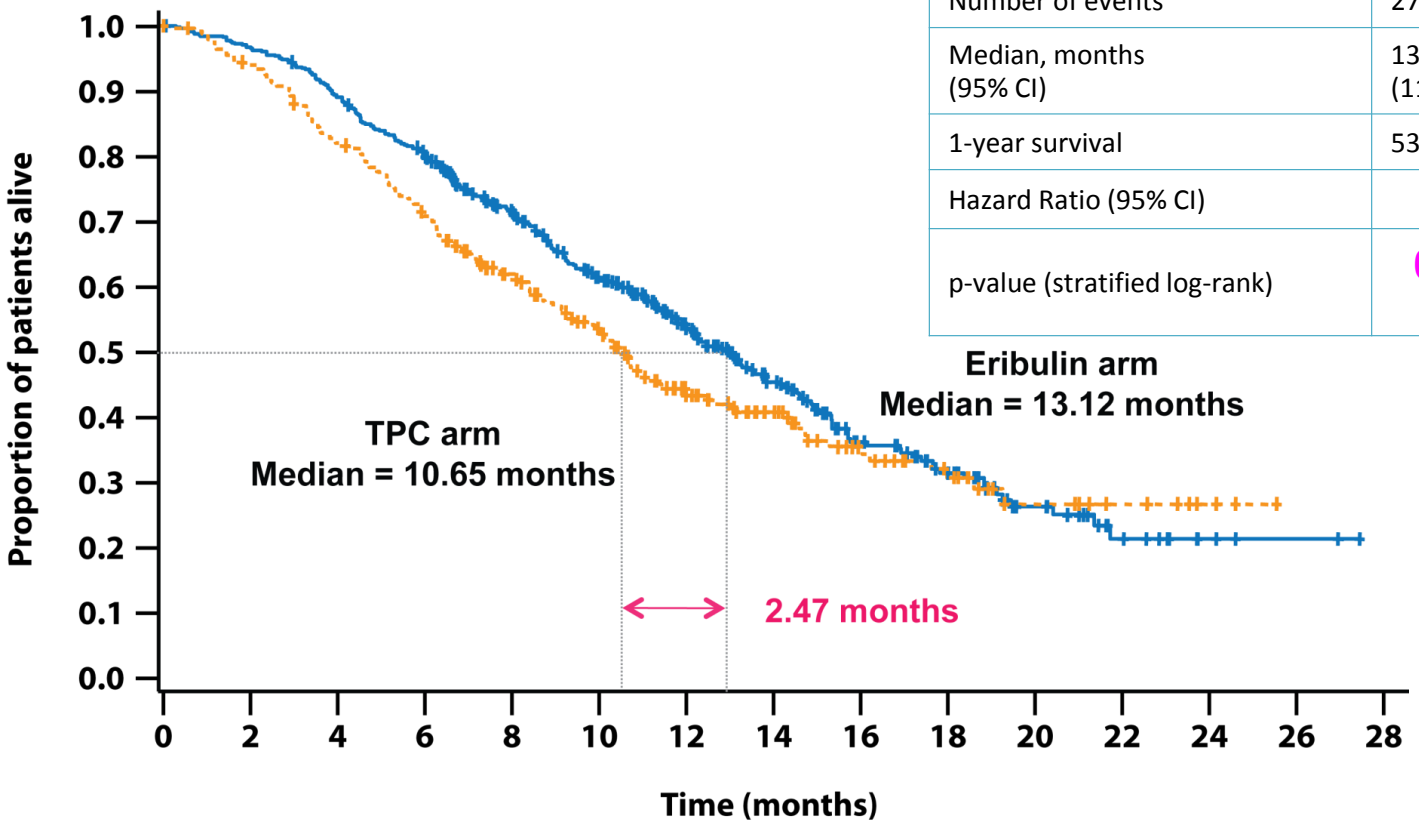
*Taxanes: paclitaxel, docetaxel, abraxane, (ixabepilone)
**Anthracyclines: doxorubicin, liposomal doxorubicin, mitoxantrone
Other Chemo: CDDP, CBDCA, CTX, ETOPOSIDE, MITO, 5-FU, MTX

Drug exposure

	Eribulin n=503	TPC: Chemotherapy n=238
Duration of exposure		
Months (median, range)	3.9 (0.7-16.3)	2.1 (0.03-21.2)
> 5 cycles received (range 1-23)	**59%**	NA

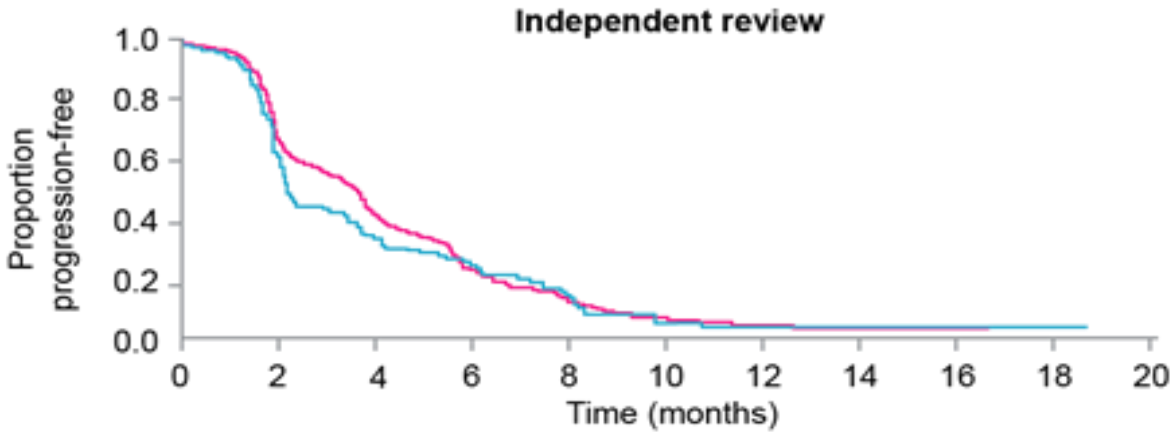
Overall Survival (ITT population)

	Eribulin n=508	TPC n=254
Number of events	274	148
Median, months (95% CI)	13.12 (11.8, 14.3)	10.65 (9.3, 12.5)
1-year survival	53.9%	43.7%
Hazard Ratio (95% CI)	0.81 (0.66, 0.99)	
p-value (stratified log-rank)	**0.041 (statisticamente significativo)**	



Questa analisi effettuata era stata programmata dopo 411 eventi, ma in realtà è stata eseguita quando 422 (55%) pazienti dello studio erano deceduti

DFS

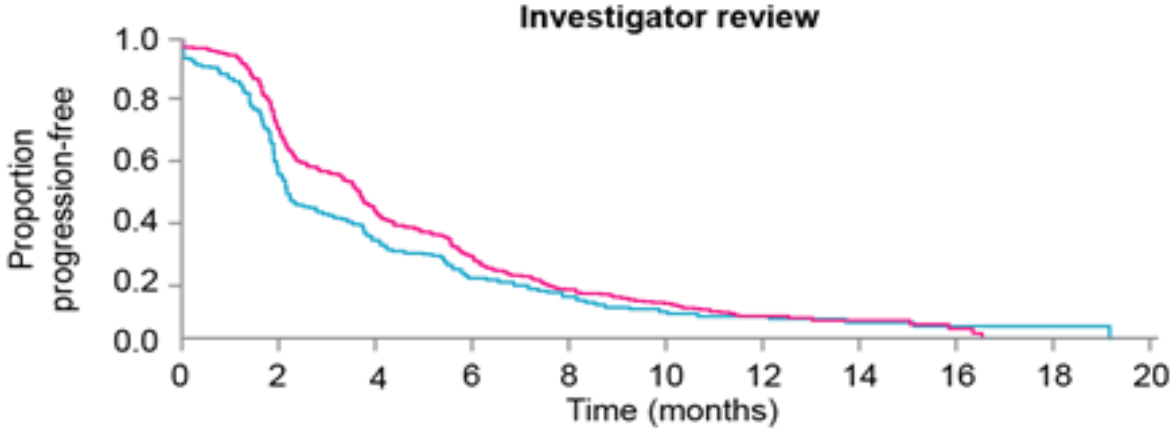


Eribulin (n=508)
TPC (n=254)

Median (months)

Eribulin	3.7
TPC	2.2

HR 0.87
(95% CI 0.71, 1.05; p = 0.14)



Eribulin (n=508)
TPC (n=254)

Median (months)

Eribulin	3.6
TPC	2.2

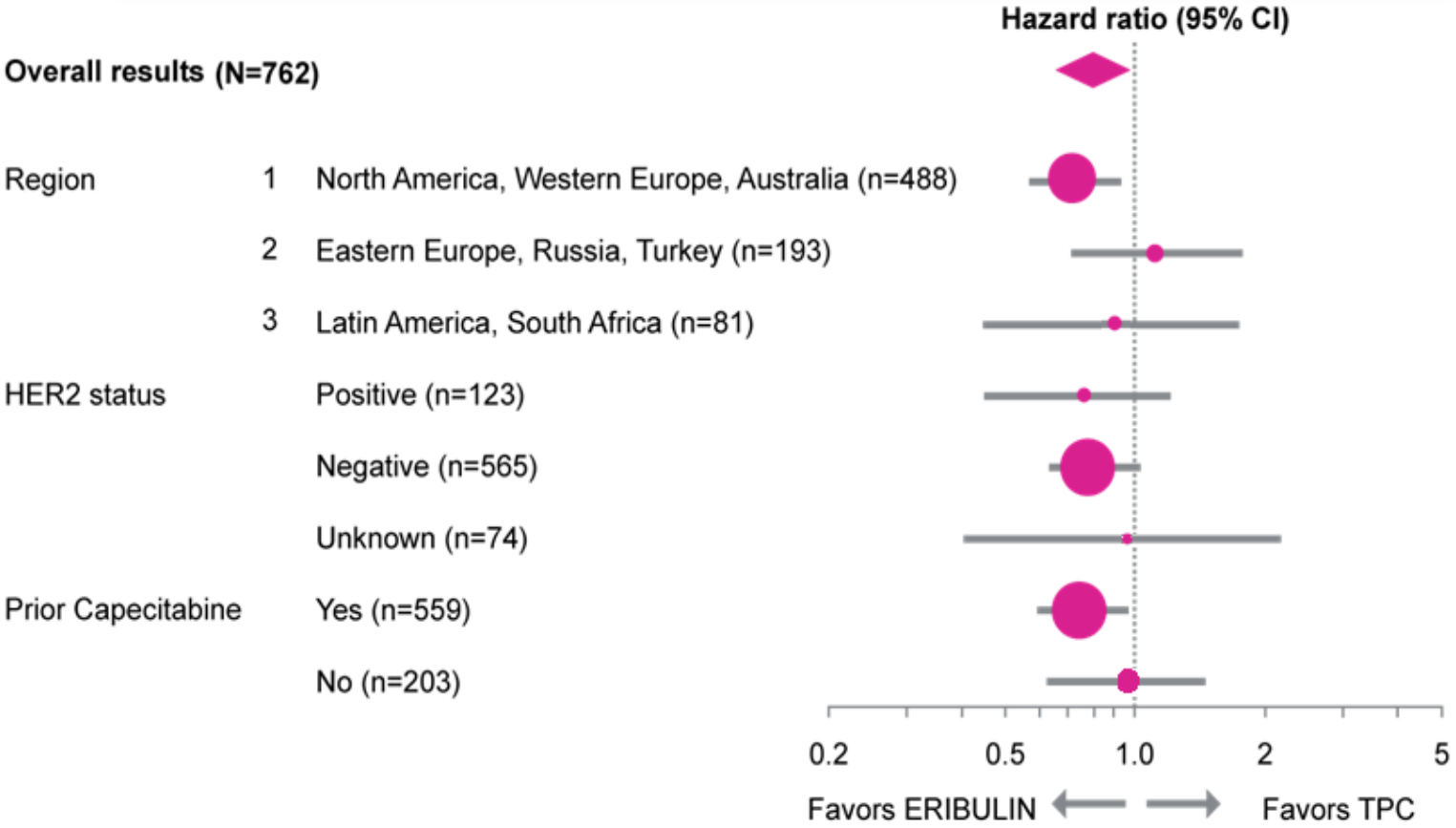
HR 0.76
(95% CI 0.64, 0.90; p = 0.002)

Best overall response

	Independent Review		Investigator Review	
	Eribulin (n=468)	TPC (n=214)	Eribulin (n=468)	TPC (n=214)
ORR (CR+PR), %	12	**5**	13	7
P value	0.002		0.028	
SD, % PD, % NE, %	44 41 3	45 49 1	47 38 2	45 45 2
Clinical benefit rate (CR+PR+SD ≥6 months), %	23	17	28	20

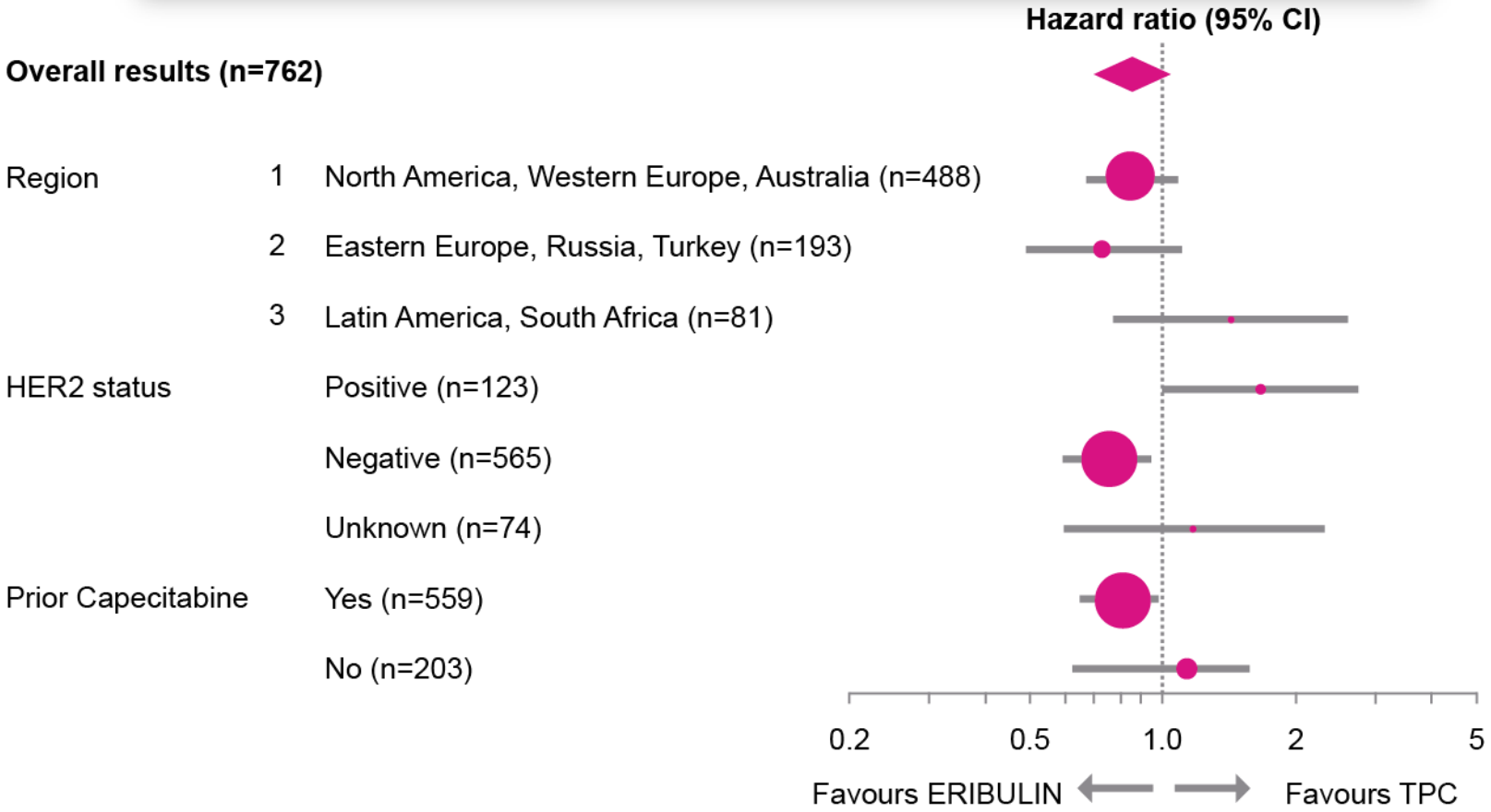
*Response evaluable population (n=682)

OS by stratification factor



*Intent-to-treat population; Based upon a stratified Cox analysis including geographic region, HER-2/neu status, and prior capecitabine therapy

PFS by stratification factor



*Based upon a stratified Cox analysis including geographic region, HER-2/neu status, and prior capecitabine therapy as strata
HER2, human epidermal growth factor receptor type 2; PFS, progression-free survival; TPC, treatment of physician's choice.
Intent-to-treat population

Twelves C et al. *Ann Oncol* 2010;**21**(suppl 8): Abstract 2750 and Oral Presentation

Safety

Adverse Event	Eribulin (n=503) n (%)	TPC (n=247) n (%)
All adverse events	497 (99)	230 (93)
Serious adverse events	126 (25)	64 (26)
Adverse events leading to		
interruption	25 (5)	25 (10)
discontinuation	67 (13)	38 (15)
dose reduction	85 (17)	39 (16)
dose delay	177 (35)	80 (32)
Fatal adverse events	20 (4)	18 (7)
Fatal adverse events (treatment-related)	5 (1)	2 (1)

Safety: hematological toxicities

Adverse event, %	Eribulin (n=503)			TPC (n=247)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Neutropenia	**52**	**21**	**24**	**30**	**14**	**7**
Leukopenia	**23**	**12**	**2**	**11**	**5**	**1**
Anaemia	**19**	**2**	**< 1**	**23**	**3**	**< 1**
Febrile neutropenia†	**5**	**3**	**1.2**	**2**	**0.8**	**0.4**
Thrombocytopenia	**2.6**	**0.6**	**0.2**	**4.9**	**0.8**	**1.6**

Safety: non hematological toxicities

Adverse event, %	Eribulin (n=503)			TPC (n=247)		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Gastrointestinal						
Nausea	**35**	**1**	**0**	**28**	**2**	**0**
Constipation	**25**	**1**	**0**	**21**	**1**	**0**
Diarrhoea	**18**	**0**	**0**	**18**	**0**	**0**
Vomiting	**18**	**1**	**<1**	**18**	**1**	**0**
General disorders and administrative site						
Asthenia/fatigue†	**54**	**8**	**1**	**40**	**10**	**0**
Pyrexia	**21**	**<1**	**0**	**13**	**<1**	**0**
Mucosal inflammation	**9**	**1**	**0**	**10**	**2**	**0**

Eribulina è stata classificata come farmaco a basso rischio emetico^

Safety: non hematological toxicities

Adverse event, %	Eribulin (n=503)			TPC (n=247)		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Nervous system disorders						
Headache	**19**	**<1**	**0**	**12**	**0**	**<1**
Peripheral neuropathy†	**35**	**8**	**<1**	**16**	**2**	**0**
Respiratory, thoracic, mediastinal						
Cough	**14**	**0**	**0**	**9**	**0**	**0**
Dyspnoea	**16**	**4**	**0**	**13**	**2**	**<1**
Skin and subcutaneous tissue						
Alopecia	**45**	**N/A**	**N/A**	**10**	**N/A**	**N/A**
Hand-foot syndrome	**1**	**<1**	**0**	**14**	**4**	**0**

Looking for efficiency rather than efficacy in randomized controlled trials in oncology

Randomized controlled trials (RCTs) are generally recognized as the gold standard for developing therapeutic agents and gaining definite data on their efficacy. When transferring the results of RCTs into practice, clinicians should consider the quality of the study design, and of the conduction, the extent of generalization of the results and the clinical relevance of the treatment effect. Considering the risk and cost–benefit profile of therapeutic agents when deciding on treatment of a patient has become even more compelling with the increasing cost of new drugs.

interest. To be considered as a true 'therapeutic breakthrough', and to justify the dramatic raise in the costs, new drugs should produce relevant improvement in clinical outcome and improve the risk–benefit profile. Methods to assess clinical relevance are available but are not implemented in the key situations where consensus is formed and adoption is decided. It is time that oncologic community shoulder his responsibilities for changing this trend.

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