The prognostic performance of PREDICT in patients with HER2-positive early-stage breast cancer

A sub-analysis of the ALTTO Trial

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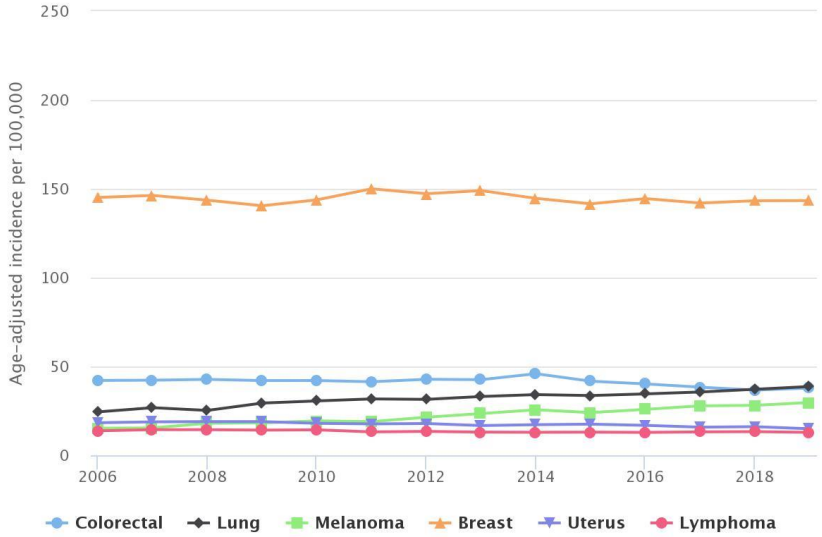
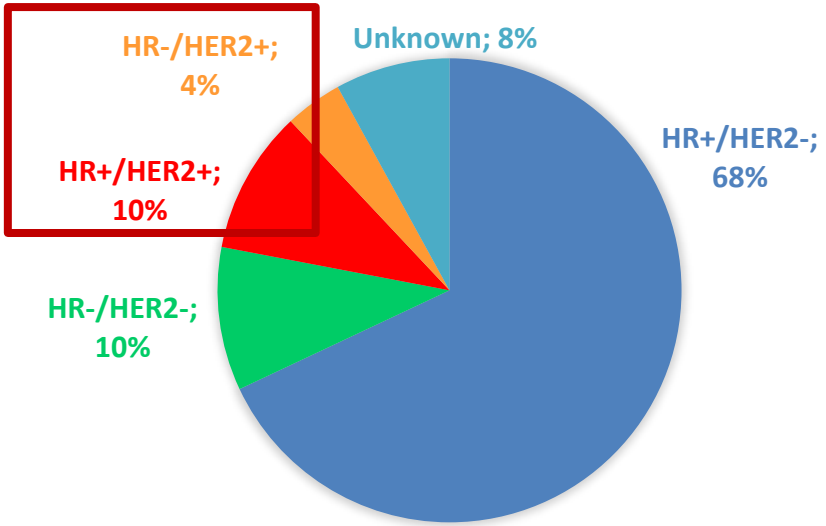
Breast Cancer: Epidemiological data

Cancer incidence in women in Belgium:
10,627 of breast cancer diagnoses per year



HER2-positive subtype accounts
for ≈14% of all breast cancers



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Surveillance, Epidemiology and End Results Program (SEER) 21, 2013-2017
Belgian Cancer Registry, 2006-2019

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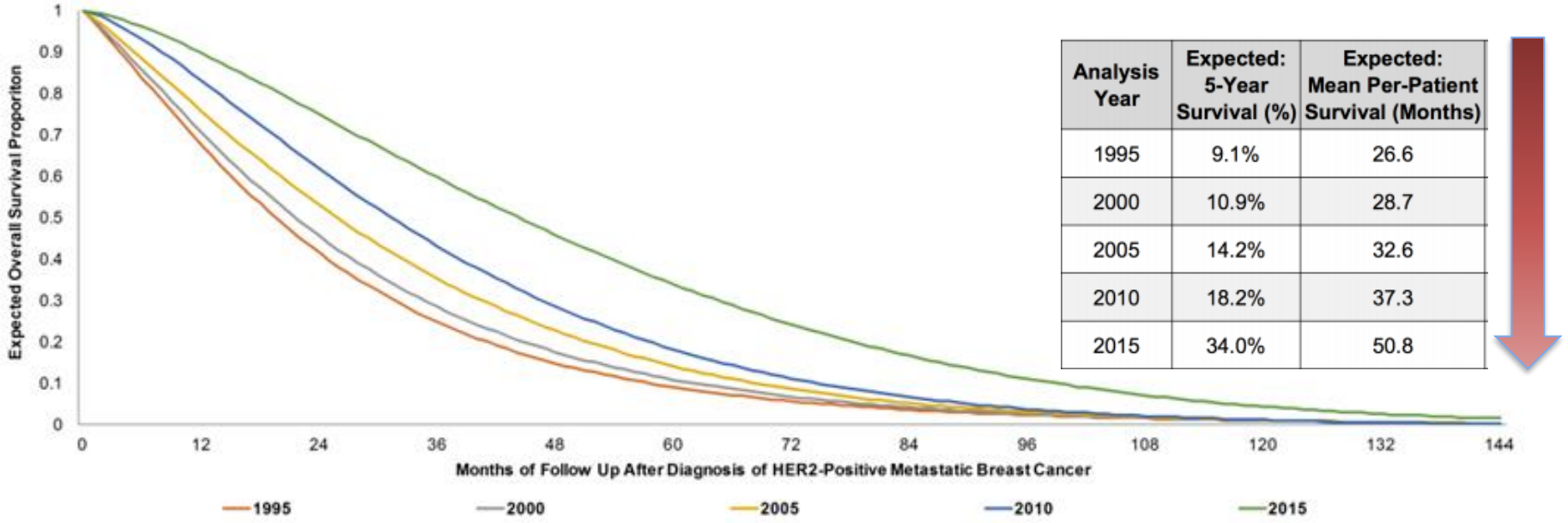
Life expectancy from HER2+ MBC diagnosis according to year analyzed: a consistent shift towards better survival



Analysis Year	Expected: 5-Year Survival (%)	Expected: Mean Per-Patient Survival (Months)
1995	9.1%	26.6
2000	10.9%	28.7
2005	14.2%	32.6
2010	18.2%	37.3
2015	34.0%	50.8

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Roth J et al, ESMO 2017

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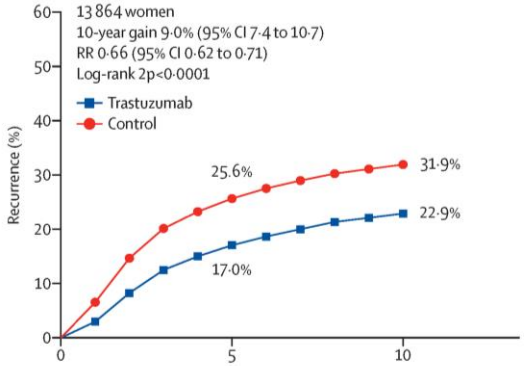
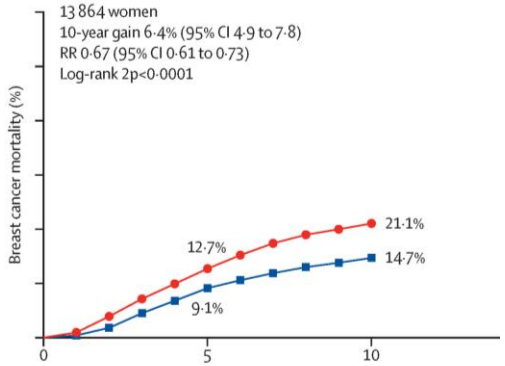
The addition of 1-yr trastuzumab to adjuvant CT reduces the risk of recurrence and mortality from breast cancer

- Meta-analysis of 13,864 women in seven randomised trials



Recurrence rates per year (% [events/woman-years]) and log-rank analyses

	Years 0–4	Years 5–9	Years ≥10
Trastuzumab	4·10 (1469/35 853)	1·53 (422/27 648)	0·95 (75/7858)
Control	6·24 (1385/22 180)	1·87 (291/15 601)	1·12 (43/3835)
Rate ratio (95% CI)	0·62 (0·58–0·66)	0·83 (0·72–0·95)	0·91 (0·63–1·31)
from (O–E)/V	−284·0/591·3	−29·6/154·9	−2·5/25·3



Death rates per year (%; 95% CI) and log-rank analyses

Years 0–4	Years 5–9	Years ≥10
1·99 (1·85–2·13)	1·38 (1·25–1·51)	0·75 (0·57–0·93)
2·73 (2·53–2·94)	2·18 (1·97–2·40)	1·15 (0·83–1·46)
0·70 (0·63–0·76)	0·63 (0·56–0·70)	0·64 (0·47–0·88)
−113·6/312·9	−84·2/179·8	−10·9/24·6

~23% of patients still present with **relapse up to 10 years from diagnosis**, and further research efforts are needed to better **refine patient selection** for adopting escalation or de-escalation treatment strategies

EBCTCG, Lancet Oncol 2021

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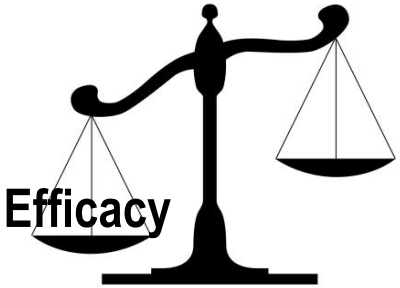
To escalate or to de-escalate? – The question in HER2-positive early breast cancer



- **High-risk** patients
- **Fit** patients

Escalation

- **Low-risk** patients
- **Frail** patients (e.g. cardiac comorbidities)

De-escalation

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PREDICT predicts **individual mortality** of pts with early breast cancer and aids **clinical decision making** for adjuvant therapy

predict breast cancer

https://breast.predict.nhs.uk/tool

DCIS or LCIS only? Yes | No

Age at diagnosis – [ ] +
Age must be between 25 and 85

Post Menopausal? Yes | No | Unknown

ER status Positive | Negative

HER2 status Positive | Negative | Unknown

Ki-67 status Positive | Negative | Unknown
Positive means more than 10%

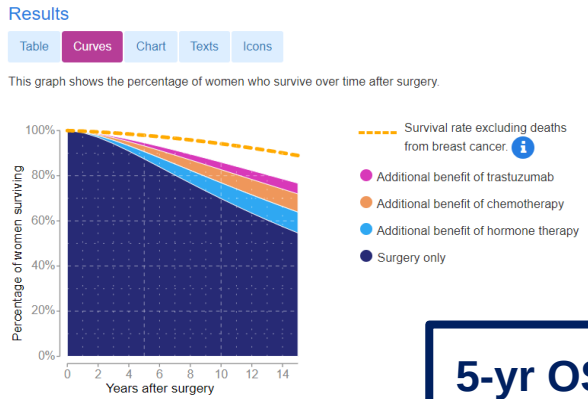
Invasive tumour size (mm) – [ ] +
If there was more than one tumour, enter the size before neo-adjuvant therapy.

Tumour grade 1 | 2 | 3

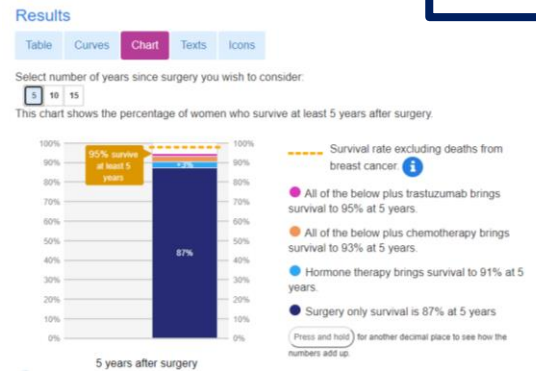
Detected by Screening | Symptoms | Unknown

Positive nodes – [ ] +

Micrometastases only Yes | No | Unknown
Enabled when positive nodes is 1.



5-yr OS estimates



Wishart GC et al., Br J Cancer 2012, 107: 800–7

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Study Objective

We aimed to investigate **the prognostic performance of PREDICT** in HER2-positive early breast cancer patients enrolled in the **ALTTO trial**[1,2] (*BIG 2-06/EGF106708 and North Central Cancer Treatment Group [Alliance] N063D*), an international, open-label, randomised phase III study testing the use of **trastuzumab and/or lapatinib** as **adjuvant anti-HER2 therapy**

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1. Piccart-Gebhart M et al., J Clin Oncol Off J Am Soc Clin Oncol 2016; 34: 1034–42.
2. Moreno-Aspitia A et al., European Journal of Cancer 148 (2021): 287-296

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ALTTO Study Design

Patients with HER2-positive early breast cancer,
either pN+ or pT≥1 cm if pN0

Anti-HER2 therapy
4 groups assigned by randomization

- Trastuzumab x 52 weeks
- Lapatinib x 52 weeks
- Trastuzumab x 12 weeks ←6 weeks→ Lapatinib x 34 weeks
- Trastuzumab x 52 weeks
  AND
  Labatinib x 52 weeks

Chemotherapy
3 administration modalities assigned per physician's choice

Design 1

- Chemotherapy
- Anti-HER2 therapy

Design 2

- Anthracycline
- Taxane
- Anti-HER2 therapy

Design 2B

- Docetaxel + Carboplatin
- Anti-HER2 therapy

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Design 1
Chemotherapy → Anti-HER2 therapy

Design 2
Anthracycline → Taxane → Anti-HER2 therapy

Design 2B
Docetaxel + Carboplatin → Anti-HER2 therapy

- Patients enrolled in the ALTTO trial and receiving **trastuzumab-based therapy** concurrently with chemotherapy (**design 2 and 2B**) were eligible for this analysis.

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Material and Methods

- We calculated PREDICT estimates using variables extracted from ALTTO database, blinded to patients' outcomes

- The prognostic performance of PREDICT was evaluated by assessing its **calibration** and **discriminatory accuracy:**

  - For **calibration**, median predicted 5-year overall survival (OS) was compared to observed 5-year OS.

  - For **discriminatory accuracy**, the area under the receiver-operator characteristic (AUC under the ROC) curve and corresponding 95% confidence intervals (CI) for predicted 5-year OS were calculated.

- **Subgroup analyses** were performed according to type of anti-HER2 therapy, type of chemotherapy, age, hormone receptor status, nodal status and tumor size.

Study Results – Patient selection and characteristics

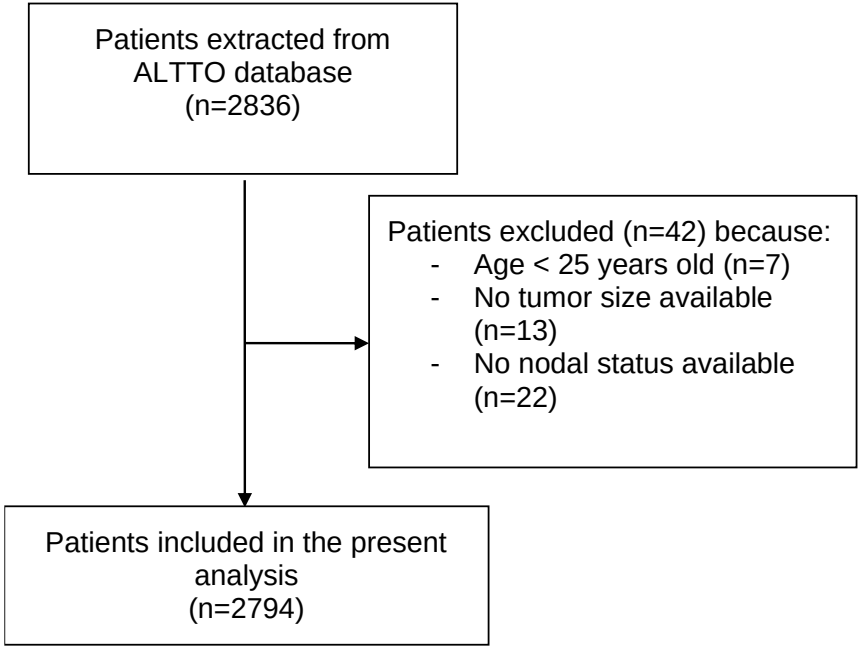


Figure. STROBE flow-chart resuming the patient selection process.

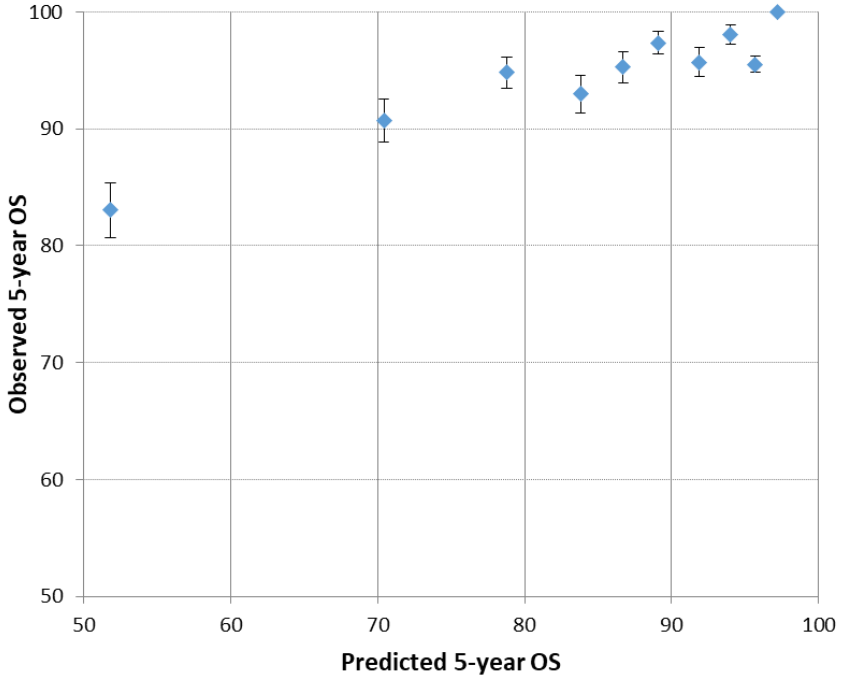
Table. Baseline patient characteristics.

		N (%)
All		**2794 (100)**
Age	**≤40**	495 (17.7)
	41-64	1989 (71.2)
	≥65	310 (11.1)
HR status	**Negative**	1185 (42.4)
	Positive	1609 (57.6)
Number of N+	**0**	567 (25.5)
	1-3	945 (42.6)
	>3	709 (31.9)
Tumor size (mm)	**≤20**	1248 (44.7)
	21-50	1356 (48.5)
	>50	190 (6.8)
Anti-HER2 Therapy	**L + T**	925 (33.1)
	T alone	936 (33.5)
	T → L	933 (33.3)
CT	**Non-anthracycline-based**	322 (11.5)
	Anthracycline-based	2472 (88.5)

L: lapatinib, T: trastuzumab; CT: chemotherapy; HR: hormone receptors; N: lymphnodes.

Study Results - Calibration

- This analysis included **2,794 pts.**
- Overall, PREDICT **underestimated 5-yr OS by 6.7%** (95% CI, 5.8-7.6)



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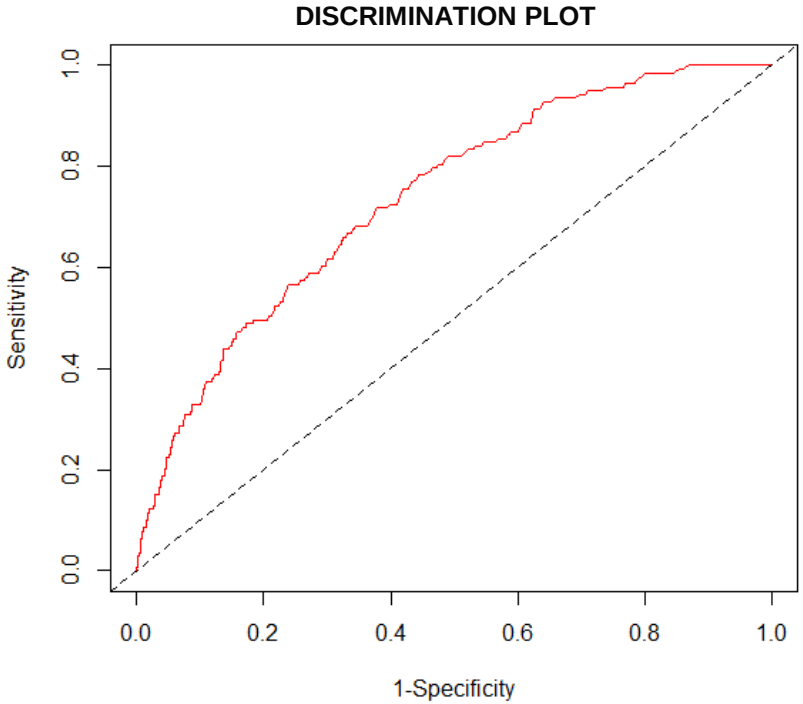
The underestimation was **consistent across all analyzed subgroups**

		N	(Predicted – Observed) 5-yr OS (%) (95% CI)
All		2794	-6.7 (-7.6; -5.8)
Anti-HER2 Therapy	**L + T**	925	-7.0 (-8.5; -5.5)
	T alone	936	-6.3 (-7.8; -4.7)
	T → L	933	-6.8 (-8.3; -5.4)
CT	**Non anthra-cycline-based**	322	-8.1 (-10.3; -5.9)
	Anthracycline-based	2472	-6.6 (-7.5; -5.6)
Age	**≤40**	495	-5.2 (-7.1; -3.4)
	41-64	1989	-6.7 (-7.7; -5.7)
	≥65	310	-9.7 (-12.9; -6.6)
HR status	**Negative**	1185	-13.0 (-14.4; -11.5)
	Positive	1609	-2.7 (-3.7; -1.7)
Number of N+	**0**	567	-6.1 (-7.4; -4.9)
	1-3	945	-9.0 (-10.2; -7.8)
	>3	709	-15.8 (-18.3; -13.3)
Tumor size (mm)	**≤20**	1248	-6.2 (-7.1; -5.3)
	21-50	1356	-7.3 (-8.7; -6.0)
	>50	190	-15.3 (-20.4; -10.2)

Study Results - Discriminatory accuracy

- 2,794 pts included in the analysis
- For discriminatory accuracy, **AUC under the ROC curve was 73.7%** (95%CI 69.7-77.8) in the overall population



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These results were **consistent across all analyzed subgroups**

		N	AUC for time-point 5 years (95% CI)
All		**2794**	**73.7 (69.7-77.8)**
Anti-HER2 Therapy	**L + T**	925	72.4 (64.3-80.4)
	T alone	936	77.7 (72.0-83.3)
	T → L	933	70.6 (63.5-77.8)
CT	**Non anthra-cycline-based**	322	65.2 (50.4-80.0)
	Anthracycline-based	2472	74.4 (70.3-78.6)
Age	**≤40**	495	76.1 (66.2-86.0)
	41-64	1989	73.7 (68.7-78.6)
	≥65	310	67.4 (56.9-77.9)

		N	AUC for time-point 5 years (95% CI)
All		**2794**	**73.7 (69.7-77.8)**
HR status	**Negative**	1185	71.9 (65.8-78.0)
	Positive	1609	76.8 (71.6-82.0)
Number of N+	**0**	567	77.3 (65.5-89.0)
	1-3	945	64.8 (54.6-75.0)
	>3	709	61.7 (55.0-68.4)
Tumor size (mm)	**≤20**	1248	70.6 (61.8-79.4)
	21-50	1356	68.6 (63.3-73.9)
	>50	190	73.0 (63.1-82.8)

Conclusions - 1

- In our ALTTO sub-analysis, PREDICT resulted in a significant **underestimation of patient survival**, and **its discriminatory accuracy** was **overall suboptimal.**

- Patients with HER2-positive breast cancer are experiencing a **consistent shift towards better survival** across the years, mainly thanks to effective therapies available for these patients, and this change might not be reflected by a prognostic tool developed and validated more than 10 years ago.

Conclusions - 2

- The current version of PREDICT **should be used with caution** to give **prognostic estimations** to HER2-positive early breast cancer patients treated in the modern era with effective chemotherapy and anti-HER2 targeted therapies.

- Further efforts are needed to develop tools able to give **prognostic estimation in HER2-positive early stage breast cancer**, where prognostication has several implications, from a therapeutic perspective (adoption of escalation or de-escalation treatment strategies) to the planning of premenopausal patients' reproductive life (affecting the choice of having or not a pregnancy).

Thank you for your attention!

BIG
Breast International Group

Acknowledgements

I would like to thank:

- All the patients and their families
- All the authors who participated in the study: L. Ameye, S. Martel, P. Aftimos, N. Pondé, C. Maurer, S. El-Abed, Y. Wang, M. Vicente, S. Chumsri, J. Bliss, J. Kroep, M. Colleoni, F. Petrelli, L. Del Mastro, A. Moreno-Aspitia, M. Piccart, M. Paesmans, E. de Azambuja, M. Lambertini
- The Jules Bordet Institute (IJB)
- The Breast International Group (BIG)
- Les Amis de l'Institut Bordet for the financial support (Grant No. 2018-09)
- The ALTTO Study sponsor GSK/Novartis
- The US National Cancer Institute (NCI)
- The North Central Cancer Treatment Group (NCCTG; Alliance)
- The ALTTO Executive and Steering Committee members

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Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial

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