STUDIO GIM2

Commento sulla metodologia

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Obiettivi

- The study was aimed at assessing two separate hypotheses:
  - Efficacy and safety of 5-FU in addition to EC->T
  - Efficacy and safety of an increase in dose-density of CT

- Primary end point: Invasive Disease Free Survival (IDFS) (events: Invasive ipsilateral breast , local/regonal recurrence, distant recurrence, Death from any cause, invasive contralayteral BC, second primary invasive cancer non breast)

- Secondary end points: Overall Survival, toxicity

- The study was designed to detect a 20% relative reduction in the incidence of relapse, second tumor or death (OR=0.80). Assuming an α error of 0.05 (two sided) and a power of 0.80, 635 events were required (2000 pts with an average follow-up of 5.5-6 years)

FACTORIAL STUDY

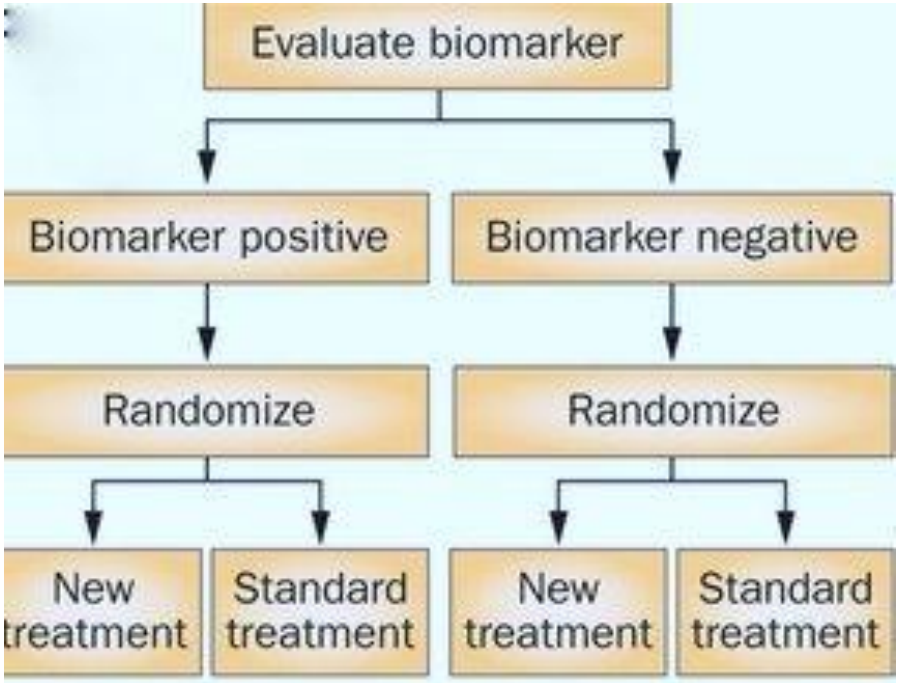
ARM A **EC x 4 cycles -> T x 4 cycles q3 wks**	**ARM C** **EC x 4 cycles -> T x 4 cycles q2 wks** **+ Pegfilgrastim**
ARM B **FEC x 4 cycles -> T x 4 cycles q3 wks**	**ARM D** **FEC x 4 cycles -> T x cycles 4 q2 wks** **+ Pegfilgrastim**

EC vs FEC

q3 wks vs q2 wks

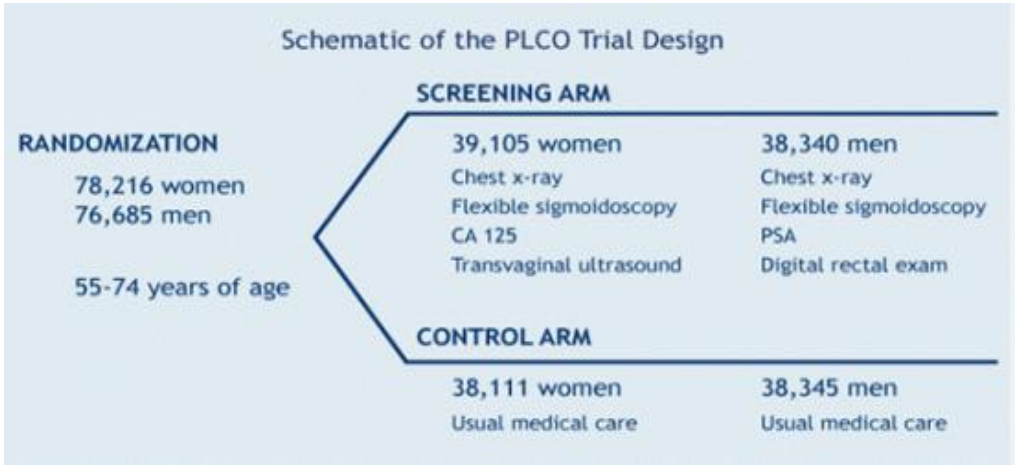
Validità del disegno

- Un disegno fattoriale è
  - un disegno in cui due o più variabili, o fattori, sono impiegate in modo che tutte le possibili combinazioni dei valori selezionati di ciascuna variabile sono utilizzati.
- Permette di rispondere a più quesiti simultaneamente
- Appropriato se
  - le interazioni sono poco probabili
  - al contrario, si vuole testare l'interazione



- Testa l'interazione
- Non tutti i fattori sono assegnati dalla randomizzazione

Disegni simili: biomarker stratified design



- I fattori sono assegnati dalla randomizzazione
- Non testa l'interazione
  - per ogni fattore uno specifico outcome

Disegni simili: reciprocal control design

- Analisi multiple
  - aumento degli errori α e β

- Bassa capacità di testare l'interazione
  - a parità di effetto
    - se per l'analisi principale potenza= 80%,
      per l'analisi di interazione potenza= 66%
  - a parità di potenza $N_{int}=4N_{princ}$

Factorial Design Considerations

By Stephanie Green, Ping-Yu Liu, and Janet O'Sullivan

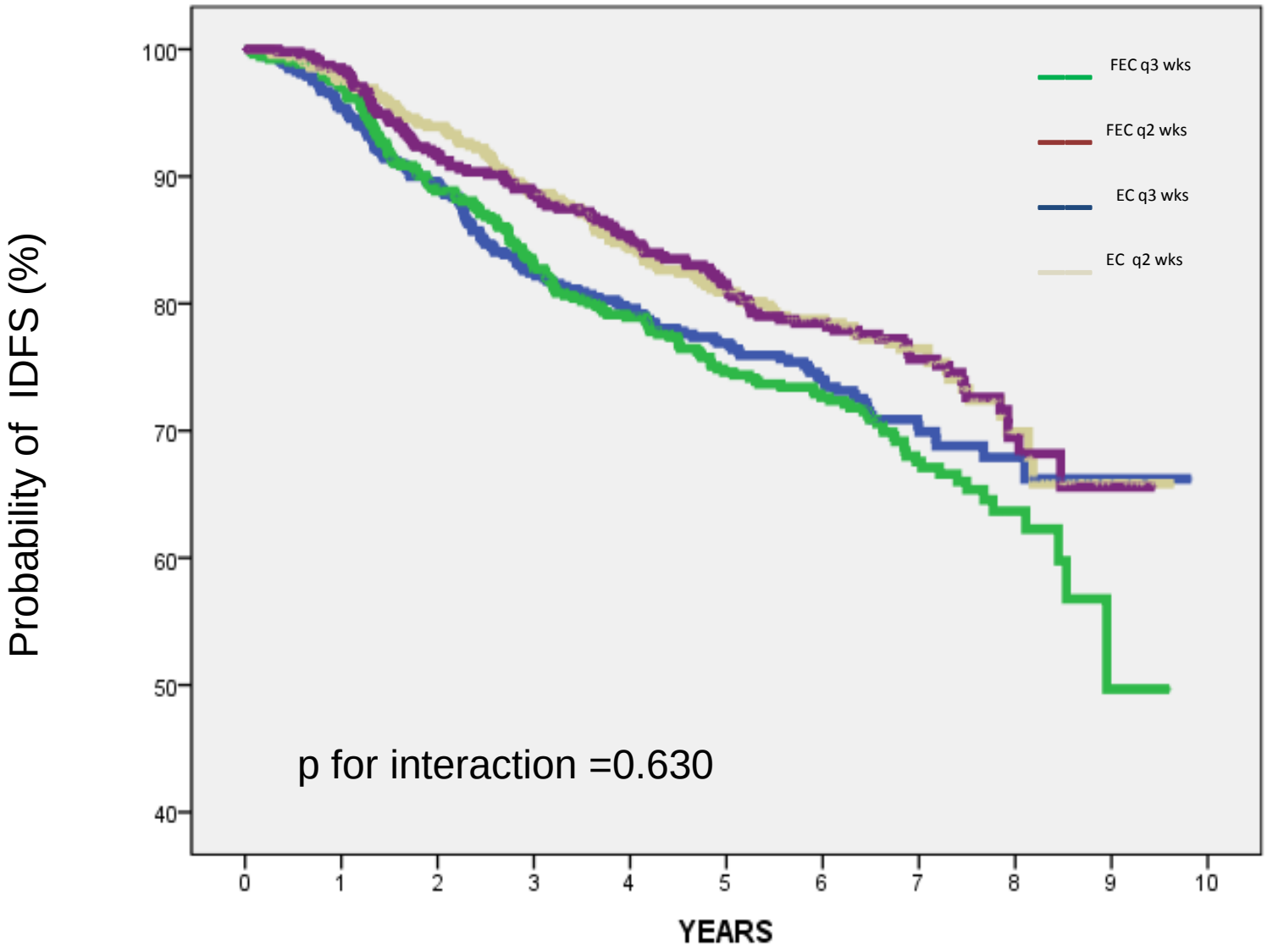
Journal of Clinical Oncology, Vol 20, No 16 (August 15), 2002: pp 3424-3430

Table 3. Probability of Correct Conclusion for the 12 Cases Summarized in Table 1*

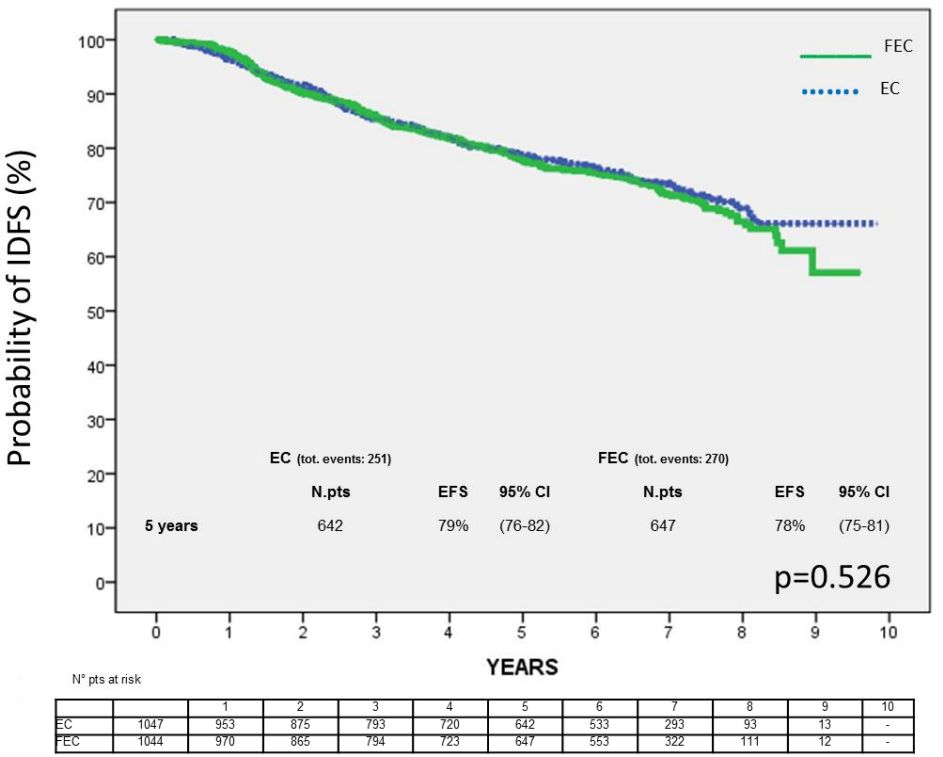
Case			Approach	Approach	Approach
Main Effect	Interaction	Best Arm	1	2	3
1: Neither CT alone nor RT alone	a: None—null case	O	0.890	0.865	0.972
effective compared with O	b. Unfavorable	O	0.999	0.914	0.926
	c: Favorable	CTRT	0.187	0.424	0.390
2: CT alone effective, RT alone not	a: None	CT	0.867	0.810	0.578
effective compared with O	b: Unfavorable	CT	0.437	0.601	0.432
	c: Favorable	CTRT	0.369	0.612	0.611
3: Each of CT alone and RT alone	a: None	CTRT	0.791	0.752	0.741
effective compared with O	b: Unfavorable	CT or RT	0.000	0.353	0.286
	c: Favorable	CTRT	0.985	0.990	0.990
4: CT alone effective, RT alone	a: None	CT	0.922	0.883	0.882
detrimental compared with O	b: Unfavorable	CT	0.422	0.659	0.659
	c: Favorable	CT	0.998	0.756	0.756

*Three approaches were used: approach 1, no test of interaction; approach 2, test of interaction; approach 3, global test followed by test of interaction. Probabilities were estimated based on 2,500 repetitions. All testing was performed at the 0.05 level except the test for interaction (0.10). All testing was one-sided except tests for CT v RT and interaction.

Risultati

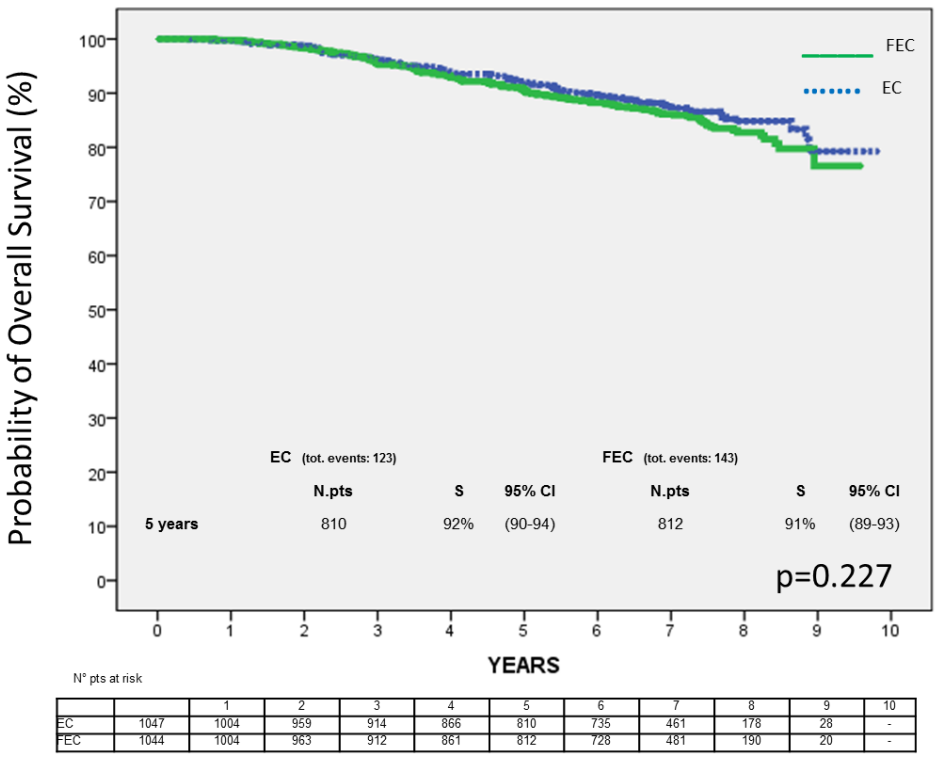


Interazione



N° pts at risk

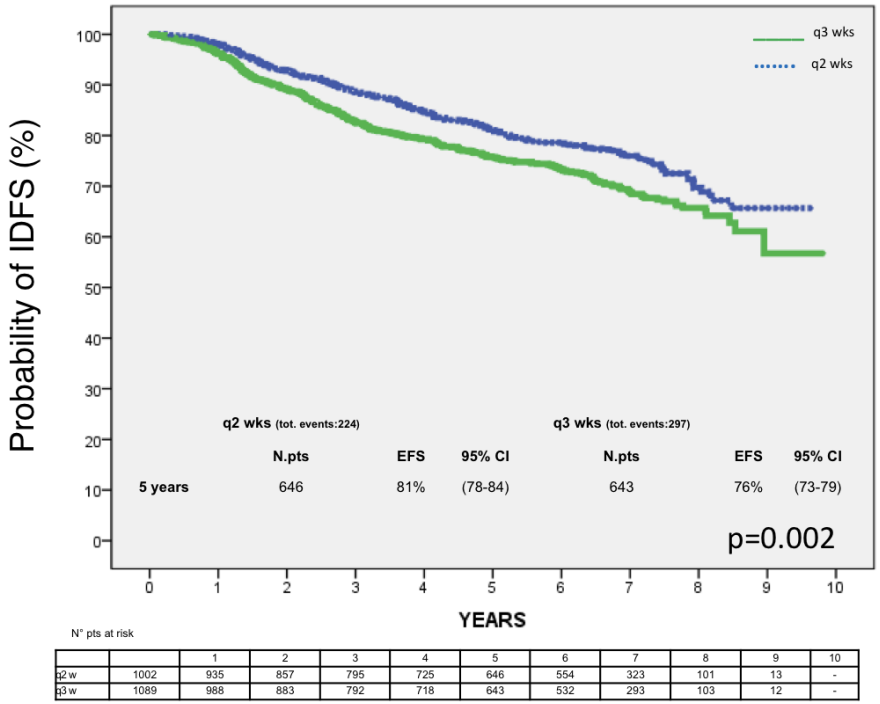
		1	2	3	4	5	6	7	8	9	10
EC	1047	953	875	793	720	642	533	293	93	13	-
FEC	1044	970	865	794	723	647	553	322	111	12	-



N° pts at risk

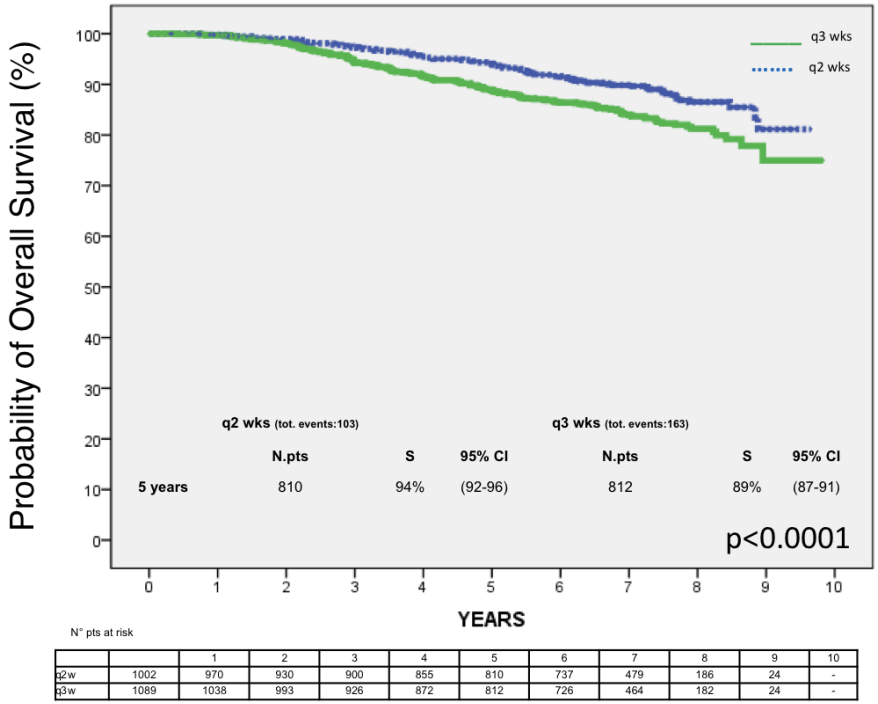
		1	2	3	4	5	6	7	8	9	10
EC	1047	1004	959	914	866	810	735	461	178	28	-
FEC	1044	1004	963	912	861	812	728	481	190	20	-

Effetti principali EC vs. FEC



N° pts at risk

		1	2	3	4	5	6	7	8	9	10
q2 w	1002	935	857	795	725	646	554	323	101	13	-
q3 w	1089	988	883	792	718	643	532	293	103	12	-

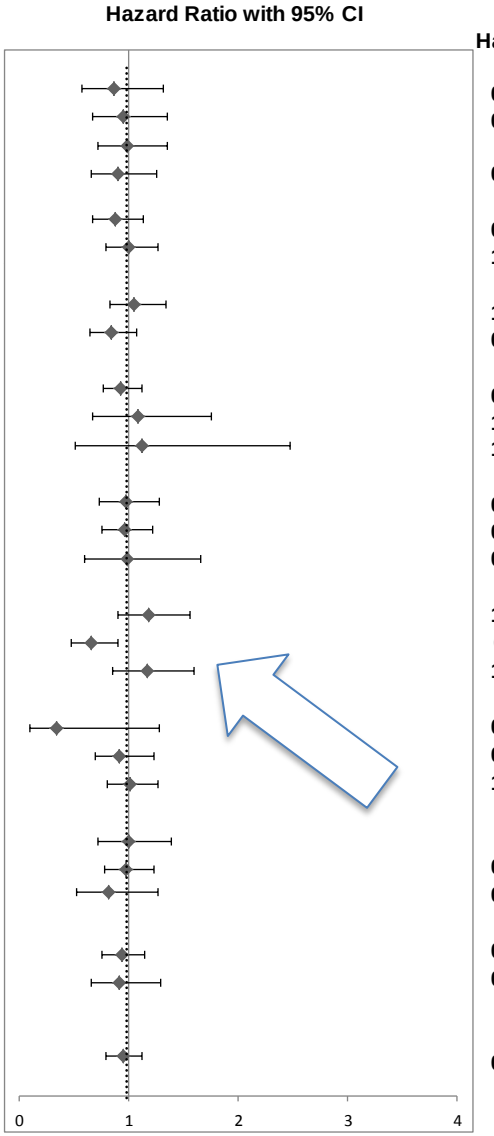


N° pts at risk

		1	2	3	4	5	6	7	8	9	10
q2 w	1002	970	930	900	855	810	737	479	186	24	-
q3 w	1089	1038	993	926	872	812	726	464	182	24	-

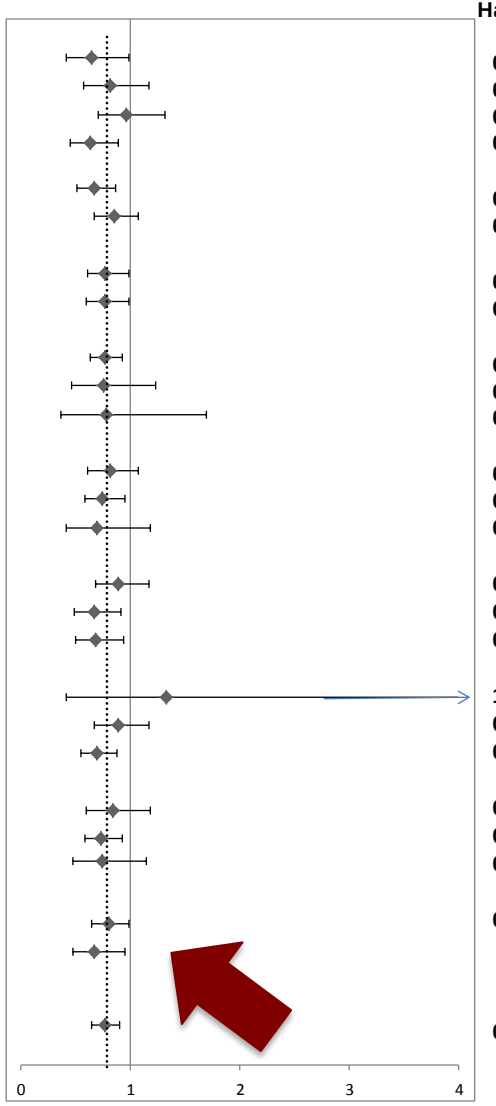
Effetti principali q14 vs. q21

	IDFS	recurrences/patients (%) EC	%	FEC	%	Hazard ratio (95% CI)	p for interaction
AGE GROUP	<40	44/146	30,1	45/132	34,1	0,867 (0,571-1,317)	0,958
	40-49	61/321	19,0	65/307	21,2	0,957 (0,674-1,358)	
	50-59	77/337	22,8	81/345	23,5	0,99 (0,725-1,354)	
	60+	69/243	28,4	79/260	30,4	0,906 (0,655-1,252)	
MENOPAUSAL STATUS	Pre	108/513	21,1	125/508	24,6	0,874 (0,675-1,131)	0,426
	Post	143/534	26,8	145/536	27,1	1,002 (0,795-1,263)	
TYPE of SURGERY	Conservative	140/636	22,0	136/633	21,5	1,055 (0,833-1,336)	0,196
	Mastectomy	111/411	27,0	134/411	32,6	0,837 (0,650-1,077)	
HISTOLOGIC TYPE	Invasive ductal carcinoma	203/845	24,0	223/847	26,3	0,925 (0,765-1,119)	0,742
	Invasive lobular carcinoma	32/118	27,1	37/140	26,4	1,091 (0,676-1,759)	
	Other	16/84	19,0	10/57	17,5	1,125 (0,510-2,479)	
TUMOR SIZE	T1	98/545	18,0	99/515	19,2	0,972 (0,735-1,285)	0,994
	T2	127/420	30,2	138/441	31,3	0,962 (0,756-1,224)	
	T3-T4	26/75	34,7	33/86	38,4	0,993 (0,593-1,662)	
N° of POSITIVE NODES	1-3	113/646	17,5	92/603	15,3	1,189 (0,903-1,566)	0,011
	4-9	62/251	24,7	99/271	36,5	0,661 (0481-0,908)	
	≥10	76/150	50,7	79/170	46,5	1,166 (0,851-1,597)	
HISTOLOGIC GRADE	Grade 1	3/69	4,3	9/68	13,2	0,347 (0,094-1,281)	0,19
	Grade 2	94/461	20,4	109/478	22,8	0,912 (0,692-1,203)	
	Grade 3	153/510	30,0	149/493	30,2	1,008 (0,804-1,263)	
HER2 STATUS	HER2+	66/228	28,6	73/252	29,0	1 (0,716-1,395)	0,736
	HER2-	150/662	22,7	150/631	23,8	0,979 (0,781-1,228)	
	Unknown	35/157	22,3	47/161	29,2	0,818 (0,528-1,268)	
HORMONAL RECEPTORS	ER+ and/or PR+	175/827	21,2	197/843	23,4	0,936 (0,763-1,148)	0,92
	ER- and PR-	68/186	36,6	65/173	37,6	0,919 (0,654-1,293)	
IDFS		251/1047	23,9	270/1044	25,8	0,947 (0,797-1,124)	



Analisi di sottogruppi EC vs FEC

	IDFS	recurrences/patients (%) q2 wks	%	q3 wks	%	Hazard ratio (95% CI)	p for interaction
AGE GROUP	<40	34/128	26,6	55/150	36,7	0,644 (0,419-0,991)	0,242
	40-49	57/305	18,7	69/323	21,4	0,822 (0,578-1,167)	
	50-59	80/343	23,3	78/339	23,0	0,961 (0,703-1,314)	
	60+	53/226	23,5	95/277	34,3	0,635 (0,454-0,889)	
MENOPAUSAL STATUS	Pre	96/495	19,4	137/526	26,0	0,667 (0,514-0,866)	0,171
	Post	128/507	25,2	160/563	28,4	0,854 (0,677-1,078)	
TYPE of SURGERY	Conservative	120/611	19,6	156/658	23,7	0,775 (0,610-0,983)	0,919
	Mastectomy	104/391	26,6	141/431	32,7	0,765 (0,594-0,987)	
HISTOLOGIC TYPE	Invasive ductal carcinoma	181/793	22,8	245/899	27,3	0,768 (0,634-0,931)	0,997
	Invasive lobular carcinoma	30/129	23,3	39/129	30,2	0,761 (0,470-1,230)	
	Other	13/80	16,2	13/61	21,3	0,784 (0,363-1,692)	
TUMOR SIZE	T1	88/515	17,1	109/545	20,0	0,814 (0,615-1,079)	0,849
	T2	113/410	27,6	152/451	33,7	0,748 (0,587-0,955)	
	T3-T4	23/73	31,5	36/88	40,9	0,702 (0,415-1,186)	
N° of POSITIVE NODES	1-3	96/603	15,9	109/646	16,9	0,893 (0,679-1,175)	0,301
	4-9	65/251	25,9	96/271	35,4	0,666 (0,486-0,913)	
	≥10	63/148	42,6	92/172	53,5	0,684 (0,496-0,944)	
HISTOLOGIC GRADE	Grade 1	7/77	9,1	5/60	8,3	1,332 (0,421-4,211)	0,29
	Grade 2	97/465	20,9	106/474	22,4	0,890 (0,675-1,172)	
	Grade 3	118/453	26,0	184/550	33,5	0,697 (0,553-0,878)	
HER2 STATUS	HER2+	62/226	27,4	77/254	30,3	0,843 (0,603-1,178)	0,8
	HER2-	125/617	20,3	175/676	25,9	0,738 (0,586-0,928)	
	Unknown	37/159	23,3	45/159	28,3	0,743 (0,481-1,149)	
HORMONAL RECEPTORS	ER+ and/or PR+	165/808	20,4	207/862	24,0	0,801 (0,653-0,983)	0,339
	ER- and PR-	53/168	31,5	80/191	41,9	0,67 (0,473-0,949)	
IDFS		224/1002	22,4	297/1089	27,3	0,764 (0,642-0,909)	



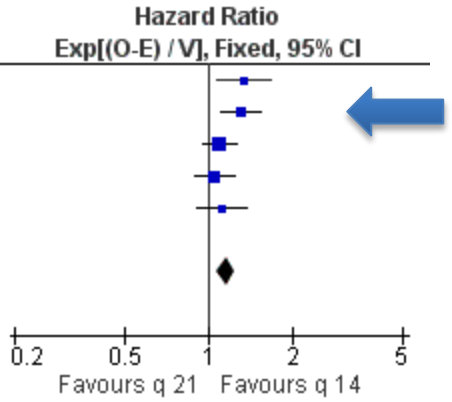
Analisi di sottogruppi q14 vs q21

Il contesto

RFS

Study or Subgroup	q 14 Events	q 14 Total	q 21 Events	q 21 Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Citron 2003	136	988	179	985	22.64	78.75	12.5%	1.33 [1.07, 1.66]
GIM2 2013	224	1002	297	1089	34.92	130.25	20.7%	1.31 [1.10, 1.55]
Linden 2007	358	1523	407	1590	17.69	191.25	30.4%	1.10 [0.95, 1.26]
TACT2 2012	282	2200	271	2200	6.17	138.25	22.0%	1.05 [0.89, 1.24]
Venturini 2005	168	604	191	610	9.6	89.75	14.3%	1.11 [0.90, 1.37]
Total (95% CI)		**6317**		**6474**			**100.0%**	**1.16 [1.07, 1.25]**
Total events	1168		1345					

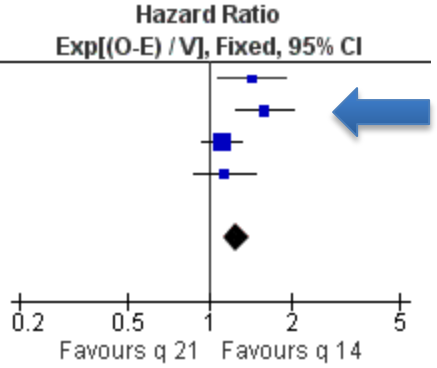
Heterogeneity: Chi² = 5.62, df = 4 (P = 0.23); I² = 29%
Test for overall effect: Z = 3.63 (P = 0.0003)



OS

Study or Subgroup	q 14 Events	q 14 Total	q 21 Events	q 21 Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Citron 2003	75	988	107	985	16.49	45.5	15.4%	1.44 [1.07, 1.92]
GIM2 2013	103	1002	163	1089	30.91	66.5	22.5%	1.59 [1.25, 2.02]
Linden 2007	237	1523	274	1590	12.97	127.75	43.3%	1.11 [0.93, 1.32]
Venturini 2005	104	604	118	610	6.95	55.5	18.8%	1.13 [0.87, 1.47]
Total (95% CI)		**4117**		**4274**			**100.0%**	**1.26 [1.12, 1.41]**
Total events	519		662					

Heterogeneity: Chi² = 7.18, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 3.92 (P < 0.0001)



Conclusioni

- Validità buona
  - potenza forse un po’ bassa per l’interazione
  - indicatori primari potenzialmente suscettibili di bias operativi
- Generalizzabilità dei risultati buona
- Risultati rilevanti per il quesito dose-density
- Consistenza con dati esterni