Lo studio di prima linea Trastuzumab + paclitaxel vs CT-P6 + paclitaxel

Dr.ssa Elena Poletto
AOU S.M. Misericordia
udine

The Oncologist®

European Perspectives

A Catalyst for Change: The European Cancer Patient's Bill of Rights

Article 2: *The right of every European citizen to optimal and timely access to appropriate specialised care, underpinned by research and innovation.*

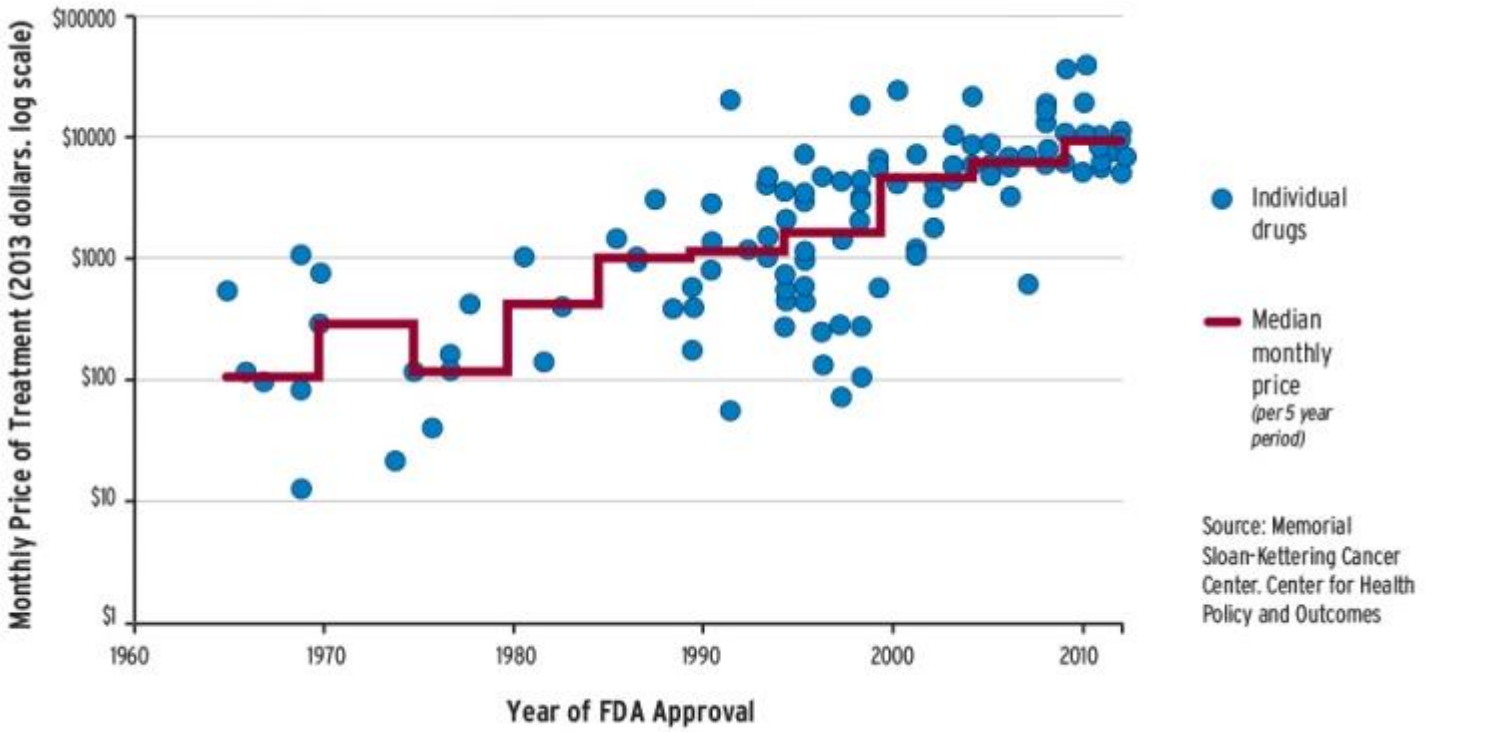
2.6: Rapid access to the latest innovations in diagnosis and treatment for the individual cancer patient following regulatory approval

2.7: the right to access care based on their need and not on their ability to pay for it

Article 3: *The right of every European citizen to receive care in health systems that ensure improved outcomes, patient rehabilitation, best quality of life and affordable healthcare*

Lawler et al, The Oncologist 2014

….but we have to consider the economic burden of cancer....



The State of Cancer Care in America: 2014, American Society of Clinical Oncology.

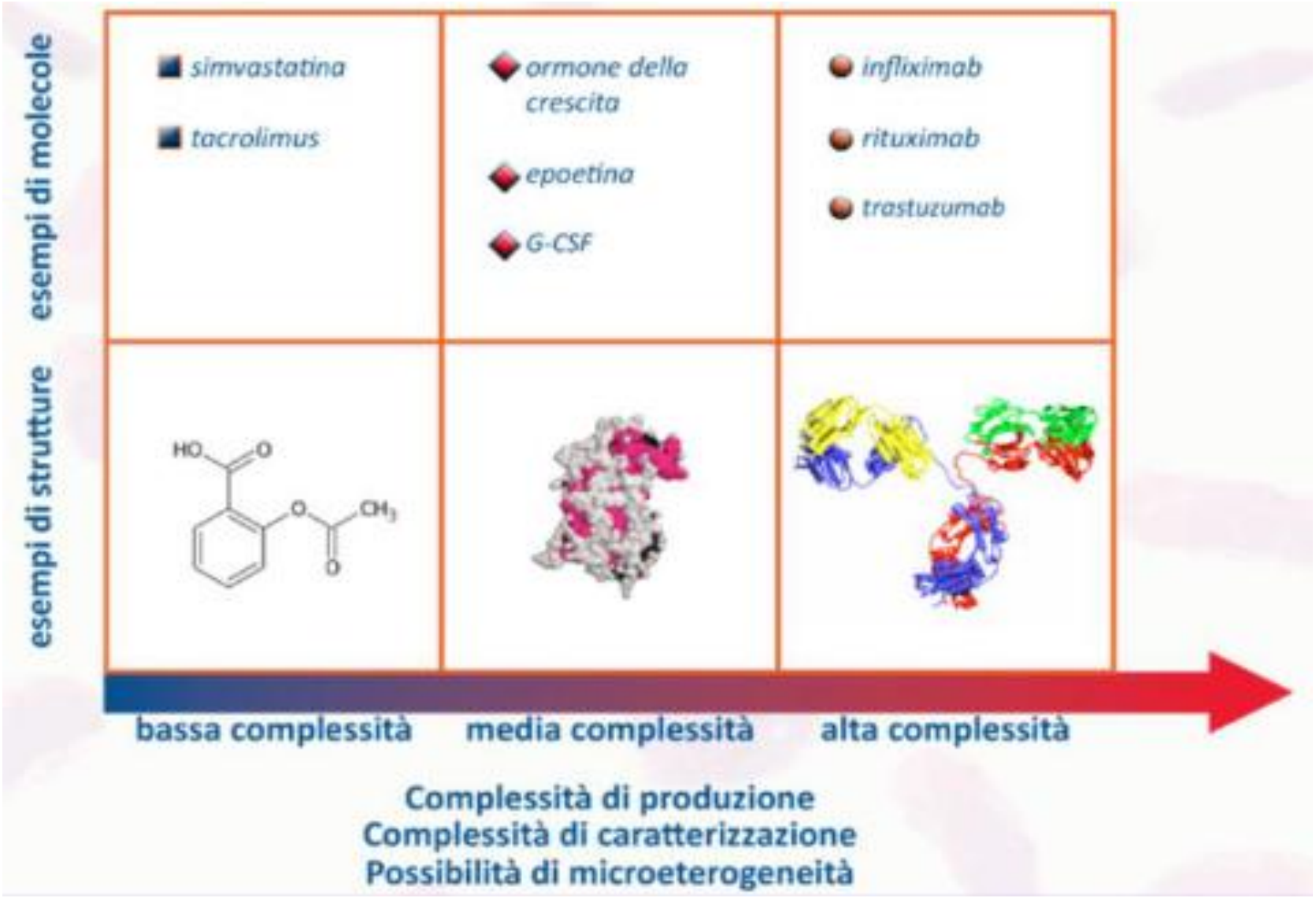
Generic Name	Brand Name	Approved Use	Precision or Targeted Therapy?[7]	Oral or Injection
Sorafenib	NEXAVAR	Differentiated thyroid carcinoma	N	Oral
Crizotinib	Xalkori	Non-small cell lung cancer, anaplastic lymphoma kinase (ALK)-positive	Y	Oral
Ibrutinib	IMBRUVICA	Mantle cell lymphoma	Y	Oral
Obinutuzumab	GAZYVA	Chronic lymphocytic leukemia	Y	Injection
Pertuzumab injection	PERJETA	HER2-positive breast cancer	Y	Injection
Paclitaxel protein-bound particles (albumin-bound)	Abraxane for injectable suspension	Adenocarcinoma of the pancreas	N	Injection
Afatinib	Gilotrif tablets	Non-small cell lung cancer, with epidermal growth factor receptor (EGFR) mutations	Y	Oral
Denosumab	Xgeva injection	Giant cell tumor of bone	N	Injection
lenalidomide capsules	REVLIMID	Mantle cell lymphoma	N	Oral
Trametinib	MEKINIST tablet	Melanoma with BRAF V600E or V600K mutation	Y	Oral
Dabrafenib	TAFINLAR capsule	Melanoma with BRAF V600E mutation	Y	Oral
Radium Ra 223 dichloride	Xofigo Injectio	Prostate cancer	N	Injection
Erlotinib	Tarceva	Non-small cell lung cancer with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations	Y	Oral
Ado-trastuzumab emtansine	KADCYLA for injection	HER2-positive, metastatic breast cancer	Y	Injection
Pomalidomide	POMALYST capsules	Multiple myeloma	N	Oral
Doxorubicin hydrochloride liposome injection	Generic version of DOXIL Injection	Ovarian cancer	N	Injection
Doxorubicin hydrochloride liposome injection	Generic version of DOXIL Injection	AIDS-related Kaposi's sarcoma	N	Injection
Bevacizumab	Avastin	Colorectal cancer	N	Injection

The State of Cancer Care in America: 2014, American Society of Clinical Oncology.

Biosimilars: definitions

- *The U.S. Food and Drug Administration*: A biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product

Biosimilar antibodies complexity



SIF guidelines

Biosimilar antibodies complexity

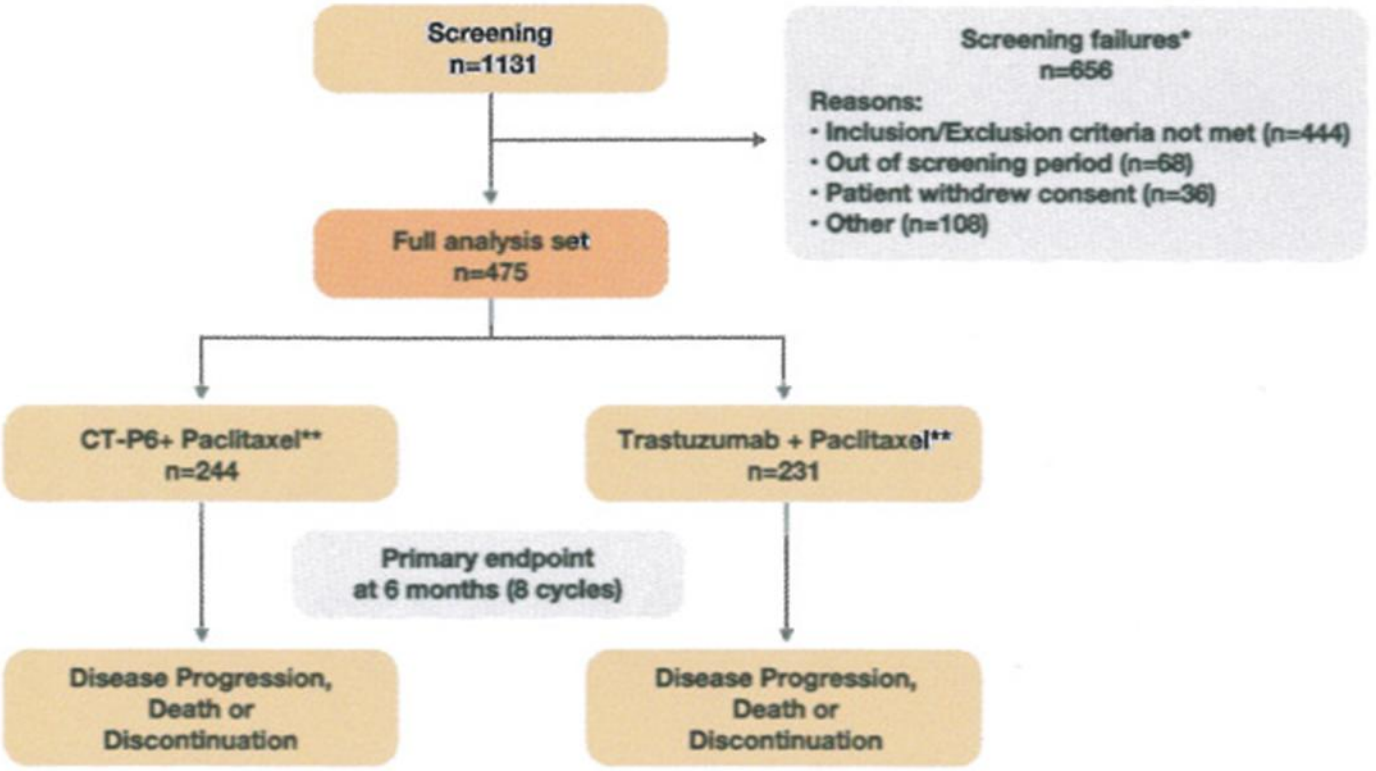
SIF guidelines

Study design

- Double blind, randomized, phase III trial
- Data were combined with data from a phase I/IIb study (NCT01084863)
  - Same inclusion/exclusion criteria
  - Same design
  - Both double blind

Study design

Figure 1. Study design



** Potentially ineligible 82 patients were excluded from analyses.*
*** CT-P6/trastuzumab: 8 mg/kg IV loading (day 1), followed by 6 mg/kg every 3 weeks, Paclitaxel : 175 mg/m2 IV every 3 weeks*

Y-H Im et al, ASCO 2013

Study aims and objective

To demonstrate equivalence of CT-P6 and trastuzumab, both given in combination with paclitaxel, as first line treatment in women with HER2-positive MBC

Study aims and objectives

- Efficacy Objectives:
  - Primary endpoint: Overall Response Rate (ORR)
  - Secondary endpoint: Time to Progression (TTP)

- Safety Objectives:
  - Secondary endpoint: cardiotoxicity
  - Tertiary endpoint: incidence and severity of adverse events

Study aims and objectives

Table 1. Statistical analysis for primary endpoint

Randomized population, no	557
Target population, no	466
Primary endpoint	**ORR (at cycle 8)**
Statistical assumptions	• Equivalence margin: 15% with alpha = 0.05 • Drop-out rate: 13% • Primary population: randomized patients receiving any study drug, having ≥1 post-baseline assessment
Analytical method for Primary endpoint	• 95% CI for difference in proportion of patients randomized to CT-P6 who have objective response (CR or PR as per RECIST 1.1 criteria) and proportion of patients randomized to trastuzumab who have objective response

Y-H Im et al, ASCO 2013

Material and methods

- Inclusion criteria:
  - Females over 18 years of age and ECOG 0-1
  - MBC with measurable lesions
  - HER2 Fluorescent In-Situ Hybridation (FISH) positive, centrally confirmed
  - No prior trastuzumab and/or chemotherapy treatment in metastatic setting
  - Prior adjuvant/neoadjuvant trastuzumab and/or chemotherapy > 12 months, allowed

Exclusion criteria

- Prior chemotherapy for MBC
- Documented CNS metastases
- History of congestive heart failure of any New York Health Association (NYHA) criteria, or serious cardiac arrhytmia requiring treatment, or recent miocardial infarction <6 months prior
- Abnormal LEVF (≤ 50%) at baseline

Results

Table 2. Patient characteristics

	CT-P6 + Paclitaxel (n=244)	Trastuzumab + Paclitaxel (n=231)
Age (years)		
Median (range)	54 (31–75)	53 (25–78)
≥ 65 years	34 (13.9)	22 (9.5)
< 65 years	210 (86.1)	209 (90.5)
Menopause status, no (%)		
Postmenopausal (not childbearing)	191 (78.3)	157 (68.0)
Premenopausal (childbearing age)	53 (21.7)	74 (32.0)
Ethnicity, no (%)		
Caucasian	158 (64.8)	141 (61.0)
Asian	86 (35.2)	90 (39.0)
Weight (kg)		
Median (range)	65.7 (36.0–140.0)	66.3 (36.0–132.0)
Body surface area (m^2)		
Median (range)	1.70 (1.18–2.55)	1.71 (1.21–2.50)
HER2 result by FISH, no (%)		
Positive	244 (100)	231 (100)
Prior neoadjuvant or adjuvant therapy, no (%)		
Yes	130 (53.3)	121 (52.4)
Trastuzumab	8 (3.3)	8 (3.5)
Taxane	33 (13.5)	31 (13.4)
Anthracycline	111 (45.5)	106 (45.9)
Baseline ECOG PS score, no (%)		
Score 0	128 (52.5)	116 (50.2)
Score 1	115 (47.1)	115 (49.8)
Metastatic site		
Lymph node	115 (47.1)	118 (51.1)
Liver	127 (52.0)	107 (46.3)
Bone	98 (40.2)	102 (44.2)
Lung	106 (43.4)	113 (48.9)
Breast	4 (1.6)	1 (0.4)
Others	84 (34.4)	72 (31.2)
Disease status		
Initial metastatic	90 (36.9)	84 (36.4)
Recurrence	154 (63.1)	147 (63.6)
Disease free interval (months, recurrence only)		
Median (range)	23.8 (0.9–148.2)	20 (0.5–384.9)

Y-H Im et al, ASCO 2013

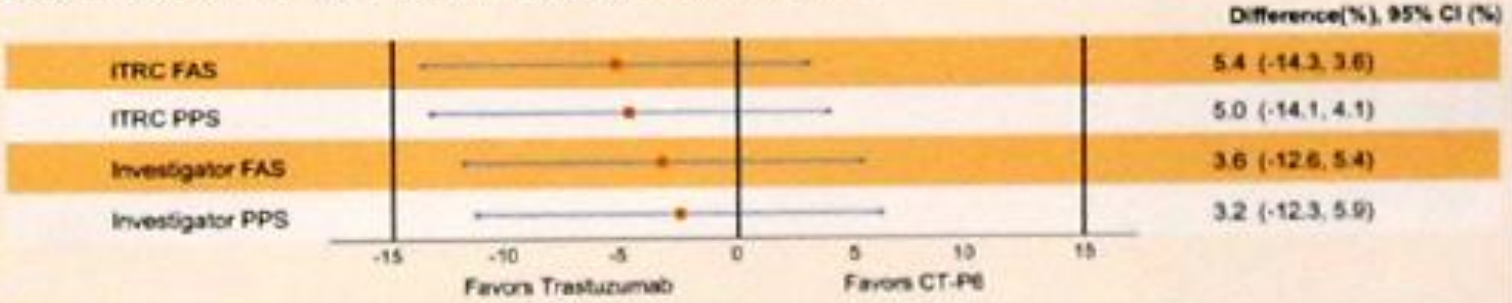
Results: efficacy endpoints

Table 3. Summary of Overall response rate during 8 cycles (Full analysis set)

Number of patients	ITRC		Investigator	
	CT-P6 + Paclitaxel (n=244)	Trastuzumab + Paclitaxel (n=231)	CT-P6 + Paclitaxel (n=244)	Trastuzumab + Paclitaxel (n=231)
Best overall response				
Complete response (CR)	9 (3.7%)	4 (1.7%)	12 (4.9%)	6 (2.6%)
Partial response (PR)	129 (52.9%)	139 (60.2%)	146 (59.8%)	152 (65.8%)
Stable disease (SD)	49 (20.1%)	38 (16.5%)	61 (25.0%)	56 (24.2%)
Overall response rate[1]				
ORR (%)	138 (56.6%)	143 (61.9%)	158 (64.8%)	158 (68.4%)
Difference (%); 95% CI (%)[2]	5.4 [-14.3, 3.6]		3.6 [-12.6, 5.4]	

CI = confidence interval, ITRC = Independent Tumour Review Committee
Patients with no post-baseline tumour assessments are counted as non-responders.
(1) Overall response rate is the proportion of patients with a best overall response of CR or PR.
(2) Difference in proportion of complete response or partial response. Confidence interval estimated using the exact method

Figure 2. Overall response rate during 8 cycles by different raters

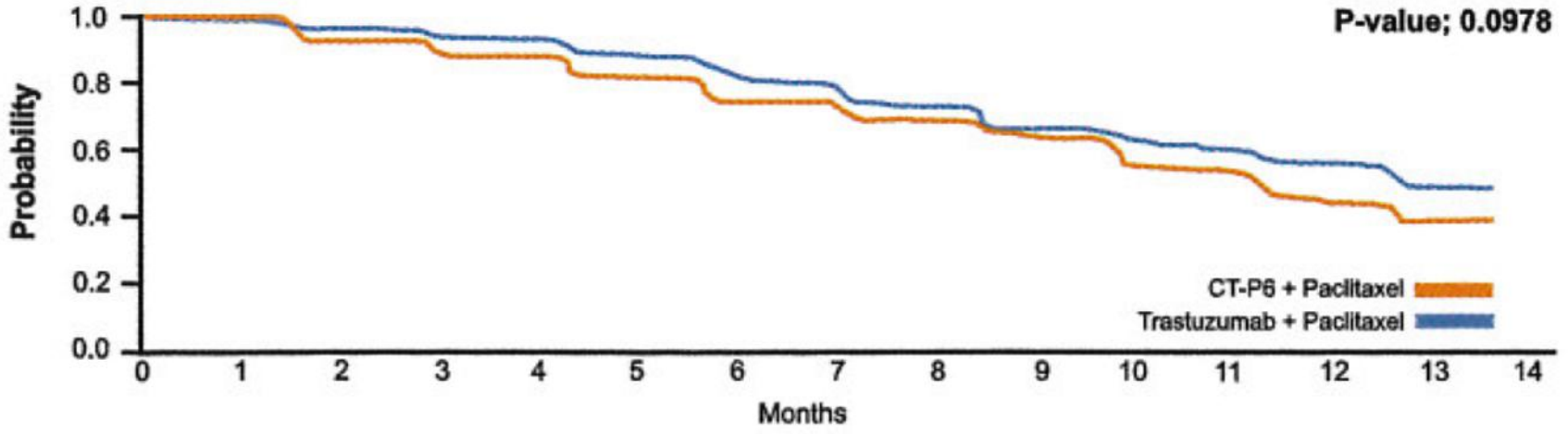


FAS = Full analysis set, PPS = per protocol patients set
Difference in proportion of complete response or partial response. Confidence interval estimated using the exact method

Y-H Im et al, ASCO 2013

Results: efficacy endpoints

Figure 3. Kaplan Meier plots of time to progression in the responder group by ITRC (Full analysis set, 1 year data)



Y-H Im et al, ASCO 2013

Results: safety endpoints

			CT-P6 + paclitaxel		Trastuzumab + paclitaxel		P value	
			All	≥ G3	All	≥ G3	All	≥ G3
Total serious adverse events (SAEs)			33	28	28	24	0.6477	0.7048
All adverse events (AEs)			224	110	214	107	0.7336	0.7865
Hematologic Events	Anaemia		187	10	180	4	0.7388	0.1274
	Neutropenia		142	81	140	82	0.5931	0.5975
	Thrombocytopenia		51	4	80	1	0.8431	0.1978
Non-hematologic events	Cardiotoxicity		15	6	14	3	0.9684	0.3539
	Infusion-related reaction/hypersensitivity		118	11	127	11	0.1492	0.8954
	Peripheral Neuropathy	sensorimotor	4	3	5	1	0.6748	0.3423
		Sensory	48	7	50	4	0.5954	0.4101
		Unspecified	63	14	56	13	0.6917	0.9587
	Nausea/vomiting		48	2	44	2	0.8633	0.9561
	Fatigue and/or Asthenia		73	5	63	3	0.5238	0.5252
	Diarrhoea		34	1	41	1	0.2545	0.9690
	Stomatitis		14	0	16	0	0.5645	NE
	Alopecia		122	0	127	3	0.2775	0.0741
	Myalgia		41	1	52	2	0.3836	0.5307
	Pain in extremity		22	2	29	6	0.2132	0.1323
	Arthralgia		21	0	30	0	0.1232	NE
	Infections		57	10	46	8	0.3622	0.7171
	ALT increased		156	8	161	5	0.1828	0.4569
	AST increased		155	8	142	3	0.6441	0.1516
	GGT increased		170	40	157	27	0.6881	0.1409
	ALP increased		149	11	150	9	0.3828	0.7399
	Creatinine increased		49	0	47	0	0.9428	NE
	Urea increased		73	NE	72	NE	0.7673	NE

Conclusions

- Equivalence of CT-P6 and trastuzumab was observed for efficacy:
  - ORR of CT-P6 + paclitaxel was equivalent to that of trastuzumab + paclitaxel during 8 cycles
  - TTP did not differ between the two arms
- CT-P6 was well tolerated with a safety profile comparable to that of trastuzumab


Grazie per l’attenzione