bjclub breast Journal Club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

20 - 21 APRILE
2023 ROMA

THE HIVE HOTEL

Via Torino, 6

THE OXFORD DEBATE EDITION

DOSE-DENSE CHEMOTHERAPY IN ADJUVANT TREATMENT OF PATIENTS WITH EARLY-STAGE BREAST CANCER: END-OF-STUDY RESULTS FROM A RANDOMISED, PHASE 3 TRIAL OF THE GRUPPO ITALIANO MAMMELLA (GIM)

L. Del Mastro, F. Poggio, E. Blondeaux, S. De Placido, M. Giuliano, M. De Laurentiis, G. Bisagni, M. Cantore, A. Turletti, C. Nisticò, Y. Urracci, O. Garrone, C. Bighin, M. Mansutti, F. Montemurro, G. Colantuoni, M. Lambertini, L. Boni on behalf of GIM group

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

Gruppo Italiano Mammella GIM

UNIVERSITÀ DEGLI STUDI DI GENOVA

Disclosure

Relationship	**Company/Organization**
Honorary, consultancy or advisory role (last 2 years)	Roche – Novartis – Pfizer – Celgene – Takeda – Ipsen – MSD – Eisai – Eli Lilly – Seagen– Daiichi Sankyo – Gilead – Exact Sciences – Pierre Fabre – Astrazeneca – GSK - Agendia

Background

- At the time of GIM2 study design (2003) but still nowadays the role of 5-fluorouracil in addition to EC/AC, was controversial. Both AC or EC and FAC or FEC used in sequential combination with taxanes are considered acceptable regimens by ASCO guidelines[1] , whilst ESMO guidelines indicate that 5-fluorouracil can be dropped from anthracycline-based regimens[2]

- Despite dose-dense chemotherapy reduces both recurrence and breast cancer mortality in high-risk early breast cancer patients, some international guidelines yet do not consider it as the optimal chemotherapy schedule to be proposed to the majority of high risk patients [1,2].

- GIM2 study at a median FU of 7.0 years showed that, in node-positive patients, addition of 5-fluorouracil to a sequential EC-P regimen does not improve efficacy, whilst 2-weekly dose-dense chemotherapy significantly improves both DFS and OS compared to 3-weekly schedule[3]

- Here we report the long-term results of the GIM2 study at a median follow up of 15.2 years

1. Denduluri N.. J Clin Oncol 34; 2016; 2. Cardoso F. Annals of Oncology 30: 1194–1220, 2019; 3. Del Mastro L. Lancet 2015; 385: 1863–72

Study design: FACTORIAL

ARM A **EC x 4 cycles -> T x 4** **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

N+ early breast cancer patients = **2091**
HR+ or HR- tumors
HER2+ or HER2 - tumors

EC- Epirubicin 90 mg/m² IV bolus, Cyclophosphamide 600 mg/m² IV bolus, every 2 or 3 weeks
T - Paclitaxel 175 mg/m² IV 3-hour infusion, every 2 or 3 weeks
FEC - Fluorouracil 600 mg/m² IV bolus, Epirubicin 90 mg/m² IV bolus, Cyclophosphamide 600 mg/m² IV bolus, every 2 or 3 weeks.

Primary end point: **DFS**
Secondary end points: **OS and safety**

Study hypotheses and sample size

- We assumed that the minimum therapeutic effect worth detecting in this study, in view of the increased toxicity associated with the experimental treatments, was a 20% relative reduction in DFS (hazard ratio[HR]=0·80), corresponding to a 4.4% absolute increase in 5-year DFS. To detect with an 80% power and a significance 5% (two-sided), a 20% relative reduction in the risk of relapse in either comparison (EC-P vs FEC-P and dose-dense vs standard interval chemotherapy), 635 DFS events had to be observed. We estimated that to observe 635 events, 2000 patients had to be enrolled with an average follow-up of 5.5–6 years.

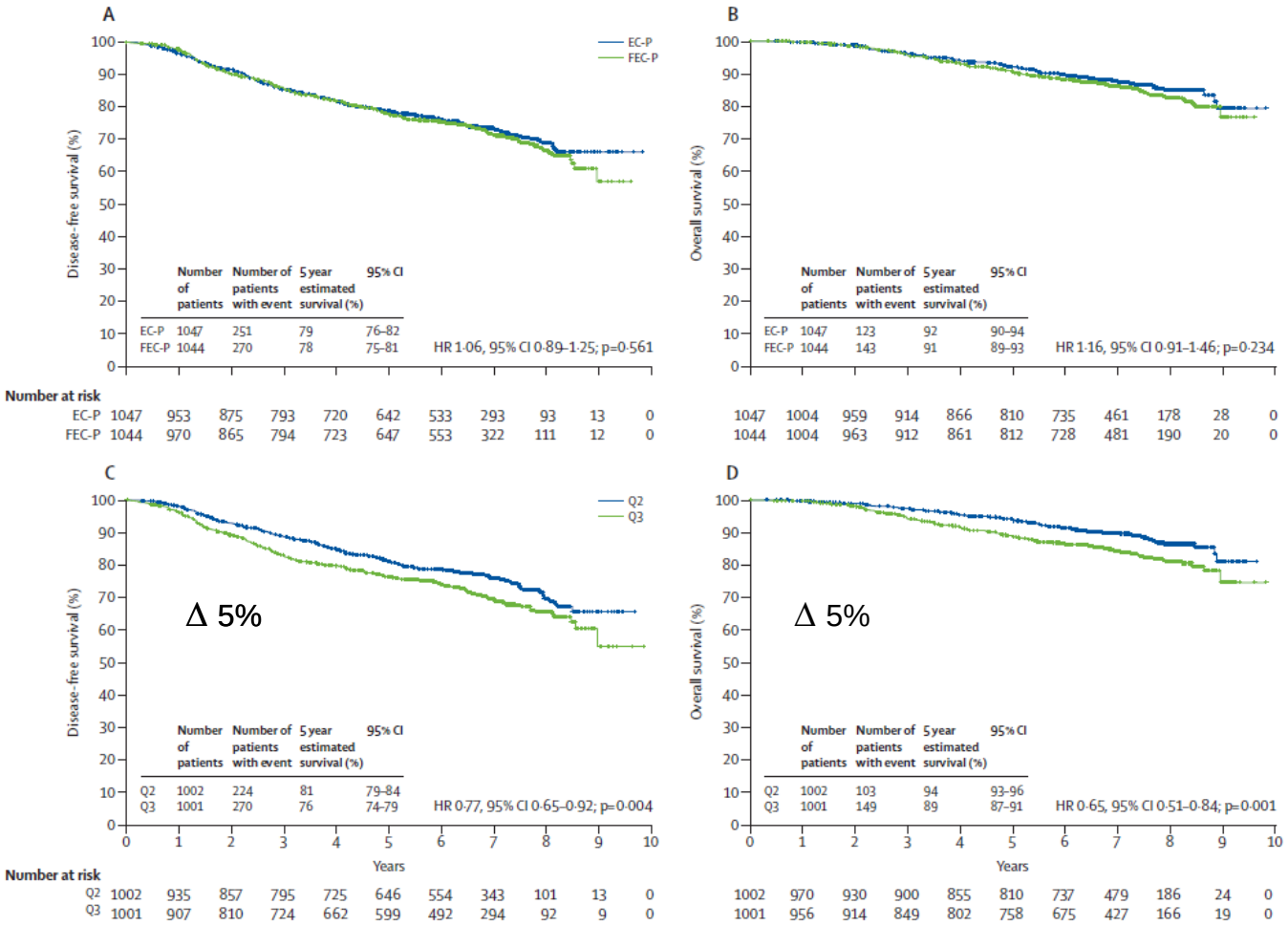
- The two primary comparisons were between FEC-P and EC-P, and between dose-dense and standard-interval chemotherapy. All statistical analyses were done on an intention-to-treat basis.

- The presence of an interaction between the two study factors (FEC-P vs EC-P) and dosing every 2 weeks vs every 3 weeks) was assessed by fitting two multivariate Cox models to the data, one for DFS and the other for OS

Patient characteristics

	q3 EC->P *N*=545 (%)	**q3 FEC->P** *N*=544 (%)	**q2 EC->P** *N*=502 (%)	**q2 FEC->P** *N*=500 (%)
Median age at randomization (IQR, years)	51 (43–60)	53 (45–61)	53 (44–59)	51 (44–59)
Nodal status				
N1	327 (60.0)	319 (58.6)	319 (63.6)	284 (56.8)
N2	**135 (24.8)**	**136 (25.0)**	**116 (23.1)**	**135 (27.0)**
N3	**83 (15.2)**	**89 (16.4)**	**67 (13.4)**	**81 (16.2)**
Tumor grade				
G1	30 (5.5)	21 (3.9)	35 (7.0)	30 (6.0)
G2	236 (43.3)	238 (43.8)	225 (44.8)	240 (48.0)
G3	**270 (49.5)**	**266 (48.9)**	**229 (45.6)**	**214 (42.8)**
Unknown	9 (1.7)	19 (3.5)	13 (2.6)	16 (3.2)
HER2 status				
Negative	344 (63.1)	332 (61.0)	318 (63.4)	299 (59.8)
Positive	**123 (22.6)**	**131 (24.1)**	**105 (20.9)**	**121 (24.2)**
Unknown	78 (14.3)	81 (14.9)	79 (15.7)	80 (16.0)
Hormone receptor status				
Negative	**103 (18.9)**	**88 (16.2)**	**83 (16.5)**	**85 (17.0)**
Positive	420 (77.1)	442 (81.3)	407 (81.1)	401 (80.2)
Unknown	22 (4.0)	14 (2.6)	12 (2.4)	14 (2.8)

Median follow up: 7.0 years

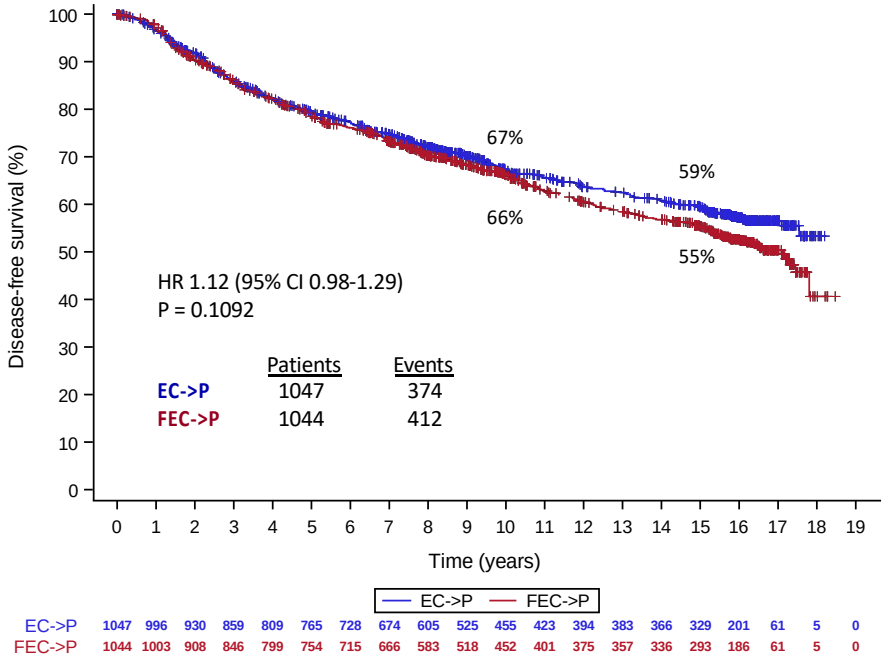


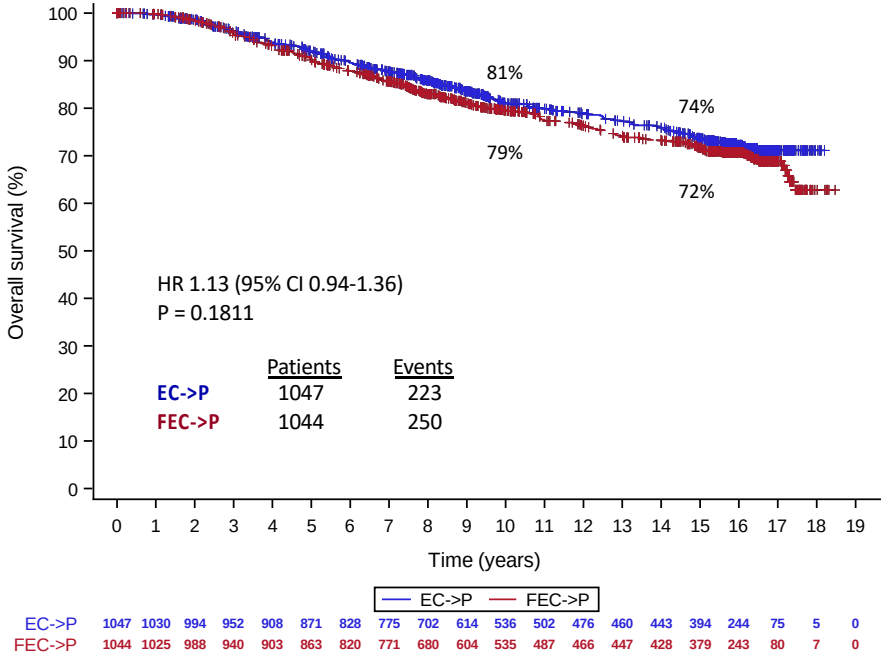
Del Mastro L. Lancet 2015; 385: 1863–72

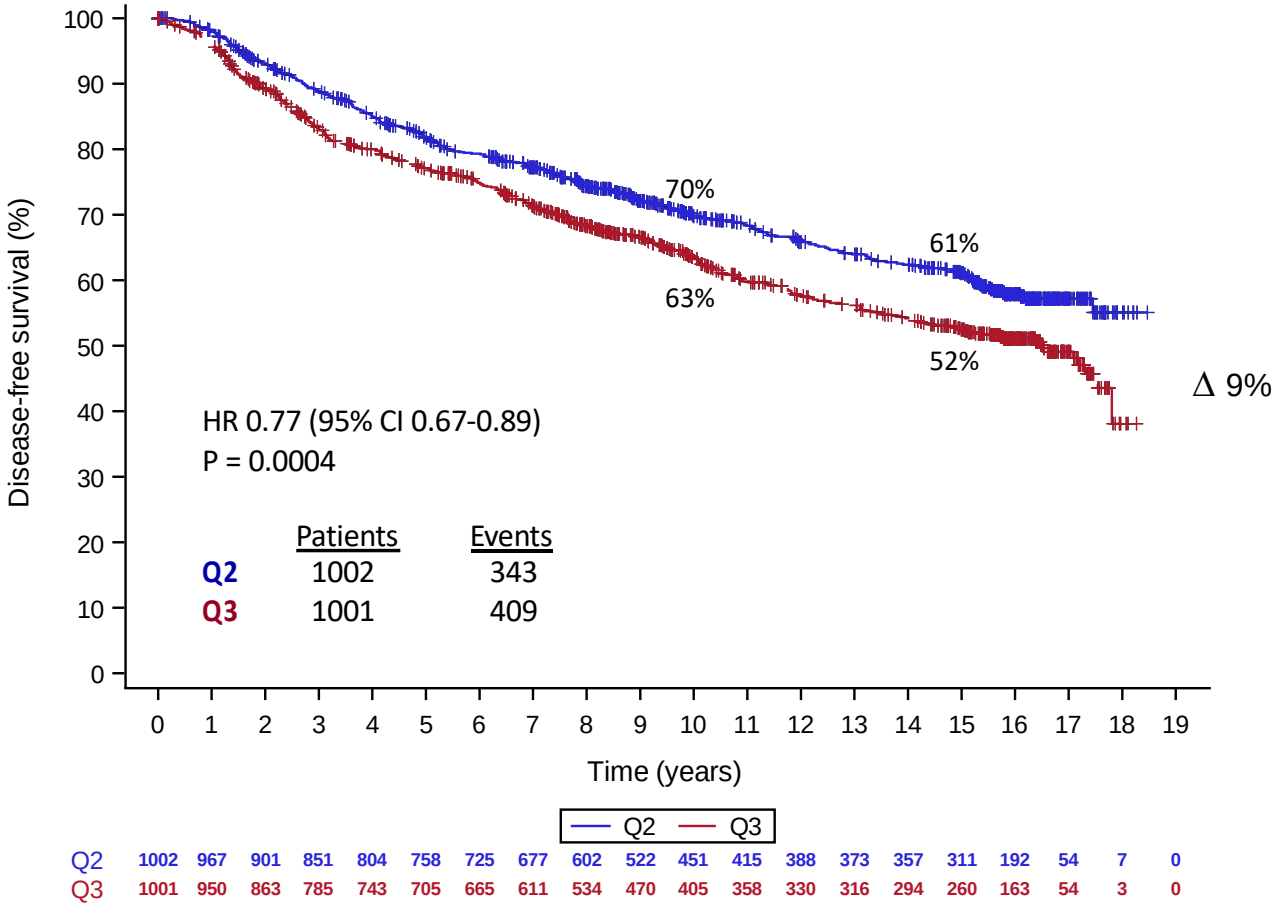
Median follow up 15.2 years

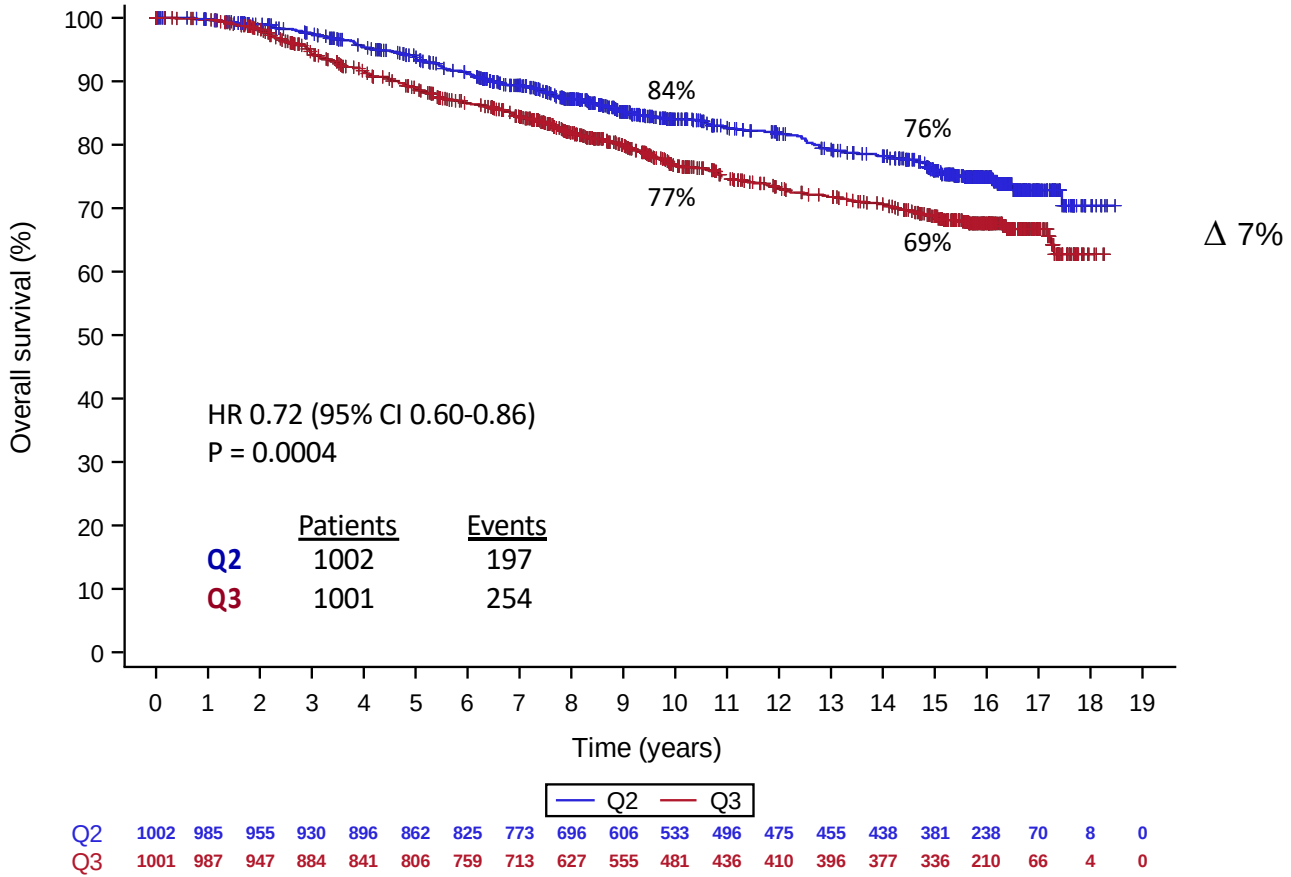
	q3 EC->P N=545 (%)	q3 FEC->P N=544 (%)	q2 EC->P N=502 (%)	q2 FEC->P N=500 (%)
No DFS event	340 (62.4)	306 (56.3)	333 (66.3)	326 (65.2)
DFS event*	205 (37.6)	238 (43.8)	169 (33.7)	174 (34.8)
Locoregional alone relapse	26 (4.8)	25 (4.6)	21 (4.2)	15 (3.0)
Distant relapse	116 (21.3)	139 (25.6)	91 (18.1)	93 (18.6)
Concurrent locoregional and distant relapse	5 (0.9)	7 (1.3)	5 (1.0)	6 (1.2)
Unknown site of relapse	3 (0.6)	0 (0.0)	3 (0.6)	0 (0.0)
Second Primary breast cancer	12 (2.2)	27 (5.0)	12 (2.4)	14 (2.8)
Second primary, non-breast cancer	21 (3.9)	15 (2.8)	15 (3.0)	27 (5.4)
Death without relapse	22 (4.0)	25 (4.6)	22 (4.4)	19 (3.8)
Overall survival events	126 (23.1)	150 (27.6)	97 (19.3)	100 (20.0)

Type of second primary	Second primary non-breast cancer N=78 (%)
Lung cancer	14 (17.9)
Colon-rectal cancer	11 (14.1)
Melanoma	8 (10.2)
Endometrial cancer	6 (7.7)
Ovarian cancer	5 (6.4)
Pancreatic cancer	4 (5.1)
Urothelial cancer	4 (5.1)
Unknown site	4 (5.1)
Leukemia	4 (5.1)
Angiosarcoma	3 (3.8)
Gist	2 (2.6)
Biliary cancer	2 (2.6)
Brain tumours	3 (3.8)
Adrenal carcinoma	1 (1.3)
Thyroid cancer	1 (1.3)
Cervical cancer	1 (1.3)
Gastric cancer	1 (1.3)
Thymoma	1 (1.3)
Head and neck cancer	1 (1.3)
Uterine leiomyosarcoma	1 (1.3)
Vulvar cancer	1 (1.3)

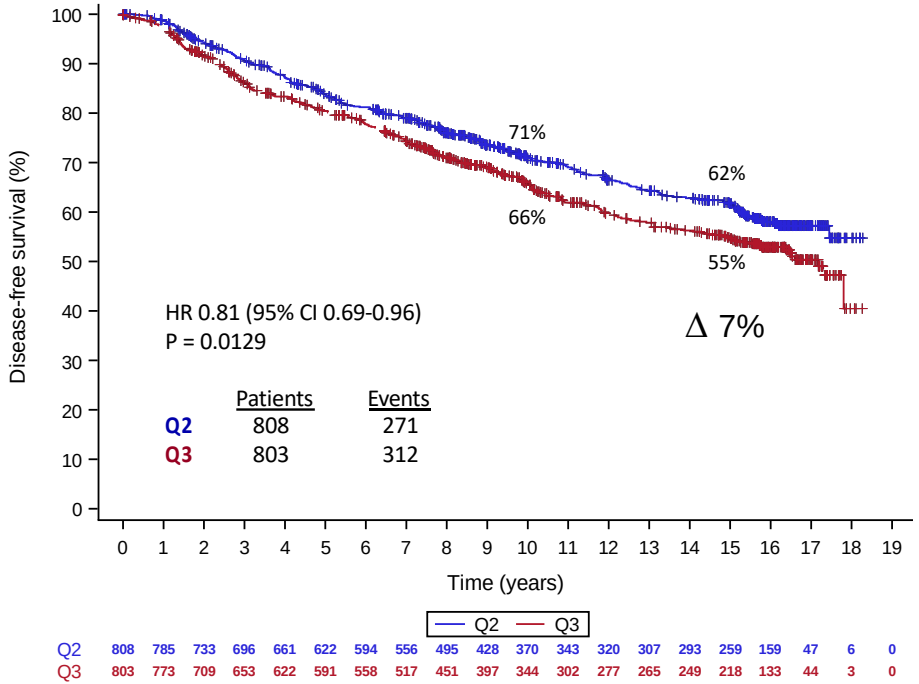

Disease-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Time (years)
67%
66%
59%
55%
HR 1.12 (95% CI 0.98-1.29)
P = 0.1092
Patients Events
EC->P 1047 374
FEC->P 1044 412
EC->P FEC->P
EC->P 1047 996 930 859 809 765 728 674 605 525 455 423 394 383 366 329 201 61 5 0
FEC->P 1044 1003 908 846 799 754 715 666 583 518 452 401 375 357 336 293 186 61 5 0


Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Time (years)
81%
79%
74%
72%
HR 1.13 (95% CI 0.94-1.36)
P = 0.1811
Patients Events
EC->P 1047 223
FEC->P 1044 250
EC->P FEC->P
EC->P 1047 1030 994 952 908 871 828 775 702 614 536 502 476 460 443 394 244 75 5 0
FEC->P 1044 1025 988 940 903 863 820 771 680 604 535 487 466 447 428 379 243 80 7 0

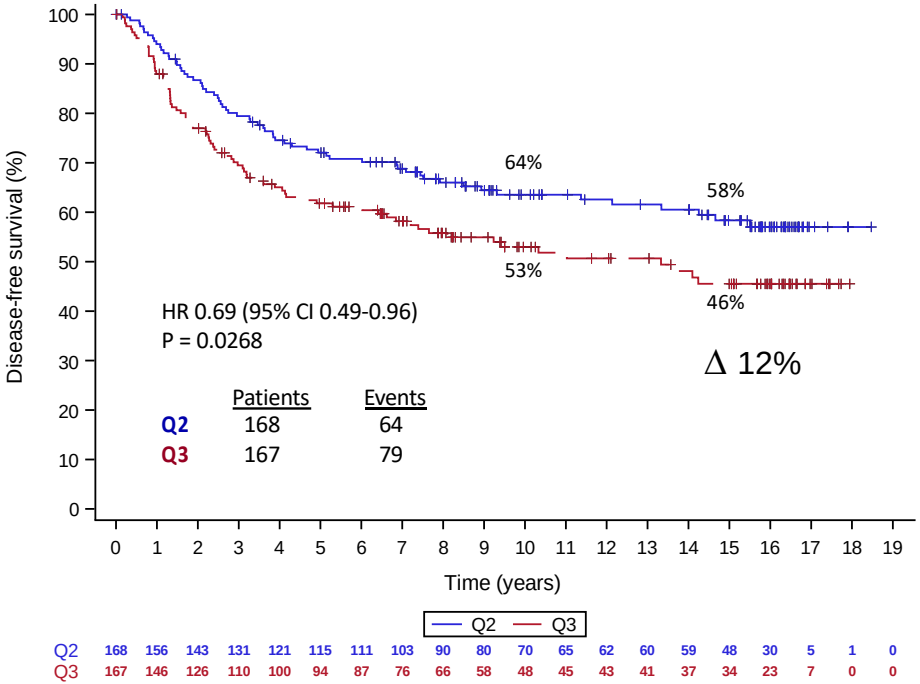

Disease-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
70%
61%
63%
52%
Δ 9%
HR 0.77 (95% CI 0.67-0.89)
P = 0.0004
Patients
Events
Q2
1002
343
Q3
1001
409
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Time (years)
Q2
Q3
Q2 1002 967 901 851 804 758 725 677 602 522 451 415 388 373 357 311 192 54 7 0
Q3 1001 950 863 785 743 705 665 611 534 470 405 358 330 316 294 260 163 54 3 0


Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
84%
76%
77%
69%
Δ 7%
HR 0.72 (95% CI 0.60-0.86)
P = 0.0004
Patients
Events
Q2
1002
197
Q3
1001
254
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Time (years)
Q2
Q3
Q2 1002 985 955 930 896 862 825 773 696 606 533 496 475 455 438 381 238 70 8 0
Q3 1001 987 947 884 841 806 759 713 627 555 481 436 410 396 377 336 210 66 4 0

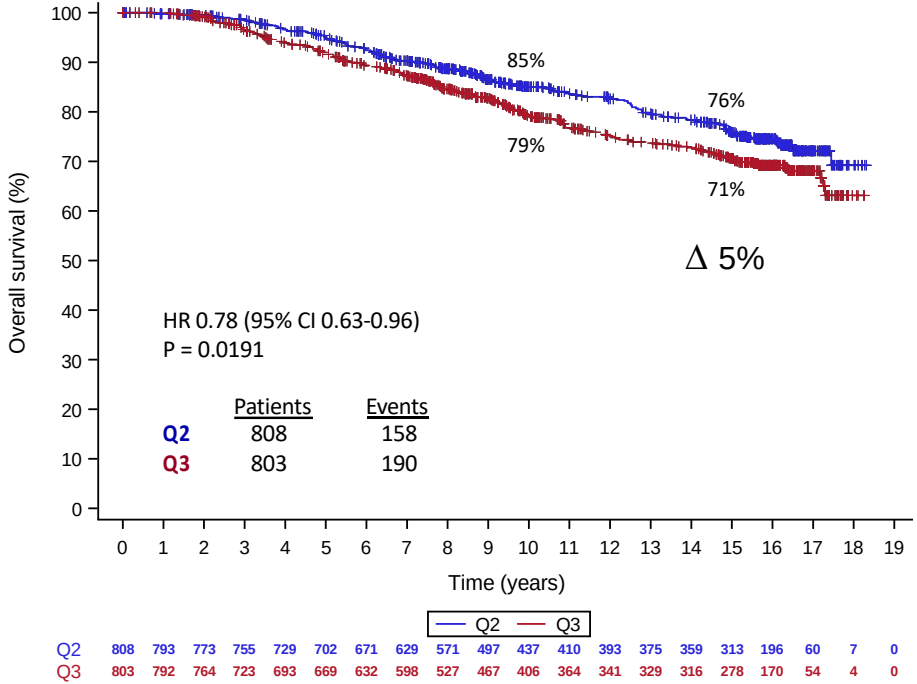
HR+


Disease-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
71%
62%
66%
55%
HR 0.81 (95% CI 0.69-0.96)
P = 0.0129
Δ 7%
Patients
Events
Q2 808 271
Q3 803 312
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Time (years)
Q2
Q3
Q2 808 785 733 696 661 622 594 556 495 428 370 343 320 307 293 259 159 47 6 0
Q3 803 773 709 653 622 591 558 517 451 397 344 302 277 265 249 218 133 44 3 0

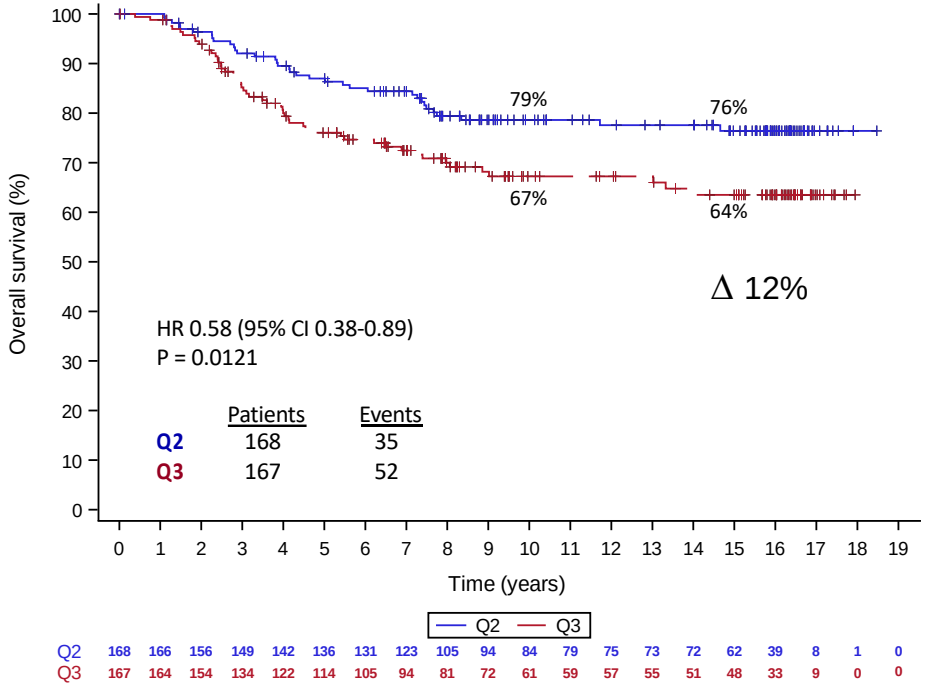
HR-


Disease-free survival (%)
100
90
80
70
60
50
40
30
20
10
0
64%
58%
53%
46%
HR 0.69 (95% CI 0.49-0.96)
P = 0.0268
Δ 12%
Patients
Events
Q2 168 64
Q3 167 79
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Time (years)
Q2
Q3
Q2 168 156 143 131 121 115 111 103 90 80 70 65 62 60 59 48 30 5 1 0
Q3 167 146 126 110 100 94 87 76 66 58 48 45 43 41 37 34 23 7 0 0

HR+


Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
85%
76%
79%
71%
Δ 5%
HR 0.78 (95% CI 0.63-0.96)
P = 0.0191
Patients
Events
Q2 808 158
Q3 803 190
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Time (years)
Q2 Q3
Q2 808 793 773 755 729 702 671 629 571 497 437 410 393 375 359 313 196 60 7 0
Q3 803 792 764 723 693 669 632 598 527 467 406 364 341 329 316 278 170 54 4 0

HR-


Overall survival (%)
100
90
80
70
60
50
40
30
20
10
0
79%
76%
67%
64%
Δ 12%
HR 0.58 (95% CI 0.38-0.89)
P = 0.0121
Patients
Events
Q2 168 35
Q3 167 52
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Time (years)
Q2 Q3
Q2 168 166 156 149 142 136 131 123 105 94 84 79 75 73 72 62 39 8 1 0
Q3 167 164 154 134 122 114 105 94 81 72 61 59 57 55 51 48 33 9 0 0

Conclusions

- **At a median follow up of 15.2 years GIM2 study**
  - **Confirms that in women with node-positive early breast cancer the addition of 5-fluorouracil to EC-P regimen does not improve DFS and OS**
  - **Confirms the huge, long-lasting benefit of dose-dense chemotherapy as compared to standard interval chemotherapy, with a 15-year absolute benefit of 9% in terms of DFS and 7% in terms of OS**

- **The benefit of dose-dense chemotherapy was observed in both HR+ (15-year absolute benefit of 7% in terms of DFS and 5% in terms of OS) and HR- tumors (15-year absolute benefit of 13% interms of both DFS and OS)**

- **Dose-dense chemotherapy should be considered the optimal regimen to propose to N+ breast cancer patients candidates for adjuvant chemotherapy, irrespective of the hormone receptor status of the disease**

Fluorouracil and dose-dense adjuvant chemotherapy in patients with early-stage breast cancer (GIM2): end-of-study results from a randomised, phase 3 trial

*Lucia Del Mastro, Francesca Poggio, Eva Blondeaux, Sabino De Placido, Mario Giuliano, Valeria Forestieri, Michelino De Laurentiis, Adriano Gravina, Giancarlo Bisagni, Anita Rimanti, Anna Turletti, Cecilia Nisticò, Angela Vaccaro, Francesco Cognetti, Alessandra Fabi, Simona Gasparro, Ornella Garrone, Maria Grazia Alicicco, Ylenia Urracci, Mauro Mansutti, Paola Poletti, Pierpaolo Correale, Claudia Bighin, Fabio Puglisi, Filippo Montemurro, Giuseppe Colantuoni, Matteo Lambertini, Luca Boni, on behalf of the Gruppo Italiano Mammella Investigators**

Lancet Oncol 2022; 23: 1571–82

Fluorouracil and dose-dense adjuvant chemotherapy in breast cancer: lessons learned from the 20-year-old GIM2 trial

*Stefania Morganti, *Sara M Tolaney*
sara_tolaney@dfci.harvard.edu

Despite these limitations, the 15 years of follow-up reported provides a rare opportunity to learn about long-term toxicity from chemotherapy. No further severe adverse events were observed, although cardiotoxicity data were not collected. 78 (4%) patients developed a secondary, non-breast malignancy, mostly colon and lung cancers, with only four cases of leukaemia. Comparing standard and dose-dense chemotherapy, there were no differences in terms of second primary cancers, death without recurrence, or chemotherapy-induced amenorrhea.

Acknowledgements

- **We thank patients, physicians, nurses, and trial coordinators who participate in the GIM2 trial.**

- **We acknowledge Giovanni Cucchiara and Carlo Panzano of Clinical Research Technology, Salerno, Italy, for clinical record online management. Simona Pastorino and Annalisa Abate provided all the technical assistance and computer work for statistical analyses.**

- **The GIM group received financial support for trial conduct from Bristol-Myers Squibb and Pharmacia. Bristol-Myers Squibb provided paclitaxel and Dompè Biotech, Italy provided filgrasti**

- Oncologi fondatori:
  - Marco Venturini
  - Francesco Cognetti
  - Sabino De Placido