The right time to stop anticancer therapy

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Breast Cancer epidemiology:

- 1.3 M new cases per year
- 0.5 M death per year

- 30 - 50% early breast cancer patients will develop metastatic disease
- 10% patients are diagnosed in IV stage disease

- Median overall survival of metastatic patients is 2-3 years
- 2% patients are alive 20 years after diagnosis of metastatic disease

- The aim of the treatment is to prolong survival and improvement the quality of live

Advanced Breast Cancer:

- Different clinical appearance
- Confirmation the diagnosis(ER PgR HER2 status)
- Choice of treatment based on

  Biology of the tumor

  Clinical data

  Previous anti cancer treatment

  Performance status

  Menopausal status
- Consider clinical trial
- Chemotherapy
- Hormonal treatment
- Targeted therapies
- Main goal of treatment is palliation
- Long term survival is possible

When the treatment should be terminated? Localization and extent of diseases

Median survival of pN1 patients. Previous adjuvant chemotherapy.

Localization	m OS (months)
Only local	No data
Opposite breast	30.2
Local and regional	20.6
bones	21.8
Visceral (no liver)	13.1
liver	5.4
CNS	4.0

First recurrences up to 3 years after mastectomy

Localization	N+ (%)	N- (%)
Local /regional	14.5	3.8
Distant	16.7	6.4
Bones	8.9	2.9
Visceral	6.8	2.6
Soft tissue	1.0	0.9
Multiple	17.3	3.0
Local /regional And distant	6.8	0.7
Multiple distant	10.5	2.3
Opposite breast	3.2	1.8
All	**51.7**	**15.0**

Chung Ch et al., Objectives in the Management of metastatic breast cancer Oncol 2003;8:514-20

Advanced Breast

- In majority of patients remission can be achieved and performance status improved
- Median response for the initial treatment is usually 8-14 months
- Progression occurs in the majority of cases

- Results of first and second line treatments are known
- The results of 3rd and later lines are not confirm

- Time of response is shorter

Quality of life

- Palliation is indicated when QoL parameters are improving even if there is no prolongation of overall survival.
- There is no data at what level of QoL the treatment is contraindicated
- Benefits from the treatment should be greater than toxicity and cost of therapy [1]
- Quality of live parameters are subjective and can change during the time.
- Comparison of QoL parameters is difficult [1, 2]

1. ASCO. Outcomes of cancer treatment for technology assesment and cancer treatment guidelines. J Clin Oncol 1996;14:671-79,
2. Waldron D et al., Quality of life measurment in advanced breast cancer: assessing the indyvidual. J Clin Oncol 1999;17:3603-11

"It matters not how long you live, but how"

Festus, Philip James Bailey

When the treatment should be terminated?

- When the treatment is not indicated?
- Prognostic and predictive factors

Cancer factors:

- ER, HER 2
- localization and extent of diseases
- previous response rate (RR)
- previous progression free survival (PFS)

Overall survival (O S), response rate (ORR) and time to progression (TTP)

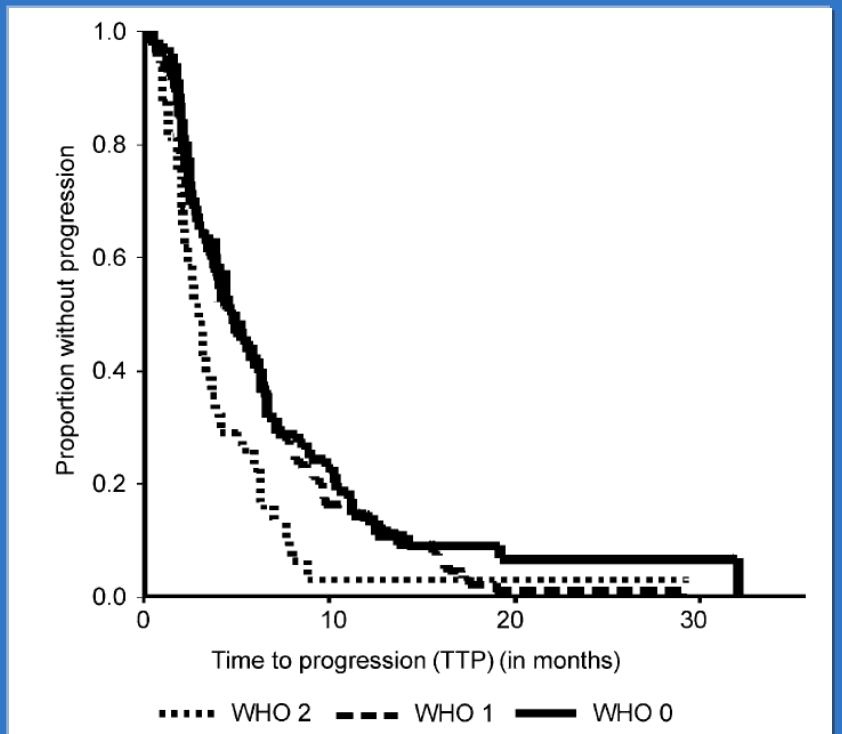
Trial	Treatment	No pts (%)	ORR	TTP (%)	OS (m)
O'Shaughnessy at a	Docetaxel + XEL	255	42% (p=0.006)	6.1 (p=0.001)	14.5 (p=0.0126)
	Docetaxel	256	30%	4.2	11.5
Albain, O'Shaughnessy	Paclitaxel + GCB	267	39% (p=0.0007)	5.4 (p=0.013)	18.5 (p=0.018)
	Paclitaxel	262	26%	3.5	15.8

O'Shaughnessy iet al., J Clin Onocl 2002;23:5542-51, Albain et al., J Clin Oncol 2004;22:5s, O'Shaughnessy et al., Proc Am Soc Clin Oncol 2003;22:7

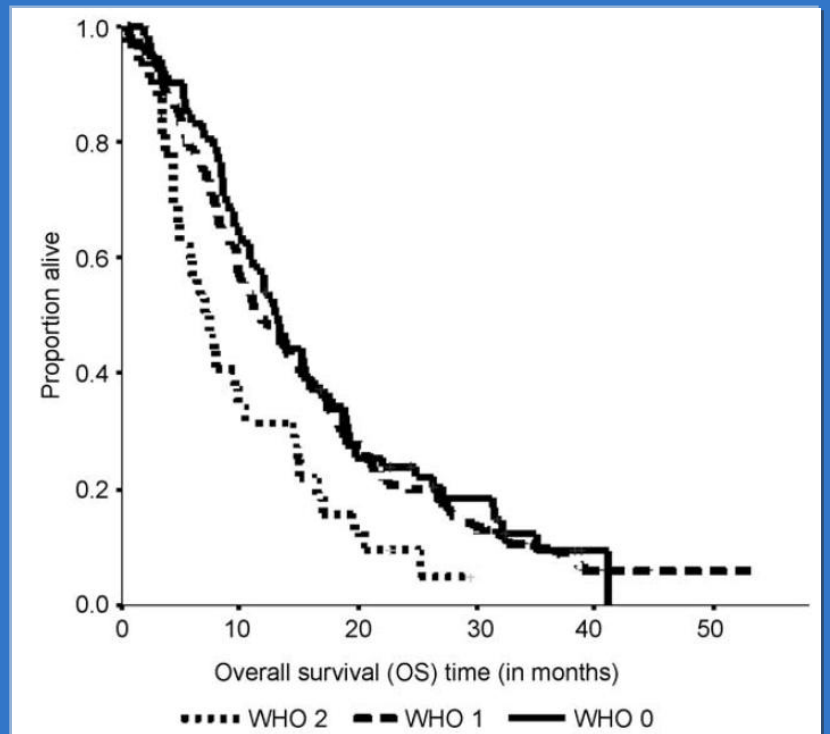
Results of treatment and performance status:

Randomized phase III trial -283 patients

DCX *vs* MTX – 5 Fu



Variable	*n*	Median TTP (months)	*P* value (bw 0&2)	*P* value (bw 1&2)
WHO 0	72	5.0	0.0092	
WHO 1	140	4.8		0.029
WHO 2	32	3.0		



Variable	*n*	Median OS (months)	P value (bw 0&2)	P value (bw 1&2)
WHO 0	72	12.9	0.0044	
WHO 1	140	11.3		
WHO 2	32	7.1		0.0073

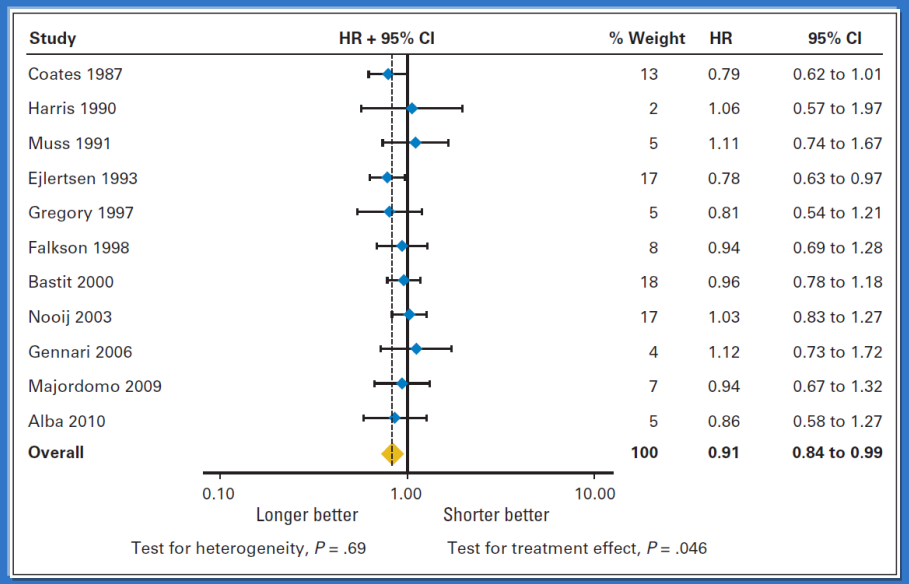
Luomaa M et al,. Prognostic value of quality of life scores for time to progression (TTP) and overall survival time (OS) in advanced breast cancer. Eur J Cancer 2003;39:1370-76

Duration of chemotherapy in MBC

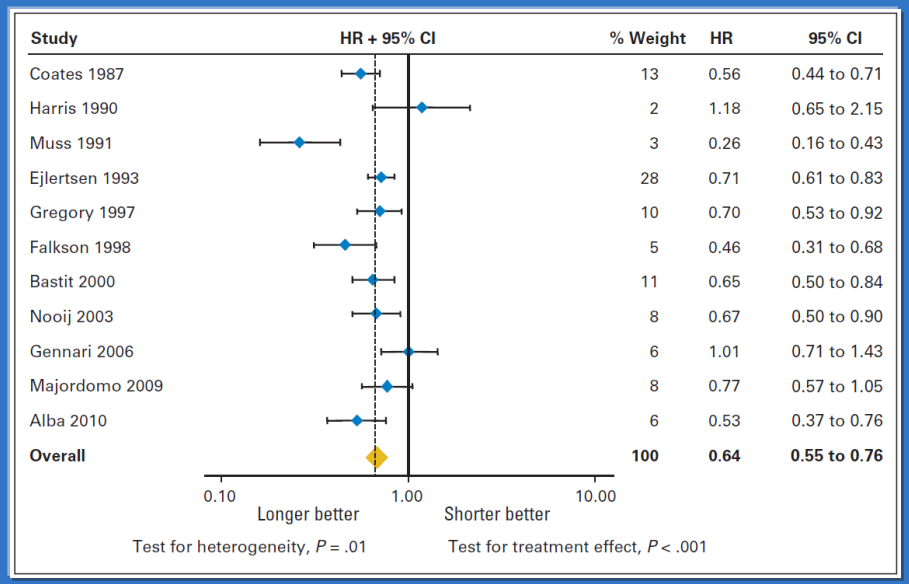
11 randomized trials

2269 patients

3-8 cycles of chemotherapy then maintenance 6 cycles to progression or unacceptable toxicity



OS



PFS

Gennari A, Stockler M, Puntoni M i wsp. Duration of Chemotherapy for Metastatic Breast Cancer: A Systematic Review and Meta-Ananlysis of Randomized Clinical Trials. J Cln Oncol 2011;29:2144-49

Randomized phase III trial of maintenance chemotherapy *vs* observation

- 324 MBC patients
- 6 cycles of gemcitabine and paclitaxel
- CR+PR+SD – randomization to chemotherapy untill progression or observation

median PFS 12 vs 8,3 m p=0.03

median OS 36.8 vs 28 m p=0.047

- No difference in QoL
- Neuritoxicity G >2 (41.7 vs 33.3 % p=0.2)

Young I et al.. A phase III, multicenter, randomized trial of maintenance versus observation after achieving clinical response in patients with metastatic breast cancer who received six cycles of gemcytabine plus paclitaxel as first-line chemotherapy. J Clin Oncol 2012;30(suppl; abstract 1003)

When the treatment should be terminated?

- Not „when to stop” but „how long to treat patients”

  Next line can give the patient additional benefit

  Eribulin > 3 lines -↑ overall survival

When the treatment should be terminated?

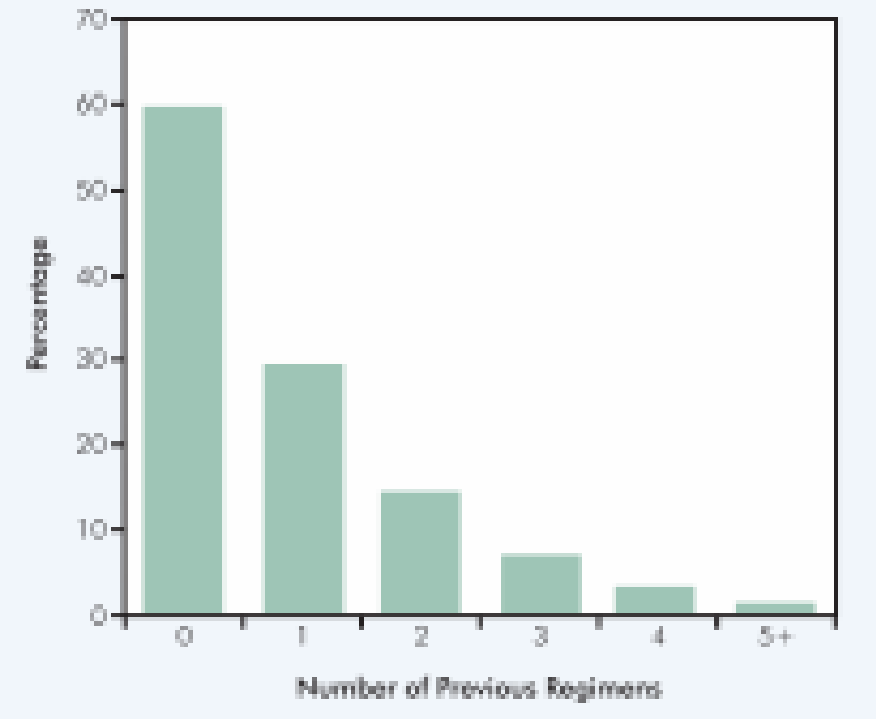
- **NCCN and ASCO**

  no response to the 3 line of treatment

  ECOG -3

National Comprehensive Cancer Network. 2009 NCCN Clinical Practice Guidelines:Breast Cancer-v.1, ASCO Giudelines 2012.

When the treatment should be terminated? Response rate in consecutive lines



- First line ORR - 60-80%
- Second line ORR 30%
- Third line ORR 15%

Soto C et al., Capecitabine (X) and taxanes in patients (pts) with anthracycline-pretreated metastatic breast cancer (MBC): sequential vs. combined therapy results from a MOSG randomised phase III trial. *J Clin Oncol 2006; 4(18 suppl):20s* (Abstract 570).

Response rate in consecutive lines

CT in consecutive lines

Treatment	Number of CT line						
	1st	2nd	3rd	4th	5th	6th	7th
anthracyclines	*46%*	*19%*	11%	10%	10%	16%	8%
taxanes	*33%*	*37%*	*25%*	*27%*	*25%*	*20%*	*20%*
vinorelbine	9%	17%	*22%*	*19%*	*17%*	*18%*	15%
gemcitabine	2%	2%	6%	7%	14%	10%	9%
capecitabine	3%	9%	9%	8%	6%	11%	9%
trastuzumab	3%	4%	8%	11%	11%	11%	16%
other	4%	12%	19%	18%	*17%*	14%	*23%*

Response rate in consecutive lines

CT line				
Response	4	5	6	7
PD	105 (46.9%)	75 (51.0%)	51 (52.6%)	35 (53.9%)
SD	39 (17.4%)	31 (21.1%)	18 (18.5%)	14 (21.5%)
PR	43 (19.2%)	15 (10.2%)	15 (15.5%)	5 (7.7%)
Clinical benefit (PR + SD)	*82 (36.6%)*	*46 (31.3%)*	*33 (34.0%)*	*19 (29.2%)*
Complete response	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nonevaluable	25 (11.2%)	15 (10.2%)	10 (10.3%)	8 (12.3%)
Chemotherapy stopped for toxicity without evaluation	12 (5.3%)	11 (7.5%)	3 (3.1%)	3 (4.6%)
Total	224 patients	147 patients	97 patients	65 patients

- **>3 lines of chemotherapy 1/3 patients has clinical benefit (SD+RR)**
- **Clinical benefit (PR and SD): Taxanes (48%), Trastuzumab (46%)**
- **Toxicity after vinorelbine and gemcitabine**

Planchat E et al., Late lines of treatment benefit survival in metastatic breast cancer in current practice? Breast 2011;20:574-8

Response rate in consecutive lines

OS in different lines 2007 and 2010r

Treatment of MBC (Number of CT line)	Number of patients	Median OS (months) from the line	Median TTF (months)	Number of patients	Median OS (months) from the line	Median TTF (months)
	Database in 2007 [8]			Database in 2010		
Ist line	487	22.5	4.0	529	28.7	3.9
2nd line	331	17.0	3.5	401	20.8	3.4
3rd line	225	12.3	2.8	304	15.6	3.1
4th line	141	9.3	2.9	226	12.6	2.8
5th line	77	8.7	3.0	149	11.7	2.8
6th line	40	8.2	2.1	99	10.4	2.6
7th line or more	25	7.5	3.7	65	11.0	2.8

OS, overall survival, CT, chemotherapy; TTF, time to treatment failure.

- **Increased number of patients treated > 3 lines of CT (30% - 2007; 43% -2010)**
- **OS 11 months in every line**
- **OS = 3x PFS**

Planchat E, et al.,. Late lines of treatment benefit survival in metastatic breast cancer in current practice? Breast 2011;20:574-8,
Kiely B et al., How long hav e I got?: A systematic Reviiew of Recent Randomized Trials. J Clin Oncol 2011;29(4):456-63

Chemotherapy in the terminal phase of disease:

Retrospective study 2005 - 2007

747 pts.

53% chemotherapy

47% best supportive care (BSC)

Disease	
Non small-cell lung cancer	19,7%
Colon cancer	16,1%
Breast cancer	11,9%
Pancreatic cancer	8,6%
Prostate cancer	6,6%
FPI	6%

1 line	2 line	3 line	4 line	5 line	CT in the last 2 weeks of life	CT in the last 4 weeks of life
64%	19%	11%	4%	2%	8%	18%

Kao S et al., Use of chemotherapy at end of life in oncology atients. J Clin Oncol 2009;20:1555-59

Chemotherapy in the terminal phase of disease

- Complex relation patient – physician
- Difficult to estimate survival for individual patient
- Physicians overestimate prognosed survival time by 27%
- It is often easier to administer chemotherapy than to terminate the treatment
- Patients and families fight to not give up
- Extra time to prepare for the unavoidable

Factors influencing decisions

Physician's point of view

Will to treat
Overall survival
Objective response
Toxicity
Symptoms
Complications of previous treatment
Age
QoL

Patient's point of view

Overall survival
Symptoms
QoL
Toxicity
Experience of previous treatment
Age

Chung Ch, Carlson R. Goals and Objectives in the Management of metastatic breast cancer Oncol 2003;8:514-20

Different views on treatment benefits Patient - Physician

- Majority of patients would accept intensive chemotherapy for 1% increase in the chance of cure or extended survival by 3 months while physicians have higher expectations [1]
- Patients want to know their prognosis, expect truth but also hope and optimism [2, 3]
- The information „I have got nothing more to offer" induces highest anxiety
- Care should not end with the termination of treatment [4]
- Patients should be aware that cancer patients who use hospice care even one day live longer than those who never use such help

1. Slevin ML, Stubbs L, Plant HJ. Br Med J 1990;300:1458-60, 2. Kutner JS, Steiner JF, Corbett KK i wsp: Information needs in terminal illness. Soc Sci Med;1999; 48:1341-1352,
3. Davey HM, Butow PN, Armstrong BK: Cancer patients' preferences for written prognostic information provided outside the clinical context. Br J Cancer 89:1450-1456, 2003,
4. Morita T, Akechi T, Ikenaga M. Communication about the ending of anticancer treatment and transition to palliative care. Ann Oncol 2004;15:1551-57

Pitfalls in making decision on termination of treatment

- Patient may be affraid to „fail her doctor” when refusing further treatment
- Physician may be affraid of ”defeat” when making decision to terminate the treatment

Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

- The aim of therapy is to decrease symptom burden, maintenance / improve QoL and to extend life if possible
- Realistic goals should be discussed with patient at the beginning of therapy
- Choice of treatment depends on patient band disease related factors
- Combination multi-drug therapy and sequential therapy may have equal effect on survival
- Treatment duration and the number of therapy lines should be individually adjusted for each patient
- Continuation of treatment beyond 3rd line in patients with good PS and response to previous chemotherapy

Cardoso F, Harbeck N, Fallofield L i wsp. Ann Oncol 2012;23(suppl 7):11-19

Decision process: treatment continuation *vs* termination