SAN ANTONIO BREAST CANCER SYMPOSIUM®
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HENRY B. GONZALEZ CONVENTION CENTER, SAN ANTONIO, TEXAS, USA

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International pooled analysis of the prognostic impact of disseminated tumor cells from the bone marrow in early breast cancer: Results from the PADDY study

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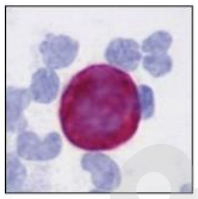
Background

Disseminated tumor cells (DTCs) from the bone marrow (BM)

- Detectable in early breast cancer
- Detection is associated with poor prognosis
  Braun et al., New Engl J Med 2005
- Regarded as early precursors of metastatic disease
  Hosseini et al., Nature 2016

Bone marrow aspiration from iliac crest



Cytokeratin staining of mononuclear cells

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Objectives

Primary Endpoint:

To asses the impact of DTC-detection on

- Overall survival (OS)

Secondary Endpoints:

To asses the impact of DTC-detection on

- Disease-free survival (DFS)
- Distant disease-free survival (DDFS)
- Locoregional relapse-free survival (LRFS)
- Impact of biological tumor subtypes on prognostic value

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Methods: Selection of study centers

International call for individual patient data

- Centers with ≥ 100 available datasets were contacted based on
  - Literature research (08/2016)
  - Centers deemed to perform bone marrow sampling

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Methods: Inclusion criteria

- Early invasive breast cancer (T1-4, N0-3, M0)
- Bone marrow aspiration had to be performed at the timepoint of primary diagnosis / during primary surgery
- DTCs had to be detected by cytokeratin staining
- No systemic treatment before bone marrow sampling

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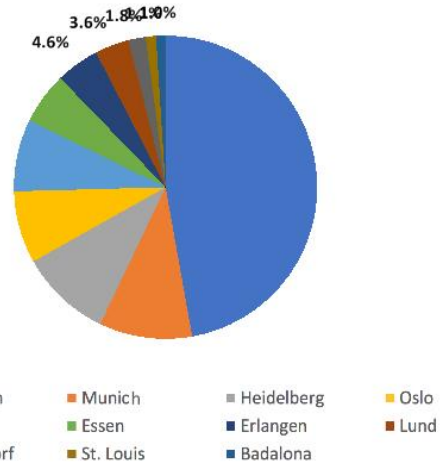
Methods: Statistics

- Patients were defined as DTC positive if at least one DTC was detected
- Survival times were measured from the time-point of bone-marrow sampling
- Univariate survival analysis (Kaplan-Meier, Log-rank test)
- Multivariate survival analysis (Cox regression stratified by center)

Data collection

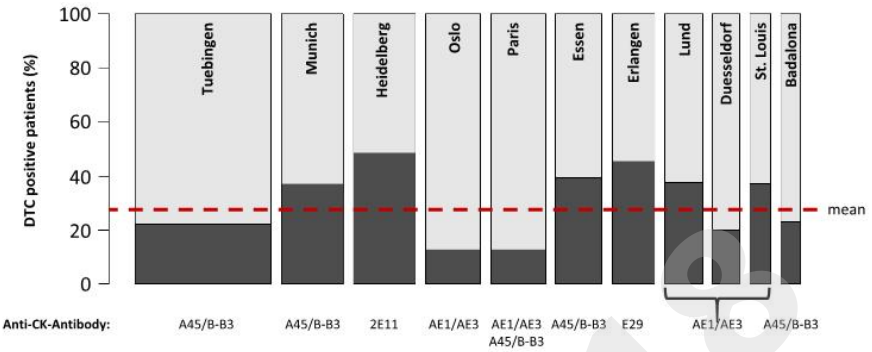
- 10,811 individual data sets were received until 06/2018
- **11 centers** from Europe and the US
- Bone marrow sampling was performed between 01/1986 and 08/2017
- After quality control, data from **n = 10,307** patients was included
- 2,590 of these patients were part of the pooled analysis from 2005*

** Braun et al. New Engl J Med 2005*



Results: DTC detection rate by center

2,814 (**27.3 %**) of 10,307 patients were DTC positive



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Results: Patient characteristics and DTC status

		n	DTC negative	DTC positive	p-value (chi²)
All **patients** (median age 57 years)		**10,307**	**72.7 %**	**27.3 %**	
Menopausal state	premenopausal	3,417	73.2 %	26.8 %	
	postmenopausal	6,458	72.3 %	27.7 %	0.323
Histology	invasive ductal	7,526	73.2 %	26.8 %	
	invasive lobular	1,828	71.1 %	28.9 %	
	other	713	71.4 %	28.6 %	0.133
Grading	G1	1,490	78.9 %	21.1 %	
	G2	5,719	72.8 %	27.2 %	
	G3	2,491	70.1 %	29.9 %	**< 0.001**

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All patients (median age 57 years)		**10,307**	**72.7 %**	**27.3 %**	
Tumor size	T1	6,324	75.3 %	24.7 %	
	T2	3,293	70.3 %	29.7 %	
	T3	403	63.0 %	37.0 %	
	T4	175	54.3 %	45.7 %	**< 0.001**
Nodal state	negative	6,414	75.6 %	24.4 %	
	positive	3,590	68.8 %	31.2 %	**< 0.001**

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Results: Patient characteristics and DTC status

		n	DTC negative	DTC positive	p-value (chi²)
All **patients** (median age 57 years)		**10,307**	**72.7 %**	**27.3 %**	
ER status	positive	7,680	75.2 %	24.8 %	
	negative	1,729	69.8 %	30.2 %	**< 0.001**
PR status	positive	6,638	75.7 %	24.3 %	
	negative	2,626	69.9 %	30.1 %	**< 0.001**
HER2 status	negative	6,526	76.8 %	23.2 %	
	positive	1,012	70.4 %	29.6 %	**< 0.001**

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Results: Prognostic value of DTCs (univariate analysis)

Median follow-up was **7.6 years**; 95% CI: [7.5; 7.7]

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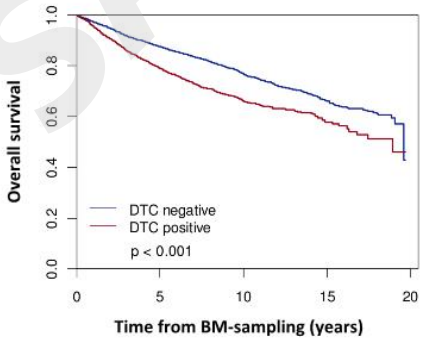

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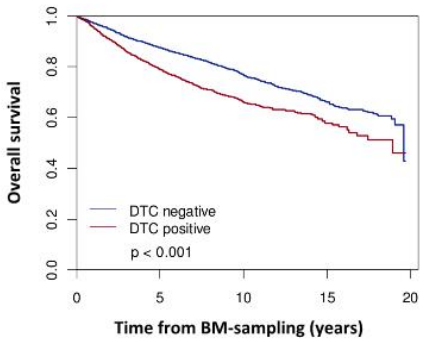

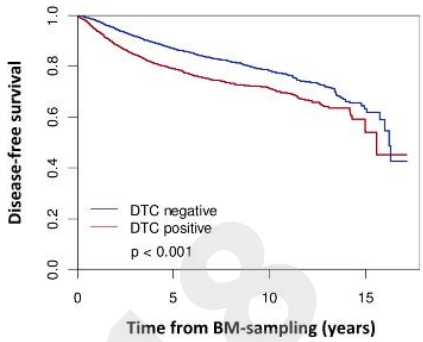

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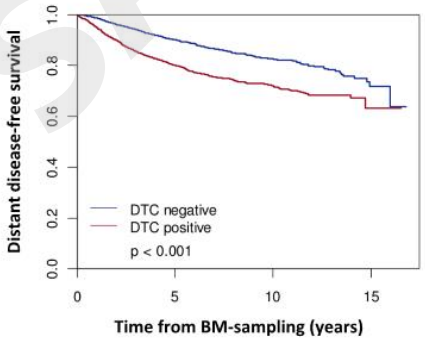

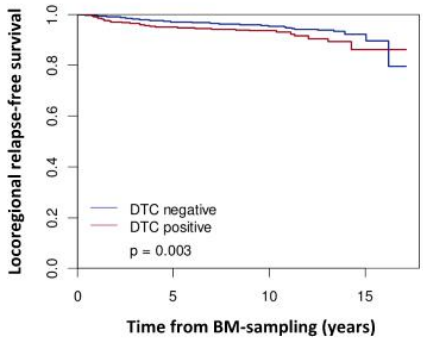

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Results: Prognostic value of DTCs (multivariate analysis)

Cox regression model (stratified by center) including age, menopausal status, histology, tumor size, nodal status, biological subtype (defined by ER, PR, HER2 and grading) and DTCs

OS (n = 7.071)		DFS (n = 6.950)		DDFS (n = 6.255)		LRFS (n = 2.309)	
HR [95%-CI]	p-value	HR [95%-CI]	p-value	HR [95%-CI]	p-value	HR [95%-CI]	p-value
1.23 [1.06; 1.43]	0.006	1.30 [1.12; 1.52]	< 0.001	1.30 [1.08; 1.56]	0.006	1.21 [0.68; 2.16]	0.512

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DTC detection is an independent factor for metastatic relapse and poor OS

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Results: Subgroups – Biological subtypes

Subtype (n = 7.466)	Definition	DTC positive patients	p-value (chi²)
Luminal A-like	Hormone receptor positive HER2 negative G1, G2	22.7 %	< 0.001
Luminal B-like	Hormone receptor positive HER2 negative G3	24.7 %	
HER2 type	HER2 positive	29.6 %	
Triple negative	Hormone receptor negative HER2 negative	25.1 %	

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Results: Subgroups – Biological subtypes

Statistically significant interaction between DTCs and subtype on DDFS
(p = 0.014)

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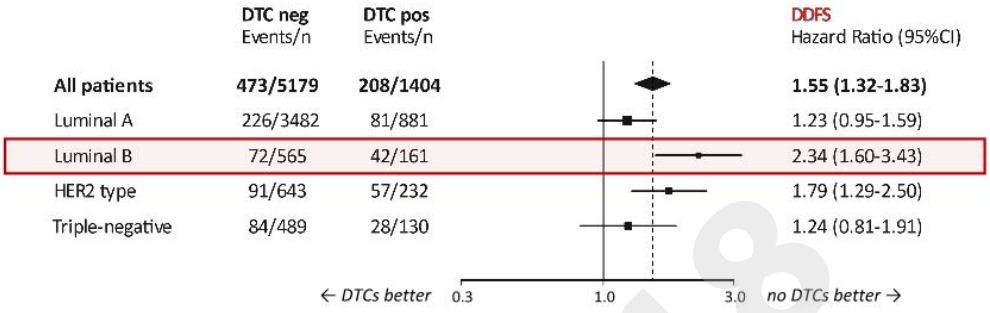

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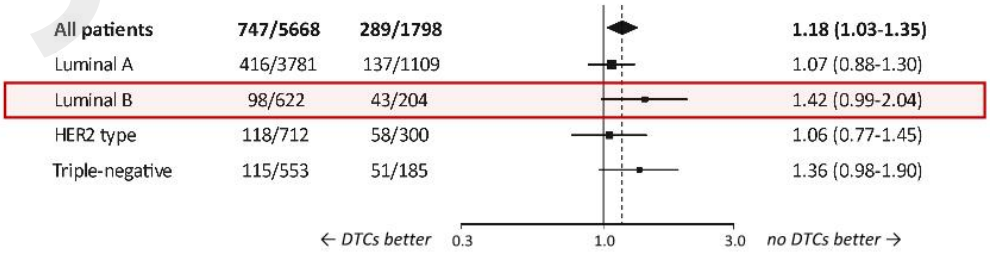
Results: Subgroups – Biological subtypes

No statistically significant interaction between DTCs and subtype on OS
(p = 0.136)



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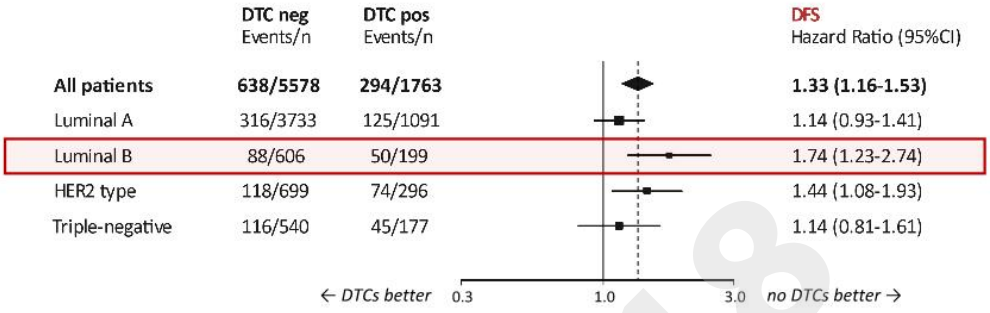
Results: Subgroups – Biological subtypes

No statistically significant interaction between DTCs and subtype on DFS
(p = 0.079)



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Summary

- DTCs were detected in the bone marrow of 2,814 (27.3 %) from 10,307 patients with early breast cancer
- DTC detection was associated with local tumor burden and biological subtype
- Presence of DTCs at primary diagnosis was an independent prognostic factor of OS, DFS, DDFS
- The impact of DTC detection on metastatic relapse was most pronounced in Luminal B patients
- Future trials must evaluate the predictive value of DTC detection and/or characterization on adjuvant therapy efficacy

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- Patients that gave consent to bone marrow sampling
- Participating study sites