Clinical utility of Circulating Tumor Cells (CTC) count to choose between 1st line hormone therapy & chemotherapy in ER+ HER2- metastatic breast cancer

Results of the phase III STIC CTC trial (NCT01710605)

FC Bidard, W Jacot, S Dureau, E Brain, T Bachelot, H Bourgeois, A Goncalves, S Ladoire, H Naman, F Dalenc, J Gligorov, M Espie, C Levy, JM Ferrero, D Loirat, P Cottu, V Dieras, C Simondi, F Berger, C Alix-Panabières, JY Pierga

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Conflicts of interest

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- Related to this study: **Menarini Silicon Biosystem** (research funding, travel grant)

- Unrelated to this study: Amgen (lecture fees, travel grant), Astra-Zeneca (consulting fees, lecture fees), Lilly (consulting fees), Novartis (research grant), Pfizer (lecture fees, consulting fees, travel grant), Roche (consulting fees, travel grant), Sanofi (consulting fees, travel grant)

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Background: first line therapy for HR+ MBC & CTCs

- **No predictive marker** to choose between hormone therapy (HT) *vs* chemoT (CT)
- 90's: CT **not superior** to HT [1]
- HT = preferred 1st line… in the absence of
  - ❑ primary endocrine resistance
  - ❑ serious concerns about the patient's prognosis

[1] Wilcken *et al*, Cochrane 2003
[2] Bidard *et al*, Lancet Oncol 2014

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CTC count (CellSearch®)

- Reproducible & FDA-cleared
- LOE I prognostic biomarker [2]
- > usual prognostic markers (beyond PS) [2]

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STIC CTC: inclusion & workup

Aim: to compare CTC-driven vs clinician's choice for 1st line therapy in HR+ MBC

Main inclusion criteria

- HR+ HER2- MBC
- No prior therapy for MBC
- Condition compatible with HT or CT
- PS 0-3
- Evaluable disease
- Informed consent

1:1 randomization stratified on PS / center / disease-free interval

Clinician's choice

CTC count: blinded

→ **HT (Clin.$_{low}$)**

→ **CT (Clin.^{high})**

The study protocol did not specify which HT or CT to use (best physician's choice)

!!! maintenance HT (after CT) was allowed in patients treated with CT

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→ **HT (Clin.$_{low}$)**

→ **CT (Clin.^{high})**

CTC count (CellSearch®) ?

Clinician's choice: dismissed

- <5 CTC /7.5mL → **HT (CTC$_{low}$)**
- ≥ 5 CTC /7.5mL → **CT (CTC^{high})**

The study protocol did not specify which HT or CT to use (best physician's choice)

!!! maintenance HT (after CT) was allowed in patients treated with CT

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Design: endpoints

Primary enpoint: PFS non-inferiority between clinically-driven and CTC-driven arms

- pre-specified non-inferiority margin:1.25
- α=0.05; β=0.2

➔ PFS events required: N= 498

➔ Patients to be included: N= 994, revised to N= 780

Secondary endpoints:

- OS
- pre-specified subgroups analyses
- cost-efficacy analyses (includ. QoL)
- budget impact analyses

All results: ITT analyses

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All results: ITT analyses

Trial opened from 02/2012 to 07/2016 in 17 centers
N= 778 pts randomized

Median follow-up: 30 months
N= 605 PFS events (78% maturity)
N= 230 OS events (30% maturity)

Results: patients characteristics by arm

	All N=778	Control Arm N=387	CTC arm N=391
Median age [IQR]	63 [55-70]	63 [55-70]	64 [54-70]
PS ≥2	7.7 %	7.9 %	7.6 %
Post-menopausal	87.2 %	87.4 %	86.9 %
PR-negative	21.1 %	23.5 %	18.7 %
Liver metastasis	20.5 %	19.7 %	21.3 %
Bone-only disease	26.3 %	28.7 %	24.0 %
Synchronous stage IV	26.7 %	25.1 %	28.4 %
LDH > normal value	29.5 %	28.9 %	30.1 %
Endocrine-sensitive	71.0 %	70.5%	71.4%
II^{ry} endocrine resistance	26.6 %	27.7 %	25.5 %
I^{ry} endocrine resistance	2.4 %	1.8 %	3.1 %

Characteristics well balanced between arms

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II^{ry} endocrine resistance	26.6 %	27.7 %	25.5 %
I^{ry} endocrine resistance	2.4 %	1.8 %	3.1 %
Clin.$_{low}$	**72.7%**		
Clin.^{high}	**27.3%**		

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IIry endocrine resistance	26.6 %	27.7 %	25.5 %
Iry endocrine resistance	2.4 %	1.8 %	3.1 %
$Clin._{low}$ / CTC_{low}	**47.5%**	46.5%	48.6%
$Clin._{low}$ / CTC^{high}	**25.2%**	26.1%	24.3%
$Clin.^{high}$ / CTC_{low}	**13.8%**	13.4%	14.0%
$Clin.^{high}$ / CTC^{high}	**13.5%**	13.9%	13.0%

← **Concordant estimates: HT in both arms**

← **Discordant estimates: HT or CT**

← **Concordant estimates: CT in both arms**

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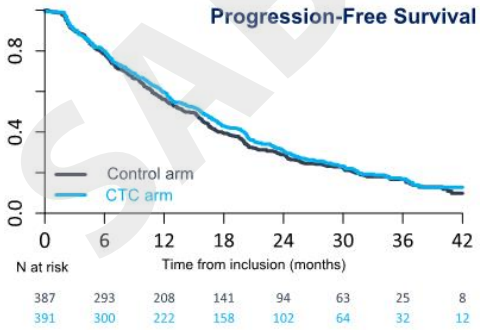
Primary endpoint: PFS in the two arms



Median PFS

CTC arm : 15.6 months [12.8-17.3]

Control arm : 14.0 months [12.2-16.0]

Primary objective met:

PFS HR=0.92, 90%CI[0.80-1.06]

No significant interaction with patient characteristics

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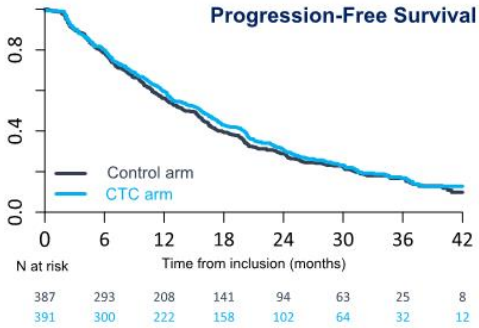
Secondary endpoint: OS in the two arms



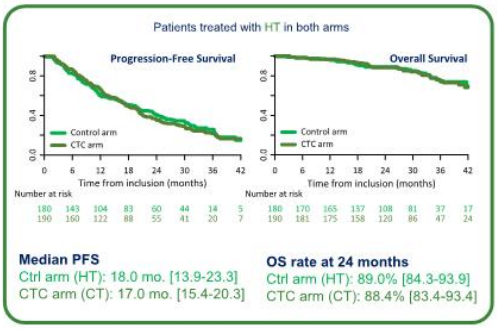
	Median PFS	OS rate at 24 months
CTC arm :	15.6 months [12.8-17.3]	82.1% [78.2-86.2]
Control arm :	14.0 months [12.2-16.0]	81.4% [77.4-85.6]

Planned subgroup analyses

	All N=778	Clin.$_{low}$ / CTC$_{low}$ N=370 (47.5%)	Clin.$_{low}$ / CTC^{high} N=196 (25.2%)	Clin.^{high} / CTC$_{low}$ N=107 (13.8%)	Clin.^{high} / CTC^{high} N=105 (13.5%)
Median age [IQR]	63 [55-70]	64 [56-71]	65 [57-73]	58 [49-64]	62 [55-68]
PS ≥2	7.7 %	3.2%	**12.8%**	5.0%	**16.8%**
Post-menopausal	87.2 %	85.0%	88.3%	**67.6%**	81.1%
PR-negative	21.1 %	21.4%	18.5%	24.0%	17.6%
Liver metastasis	20.5 %	**11.6%**	20.9%	28.0%	**42.9%**
Bone-only disease	26.3 %	28.5%	35.6%	**15.9%**	**12.4%**
Synchronous stage IV	26.7 %	26.2%	24.0%	25.2%	35.2%
LDH > normal value	29.5 %	21.5%	**35.8%**	28.2%	**45.4%**
Endocrine-sensitive	71.0 %	74.1%	76.0%	54.2%	67.6%
II^{ry} endocrine resistance	26.6 %	24.3%	23.0%	**39.3%**	28.6%
I^{ry} endocrine resistance	2.4 %	1.6%	1.0%	6.5%	3.8%
Chemo. Regimen					
Taxanes or Anthra.	82.9%	-	73.3%	94.0%	86.0%
Capecitabine	17.1%	-	26.7%	6.0%	14.0%

Planned subgroups analyses: (1) concordant groups

	Clin.$_{low}$/CTC$_{low}$	Clin.$_{low}$/CTC^{high}	Clin.^{high}/CTC$_{low}$	Clin.^{high}/CTC^{high}
Control arm	HT	HT	CT	CT
CTC arm	HT	CT	HT	CT
N pts total (%)	370 (47.5%)			



Median PFS
Ctrl arm (HT): 18.0 mo. [13.9-23.3]
CTC arm (CT): 17.0 mo. [15.4-20.3]

OS rate at 24 months
Ctrl arm (HT): 89.0% [84.3-93.9]
CTC arm (CT): 88.4% [83.4-93.4]

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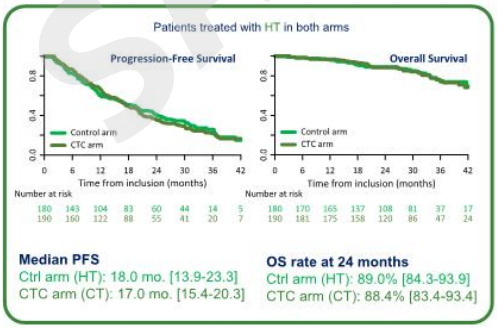
Planned subgroups analyses: (1) concordant groups

	Clin.$_{low}$/CTC$_{low}$	Clin.$_{low}$/CTC^{high}	Clin.^{high}/CTC$_{low}$	Clin.^{high}/CTC^{high}
Control arm	HT	HT	CT	CT
CTC arm	HT	CT	HT	CT
N pts total (%)	370 (47.5%)			105 (13.5%)



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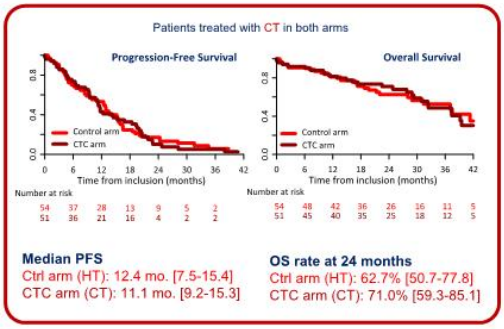

Median PFS
Ctrl arm (HT): 12.4 mo. [7.5-15.4]
CTC arm (CT): 11.1 mo. [9.2-15.3]

OS rate at 24 months
Ctrl arm (HT): 62.7% [50.7-77.8]
CTC arm (CT): 71.0% [59.3-85.1]

➔ **CTC count complements the prognostic estimate and isolate patients with excellent / poorer outcome**

Planned subgroups analyses: (2) discordant groups

	$Clin._{low}/CTC_{low}$	$Clin._{low}/CTC^{high}$	$Clin.^{high}/CTC_{low}$	$Clin.^{high}/CTC^{high}$
Control arm	HT	HT	CT	CT
CTC arm	HT	CT	HT	CT
N pts total (%)	370 (47.5%)	196 (25.2%)		105 (13.5%)

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Planned subgroups analyses: (2) discordant groups

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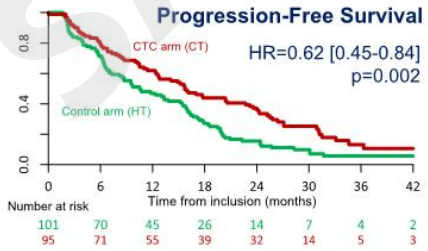

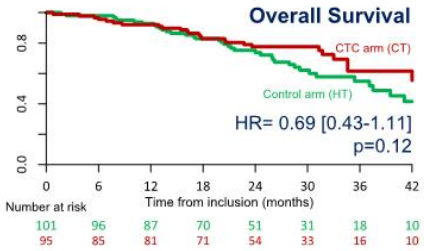

Median PFS
CTC arm (CT): 15.6 mo. [12.2-22.7]
Control arm (HT): 10.5 mo. [7.3-15.4]

OS rate at 24 months
CTC arm (CT): 77.6% [69.2-87.1]
Control arm (HT): 73.7% [64.9-83.7]

Planned subgroups analyses: (2) discordant groups

	$Clin._{low}/CTC_{low}$	$Clin._{low}/CTC^{high}$	$Clin.^{high}/CTC_{low}$	$Clin.^{high}/CTC^{high}$
Control arm	HT	HT	CT	CT
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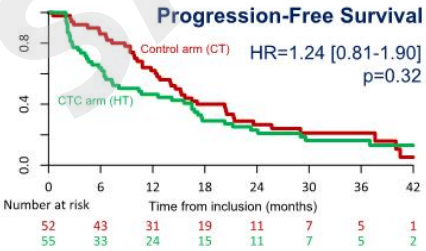

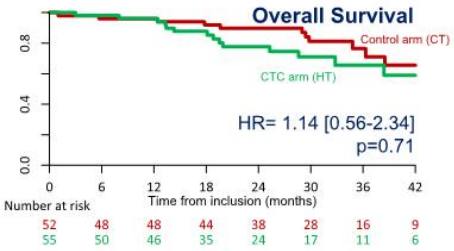

Median PFS
CTC arm (HT): 8.1 mo. [6.1-16.8]
Control arm (CT): 14.6 mo. [10.8-20.4]

OS rate at 24 months
CTC arm (HT): 77.7% [66.3-91.1]
Control arm (CT): 89.8% [81.7-98.7]

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Exploratory analysis: discordant groups pooled

	$Clin._{low}/CTC_{low}$	$Clin._{low}/CTC^{high}$	$Clin.^{high}/CTC_{low}$	$Clin.^{high}/CTC^{high}$
Control arm	HT	HT vs CT		CT
CTC arm	HT			CT
N pts total (%)	370 (47.5%)	303 (38.9%)		105 (13.5%)

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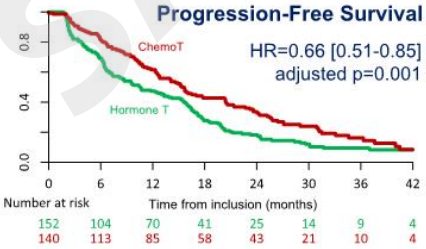

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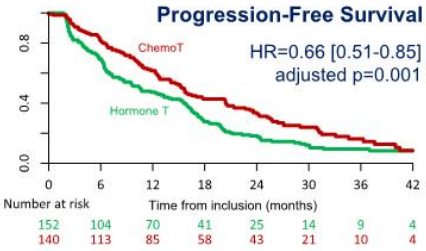

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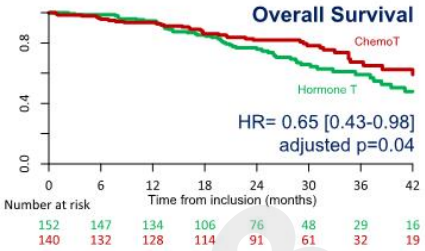

OS rate at 24 months
HT: 74.4% [67.5-82.7]
CT: 82.9% [75.6-88.8]

STIC CTC: conclusions

- **CTC count was tested as a standalone biomarker *vs* clinicians' estimate**

  In the overall population, this reproducible biomarker is clinically reliable

  Room for improvement: combination / integration into multiparametric decision tools

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  Further studies are worthy, especially with CDK4/6 inhibitors added to maintenance therapy

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- **Looking further into discordant subgroups, this is the first contemporary study reporting a significant reduction in the risk of death with frontline chemotherapy**
  This result was obtained in #300 patients randomized between HT and CT and challenges current standards

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- **CTC count should be included in the decision algorithm for HR+ HER2- MBC patients**

Acknowledgements: STIC CTC study

Patients & nurses

Co-authors W Jacot, S Dureau, E Brain, T Bachelot, H Bourgeois, A Goncalves, S Ladoire, H Naman, F Dalenc, J Gligorov, M Espie, C Levy, JM Ferrero, D Loirat, P Cottu, V Dieras, C Simondi, F Berger, C Alix-Panabières, JY Pierga

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