Circulating Tumor Cells-driven choice of first line therapy for HR+ HER2- metastatic breast cancer

Overall Survival analysis of the phase 3 STIC CTC trial

FC Bidard, N Kiavue, C Alix-Panabières, S Dureau, T Bachelot, H Bourgeois, A Goncalves, E Brain, S Ladoire, F Dalenc, J Gligorov, L Teixeira, G Emile, JM Ferrero, D Loirat, L Cabel, V Diéras, F Berger, W Jacot, JY Pierga

institut Curie

Disclosures

FC Bidard	**Menarini Silicon Biosystems (institutional research grant)** Astra-Zeneca, Daichii-Sankyo, Exact Sciences, General Electrics Healthcare, GSK, Lilly, Menarini/Stemline, Novartis, Prolynx, Rain Therapeutics, Roche, Seagen, Sanofi (boards, lectures, travel support, research support)
C Alix-Panabieres	Menarini Silicon Biosystems (honoraria)
JY Pierga	Menarini Silicon Biosystems (institutional research support)

The other authors did not report any COI

Background: CTC and treatment choice in mBC

Treatment choice between chemotherapy (CT) *vs* endocrine therapy (ET) in HR+ HER2- mBC

- ET is the prefered therapy (few side effects)
- CT is an option for patients with unfavorable prognosis
- No validated decision-making algorithm ➔ highly heterogenous treatment decisions

CTC count (CellSearch®)

- Standardized liquid biopsy biomarker (FDA-cleared / run in CLIA labs)
- ≥5 CTC/7.5ml (CTC^{high}) is a LoE I adverse prognostic factor – whatever the line of therapy [1,2]

  strong impact on OS (HR=2.9) [1,2]

  complements *and not duplicates* standard clinico-pathological prognostic factors [2]

STIC CTC concept:

CTC count as an aid to treatment decisions (ET vs CT) in HR+ HER2- mBC

[1] Cristofanilli *et al.*, N Engl J Med 2004

[2] Bidard FC *et al.*, Lancet Oncol 2014

STIC CTC design

Main inclusion criteria
- Pre / post menopausal women
- 1st line HR+ (>10%) HER2- mBC
- PS 0-3
- Could receive either Endoc.T. or ChemoT. (investigator assessment)

Assesments before randomization
- Investigator's choice: **Endoc.T. (« $Clin_{low}$ ») or ChemoT. (« $Clin^{high}$ »)**
- CTC count (CellSearch®) at central platforms

R

Standard arm

Investigators' choice:
- Endoc.T. ($Clin_{low}$)
- ChemoT. ($Clin^{high}$)

CTC arm

Treatment driven by CTC count
- Endoc.T. if CTC_{low} (<5 CTC/7.5mL)
- ChemoT. if CTC^{high} (≥5 CTC/7.5mL)

755 patients, enrolled 02.2012-07.2016 at 17 sites in France

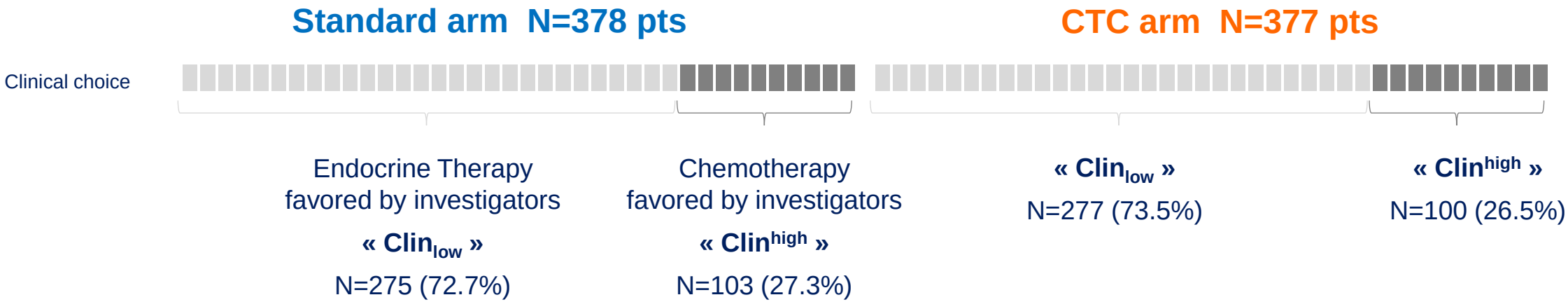
Primary objective – already achieved [3]
- Progression-Free Survival (non-inferiority)

This (final) analysis
- Patient follow-up was stopped in 2021
- Median FU: 57 months
- Updated PFS data: 664 PFS events (87.9% maturity)
- **OS data: 382 OS events (50.6% maturity)**
- **Pre-planned subgroup analyses on PFS & OS**

[3] Bidard FC *et al.*, JAMA Oncol 2021

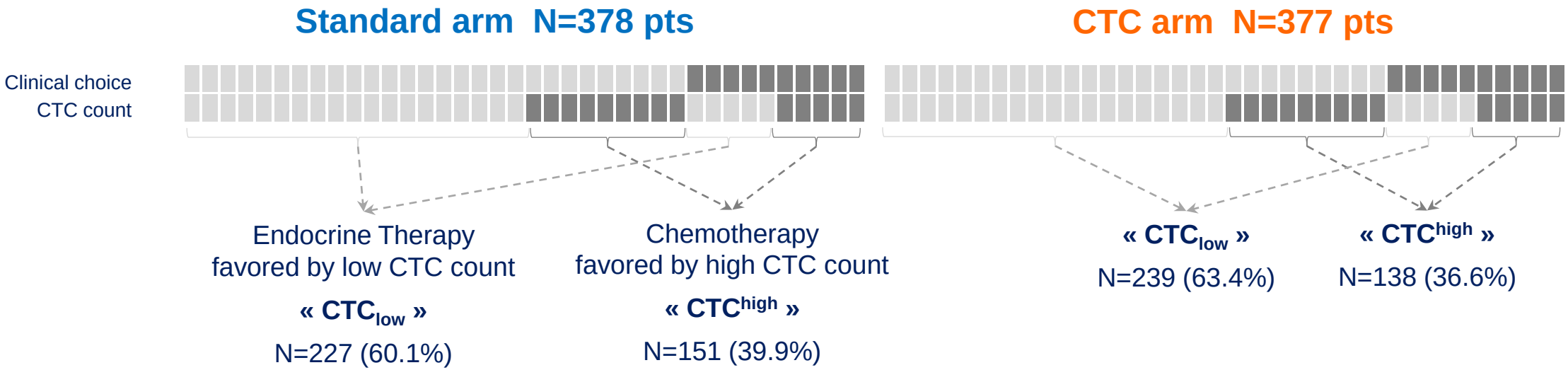
Patient characteristics

	$Clin_{low}$ patients	$Clin^{high}$ patients
PS 2-3	5.8% of $Clin_{low}$ pts	9.9% of $Clin^{high}$ pts
Bone-only disease	31.2%	12.8%
Endocrine-resistance	25.2%	37.9%

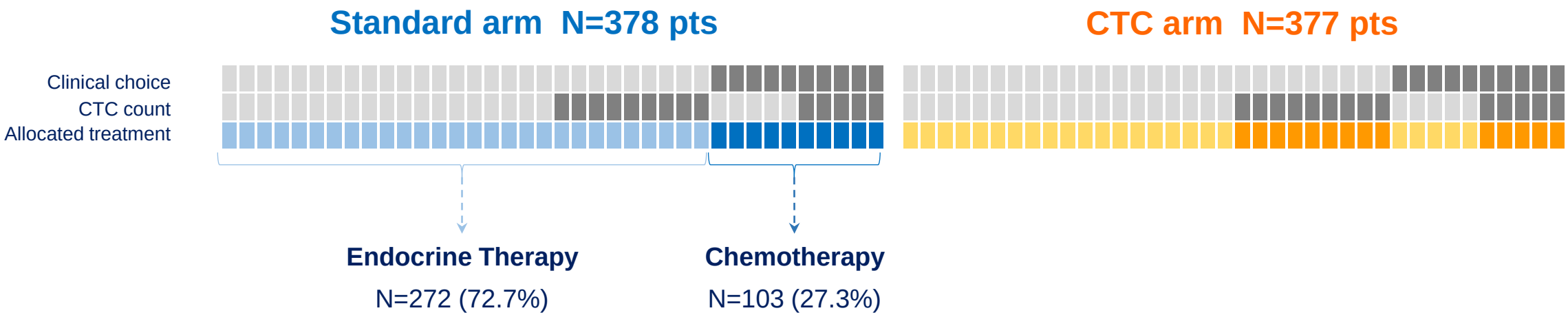


Patient characteristics

	CTC_{low} patients	CTC^{high} patients
PS 2-3	3.4% of $Clin_{low}$ pts	14.5% of $Clin^{high}$ pts
Bone-only disease	25.8%	27.1%
Endocrine-resistance	30.2%	26.0%



Allocated treatments [3]

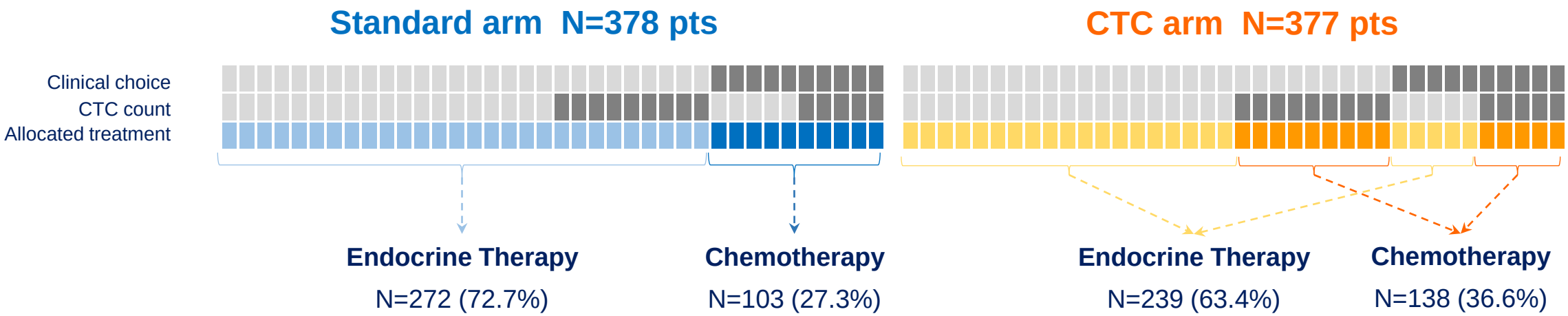


- ✓ Once the allocated treatment type was known (ET or CT), investigators were free to decide which ET or CT to use
- ✓ ET mostly consisted in single agent aromatase inhibitor or fulvestrant

  CDK4/6i were not approved at time of accrual; 42.2% of pts received CDK4/6i as ≥2nd line therapy (no difference between arms)
- ✓ CT mostly consisted in paclitaxel or capecitabine

[3] Bidard FC *et al.*, JAMA Oncol 2021

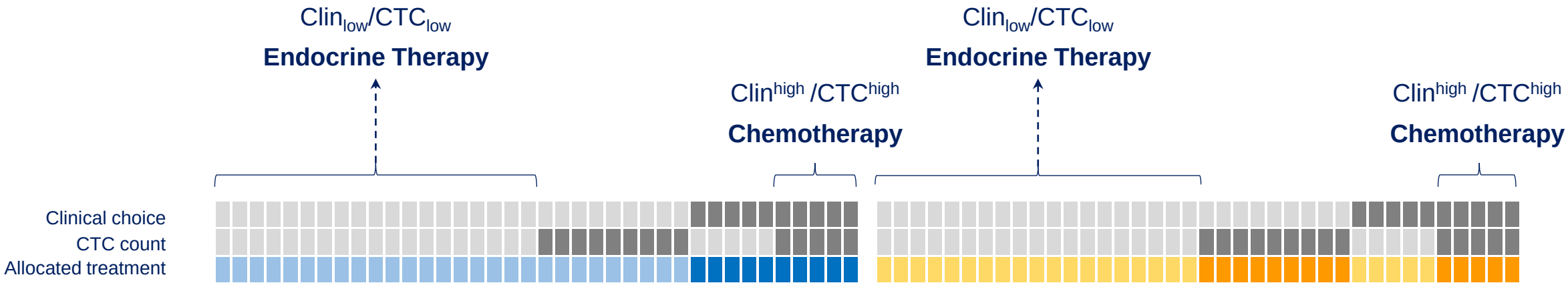
Allocated treatments



Overall, more patients were assigned to chemotherapy in the CTC arm (Δ= +9.7%)

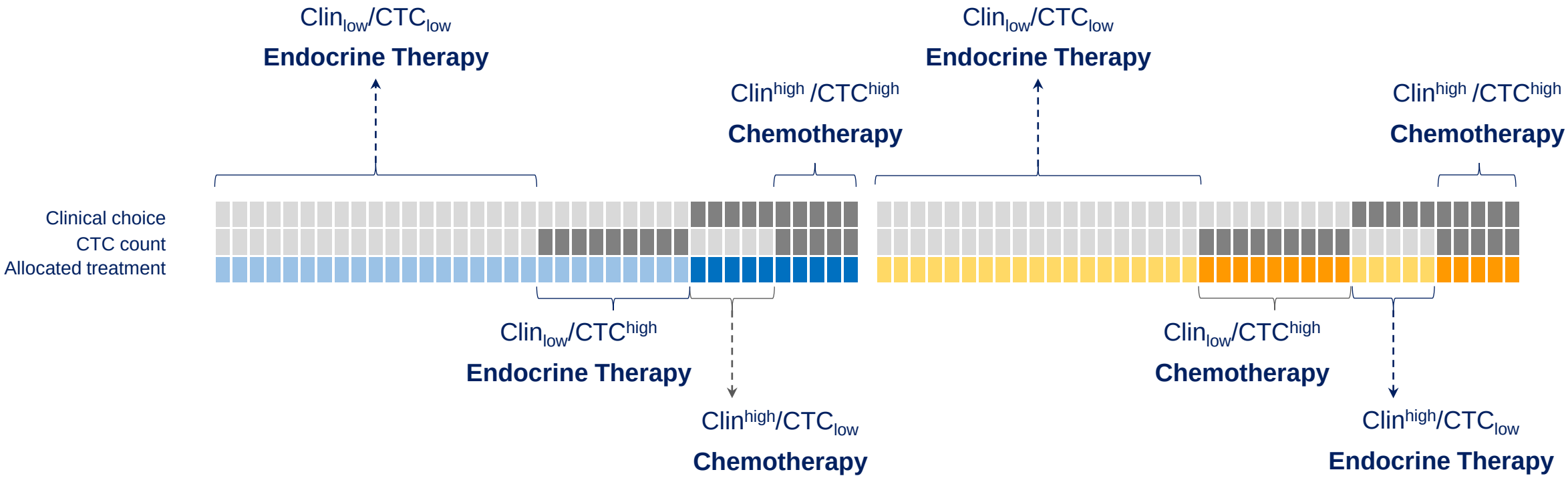
~ 60% concordance between investigators and CTC count

***i.e.* same treatment received in both arms**



~ 60% concordance between investigators and CTC count

***i.e.* same treatment received in both arms**



~ 40% discordance between investigators and CTC count

i.e. treatment differed between arms

Pre-planned subgroup analyses

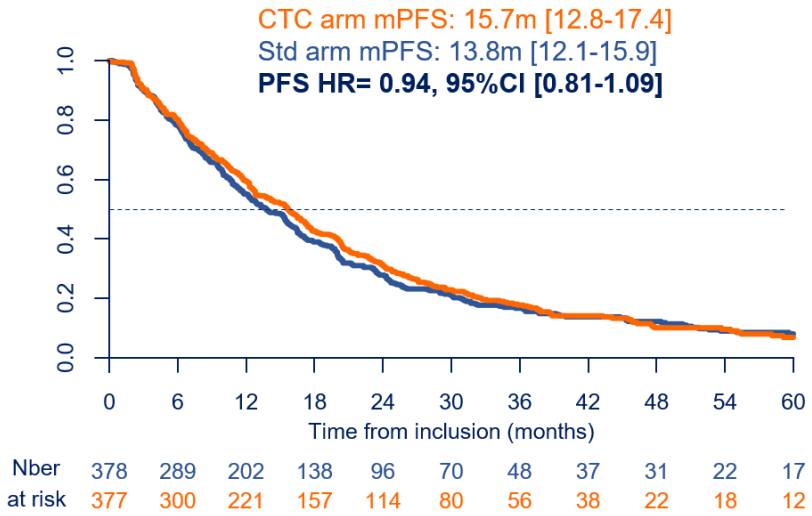
Clin$_{low}$/CTC$_{low}$ Clin^{high} /CTC^{high}

Clin$_{low}$/CTC^{high} Clin^{high}/CTC$_{low}$

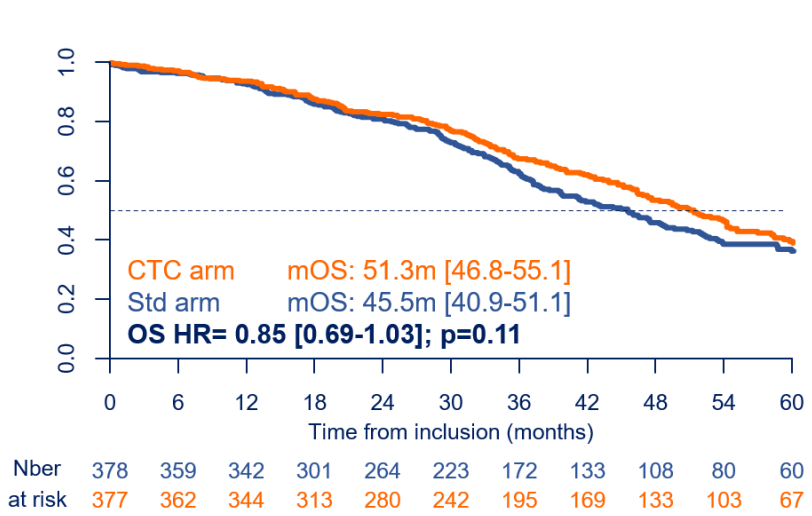
Outcome, all patients – including patients with no treatment change (~60%)

Standard arm N=378 of 378 pts **CTC arm N=377 of 377 pts**

Progression-Free Survival



Overall Survival



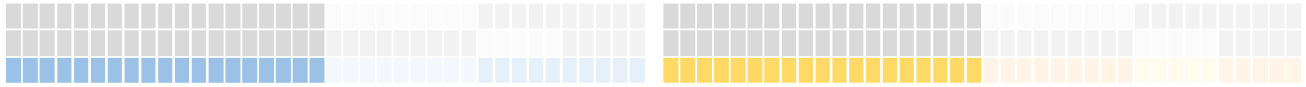
Non-inferiority was previously demonstrated for PFS [3]

Longer follow-up substantiates that CTC-based choice is safe

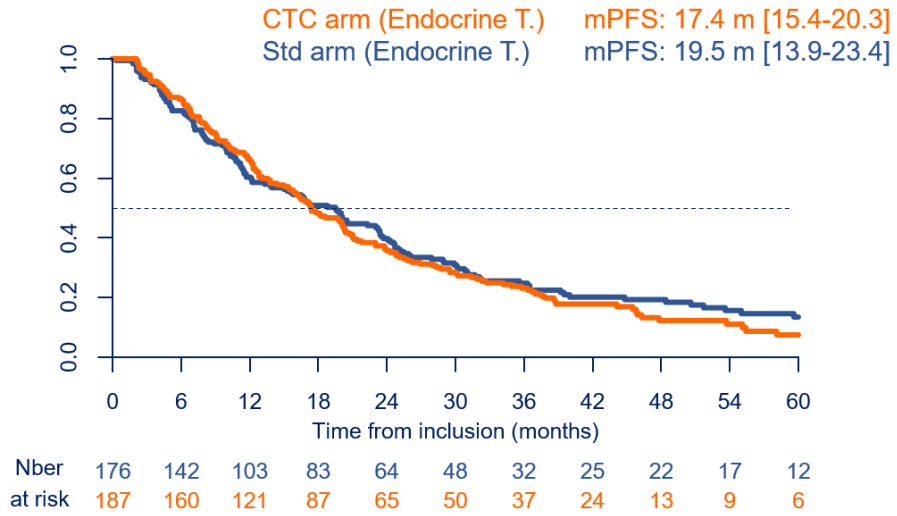
[3] Bidard FC *et al.*, JAMA Oncol 2021

Pre-specified subgroup analysis: $Clin_{low}/CTC_{low}$ (48.2% of patients)

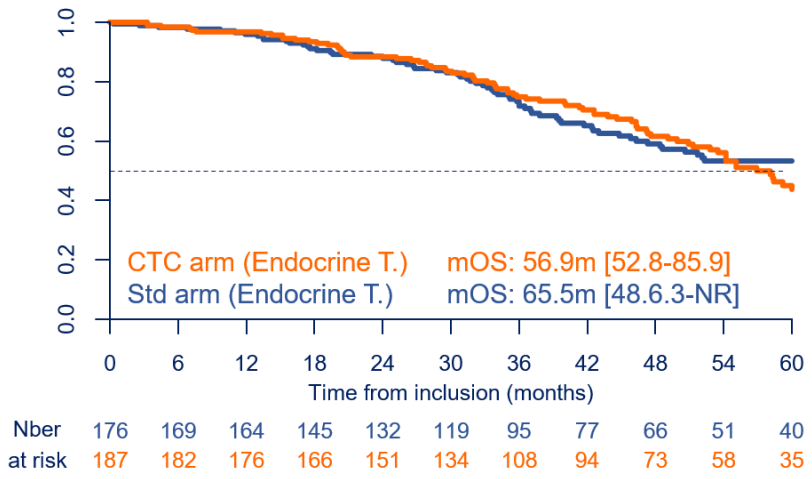
Standard arm N=176 of 378 pts **CTC arm N=187 of 377 pts**



Progression-Free Survival



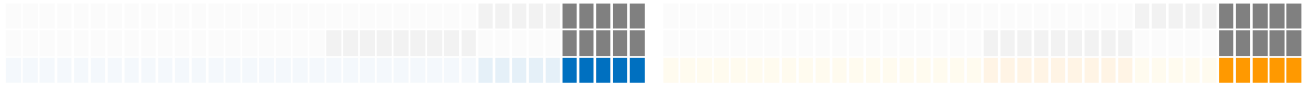
Overall Survival



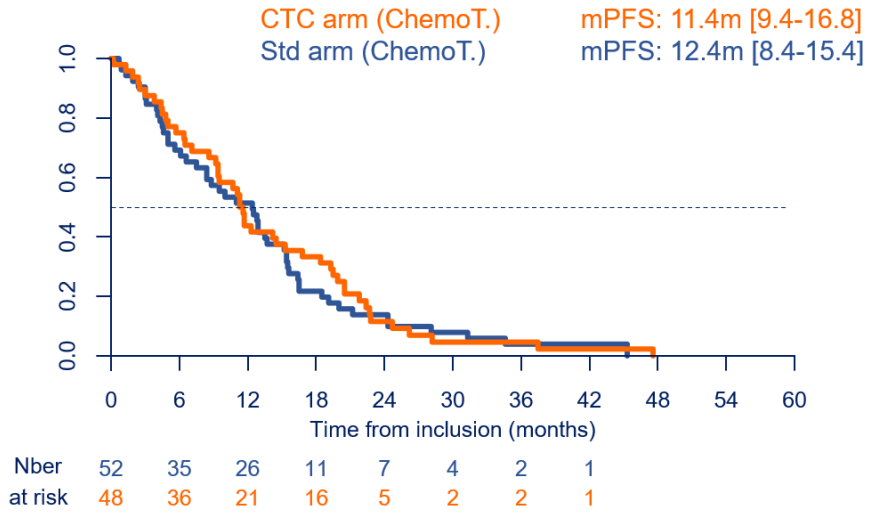
Similar treatment (endocrine therapy) in the two arms led to similar outcomes

Pre-specified subgroup analysis: Clin^{high}/CTC^{high} (13.2% of patients)

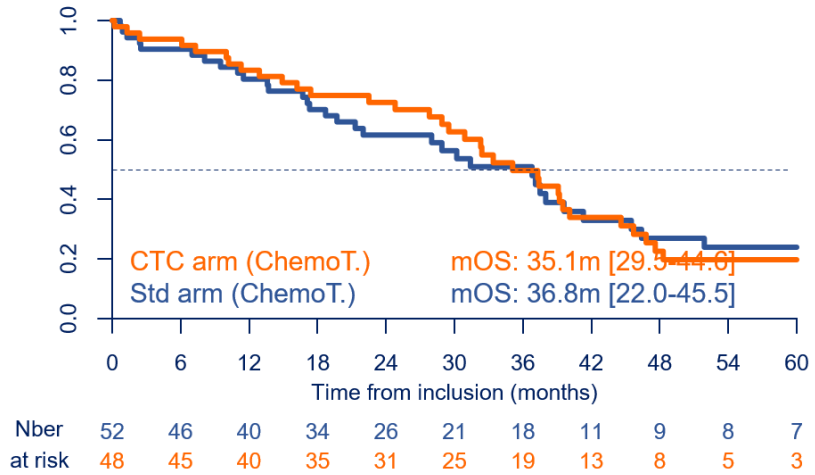
Standard arm N=52 of 378 pts **CTC arm N=48 of 377 pts**



Progression-Free Survival



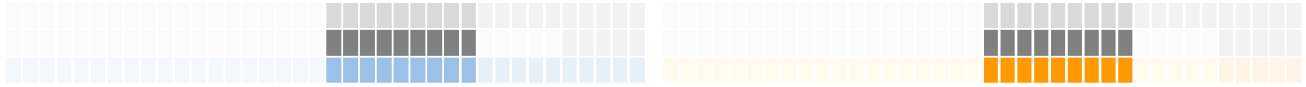
Overall Survival



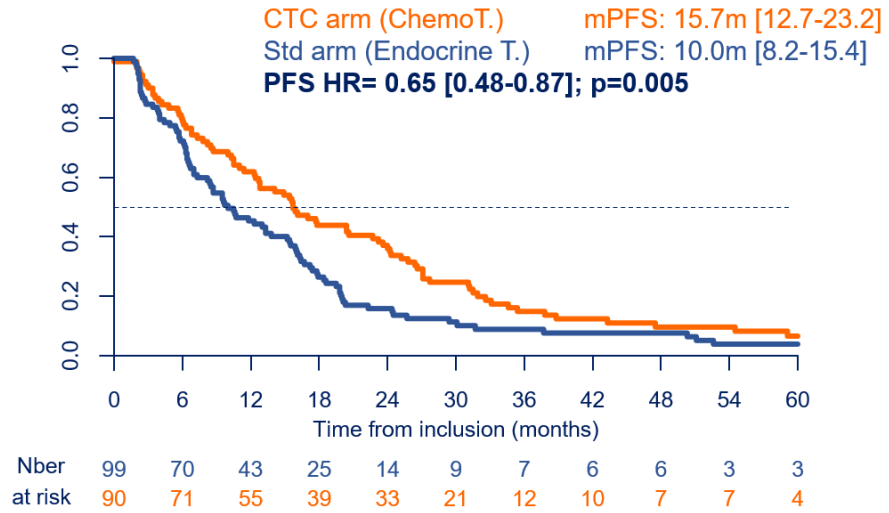
Similar treatment (chemotherapy) in the two arms led to similar outcomes

Pre-specified subgroup analysis: $Clin_{low}/CTC^{high}$ (25.0% of patients)

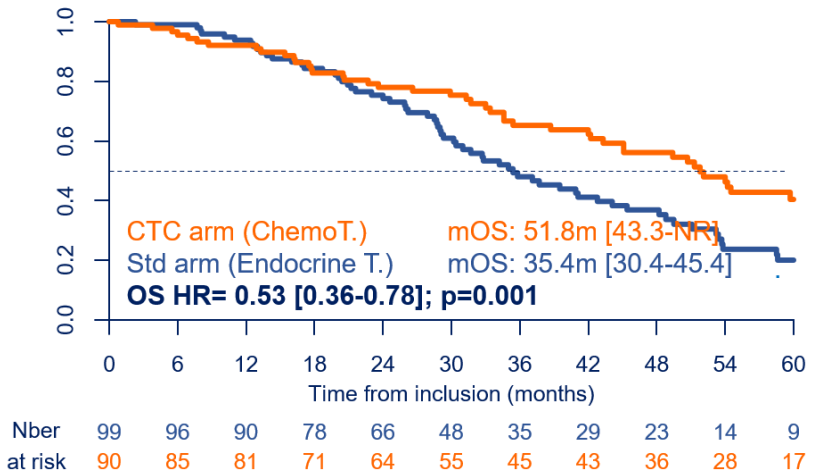
Standard arm N=99 of 378 pts **CTC arm N=90 of 377 pts**



Progression-Free Survival



Overall Survival

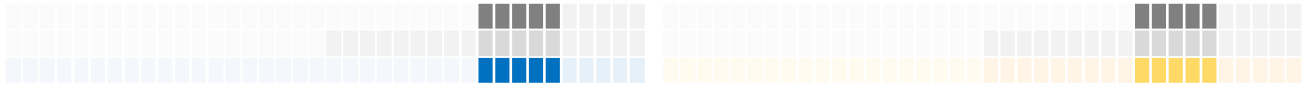


Statistically significant and clinically meaningful survival benefit (PFS & OS)
in patients with high CTC count treated with chemotherapy

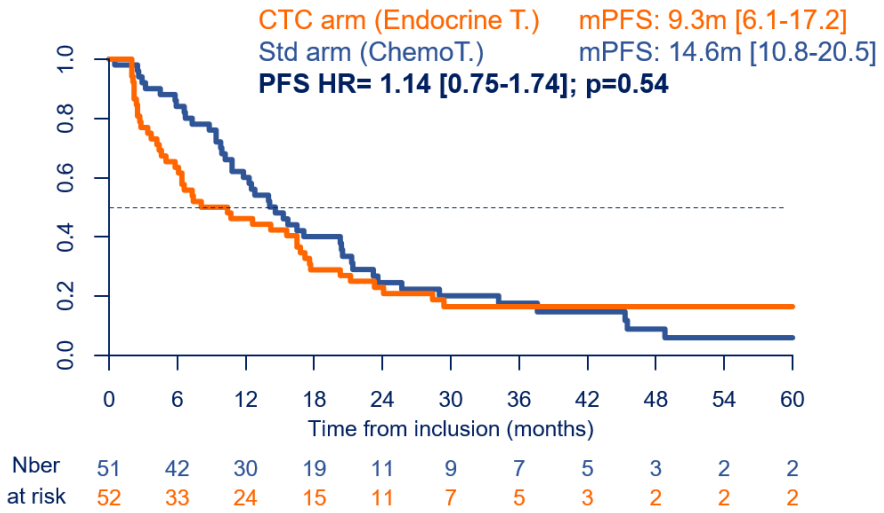
Pre-specified subgroup analysis: $Clin^{high}/CTC_{low}$ (13.6% of patients)

Standard arm N=51 of 378 pts

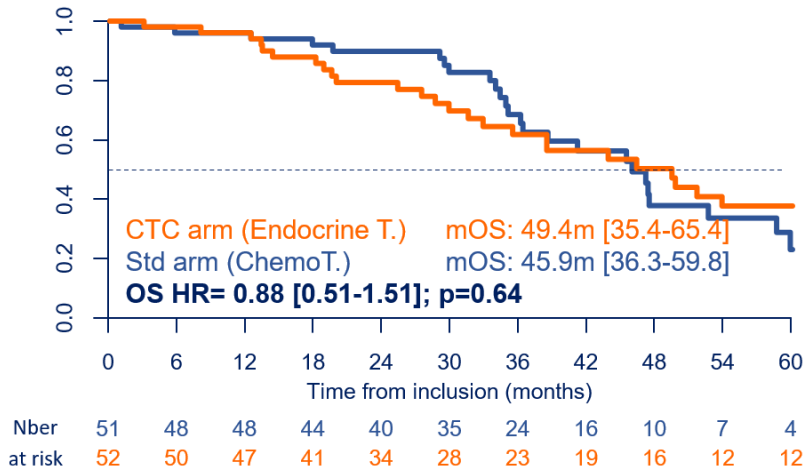
CTC arm N=52 of 377 pts



Progression-Free Survival



Overall Survival

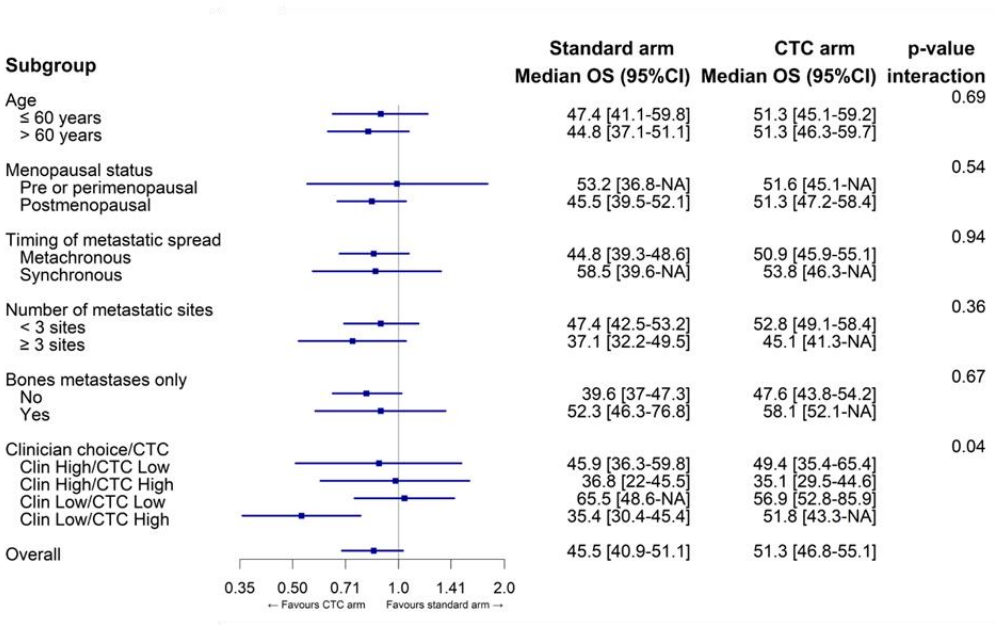


No survival benefit (PFS & OS)

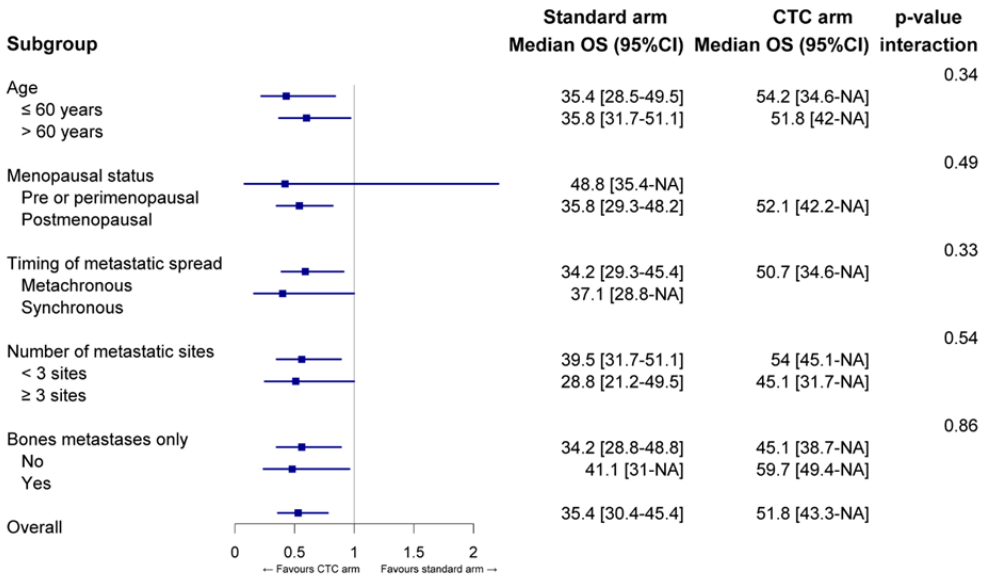
of chemotherapy (investigator's choice) over endocrine therapy (low CTC count)

Other subgroup analyses

All patients (N=755 pts)



$Clin_{low}/CTC^{high}$ patients (N=189 pts)



Treatment effect was consistent accross other pre-specified subgroups

STIC CTC: Conclusions

First prospective trial to support with a high LoE the clinical utility of CTC count in HR+ HER2- mBC

The primary objective was previously reached -- Now, with long term follow-up:

$Clin_{low}/CTC^{high}$ patients (25.0%)	$Clin^{high}/CTC_{low}$ patients (13.6%)
Major OS benefit with chemotherapy	Chemotherapy not beneficial
ΔmOS = 16 months	**Endocrine Therapy remains standard of care**

Main limitation

Trial run in 1st line without CDK4/6 inhibitors – the standard of care for CDK4/6i-naïve patients

➔ The dilemma between ET and CT remains intact in patients who received CDK4/6i as adjuvant or 1st line therapy

New opportunities in the post-CDK4/6i setting

- Short PFS with targeted endocrine therapy
- Vectorized chemotherapy (ADCs) is likely to become a very attractive option

➔ **CTC count before therapy as a standardized biomarker to find patients with aggressive disease**

Acknowledgements

- Patients and their family
- Investigators & clinical research staff at 17 sites in France
- CTC platforms
- Study project managers

Trial funding:

- INCa (STIC 2011)
- Menarini Silicon Biosystems

Institutional support:

- Institut Curie SIRIC2
- Inserm CIC-BT 1428
- Université de Versailles / Paris-Saclay