# La Chemioterapia Adiuvante Dose-Dense

# Lo studio GIM 2


**Alessandra Fabi**

# GIM 2 study

**Epirubicin and Cyclophosphamide (EC) followed by Paclitaxel (T) versus Fluorouracil, Epirubicin and Cyclophosphamide (FEC) followed by T, all given every 3 weeks or 2 weeks, in node-positive early breast cancer (BC) patients (pts). Final results of the Gruppo Italiano Mammella (GIM)-2 randomized phase III study**

Francesco Cognetti, Paolo Bruzzi, Sabino De Palcido, Michele De Laurentiis, Corrado Boni, Enrico Aitini, Antonio Durando, Anna Turletti, Enrichetta Valle, Ornella Garrone, Fabio Puglisi, Filippo Montemurro, Sandro Barni, Beatrice Di Blasio, Teresa Gamucci, Cesare Gridelli, Nina Olmeo, Carlo Tondini, Anna Maria Parisi, Claudia Bighin, Simona Pastorino, Matteo Lambertini, Lucia Del Mastro, on behalf of GIM group


SAN ANTONIO
BREAST CANCER
SYMPOSIUM

**Valter Torri**
**"PM"**

**"Giudici"**

**"Testimone"**

**"Persona informata sui fatti"**

# Assumption and Background

- Anthracyclines and taxanes are mainstays in treating women with axillary node-positive breast cancer,

- Hryniuk and Levine, first suggested that dose-dense adjuvant CT was correlated to disease-free survival in breast cancer [1]. Based on mathematical modeling of tumor growth [2,3], shortening the interval between treatment cycles from every 3 weeks to 2 weeks, or using a dose-dense schedule, improved the outcome for patients with breast cancer with axillary node-positive disease [4].

- Randomized trials demonstrated a significant survival for pts with LN+ BC breast, treated with dose-dense (2 week intervals) CT + G-CSF support compared to conventional 3-week schedules [4].

- Despite pooled analysis of phase III trials showed that dose-dense CT is superior to standard interval CT, additional data from randomized controlled trials are needed before dose-dense chemotherapy can be considered as the standard of care [5]

- Among the different antracycline-based regimens commonly used before taxanes, both AC/EC and FAC/FEC are administered and no data are available on the usefulness of adding 5-fluorouracil to AC/EC

[1]Hryniuk and Levine, *Clin Oncol* 1986; [2]Norton & Simon, *Cancer Treat Reports 1986,* Norton, [3]*Cancer Res*, 1988, [4]Citron et al, J Ckin Oncol 2003, [5]Bonilla, *J Nat Cancer Inst 2010*

# Aims and statistical considerations

- ✔The study was aimed at assessing two separate hypotheses:
  - Efficacy and safety of 5-FU in addition to EC->T
  - Efficacy and safety of a dose-dense CT vs conventional 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 alpha 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)

# Study design: FACTORIAL

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

EC vs FEC

q3 wks vs q2 wks

*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.


***Operable breast cancer***
***Histologically positive nodes***

**2091 Patients randomized**

- EC q3 wks* n=545
- FEC q3 wks* n=544
- EC q2 wks n=502
- FEC q2 wks n=500

q3 wks vs q2 wks Comparison → ITT Analysed : 1089 vs 1002 pts

FEC vs EC Comparison → ITT Analysed : 1044 vs 1047 pts

* 5 out of 81 centers choosed to randomize pts only in the 2-arm study (FEC q3 wks vs EC q3 wks)

# General overview

| | |
|---|---|
| • First patient in | 24/04/2003 |
| • Last patient in | 03/07/2006 |
| • Total patients | 2091 |
| • Total number of centers | 91 |
| • Centers no pts | 10 |
| • Centers with pts (at least 1 randomized pt) | 81 |

# Patients Characteristics according to Regimen

| | EC21 | | FEC21 | | EC14 | | FEC14 | |
|---|---|---|---|---|---|---|---|---|
| | No Pz | % | No Pz | % | No Pz | % | No Pz | % |
| **Total enrolled** | **545** | | **544** | | **502** | | **500** | |
| **AGE** | | | | | | | | |
| Median | 51 | | 53 | | 53 | | 51 | |
| Range | 24-71 | | 26-71 | | 27-71 | | 25-71 | |
| **MENOPAUSAL STATUS** | | | | | | | | |
| Pre | 281 | 51.6 | 245 | 45.0 | 232 | 46.2 | 263 | 52.6 |
| Post | 264 | 48.4 | 299 | 55.0 | 270 | 53.8 | 237 | 47.4 |
| **SURGERY** | | | | | | | | |
| Conservative | 338 | 62.0 | 320 | 58.8 | 298 | 59.4 | 313 | 62.6 |
| Mastectomy | 207 | 38.0 | 224 | 41.2 | 204 | 40.6 | 187 | 37.4 |
| **HISTOLOGIC TYPE** | | | | | | | | |
| Invasive ductal carcinoma | 456 | 83.7 | 443 | 81.4 | 389 | 77.5 | 404 | 80.8 |
| Invasive lobular carcinoma | 53 | 9.7 | 76 | 14.0 | 65 | 12.9 | 64 | 12.8 |
| Other | 36 | 6.6 | 25 | 4.6 | 48 | 9.6 | 32 | 6.4 |
| **TUMOR SIZE** | | | | | | | | |
| T1 | 283 | 51.9 | 262 | 48.2 | 262 | 52.2 | 253 | 50.6 |
| T2 | 218 | 40.0 | 233 | 42.8 | 202 | 40.2 | 208 | 41.6 |
| T3 | 21 | 3.9 | 25 | 4.6 | 25 | 5.0 | 29 | 5.8 |
| T4 | 19 | 3.5 | 23 | 4.2 | 10 | 2.0 | 9 | 1.8 |
| Unknown | 4 | 0.7 | 1 | 0.2 | 3 | 0.6 | 1 | 0.2 |
| **N° of POSITIVE NODES** | | | | | | | | |
| 1-3 | 327 | 60.0 | 319 | 58.6 | 319 | 63.5 | 284 | 56.8 |
| 4-9 | 135 | 24.8 | 136 | 25.0 | 116 | 23.1 | 135 | 27.0 |
| ≥10 | 83 | 15.2 | 89 | 16.4 | 67 | 13.3 | 81 | 16.2 |
| Unknown | 1 | 0.2 | 1 | 0.2 | - | - | - | - |

# Patients Characteristics according to Regimen

| | EC21 | | FEC21 | | EC14 | | FEC14 | |
|---|---|---|---|---|---|---|---|---|
| | **No Pz** | **%** | **No Pz** | **%** | **No Pz** | **%** | **No Pz** | **%** |
| **Total enrolled** | **545** | | **544** | | **502** | | **500** | |
| **HISTOLOGIC GRADE** | | | | | | | | |
| Grade 1 | 32 | 5.9 | 28 | 5.1 | 37 | 7.4 | 40 | 8.0 |
| Grade 2 | 236 | 43.3 | 238 | 43.8 | 225 | 44.8 | 240 | 48.0 |
| Grade 3 | 275 | 50.5 | 275 | 50.6 | 235 | 46.8 | 218 | 43.6 |
| Unknown | 2 | 0.4 | 3 | 0.6 | 5 | 1.0 | 2 | 0.4 |
| **HER2 STATUS** | | | | | | | | |
| HER2+ | 123 | 22.6 | 131 | 24.1 | 105 | 20.9 | 121 | 24.2 |
| HER2- | 344 | 63.1 | 332 | 61.0 | 318 | 63.3 | 299 | 59.8 |
| Unknown | 78 | 14.3 | 81 | 14.9 | 79 | 15.7 | 80 | 16.0 |
| **HORMONAL RECEPTORS** | | | | | | | | |
| ER+ and/or PR+ | 420 | 77.1 | 442 | 81.2 | 407 | 81.1 | 401 | 80.2 |
| ER- and PR- | 103 | 18.9 | 88 | 16.2 | 83 | 16.5 | 85 | 17.0 |
| Unknown | 22 | 4.0 | 14 | 2.6 | 12 | 2.4 | 14 | 2.8 |
| **Ki67 value (% of positive cells)** | | | | | | | | |
| 0-14 | 120 | 22.0 | 113 | 20.8 | 142 | 28.3 | 132 | 26.4 |
| 15-20 | 33 | 6.1 | 51 | 9.4 | 44 | 8.8 | 41 | 8.2 |
| ≥20 | 273 | 50.1 | 269 | 49.4 | 214 | 42.6 | 232 | 46.4 |
| Unknown | 119 | 21.8 | 111 | 20.4 | 102 | 20.3 | 95 | 19.0 |

# COMPLIANCE WITH THERAPY

| | EC21 | | FEC21 | | EC14 | | FEC14 | |
|---|---|---|---|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % | No. of Patients | % | No. of Patients | % |
| **Total enrolled** | 545 | | 544 | | 502 | | 500 | |
| **Completed 8 cycles** | 476 | 87.3 | 483 | 88.8 | 451 | 89.8 | 441 | 88.2 |
| With no delay and/or dose reduction | 456 | | 464 | | 426 | | 419 | |
| With some delay | 4 | | 1 | | 6 | | 1 | |
| With some dose reduction | 16 | | 17 | | 18 | | 19 | |
| With delay and dose reduction | 0 | | 1 | | 1 | | 2 | |
| **Discontinued** | 62 | 11.4 | 50 | 9.1 | 46 | 9.2 | 51 | 10.2 |
| Toxicity | 23 | | 26 | | 23 | | 27 | |
| Early relapse | 5 | | 2 | | 0 | | 1 | |
| Refusal | 14 | | 10 | | 13 | | 10 | |
| Other | 20 | | 12 | | 10 | | 13 | |
| **Not begun** | 7 | 1.3 | 11 | 2.1 | 5 | 1.0 | 8 | 1.6 |

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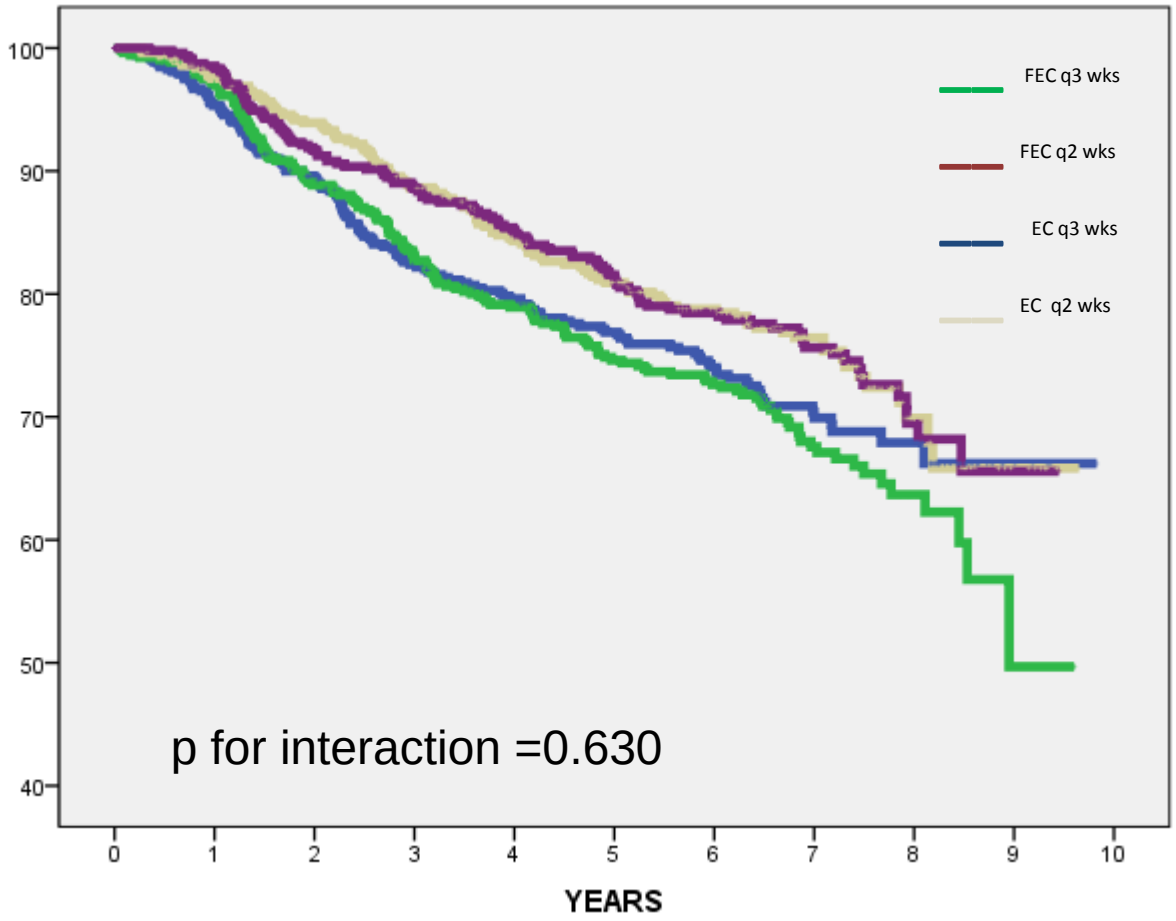
# Event in the intention to Treat Population

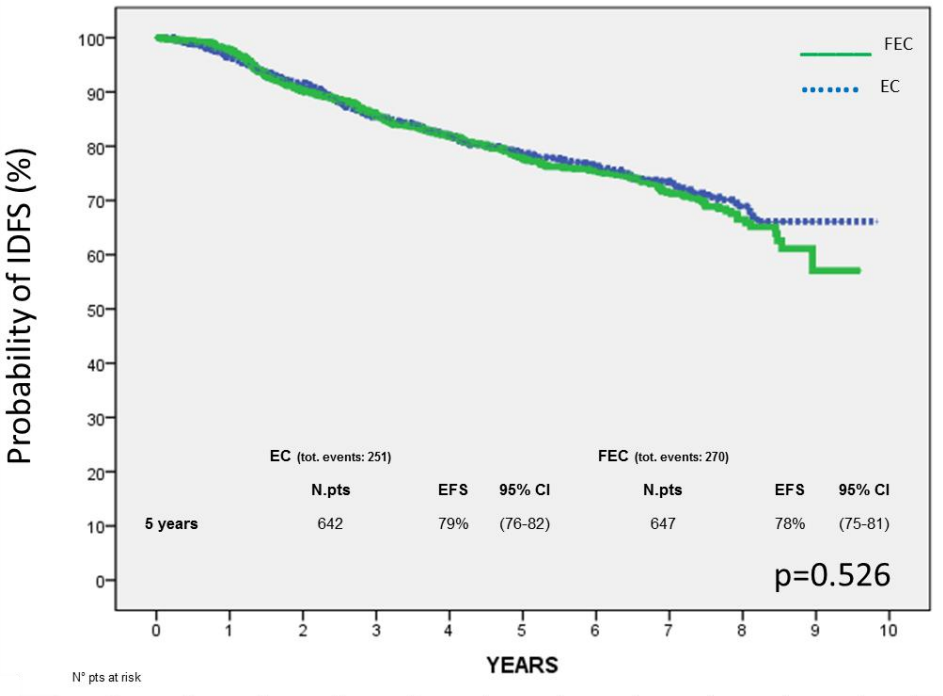
| | EC21 | | FEC21 | | EC14 | | FEC14 | |
|---|---|---|---|---|---|---|---|---|
| | No. Pz | % | No. Pz | % | No. Pz | % | No. Pz | % |
| **Total enrolled** | **545** | | **544** | | **502** | | **500** | |
| **OS** | | | | | | | | |
| **Total deaths** | **75** | **13.8** | **88** | **16.2** | **48** | **9.6** | **55** | **11.0** |
| **IDFS** | | | | | | | | |
| ***Total events*** | **140** | **25.7** | **157** | **28.9** | **111** | **22.1** | **113** | **22.6** |
| *Relapse* | | | | | | | | |
| Local only, regional only, or both | 13 | 2.4 | 18 | 3.3 | 10 | 2.0 | 12 | 2.4 |
| Distant | 93 | 17.1 | 102 | 18.8 | 74 | 14.7 | 74 | 14.8 |
| Concurrent Distant and + Locoregional relapse | 11 | 2.0 | 13 | 2.4 | 8 | 1.6 | 5 | 1.0 |
| Unknown | 4 | 0.7 | 5 | 0.9 | 2 | 0.4 | 2 | 0.4 |
| *Second primary malignancy* | | | | | | | | |
| Primary breast cancer | 7 | 1.3 | 11 | 2.0 | 4 | 0.8 | 6 | 1.2 |
| Second primary tumor, non-breast | 12 | 2.2 | 4 | 0.7 | 8 | 1.6 | 10 | 2.0 |
| *Death without relapse* | - | - | 4 | 0.7 | 5 | 0.9 | 4 | 0.8 |

OS= OVERALL SURVIVAL; IDFS= INVASIVE DISEASE SURVIVAL

# Results

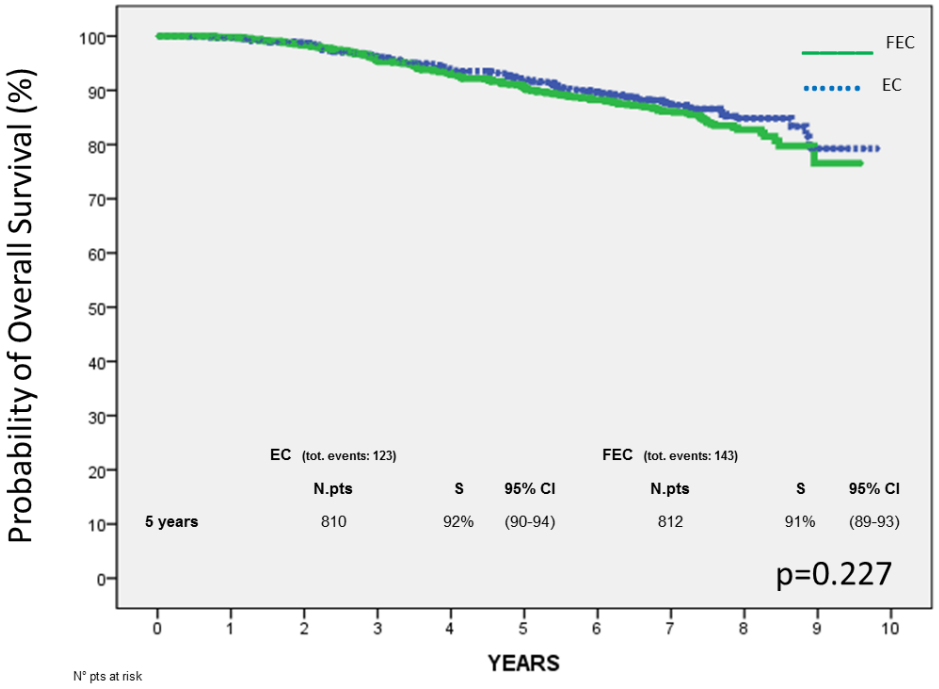

Probability of IDFS (%)
100
90
80
70
60
50
40
0
1
2
3
4
5
6
7
8
9
10
YEARS
FEC q3 wks
FEC q2 wks
EC q3 wks
EC q2 wks
p for interaction =0.630

# EC vs FEC




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 | - |

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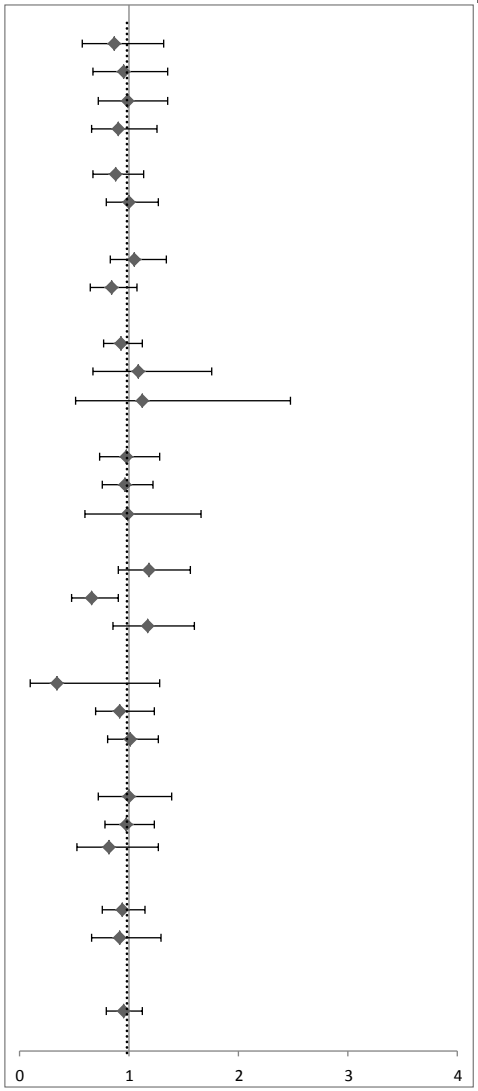
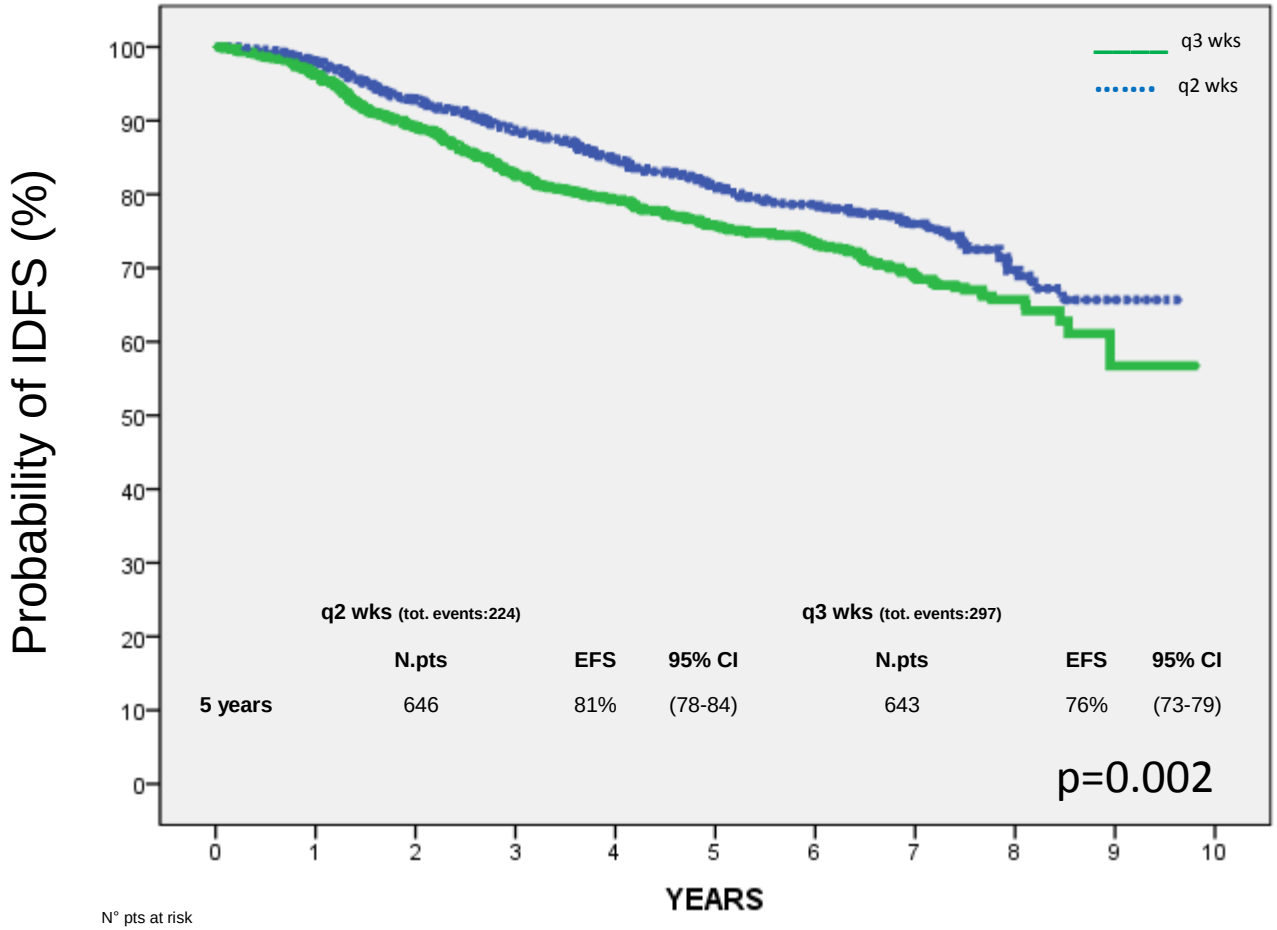
# Risk of recurrence : EC vs FEC

| | 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) | |



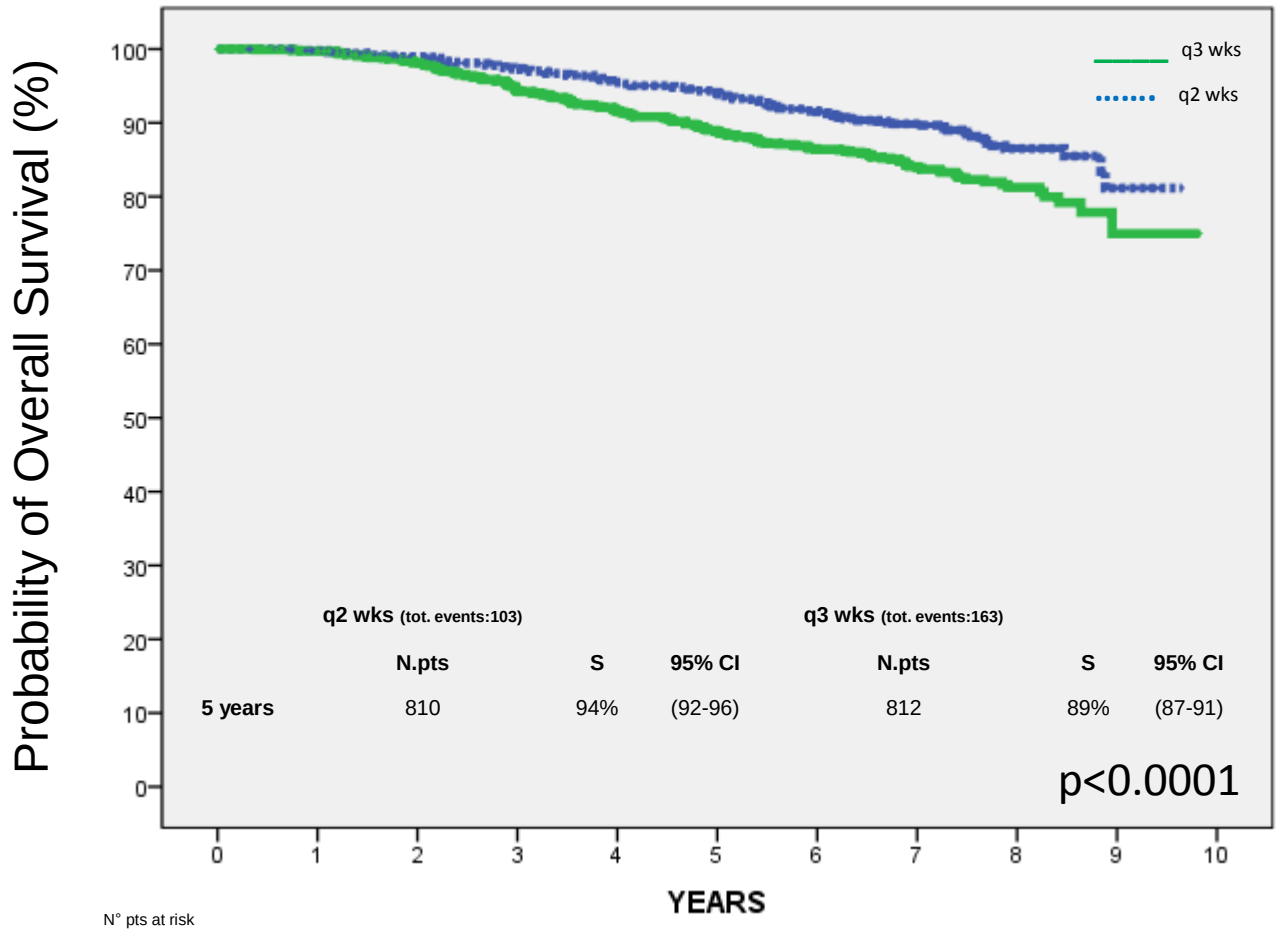
# 3 wks vs 2 wks




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 | - |

# 3 wks vs 2 wks

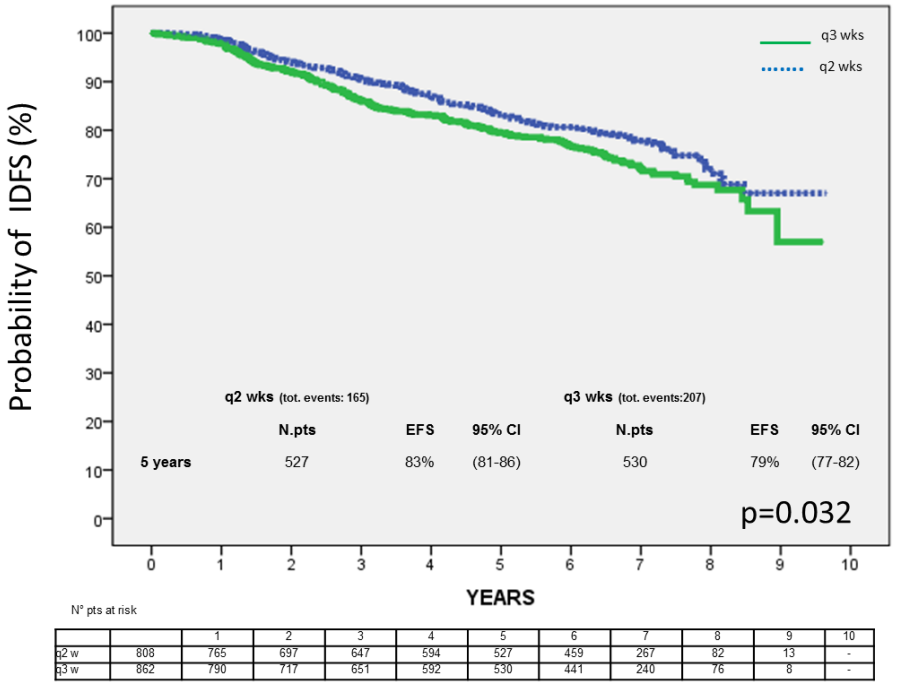



N° pts at risk

| | | 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 | - |

# IDFS 3 wks vs 2 wks and HR status

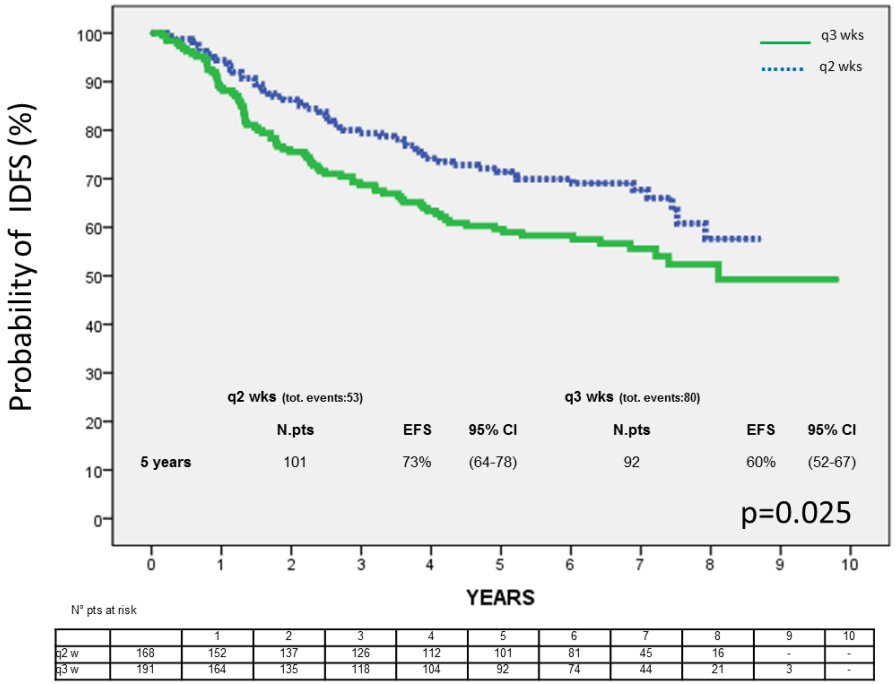
HR+




N° pts at risk

| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| q2 w | 808 | 765 | 697 | 647 | 594 | 527 | 459 | 267 | 82 | 13 | - |
| q3 w | 862 | 790 | 717 | 651 | 592 | 530 | 441 | 240 | 76 | 8 | - |

HR-

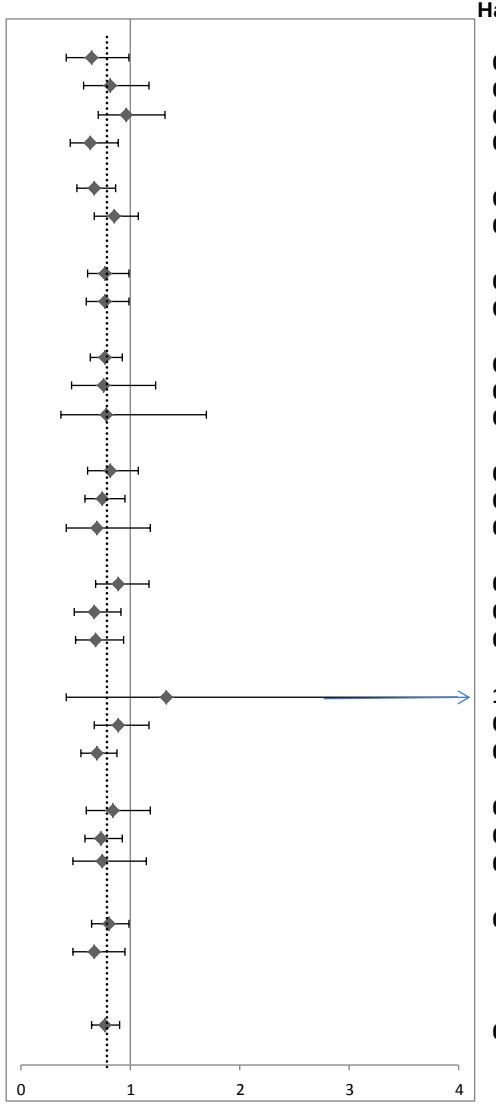



N° pts at risk

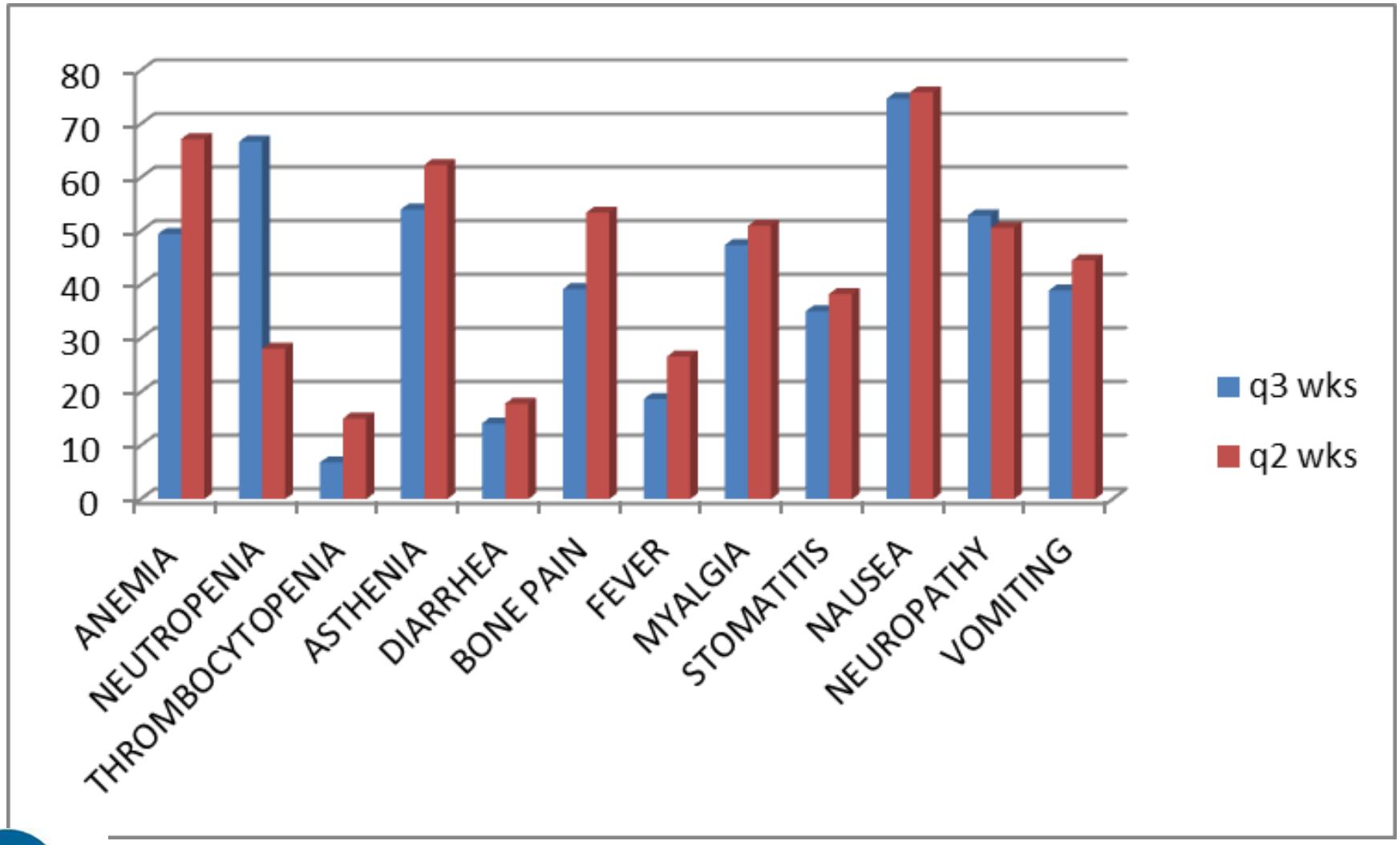
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| q2 w | 168 | 152 | 137 | 126 | 112 | 101 | 81 | 45 | 16 | - | - |
| q3 w | 191 | 164 | 135 | 118 | 104 | 92 | 74 | 44 | 21 | 3 | - |

# Risk of recurrence : q2 wks vs q3 wks

| | 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) | |



# Major all grade toxicities by treatment arm

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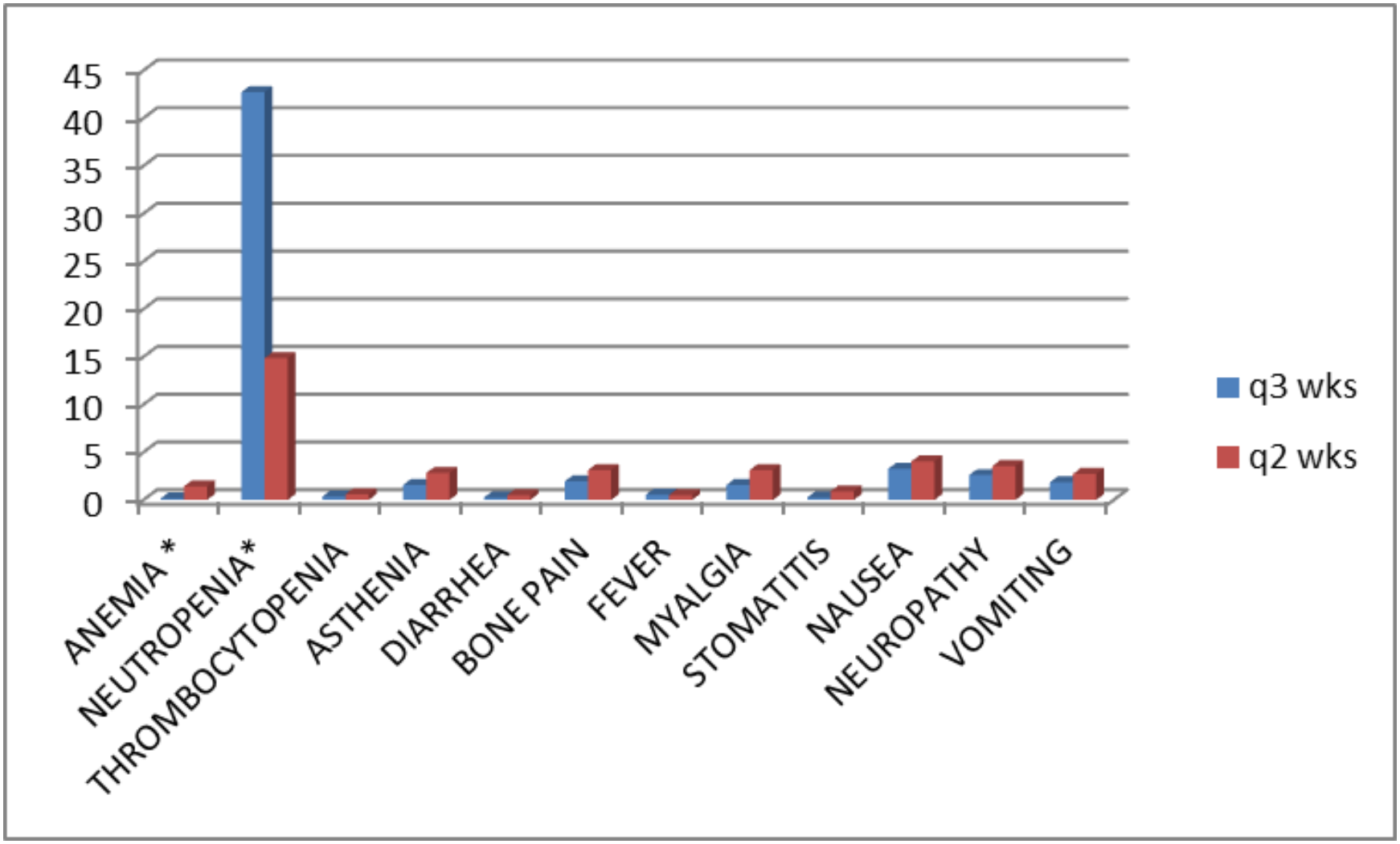
# Grade 3 and 4 toxicities effects




* Statistically significant difference

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# GIM 2: Conclusions

- **Dose-dense CT** as adjuvant treatment in node positive BC patients **improves significantly DFS and OS**

- The **advantage is independent** by clinical and histopathological factors

- The addition of **Fluorouracil to EC does not improve** clinical outcomes

- The **use of Pegfilgrastim** allowed the **safe administration** in accelerated regimen

- The **dose-dense CT regimen** used in the present trial **is an optimal option in the clinical practice** for the adjuvant treatment of node positive BC patients

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# Thanks to

**All the investigators**

**All the patients**

Marco Venturini