LECTURES FOR TRAINING: Determinants of Last-line Treatment in Metastatic Breast Cancer

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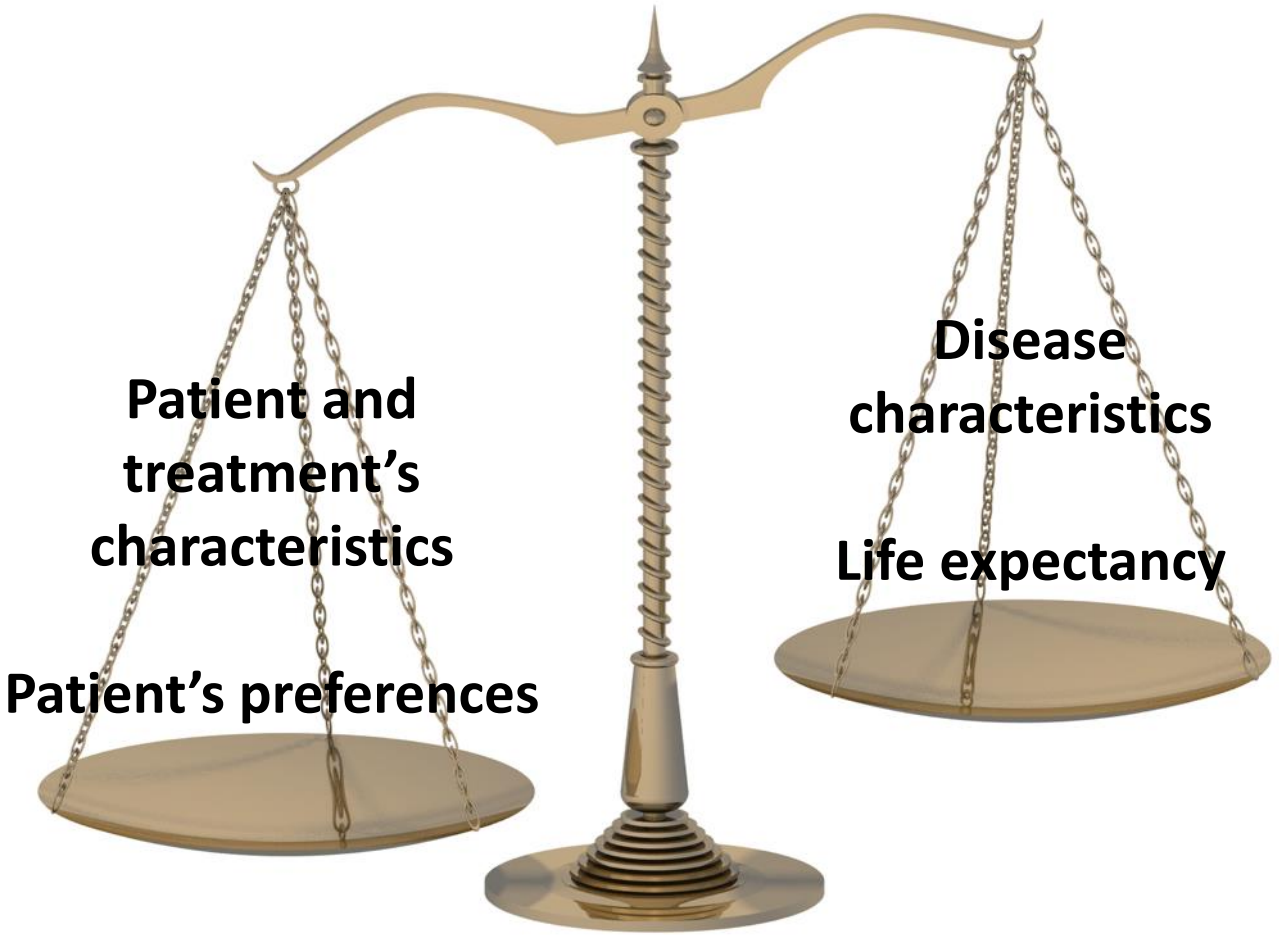
Last-line decision making



The criteria driving clinical decision are still highly debated and no consensus has yet been reached regarding when to switch to BSC.

The usefulness of prognostication

- Accurate prognostication is important for decision making and to determine the goals of care
- Clinical prediction of survival is not enough
- Various prognostic tools can be used to enhance prognostication and improve the accuracy of clinician's survival prediction estimates
- The most appropriate care in the best possible setting

What tool?

- Karnofsky Performance Scale (KPS) and Eastern Cooperative Oncology Group (ECOG) Performance Scale
- Palliative Prognostic Score (PaP)
- Palliative Prognostic Index (PPI)
- Palliative Performance Score (PPS)

Accuracy of the prognostic scores

Score[a]	Cutoff[b]	% Sensitivity (95% CI)	% Specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)	% Accuracy (95% CI)
21 days						
PaP score	9	69.9 (64.4–75.4)	83.7 (79.3–88.2)	80.2 (75.0–85.3)	74.8 (70.0–79.5)	77.0 (73.0–81.0)
D-PaP score	9	72.9 (67.6–78.3)	80.2 (75.6–84.9)	77.6 (72.4–82.8)	75.9 (71.1–80.8)	76.7 (72.7–80.7)
PPI	5	73.7 (68.4–79.0)	67.1 (61.7–72.6)	67.8 (62.4–73.2)	73.1 (67.7–78.5)	70.3 (65.7–74.9)
30 days						
PaP score	5	91.5 (88.5–94.5)	57.7 (51.2–64.3)	76.4 (71.4–81.4)	81.9 (75.9–88.0)	88.0 (84.9–91.1)
D-PaP score	6	87.5 (83.6–90.8)	68.2 (62.0–74.3)	80.4 (76.3–84.5)	78.1 (72.3–84.0)	79.6 (75.8–83.4)
PPI	4	84.8 (80.9–88.7)	53.6 (47.1–60.2)	73.2 (68.8–77.7)	70.2 (63.3–77.2)	72.3 (67.9–76.7)

[a]PPS alone accuracy <50% (see text).
[b]We chose to show the best performance cutoff for each score.
Abbreviations: CI, confidence intervals; D-PaP, PaP Score including delirium; NPV, negative predictive value; PaP, Palliative Prognostic Score; PPI, Palliative Prognostic Index; PPV, positive predictive value.

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Abbreviations: CI, confidence intervals; D-PaP, PaP Score including delirium; NPV, negative predictive value; PaP, Palliative Prognostic Score; PPI, Palliative Prognostic Index; PPV, positive predictive value.

PaP score *C* index = 0.73 (95% CI 0.71–0.74)
D-PaP score C index 0.72 (95% CI 0.70–0.73)

PPI score C index 0.62; **PPS score** C index 0.63

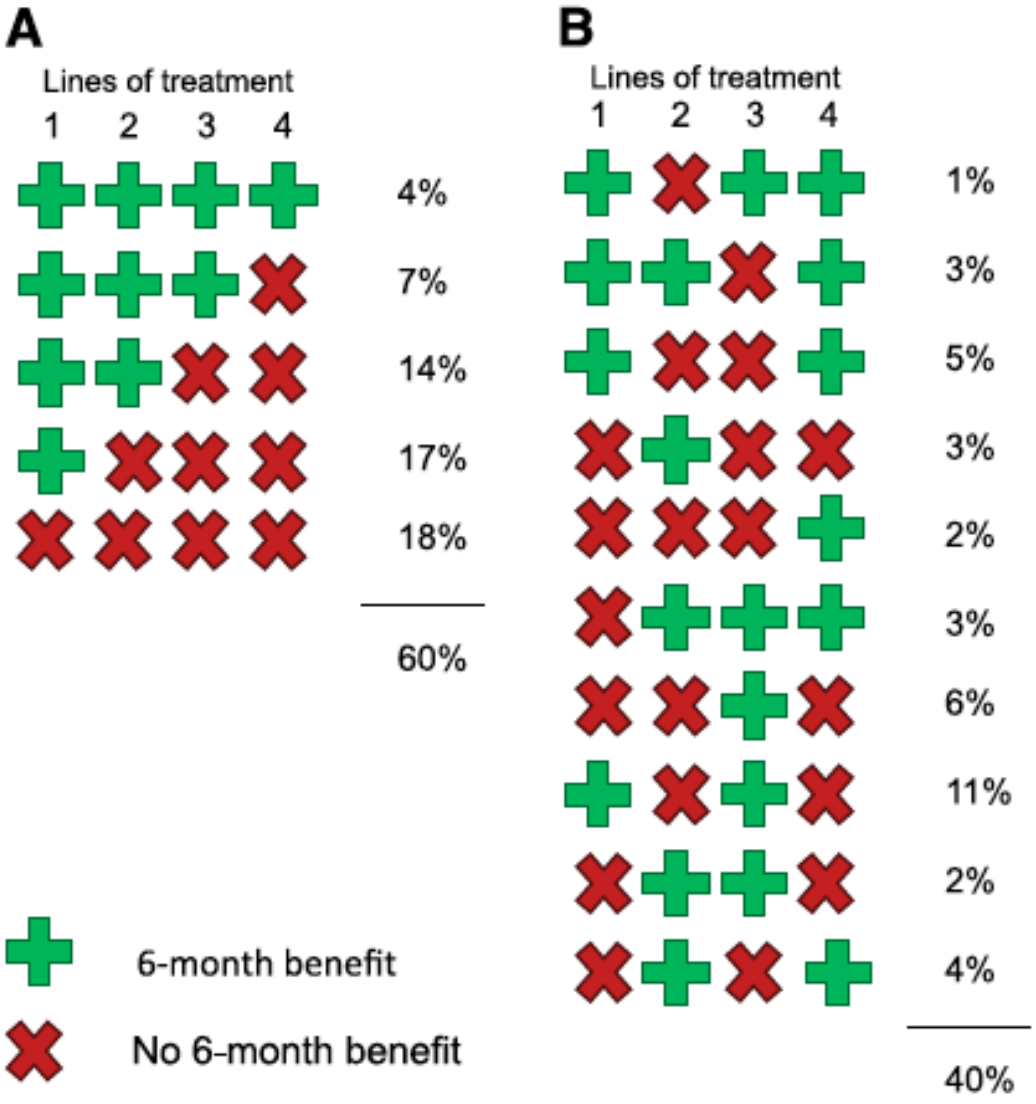
***Δ* < 10% in discriminating accuracy**

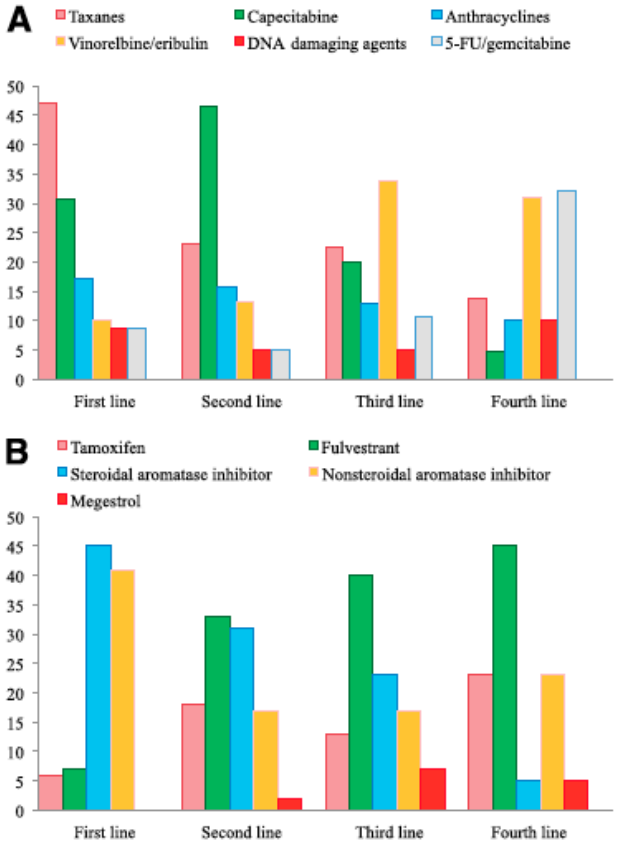
Maltoni M et al. The Oncologist 2012

But…

- Which tool is best?
- Approach to prognostication is not standardized;
- Temporal approach to prognostication (e.g. <6 weeks) vs. expression of prognosis in terms of chance of survival (e.g. 30% -70% by 30 days);
- Some symptoms (dyspnea, anorexia..) are difficult to dichotomize as present or absent;
- patient's reporting of symptoms *versus* systematic assessment (Edmonton Symptom Assessment Scale – ESAS);
- Clinicians need a tool that is capable of identifying patients at both good and bad prognosis.

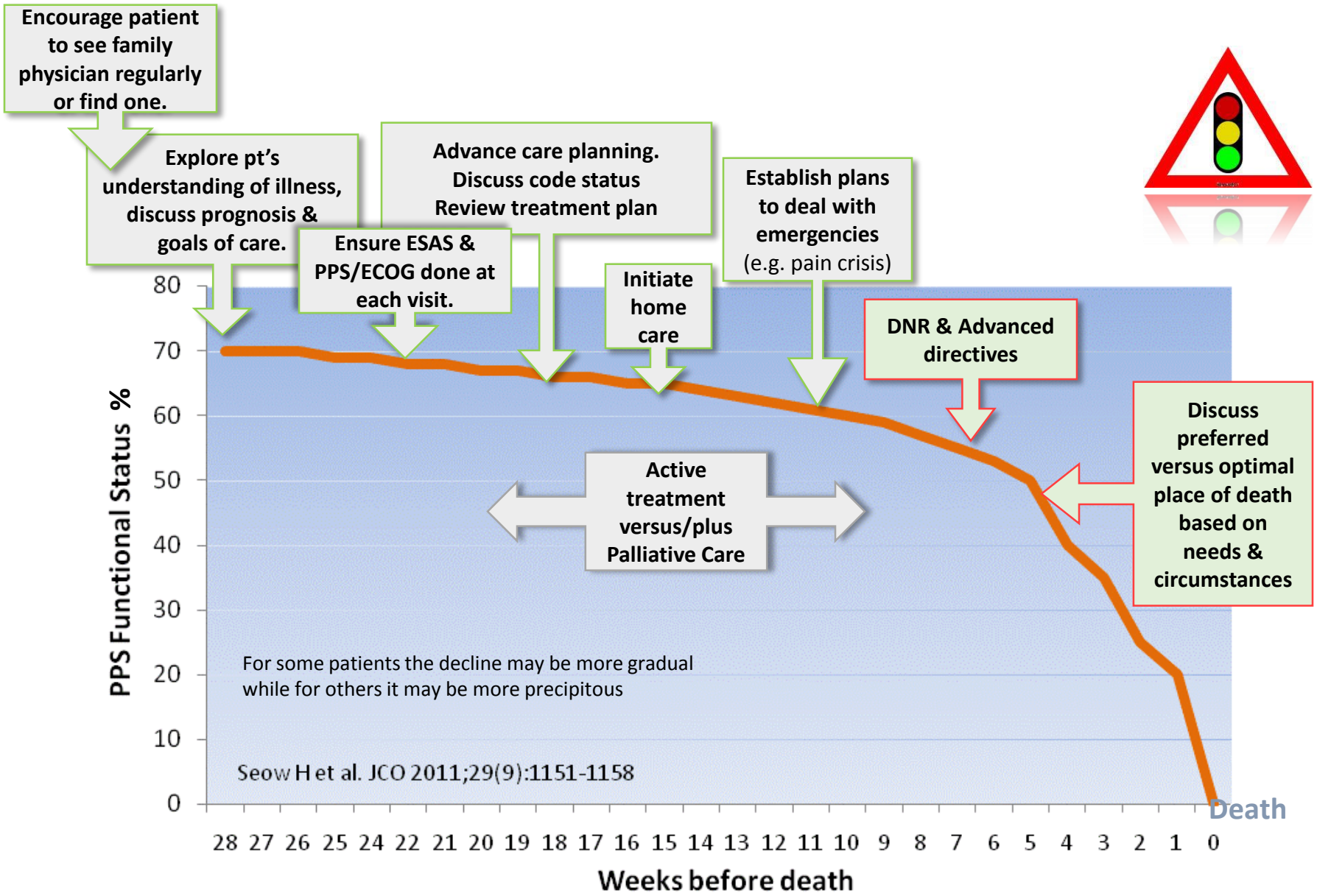
Advanced line ≠ absence of benefit





Bonotto M et al. The Oncologist 2015

Illness trajectory in progressive cancer



Original Study

Determinants of Last-line Treatment in Metastatic Breast Cancer

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Clinical Breast Cancer, June 2018

Aim of the study

To identify the clinicopathologic factors that could improve the prognostic valuation of MBC patients and the clinical decision-making at the end of life;

To test the association between clinicopathologic variables and the interval from the last-line treatment prescription to death.

Patients

Retrospective analysis of the data from 593 consecutive patients with MBC treated at the Department of Oncology of Udine from January 2004 to June 2014;

Patients' data extracted from electronical medical records

- Primary tumor hystotipe
- Molecular subtype
- Comorbidities (cardiovascular, diabetes, pulmonary, renal disease)
- Presence of symptoms or laboratory abnormalities
- ECOG PS at last-line (0-1 versus 2-3)
- Age at last line (<70 versus ≥70)

Methods

Patient characteristics summarized through descriptive analysis

Last-line survival (LLS): interval between the start of last-line and death from any cause.

The association between clinicopathological features and death within **30 or 90 days** after last-line prescription was explored through uni- and multivariate logistic regression models

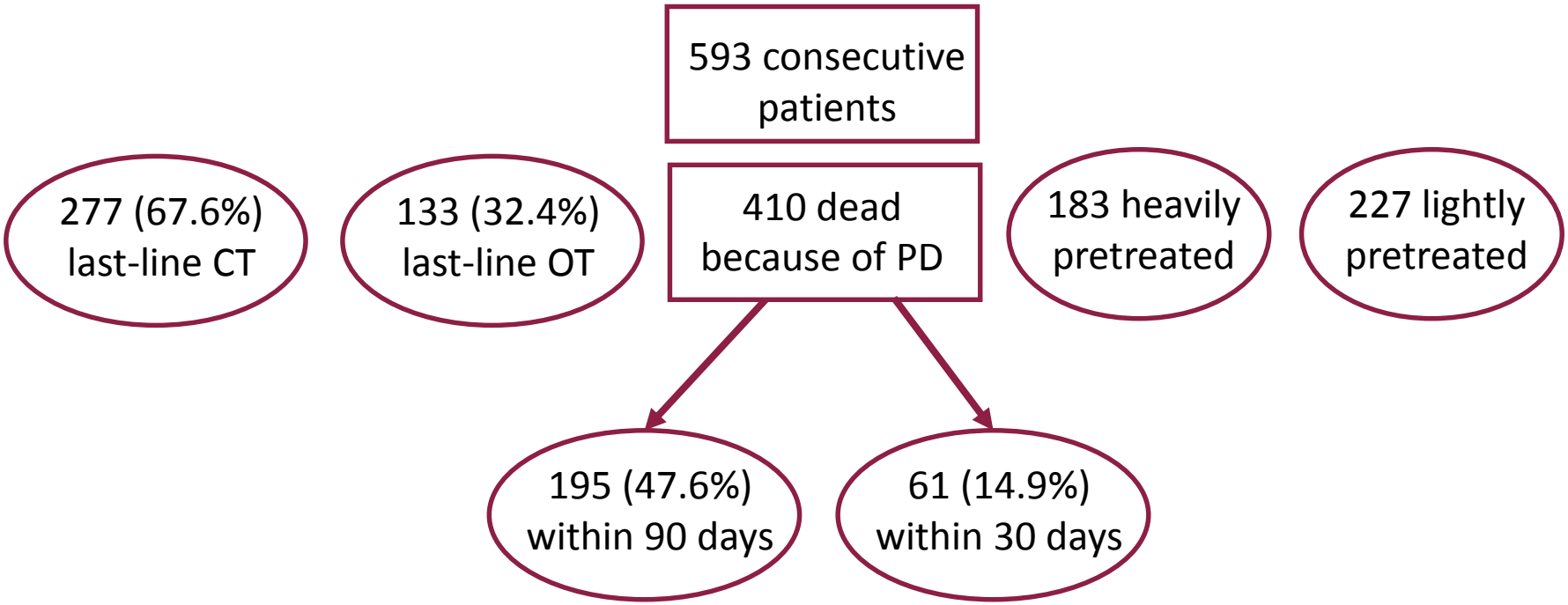
Factors affecting treatment choice were investigated using uni- and multivariate logistic regression analysis.

Subgroup analysis of 2 distinct cohorts: **lightly (≤ 3 lines) and heavily (> 3 lines) pretreated patients** → contingency tables and $\chi 2$ test.

The prognostic role of penultimate line-PFS analyzed through the Kaplan-Meier estimator plot and log-rank test.

Results

- Median age at the last-line of treatment: 67.15 years (31-92 years)
- Median number of treatment lines: 3 (1-13)
- Median LLS: 100 days



Patient and disease characteristics

Variable	Total Population	Lightly Pretreated[a]	Heavily Pretreated[a]	*P* Value[b]
Primary tumor histotype (n = 404)				.333
Ductal	75.99 (307)	76.23 (170)	75.69 (137)	
Lobular				
NOS				
ER status (n = 378)				
Negative				
Positive				
PR status (n = 379)				
Negative				
Positive				
HR status (n = 410)				
Negative				
Positive				
Ki-67 (n = 308)				
<14%				
≥14%				
HER2 status (n = 371)				
Negative				
Positive				
Luminal type (n = 330)				
Luminal A-like				
Luminal B-like, HER2$^-$				
Luminal B-like, HER2$^+$				
HER2$^+$, nonluminal				
Triple negative				
Diabetes mellitus (n = 406)				
No				
Yes				

Variable	Total Population	Lightly Pretreated[a]	Heavily Pretreated[a]	*P* Value[b]
Ascites (n = 322)				.7438
No	91.30 (294)	90.80 (148)	91.82 (146)	
Yes	8.70 (28)	9.20 (15)	8.18 (13)	
Pain (n = 352)				.8366
No	38.92 (137)	39.44 (71)	38.37 (66)	
Yes	61.08 (215)	60.56 (109)	61.63 (106)	
Anorexia, weight loss, cachexia (n = 337)				.4024
No	73.29 (247)	75.29 (128)	71.26 (119)	
Yes	26.71 (90)	24.71 (42)	28.74 (48)	
Liver function impairment (n = 278)				.6914
No	86.33 (240)	85.51 (118)	85.51 (122)	
Yes	13.67 (38)	14.49 (20)	12.86 (18)	
Edema (n = 319)				.2448
No	88.40 (282)	86.34 (139)	90.51 (143)	
Yes	11.60 (37)	13.66 (22)	9.49 (15)	
Pleural effusion (n = 317)				.1612
No	84.86 (269)	82.10 (133)	87.74 (136)	
Yes	15.14 (48)	17.90 (29)	12.26 (19)	
Neurologic symptoms (n = 330)				<.0001
No	74.24 (245)	84.24 (139)	64.24 (106)	
Yes	25.76 (85)	15.76 (26)	35.76 (59)	
CNS symptoms (n = 158)				.352
No	85.44 (135)	88.16 (67)	82.93 (68)	
Yes	14.56 (23)	11.84 (9)	17.07 (14)	
Pathologic fractures (n = 300)				.2625
No	95.33 (286)	93.96 (140)	96.69 (146)	
Yes	4.67 (14)	6.04 (9)	3.31 (5)	
ECOG PS at last line (n = 404)				.6321
0-1	65.35 (264)	66.37 (148)	64.09 (116)	
2-3	34.65 (140)	33.63 (75)	35.91 (65)	
Age at last line (n = 410)				.0029
<70 y	58.05 (238)	51.54 (117)	66.12 (121)	
≥70 y	41.95 (172)	48.46 (110)	33.88 (62)	

[a]Lightly pretreated: ≤ 3 lines; heavily pretreated: > 3 lines [b] $\chi 2$ test.

Multivariate analysis: predictors of death < 30 days

Total population

Variable	OR	95% CI	*P* Value	Variable	OR	95% CI	*P* Value
Death <30 d				Death <30 d			
Prescribing physician			.177	Liver function impairment			.159
Other	1	Ref		No	1	Ref	
Breast cancer specialist	0.51	0.19-1.35		Yes	2.31	0.72-7.36	
Asthenia			.475	Edema			.152
No	1	Ref		No	1	Ref	
Yes	1.36	0.58-3.18		Yes	2.17	0.75-6.27	
Jaundice			.033	Pleural effusion			.642
No	1	Ref		No	1	Ref	
Yes	6.63	1.17-37.66		Yes	1.28	0.45-3.69	
Ascites			.637	Visceral localization			.431
No	1	Ref		No	1	Ref	
Yes	1.37	0.37-5.03		Yes	1.39	0.62-3.12	
Anorexia, weight loss, cachexia			.391	ECOG PS at last line			<.001
No	1	Ref		0-1	1	Ref	
Yes	1.47	0.61-3.54		2-3	4.72	2.04-10.90	

Multivariate analysis: predictors of death < 90 days

Total population

Variable	OR	95% CI	*P* Value
Death <90 d			
Prescribing physician			.404
Other	1	Ref	
Breast cancer specialist	1.49	0.59-3.76	
Pulmonary disease			.294
No	1	Ref	
Yes	0.51	0.15-1.77	
Asthenia			.276
No	1	Ref	
Yes	1.41	0.76-2.59	
Jaundice			.170
No	1	Ref	
Yes	5.05	0.50-50.92	
Ascites			.207
No	1	Ref	
Yes	2.16	0.65-7.18	
Pain			.052
No	1	Ref	
Yes	1.84	0.99-3.41	

Variable	OR	95% CI	*P* Value
Anorexia, weight loss, cachexia			.913
No	1	Ref	
Yes	1.04	0.51-2.12	
Liver function impairment			.184
No	1	Ref	
Yes	1.96	0.73-5.32	
Pleural effusion			.080
No	1	Ref	
Yes	2.10	0.92-4.81	
Visceral localization			.431
No	1	Ref	
Yes	1.39	0.62-3.12	
ECOG PS at last line			.022
0-1	1	Ref	
2-3	2.16	1.12-4.19	
Age at last line			.440
≥70 y	1	Ref	
<70 y	1.27	0.69-2.33	
Total lines			
Per unit	1.06	0.97-1.19	.371

Multivariate analysis: lightly pretreated patients

Death < 30 days

Variable	OR	95% CI	*P* Value
Death <30 d			
Asthenia			.399
No	1	Ref	
Yes	1.65	0.52-5.30	
Jaundice			.092
No	1	Ref	
Yes	5.82	0.75-45.0	
Ascites			.370
No	1	Ref	
Yes	2.26	0.38-13.32	
Edema			.122
No	1	Ref	
Yes	3.10	0.74-12	
Visceral localization			.280
No	1	Ref	
Yes	2.16	0.53-8.78	
ECOG PS at last line			.010
0-1	1	Ref	
2-3	4.69	1.46-15.13	
Age at last line			.110
≥70 y	1	Ref	
<70 y	2.78	0.79-9.76	

Death < 90 days

Variable	OR	95% CI	*P* Value
Death within 90 d			
Asthenia			.360
No	1	Ref	
Yes	1.45	0.66-3.2	
Ascites			.276
No	1	Ref	
Yes	2.59	0.47-14.29	
Liver function impairment			.021
No	1	Ref	
Yes	4.17	1.24-14.04	
Pleural effusion			.139
No	1	Ref	
Yes	2.11	0.78-5.69	
Visceral localization			.062
No	1	Ref	
Yes	2.13	0.96-4.72	
Age at last line			.105
≥70 y	1	Ref	
<70 y	1.91	0.87-4.19	

Multivariate analysis: heavily pretreated patients

Death < 30 days

Variable	OR	95% CI	*P* Value
Death within 30 d			
Prescribing physician			.001
Other	1	Ref	
→ Breast cancer specialist	0.09	0.02-0.39	
Asthenia			.475
No	1	Ref	
Yes	1.58	0.45-5.57	
Jaundice			.378
No	1	Ref	
Yes	2.91	0.27-31.37	
Anorexia, weight loss, cachexia			.659
No	1	Ref	
Yes	1.31	0.39-4.46	
Liver function impairment			.045
No	1	Ref	
→ Yes	4.63	1.03-20.77	
ECOG PS at last line			.001
0/1	1	Ref	
→ 2/3	7.50	2.25-25.11	

Death < 90 days

Variable	OR	95% CI	*P* Value
Death within 90 d			
Pain			.216
No	1	Ref	
Yes	1.54	0.78-3.03	
Anorexia, weight loss, cachexia			.022
No	1	Ref	
→ Yes	2.41	1.13-5.12	
ECOG PS at last line			.007
0-1	1	Ref	
→ 2-3	2.59	1.30-5.14	

Multivariate analysis: luminal lightly pretreated pts

CT

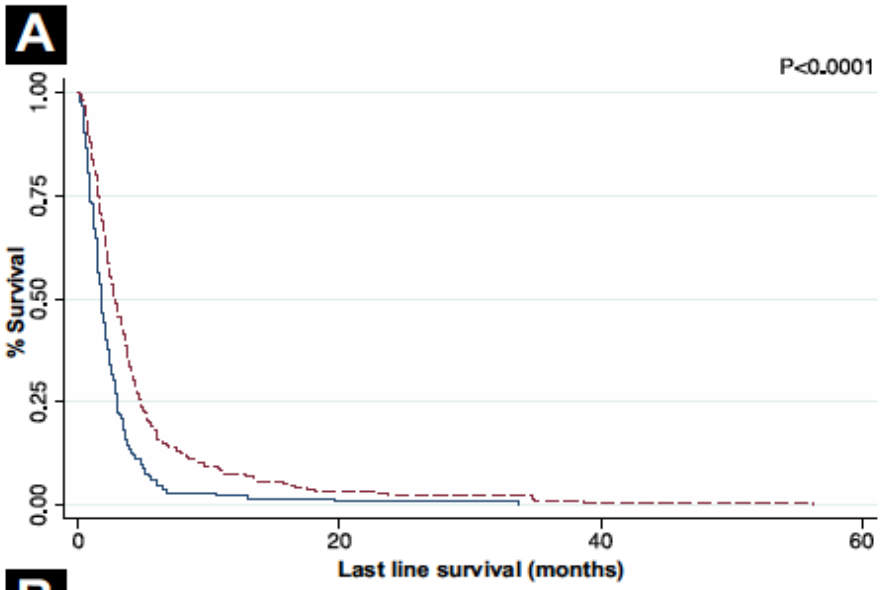
- **Age < 70** years: OR 7.49; 95% CI 2.77-20.24; P < 0.0001
- **Luminal B-like disease**
  - ***HER2^{+} disease***: OR 4.85; 95% CI 1.36-17.30; P 0.015
  - ***HER2^{-} disease***: OR 11; 95% CI, 1.79-67.48; P 0.010
- **Number of previous lines** as a continuous variable: OR 1.78; 95% CI 1.02-3.09; P 0.042

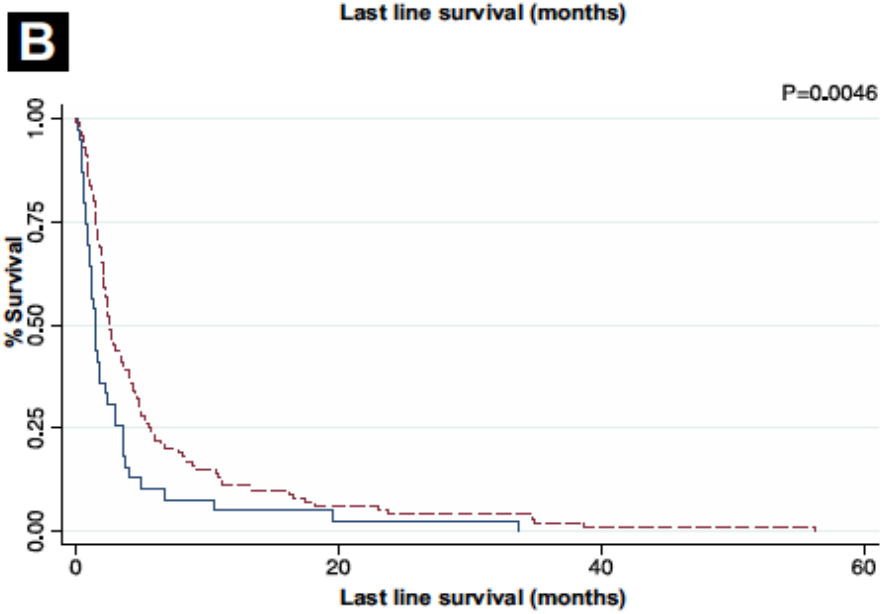
CT

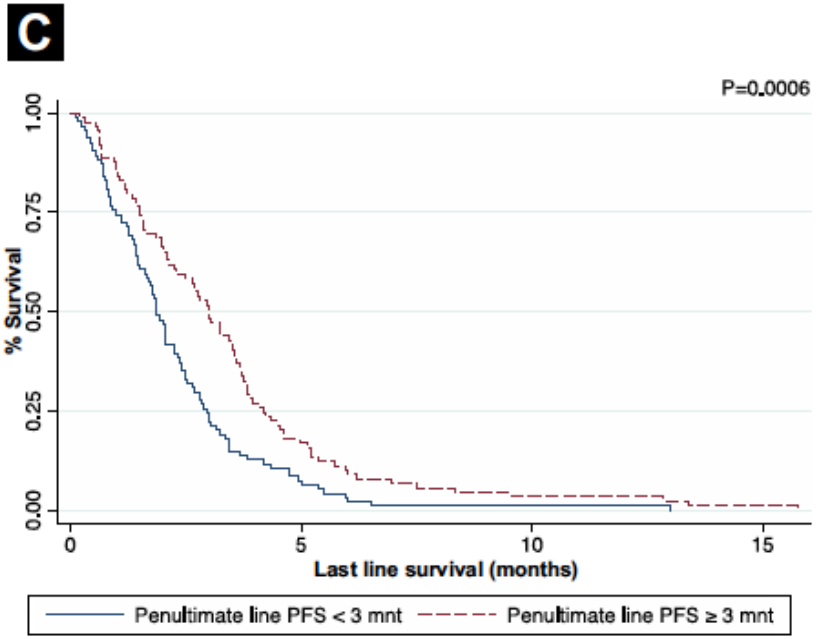
- Patients with **cardiovascular disease** were less likely to receive CT: OR 0.33; 95% CI 0.13-0.83; P 0.018

Heavily pretreated patients: only **ECOG PS > 1** was associated with the therapeutic choice: OR 0.28; 95% CI 0.14-0.60; P 0.001

Last-line survival according to PFS in penultimate line







A Total population

B Lightly pretreated patients

C Heavily pretreated patients

Discussion

ECOG PS > 1 at the last-line treatment associated with increased risk of death within 30 days both in lightly and heavily pretreated patients and with increased risk of death within 90 days among heavily pretreated patients.

VOLUME 30 · NUMBER 14 · MAY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Identifies Five Key Opportunities to Improve Care and Reduce Costs: The Top Five List for Oncology

Lowell E. Schnipper, Thomas J. Smith, Derek Raghavan, Douglas W. Blayney, Patricia A. Ganz, Therese Marie Mulvey, and Dana S. Wollins

1. **Don't use cancer-directed therapy for solid tumor patients with the following characteristics: low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and no strong evidence supporting the clinical value of further anti-cancer treatment.[10-15]**
   - Studies show that cancer directed treatments are likely to be ineffective for solid tumor patients who meet the above stated criteria.
   - Exceptions include patients with functional limitations due to other conditions resulting in a low performance status or those with disease characteristics (e.g. mutations) that suggest a high likelihood of response to therapy.
   - Implementation of this approach should be accompanied with appropriate palliative and supportive care.

Sources:

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Discussion

Anorexia and weight loss associated with death < 90 days among heavily pretreated patients

Liver function impairment associated with

- death < 90 days among lightly pretreated patients
- death < 30 days among heavily pretreated patients

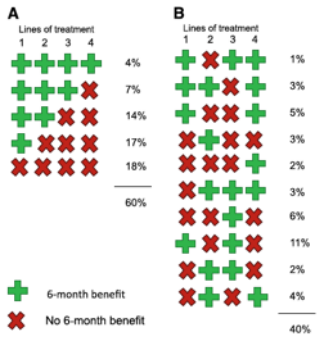
In line with Grunfeld EA, JCO 2006

Age < 70 years

- not associated with an excessive use of aggressive therapies at the end of life among the whole population
- associated with CT prescription in the lightly pretreated subset → not confirmed after correction for the ECOG PS and the presence of symptoms

In contrast with Hashimoto K, The Oncologist 2009

Significant effect of PFS achieved in the penultimate line on the outcome



Bonotto M, The Oncologist 2015

Discussion

Breast cancer oncologists tended to prescribe less active treatments within the patients' last month of life.

- More able to recognize clinical features of terminal breast cancer patients
- More accurate prognostication of heavily pretreated patients
- The prognosis of heavily pretreated patients was driven also by the previous lines of therapy

In line with Zdenkowski N, Intern Med J 2013
Hashimoto K, The Oncologist 2009
Pacetti C, Support Care Cancer 2015

Conclusions

- Our results have confirmed **ECOG PS** as the most robust independent factor driving both therapeutic choice and outcome for MBC patients;
- The **molecular subtype** influences clinical decision-making, not only in the early phase of advanced disease, but also for later treatment lines;
- Younger age seemed not to be associated with the use of aggressive therapies in the end of life period after correction for ECOG PS and the presence of symptoms;
- Our data have highlighted the importance of **oncologist specialization** in the management of end of life care among patients with particularly complex cases;
- To the best of our knowledge, the present study is the first with results to suggest the **significant effect of PFS** achieved in previous lines on the last-line outcomes.

Conclusions

- Improvement of end of life care is 1 of the 3 main strategies for the sustainability of cancer care → prolonging the follow-up period and the integration of data from territorial and hospice care institutes could help in the development of evidence-based guidelines to support clinical decision-making to optimize resources and enhance patient care;

- The identification of factors influencing the decision-making process regarding active treatment prescription in this setting could be the first step toward decreasing the number of unnecessary therapies and improving palliative care.


#focus2018