Progetto Canoa

Carcinoma Mammario

Gruppo A

QUESITO GRADE:

Nelle pazienti con carcinoma mammario N+ operato, la chemioterapia dose-dense è raccomandabile rispetto alla chemioterapia standard?

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Pescantina- Villa Quaranta (VR)

10-11 aprile 2015

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Nelle pazienti con carcinoma mammario N+ operato, la chemioterapia dose-dense è raccomandabile rispetto alla chemioterapia standard?

1. **Presentazione del quesito strutturato**

2. **Tavola delle evidenze**

1. Presentazione del quesito strutturato

PICO

P opulation	**Pazienti con carcinoma mammario operato N+**
I ntervention	**CHT Dose dense**
C omparison	**CHT standard**
O utcomes	**•Importanti ed essenziali** **•Importanti ma non essenziali** **•Non importanti** **• di beneficio** **• di danno**

Dose-dense chemotherapy

- Dose density refers to the administration of drugs with a shortened intertreatment interval
- In experimental models, a given dose of drug always kills a certain fraction, rather than a certain number, of exponentially growing cancer cells
- Breast cancer cells proliferate by nonexponential gompertzian kinetics and regrowth of cancer cells between cycles of cytoreduction is more rapid than in exponential model
- Treatment designed to kill exponentially growing cells may not be able to kill all gompertzian growing cells
- More frequent administration of cytotoxic therapy would be more effective way of minimizing residual tumor burden than dose escalation

Norton, Oncologist 2001

Outcomes

- **Importanti ed essenziali** **(9-7)**
  - OS 9
  - DFS 9
- **Importanti ma non essenziali** **(6-4)**
  - Anemia G 3/4 5
  - Neutropenia G 3/4 5
  - Trombocitopenia G 3/4 5
  - Mucositi 4,5
  - Tossicità neurologica 5
- **Non importanti** **(3-1)**
  - LAM/SMD 3

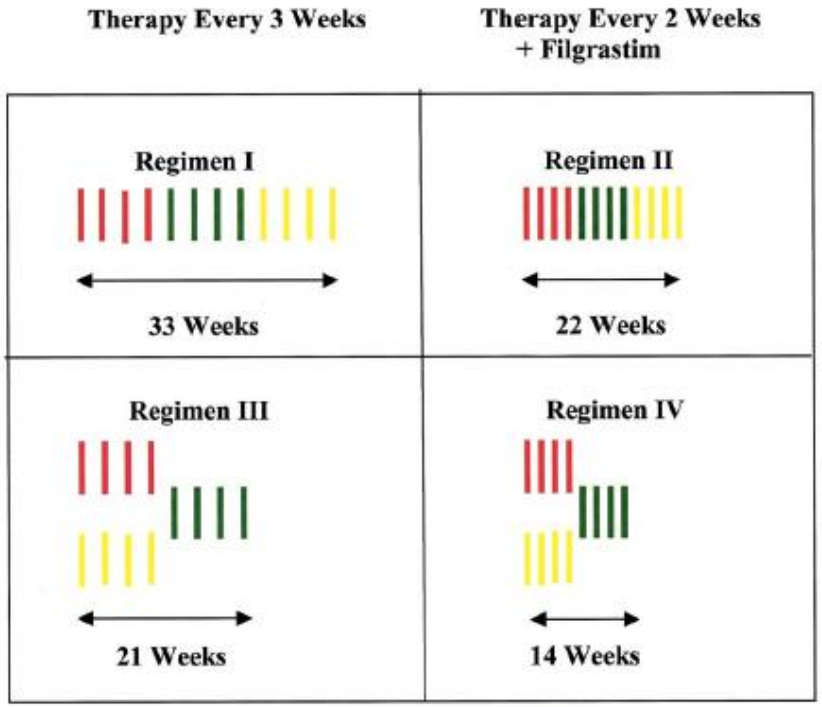
2. Tavola delle evidenze

Trial	Pts	Ln	F. U.	DDCht	Standard Cht	Endpoints	Toxicity	MDS AML
Citron, 2003 C9741	2005	100%	36 m	A→T→C q14 + FILGRASTIM AC→T q14 + FILGRASTIM	A→T→C q21 AC→T q21	DFS RR 0.74, p .010 (primary) OS RR 0.69, p .013 (secondary)	More severe neutropenia in ddCHT	11 cases
Burnell, 2010 MA21	2104	72%	30.4 m	ddEC + filgrastim→T	CEF AC→T	3 years RFS AC/T vs CEF 1.49, p=.005 AC/T vs ddEC/T 1.68, p=.0006 ddEC/T vs CEF 0.89, P=46	CEF and ddEC/T: febrile neutrop. and trasfusions T regimens: neuropathy	4 AML in CEF 4 MDS in ddEC→T
Moebus, 2010 AGO	1284	100% N2,N3	62 m	E→T→C q14 + filgrastim	EC→T q21	EFS HR 0.72 (0.59-0.87), (primary) p <.001 OS HR 0.76 (0.59-0.97), (primary) p .029	More H and non H toxicities in ddCHT	Total 4 AML-MDS
Swain, 2013 NSABP B-38	4894	100%	64 m	ddAC→ddP + G-CSF ddAC→ddPG + G-CSF	TAC	5 year DFS (primary) ddAC → PG vs ddAC→P 80.6% vs 82.2%,HR 1.07 ddAC → PG vs TAC 80.6% vs 80.1%, HR 0.93 ddAC → P vs TAC HR 0.87 5 year OS (secondary) ddAC → PG vs ddAC→P 90.8% vs 89.1%, HR 0.85 ddAC → PG vs TAC 90.8% vs 89.6%, HR 0.86 ddAC → P vs TAC HR 1.01	TAC→ febrile neutropenia and diarrhea P→neuropathy ddCHT→anemia	TAC=5 AC→P=8 AC→PG =11
Del Mastro, 2015 GIM2	2091	100%	7 y	FEC→T q14 + pegfilgrastim EC→T q14+ pegfilgrastim	FEC→T q21 EC→T q21	DFS HR 0.77 CI 0.65-0.92, p 0.004 (primary) OS HR 0.65 CI 0.51-0.84, p0.001	ddCHT: anemia, transaminitis, myalgias	1 AML 1 MDS

Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741

By Marc L. Citron, Donald A. Berry, Constance Cirrincione, Clifford Hudis, Eric P. Winer, William J. Gradishar, Nancy E. Davidson, Silvana Martino, Robert Livingston, James N. Ingle, Edith A. Perez, John Carpenter, David Hurd, James F. Holland, Barbara L. Smith, Carolyn I. Sartor, Eleanor H. Leung, Jeffrey Abrams, Richard L. Schilsky, Hyman B. Muss, and Larry Norton

2 x 2 factorial design
2005 patients
Sep 1997→ March 1999



A→T→C
vs
AC → T

q 3 weeks vs q 2 weeks

Doxorubicin 60 mg/m^2 i.v.
Cyclophosphamide 600 mg/m^2 i.v.
Paclitaxel 175 mg/m^2 i.v. over 3 hours

Citron, *JCO* 2003

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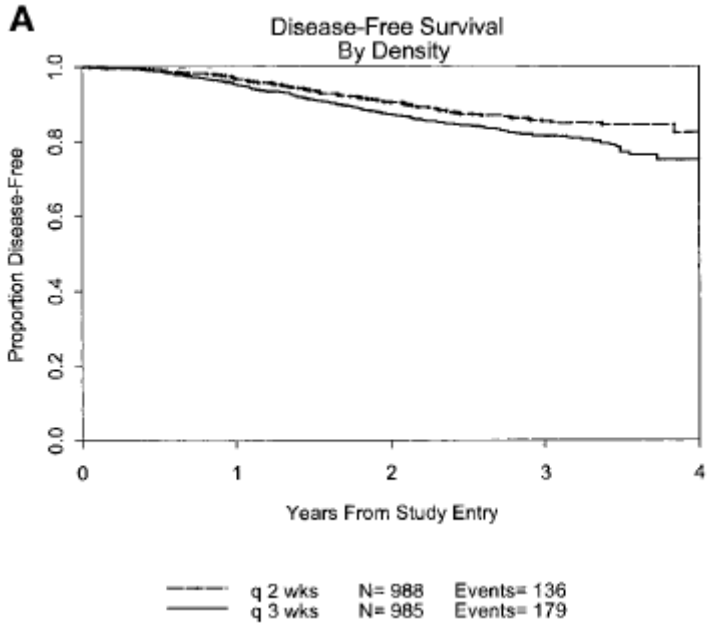
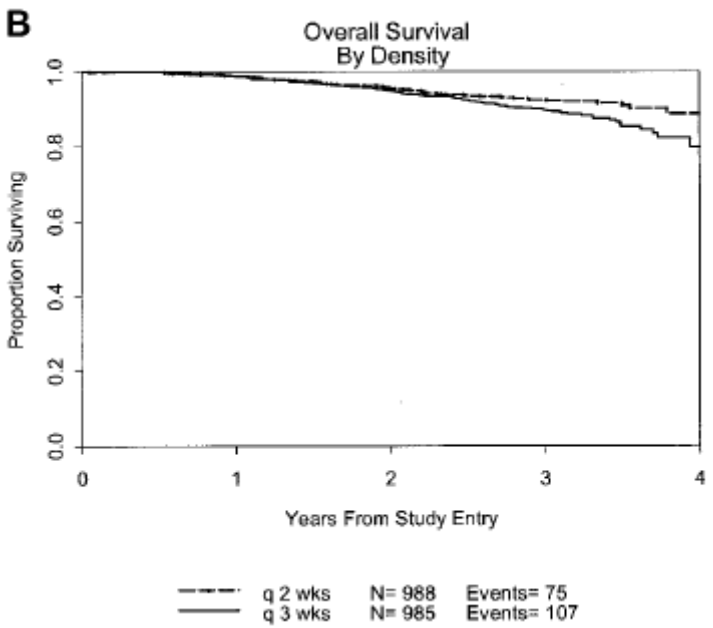


Risk ratio=0.74, p=.010



Risk ratio=0.69, p=.013

Median follow up 36 months

DFS→study entry until local recurrence, distant relapse or death without relapse (primary end point) and OS (secondary end point) were significantly prolonged for the dose dense regimens

4-year DFS was 82% for dose dense regimens and 75% for conventionally scheduled

No difference in DFS or OS between concurrent and sequential schedules

Citron, JCO 2003

Randomized Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741

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Toxicities

	Grade of Toxicity						
	3		4		5		
	n	%	n	%	n	%	Total No.
WBC							
Arm 1 (A → T → C q 3 weeks)	2	—	4	1	0	0	479
Arm 2 (A → T → C q 2 weeks)	0	0	1	—	0	0	490
Arm 3 (AC → T q 3 weeks)	3	1	57	11	0	0	500
Arm 4 (AC → T q 2 weeks)	1	—	28	6	0	0	493
Platelets							
Arm 1 (A → T → C q 3 weeks)	0	0	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	0	0	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	2	—	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	1	—	3	—	0	0	493
Hemoglobin							
Arm 1 (A → T → C q 3 weeks)	0	0	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	0	0	1	—	0	0	490
Arm 3 (AC → T q 3 weeks)	1	—	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	0	0	1	—	0	0	493
Granulocytes/bands							
Arm 1 (A → T → C q 3 weeks)	0	0	113	24	0	0	479
Arm 2 (A → T → C q 2 weeks)	1	—	14	3	0	0	490
Arm 3 (AC → T q 3 weeks)	0	0	214	43	0	0	500
Arm 4 (AC → T q 2 weeks)	1	—	46	9	0	0	493
Nausea							
Arm 1 (A → T → C q 3 weeks)	22	5	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	34	7	1	—	0	0	490
Arm 3 (AC → T q 3 weeks)	41	8	3	1	0	0	500
Arm 4 (AC → T q 2 weeks)	41	8	0	0	0	0	493
Vomiting							
Arm 1 (A → T → C q 3 weeks)	10	2	4	1	0	0	479
Arm 2 (A → T → C q 2 weeks)	14	3	4	1	0	0	490
Arm 3 (AC → T q 3 weeks)	32	6	8	2	0	0	500
Arm 4 (AC → T q 2 weeks)	18	4	12	2	0	0	493
Diarrhea							
Arm 1 (A → T → C q 3 weeks)	5	1	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	8	2	4	1	0	0	490
Arm 3 (AC → T q 3 weeks)	7	1	5	1	0	0	500
Arm 4 (AC → T q 2 weeks)	5	1	0	0	0	0	493
Stomatitis							
Arm 1 (A → T → C q 3 weeks)	5	1	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	4	1	2	—	0	0	490
Arm 3 (AC → T q 3 weeks)	14	3	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	9	2	4	1	0	0	493
Cardiac function							
Arm 1 (A → T → C q 3 weeks)	5	1	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	4	1	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	1	—	1	—	0	0	500
Arm 4 (AC → T q 2 weeks)	0	0	1	—	0	0	493

Citron, *JCO* 2003

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Toxicities

	Grade of Toxicity						
	3		4		5		
	n	%	n	%	n	%	Total No.
Other cardiac							
Arm 1 (A → T → C q 3 weeks)	2	—	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	0	0	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	0	0	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	1	—	0	0	0	0	493
Phlebitis/thrombosis							
Arm 1 (A → T → C q 3 weeks)	3	1	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	4	1	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	3	1	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	4	1	0	0	0	0	493
Sensory							
Arm 1 (A → T → C q 3 weeks)	21	4	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	19	4	1	—	0	0	490
Arm 3 (AC → T q 3 weeks)	25	5	2	—	0	0	500
Arm 4 (AC → T q 2 weeks)	19	4	0	0	0	0	493
Motor							
Arm 1 (A → T → C q 3 weeks)	4	1	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	4	1	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	8	2	1	—	0	0	500
Arm 4 (AC → T q 2 weeks)	5	1	0	0	0	0	493
Pain							
Arm 1 (A → T → C q 3 weeks)	19	4	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	33	7	1	—	0	0	490
Arm 3 (AC → T q 3 weeks)	31	6	3	1	0	0	500
Arm 4 (AC → T q 2 weeks)	46	9	1	—	0	0	493
Skin							
Arm 1 (A → T → C q 3 weeks)	8	2	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	15	3	3	1	0	0	490
Arm 3 (AC → T q 3 weeks)	2	—	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	11	2	1	—	0	0	493
Myalgias/arthralgias							
Arm 1 (A → T → C q 3 weeks)	23	5	0	0	0	0	479
Arm 2 (A → T → C q 2 weeks)	25	5	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	25	5	2	—	0	0	500
Arm 4 (AC → T q 2 weeks)	26	5	0	0	0	0	493
Infection							
Arm 1 (A → T → C q 3 weeks)	14	3	1	—	0	0	479
Arm 2 (A → T → C q 2 weeks)	19	4	0	0	0	0	490
Arm 3 (AC → T q 3 weeks)	27	5	0	0	0	0	500
Arm 4 (AC → T q 2 weeks)	13	3	2	—	0	0	493

Citron, *JCO* 2003

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cyclophosphamide, Epirubicin, and Fluorouracil Versus Dose-Dense Epirubicin and Cyclophosphamide Followed by Paclitaxel Versus Doxorubicin and Cyclophosphamide Followed by Paclitaxel in Node-Positive or High-Risk Node-Negative Breast Cancer

Margot Burnell, Mark N. Levine, Judith-Anne W. Chapman, Vivien Bramwell, Karen Gelmon, Barbara Walley, Ted Vandenberg, Haji Chalchal, Kathy S. Albain, Edith A. Perez, Hope Rugo, Kathleen Pritchard, Patti O'Brien, and Lois E. Shepherd

Burnell, *JCO*, 2010

Cyclophosphamide, Epirubicin, and Fluorouracil Versus Dose-Dense Epirubicin and Cyclophosphamide Followed by Paclitaxel Versus Doxorubicin and Cyclophosphamide Followed by Paclitaxel in Node-Positive or High-Risk Node-Negative Breast Cancer

Treatment regimens

CEF	EC/T	AC/T
Cyclophosphamide 75 mg/m^2 orally, days 1-14	Epirubicin 120 mg/m^2 IV, day 1	Doxorubicin 60 mg/m^2 IV, day 1
Epirubicin 60 mg/m^2 IV, days 1 and 8	Cyclophosphamide 830 mg/m^2 IV, day 1	Cyclophosphamide 600 mg/m^2 IV, day 1
Fluorouracil 500 mg/m^2 IV, days 1 and 8	EC administered every 14 days for 6 cycles	AC administered every 21 days for 4 cycles
Cotrimoxazole 2 tablets orally bid or ciprofloxacin 500 mg orally bid for duration of chemotherapy	Paclitaxel 175 mg/m^2 IV, every 21 days for 4 cycles	Paclitaxel 175 mg/m^2 IV, every 21 days for 4 cycles
Duration = six 28-day cycles	Filgrastim 5 μg/kg subcutaneously, days 2-13	Filgrastim and epoetin permitted
Filgrastim and epoetin permitted	Epoetin 40,000 U subcutaneously weekly	

NOTE. A complete blood count with differential and platelet count was performed at the beginning of each cycle of chemotherapy. Dose modifications were performed according to predefined guidelines based on hematologic and non-hematologic toxicity.

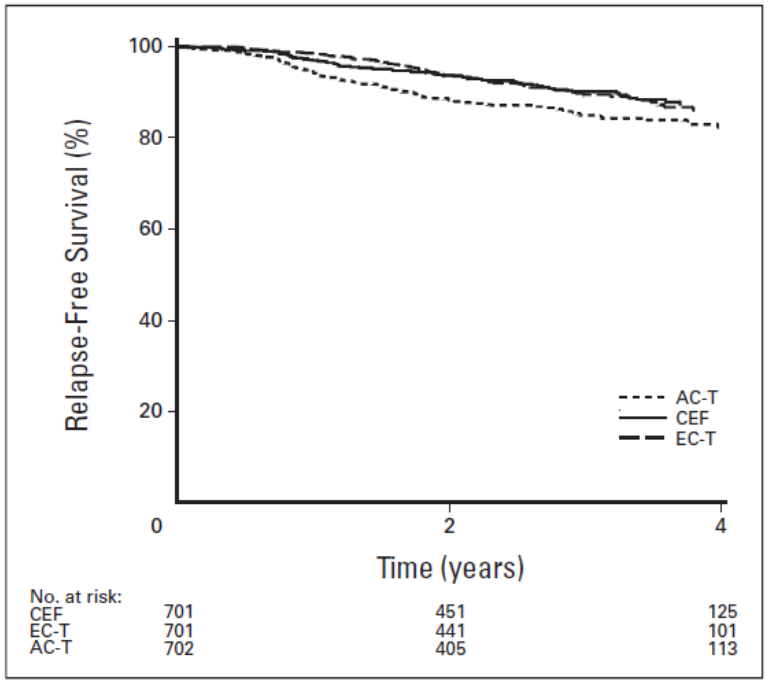
Abbreviations: CEF, cyclophosphamide, epirubicin, and fluorouracil; EC/T, dose-dense epirubicin and cyclophosphamide followed by paclitaxel; AC/T, doxorubicin and cyclophosphamide followed by paclitaxel; IV, intravenously; bid, twice per day.

2104 patients
Dec 2000→ May 2005
Median follow up 30.4 months
Interim analysis

Burnell, *JCO*, 2010

Cyclophosphamide, Epirubicin, and Fluorouracil Versus Dose-Dense Epirubicin and Cyclophosphamide Followed by Paclitaxel Versus Doxorubicin and Cyclophosphamide Followed by Paclitaxel in Node-Positive or High-Risk Node-Negative Breast Cancer

Three-year adjusted relapse free survival



3-year RFS (local/nodal or distant recurrences)
for CEF, ddEC/T and AC/T were 90.1%, 89.5% and 85% (p=.001)
HRs for recurrence are as follows:
AC/T vs CEF 1.49, p=.005
AC/T vs ddEC/T 1.68, p=.0006
ddEC/T vs CEF 0.89, p=.46

Burnell, JCO, 2010

Cyclophosphamide, Epirubicin, and Fluorouracil Versus Dose-Dense Epirubicin and Cyclophosphamide Followed by Paclitaxel Versus Doxorubicin and Cyclophosphamide Followed by Paclitaxel in Node-Positive or High-Risk Node-Negative Breast Cancer

Toxicities

Toxicity and Grade	CEF		EC/T		AC/T		*P**
	No.	%	No.	%	No.	%	
Patients with toxicity	680	100	688	100	674	100	
Nausea, grade 3/4	34	5.0	98	14.2	37	5.5	< .001
Vomiting, grade 3/4	38	5.6	103	15.0	42	6.2	< .001
Diarrhea, grade 3/4	18	2.7	25	3.6	8	1.2	< .001
Stomatitis, grade 3/4	61	9.0	68	9.9	5	0.7	< .001
Granulocytes, grade 3/4†	412	60.9	379	55.3	287	42.6	< .001
Platelets, grade 3/4†	96	14.1	165	24.1	10	1.5	< .001
Thrombosis, grade 3/4	22	3.2	18	2.6	3	0.5	< .001
Sensory neuropathy, grade 3/4	2	0.3	41	6.0	37	5.5	< .001
Motor neuropathy, grade 3/4	2	0.3	10	1.5	2	0.3	< .001
Febrile neutropenia, grade 3/4	153	22.5	111	16.1	32	4.8	< .001
Decreased LVEF (acute), grade 3/4	3	0.4	2	0.3	2	0.3	.02
Decreased LVEF (delayed), grade 3/4	14	2.1	5	0.7	2	0.3	< .001
Hemoglobin, grade 3/4†	112	16.5	199	29.0	7	1.0	< .001
Acute leukemia	4	0.57	4	0.57	0	0.0	.14

Abbreviations: CEF, cyclophosphamide, epirubicin, and fluorouracil; EC/T, dose-dense epirubicin and cyclophosphamide followed by paclitaxel; AC/T, doxorubicin and cyclophosphamide followed by paclitaxel; LVEF, left ventricular ejection fraction.

**P* value based on Fisher's exact test to compare toxicities between the three arms.

†Respectively, N for granulocytes are 677, 686, and 674; for platelets, 680, 686, and 674; for delayed decreased LVEF, 670, 682, and 659; for hemoglobin, 680, 687, and 674.

Burnell, *JCO*, 2010

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

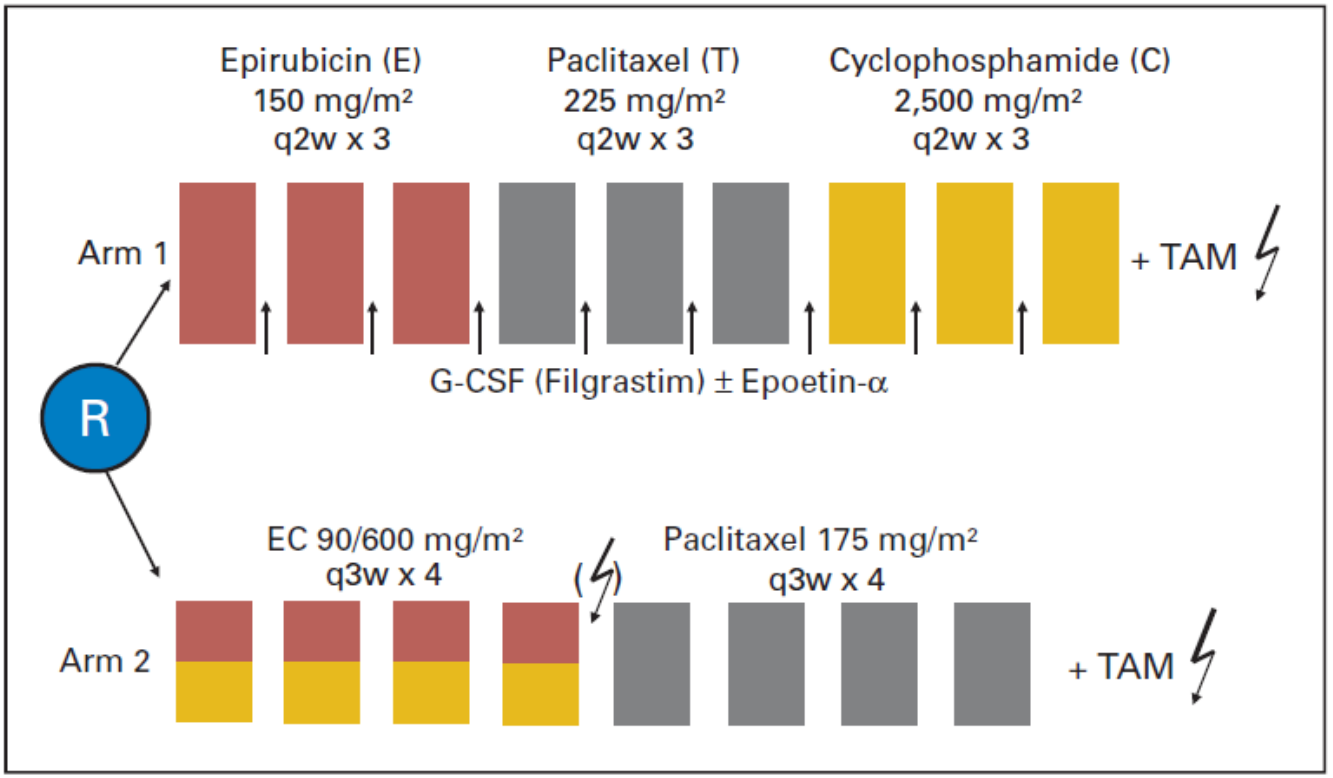
Intense Dose-Dense Sequential Chemotherapy With Epirubicin, Paclitaxel, and Cyclophosphamide Compared With Conventionally Scheduled Chemotherapy in High-Risk Primary Breast Cancer: Mature Results of an AGO Phase III Study

Volker Moebus, Christian Jackisch, Hans-Joachim Lueck, Andreas du Bois, Christoph Thomssen, Christian Kurbacher, Walther Kuhn, Ulrike Nitz, Andreas Schneeweiss, Jens Huober, Nadia Harbeck, Gunter von Minckwitz, Ingo B. Runnebaum, Axel Hinke, Rolf Kreienberg, Gottfried E. Konecny, and Michael Untch

Moebus, *JCO*, 2010

Intense Dose-Dense Sequential Chemotherapy With Epirubicin, Paclitaxel, and Cyclophosphamide Compared With Conventionally Scheduled Chemotherapy in High-Risk Primary Breast Cancer: Mature Results of an AGO Phase III Study

Trial design

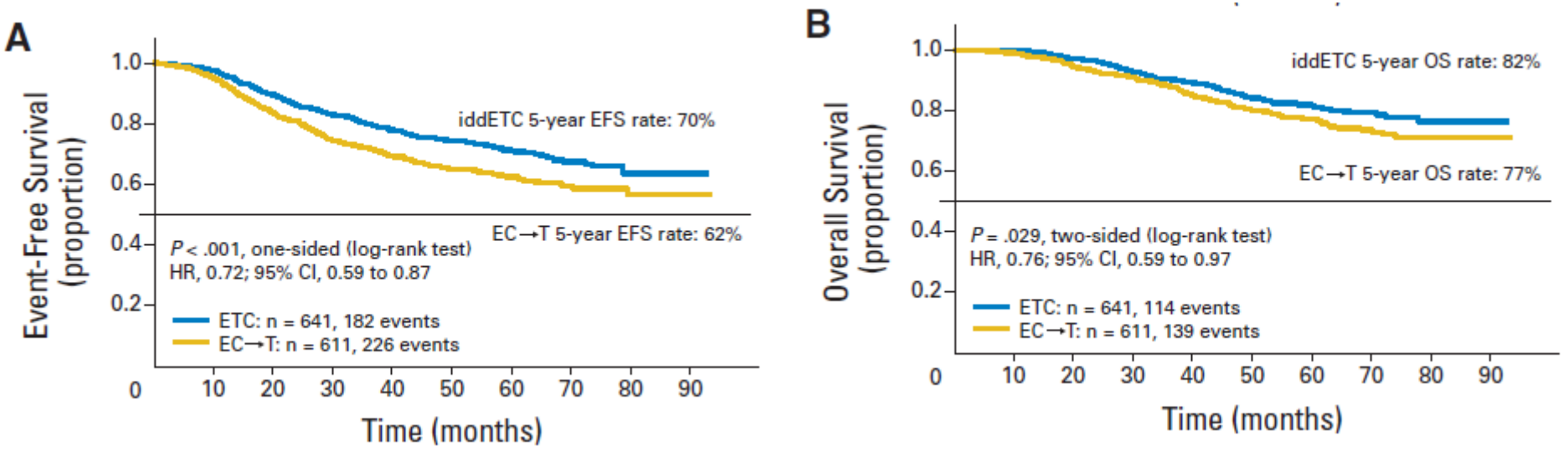


From Nov 1998 to April 2003→ 1284 pts

Moebus, *JCO*, 2010

Intense Dose-Dense Sequential Chemotherapy With Epirubicin, Paclitaxel, and Cyclophosphamide Compared With Conventionally Scheduled Chemotherapy in High-Risk Primary Breast Cancer: Mature Results of an AGO Phase III Study

Event-free survival (EFS) and overall survival (OS) by treatment arm



Median follow up: 62 months

Event free survival primary endpoint

(locoregional or distant relapse, contralateral breast cancer, second primary cancer or death)

5 year EFS rate: ddETC 70% vs EC/T 62%

5 year OS rate: ddETC 82% vs EC/T 77%

Moebus, *JCO*, 2010

Intense Dose-Dense Sequential Chemotherapy With Epirubicin, Paclitaxel, and Cyclophosphamide Compared With Conventionally Scheduled Chemotherapy in High-Risk Primary Breast Cancer: Mature Results of an AGO Phase III Study

Toxicities

- ✓ Hematologic toxicity → more pronounced in the IDD arm (p<.001)
  - *Febrile neutropenia idd-ETC 7% vs EC→T 2% (p <.001)*
  - *Red blood cell transfusions idd-ETC 20% vs EC→T 1% (p <.001)*

- ✓ Non hematologic toxicity → more pronounced in the IDD arm

Moebus, JCO, 2010

VOLUME 31 · NUMBER 26 · SEPTEMBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY

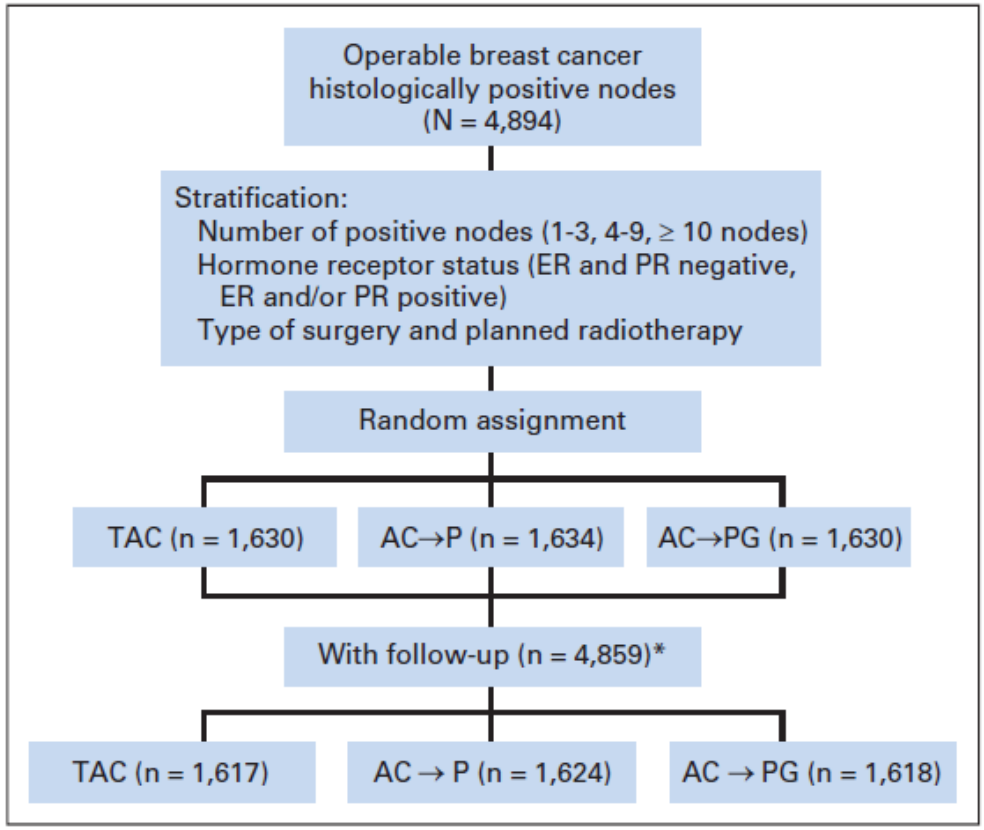
ORIGINAL REPORT

Definitive Results of a Phase III Adjuvant Trial Comparing Three Chemotherapy Regimens in Women With Operable, Node-Positive Breast Cancer: The NSABP B-38 Trial

Sandra M. Swain, Gong Tang, Charles E. Geyer Jr, Priya Rastogi, James N. Atkins, Paul P. Donnellan, Louis Fehrenbacher, Catherine A. Azar, André Robidoux, Jonathan A. Polikoff, Adam M. Brufsky, David D. Biggs, Edward A. Levine, John L. Zapas, Louise Provencher, Donald W. Northfelt, Soonmyung Paik, Joseph P. Costantino, Eleftherios P. Mamounas, and Norman Wolmark

Swain, *JCO*, 2013

Definitive Results of a Phase III Adjuvant Trial Comparing Three Chemotherapy Regimens in Women With Operable, Node-Positive Breast Cancer: The NSABP B-38 Trial



Enrollement: Nov 2004 → May 2007
Amendment (2005) exclude HER2 +
Median follow up: 64 months

Primary prophylaxis with pegfilgrastim/filgrastim

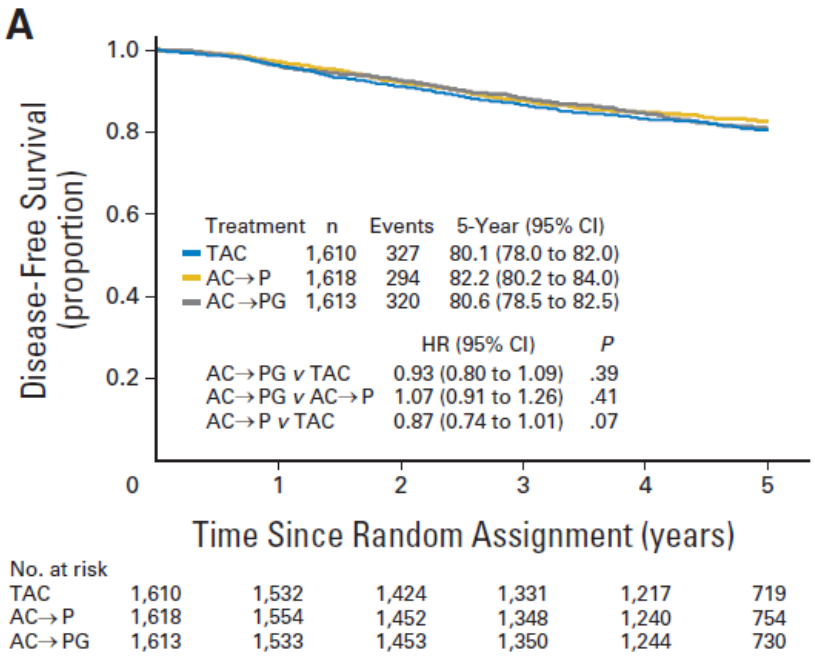
TAC
T = docetaxel 75 mg/mq, *A*= doxorubicin 50 mg/mq, *C*= cyclophosphamide 500 mg/mq q 21 x 6 cycles
dd *AC* → *P*
A= doxorubicin 60 mg/mq, *C*= cyclophosphamide 600 mg/mq q 14 x 4 cycles→ P= paclitaxel 175 mg/mq q 14 x 4 cycles
dd *AC* → *PG*
A= doxorubicin 60 mg/mq, *C*= cyclophosphamide 600 mg/mq q 14 x 4 cycles → P= paclitaxel 175 mg/mq, *G* = gemcitabine 2000 mg/mq q 14 x 4 cycles

Swain, *JCO*, 2013

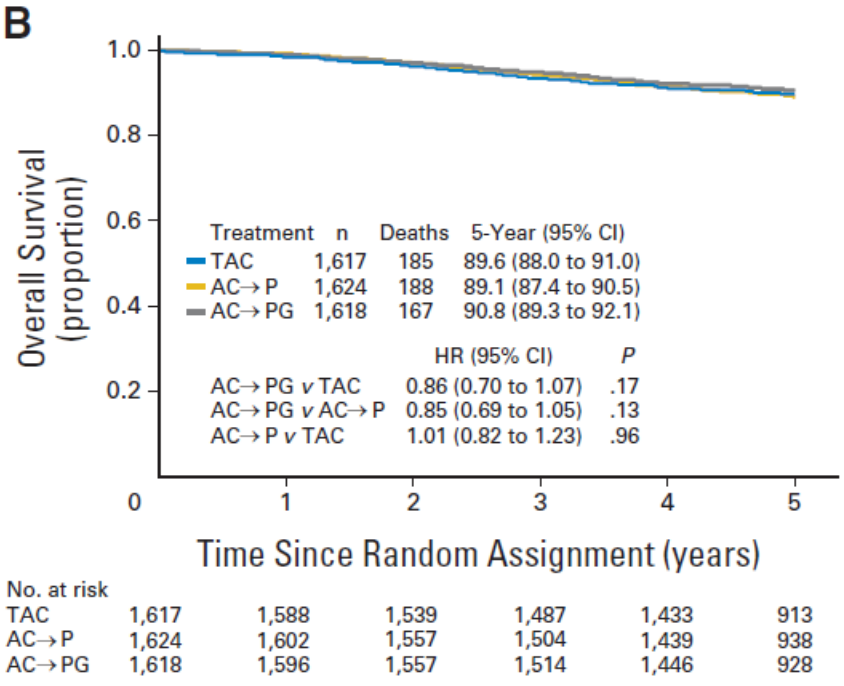
Definitive Results of a Phase III Adjuvant Trial Comparing Three Chemotherapy Regimens in Women With Operable, Node-Positive Breast Cancer: The NSABP B-38 Trial

DFS (primary endpoint)

local, regional, distant breast cancer, second primary and death for any cause



OS (secondary endpoint)



5 year DFS

ddAC → PG vs ddAC→P	80.6% vs 82.2%,	HR 1.07
ddAC → PG vs TAC	80.6% vs 80.1%,	HR 0.93
ddAC → P vs TAC		HR 0.87

5 year OS

ddAC → PG vs ddAC→P	90.8% vs 89.1%,	HR 0.85
ddAC → PG vs TAC	90.8% vs 89.6%,	HR 0.86
ddAC → P vs TAC		HR 1.01

No significant differences in 5-year DFS

Swain, JCO, 2013

Definitive Results of a Phase III Adjuvant Trial Comparing Three Chemotherapy Regimens in Women With Operable, Node-Positive Breast Cancer: The NSABP B-38 Trial

Grade 3 or 4 Adverse Events, According to treatment Group

Adverse Event	TAC (n = 1,607) No.	TAC (n = 1,607) %	AC→P (n = 1,623) No.	AC→P (n = 1,623) %	AC→PG (n = 1,612) No.	AC→PG (n = 1,612) %	P
Febrile neutropenia	144	9	48	3	51	3	< .001
Infection with neutropenia	22	1	8	< 1	3	< 1	< .001
Allergic reaction	9	< 1	26	2	18	< 1	.03
Anemia (hemoglobin < 8 g/dL)	3	< 1	27	2	25	2	< .001
Arthralgia/ myalgia	66	4	186	11	196	12	< .001
Fatigue	148	9	132	8	164	10	.15
Nausea	63	4	50	3	52	3	.43
Vomiting	45	3	45	3	49	3	.93
Mucositis	15	< 1	8	< 1	18	1	.21
Diarrhea	110	7	33	2	38	2	< .001
Thrombosis or embolism	37	2*	25	2	43	3	.23
Sensory neuropathy	16	< 1	117	7	99	6	< .001
Left ventricular dysfunction	5	< 1	0	0	0	0	.04

25 deaths on treatment: 13 in TAC, 5 in ddAC→P, 7 in ddAC→PG (p=.2)
AML or MDS: 5 in TAC, 8 in ddAC→P, 11 in ddAC→PG (p=.46)

Swain, JCO, 2013

GIM 2

Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial

Lucia Del Mastro, Sabino De Placido*, Paolo Bruzzi, Michele De Laurentiis, Corrado Boni, Giovanna Cavazzini, Antonio Durando, Anna Turletti, Cecilia Nisticò, Enrichetta Valle, Ornella Garrone, Fabio Puglisi, Filippo Montemurro, Sandro Barni, Andrea Ardizzoni, Teresa Gamucci, Giuseppe Colantuoni, Mario Giuliano, Adriano Gravina, Paola Papaldo, Claudia Bighin, Giancarlo Bisagni, Valeria Forestieri, Francesco Cognetti, for the Gruppo Italiano Mammella (GIM) investigators†*

Del Mastro, Lancet 2015

GIM 2

Study design: factorial

ARM A	ARM C
EC x 4 → T x 4 q 3 weeks	EC x 4 → T x 4 q 2 weeks + Pegfilgrastim
545 pts	502 pts
ARM B	ARM D
FEC x 4 → T x 4 q 3 weeks	FEC x 4 → T x 4 q 2 weeks + Pegfilgrastim
544 pts	500 pts

EC vs FEC

q 3 weeks vs q 2 weeks

First patient: 24/04/2003
Last patient: 03/07/2006
Median follow up: 7 years

*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.

Del Mastro, Lancet 2015

GIM 2

✓ **Primary endpoint: DFS**
(local recurrence, distant metastases, contralateral or ipsilateral breast tumor, second primary malignancy, death from any cause, loss to follow up or end of study)

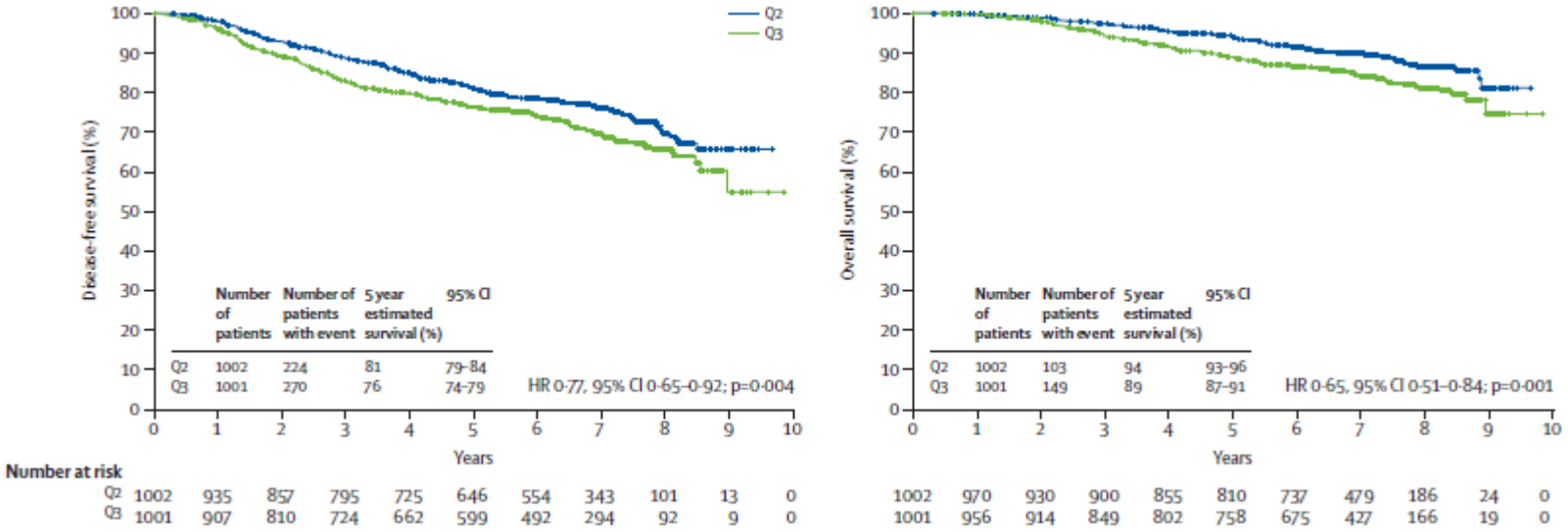
✓ **Secondary endpoint: OS and safety**

- The study was designed to detect a 20% relative reduction in DFS 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 DD vs standard), 635 DFS events had to be observed (1500 pts needed to be enrolled with an average follow up of 7-8 years or 2000 pts with an average follow up of 5.5-6 years)

Del Mastro, Lancet 2015

GIM 2

3 weeks vs 2 weeks



DFS at 5 years: 76% vs 81%

OS at 5 years: 89% vs 94%

Del Mastro, Lancet 2015

GIM 2

Adverse events occurring in at least 5% of any one group

	q3EC-P group (n=536)		q3FEC-P group (n=533)		q2EC-P group (n=496)		q2FEC-P group (n=492)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Anaemia	264 (49%)	0	263 (49%)	2 (<1%)	329 (66%)	6 (1%)	321 (65%)	8 (2%)
Neutropenia	153 (29%)	200 (37%)	103 (19%)	257 (48%)	69 (14%)	50 (10%)	61 (12%)	97 (20%)
Thrombocytopenia	29 (5%)	2 (<1%)	40 (8%)	2 (<1%)	57 (11%)	1 (<1%)	86 (17%)	5 (1%)
Asthenia	275 (51%)	5 (1%)	286 (54%)	12 (2%)	294 (59%)	13 (3%)	294 (60%)	15 (3%)
Diarrhoea	79 (15%)	1 (<1%)	69 (13%)	2 (<1%)	77 (16%)	2 (<1%)	94 (19%)	3 (1%)
Bone pain	200 (37%)	10 (2%)	198 (37%)	11 (2%)	263 (53%)	11 (2%)	234 (48%)	20 (4%)
Fever	91 (17%)	1 (<1%)	103 (19%)	5 (1%)	131 (26%)	1 (<1%)	127 (26%)	4 (1%)
Myalgia	248 (46%)	9 (2%)	242 (45%)	8 (2%)	237 (48%)	15 (3%)	236 (48%)	16 (3%)
Stomatitis	164 (31%)	0	208 (39%)	3 (1%)	180 (36%)	4 (1%)	189 (38%)	5 (1%)
Nausea	390 (73%)	13 (2%)	374 (70%)	22 (4%)	365 (74%)	15 (3%)	345 (70%)	25 (5%)
Vomiting	199 (37%)	8 (1%)	197 (37%)	12 (2%)	203 (41%)	7 (1%)	210 (43%)	20 (4%)
Neuropathy	269 (50%)	16 (3%)	269 (50%)	12 (2%)	232 (47%)	19 (4%)	233 (47%)	16 (3%)
Transaminase elevation	130 (24%)	3 (1%)	159 (30%)	2 (<1%)	174 (35%)	11 (2%)	196 (40%)	8 (2%)

Comparison between EC-P and FEC-P in terms of grade 3–4 toxicity is reported in the appendix. Comparison between dose dense and standard interval regimens in terms of grade 3–4 toxic effects is reported in the appendix.

Del Mastro, Lancet 2015

2. Tavola delle evidenze

Trial	Pts	Ln	F. U.	DDCht	Standard Cht	Endpoints	Toxicity	MDS AML
Citron, 2003 C9741	2005	100%	36 m	A→T→C q14 + FILGRASTIM AC→T q14 + FILGRASTIM	A→T→C q21 AC→T q21	DFS RR 0.74, p .010 (primary) OS RR 0.69, p .013 (secondary)	More severe neutropenia in ddCHT	11 cases
Burnell, 2010 MA21	2104	72%	30.4 m	ddEC + filgrastim→T	CEF AC→T	3 years RFS AC/T vs CEF 1.49, p=.005 AC/T vs ddEC/T 1.68, p=.0006 ddEC/T vs CEF 0.89, P=46	CEF and ddEC/T: febrile neutrop. and trasfusions T regimens: neuropathy	4 AML in CEF 4 MDS in ddEC→T
Moebus, 2010 AGO	1284	100% N2,N3	62 m	E→T→C q14 + filgrastim	EC→T q21	EFS HR 0.72 (0.59-0.87), (primary) p <.001 OS HR 0.76 (0.59-0.97), (primary) p .029	More H and non H toxicities in ddCHT	Total 4 AML-MDS
Swain, 2013 NSABP B-38	4894	100%	64 m	ddAC→ddP + G-CSF ddAC→ddPG + G-CSF	TAC	5 year DFS (primary) ddAC → PG vs ddAC→P 80.6% vs 82.2%,HR 1.07 ddAC → PG vs TAC 80.6% vs 80.1%, HR 0.93 ddAC → P vs TAC HR 0.87 5 year OS (secondary) ddAC → PG vs ddAC→P 90.8% vs 89.1%, HR 0.85 ddAC → PG vs TAC 90.8% vs 89.6%, HR 0.86 ddAC → P vs TAC HR 1.01	TAC→ febrile neutropenia and diarrhea P→neuropathy ddCHT→anemia	TAC=5 AC→P=8 AC→PG =11
Del Mastro, 2015 GIM2	2091	100%	7 y	FEC→T q14 + pegfilgrastim EC→T q14+ pegfilgrastim	FEC→T q21 EC→T q21	DFS HR 0.77 CI 0.65-0.92, p 0.004 (primary) OS HR 0.65 CI 0.51-0.84, p0.001	ddCHT: anemia, transaminitis, myalgias	1 AML 1 MDS

Grazie per l'attenzione