GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

INSTITUT
JULES BORDET
INSTITUUT

ESMO Clinical Research Fellowship
09/2018 to 09/2019

Long-term cardiac outcomes of HER2 positive breast cancer patients treated in the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial – the ALTTO Cardiac sub-analysis

Daniel Eiger, MD

FINAL REPORT

Host Institute: Institut Jules Bordet, Brussels, Belgium
Mentor: Evandro de Azambuja, MD, PhD

Home Institute – Head of department: Centro Paulista de Oncologia, Sao Paulo, Brazil – Daniel Luiz Gimenes, MD

Introduction

Treatment with trastuzumab in HER2-positive breast cancer has greatly impacted on the outcomes of early stage disease, reducing the risk of recurrence by 40% and risk of death by 34%. [1] Cardiotoxicity is an important drug-related adverse event, which is manifested most commonly as asymptomatic reduction in left ventricular ejection fraction (LVEF), although a minor fraction of patients experiences congestive heart failure (CHF) and, rarely, cardiac death.[2]

Currently, HER2 dual blockade combining trastuzumab with pertuzumab (early and metastatic disease) and trastuzumab with lapatinib (metastatic setting) has been proven better than single HER2 blockade.[3–5] Lapatinib (L), a tyrosine kinase inhibitor (TKI) of HER1 and 2 is approved for the treatment of HER2-positive, trastuzumab-resistant metastatic breast cancer in combination with trastuzumab (T), capecitabine or endocrine therapy.[6–8] Nevertheless, there is less data on cardiotoxicity of dual HER2 blockade with T+L.[7,8] Therefore, the objective of this sub-analysis of the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial (ALTTO) is to provide a detailed picture of cardiotoxicity associated with the combination of T+L, and also to compare it to T alone.

Methods

Study design

ALTTO was an international multi-center, open-label, phase 3 randomized clinical trial in patients with HER2-positive early breast cancer, which has previously been reported.[5] Briefly, 8381 patients with early HER2-positive breast cancer were randomized into 4 different arms of treatment, each given for one year: (1) T monotherapy; (2) L monotherapy; (3) a sequence of the two drugs (T→L); (4) the concomitant administration of the two drugs (T+L). Anti-HER2 treatment could be given at the completion of all chemotherapy or concomitantly with taxanes, after the anthracycline component in case doxorubicin or epirubicin was given.

Patients had to have a baseline LVEF ≥ 50% measured by either echocardiography (ECHO) or multiple-gated acquisition (MUGA) scan, prior to anti-HER2 therapy. Patients treated with an anthracycline-based chemotherapy were eligible if cumulative doses of doxorubicin were ≤ 360mg/m^2 or epirubicin ≤ 720mg/m^2. Those with serious cardiac illness were not eligible. Further details regarding patients` selection and study design were provided elsewhere.[5]

The ALTTO cardiac population consists of patients randomized to T (2097 patients) and T+L (2093 patients) arms, as T→L and L treatments are not used in current clinical practice, thus having no relevance in terms of contemporary cardiotoxicity.

Cardiac Monitoring

LVEF was assessed consistently with the same method (ECHO or MUGA) at baseline, weeks 13, 25, 37 and 52, and during follow up at months 18, 24, 36, 48 and 60. After this period, LVEF was assessed yearly until year 10. After a protocol amendment in March 2016, LVEF assessment after 5 years of follow-up was no longer mandatory.
Should a patient develop clinical signs or symptoms of congestive heart failure (CHF), unscheduled LVEF assessment and electrocardiogram (ECG) were performed. Furthermore, anti-HER2 treatment was to be permanently discontinued upon the occurrence of CHF NYHA class III or IV, and it could be temporarily stopped and re-introduced, depending on the degree of LVEF decrement in asymptomatic left ventricular dysfunction or CHF NYHA class II.[5]

Cardiac endpoints

Cardiac events (CEs) were defined for the purpose of this analysis as follows:
Asymptomatic CE: asymptomatic significant LVEF drop, defined as an absolute decline of at least 10 percentage points from baseline and to below 50%, either by MUGA or ECHO. This event had to be confirmed with a 2nd LVEF assessment after 3 weeks of the 1st significant LVEF drop.
Symptomatic CE: New York Heart Association (NYHA) class II, III or IV HF associated with a significant LVEF drop. Symptomatic CE NYHA class II had to be confirmed with a 2nd LVEF assessment after 3 weeks of the 1st significant LVEF drop.
Cardiac death: death definitely due to HF, myocardial infarction or documented arrhythmia, or probable cardiac death within 24 hours of a CE.
The following outcomes were further assessed, according to definitions below:
Acute recovery from CE: two or more consecutive LVEF assessments of 50% or greater after a CE, irrespective of (cardiovascular) treatment. The date of the first LVEF assessment showing an increase of LVEF above 50% was considered the recovery date.
Occurrence of LVEF drop to less than 50% following acute recovery: after a patient reaches criteria for acute recovery from a CE, this event is defined as a 2nd LVEF drop to < 50%, regardless of anti-HER2 treatment re-exposure or association with symptoms. Importantly, this outcome definition precludes capturing more than one CE per patient.
Time to development of CE: time elapsed between the start of anti-HER2 treatment and the date of occurrence of a CE.
Time to recovery from CE: time elapsed between the start of a CE and the recovery date.
Anti-HER2 treatment completion: defined as completion of the pre-planned 52 weeks of anti-HER2 treatment.
Reasons for anti-HER2 non-completion: defined as safety reason, recurrence of disease or other reasons (defined as a reason qualified as none of the two previous). Safety reason was further divided into cardiac safety (defined as permanent discontinuation due to a CE) and other safety (defined as permanent discontinuation due to an adverse event [AE]).

Statistical Analysis

Data was extracted from the second analysis dataset, of Q12017. Baseline characteristics are described by treatment arms (T; T+L). The distribution of CEs, the median time for development of CEs, the incidence of recovery from CEs, and the incidence of permanent treatment discontinuations are described by treatment arms (T, T+L). Categorical data were cross-tabulated to generate proportion, then chi-square tests to assess the stability of patients' characteristics across treatment arms (T; T+L).
The reverse Kaplan-Meier method was used to determine the median follow-up (FU) time for the entire cohort and by treatment arms.
The primary endpoint was the incidence of CEs, defined as the sum of asymptomatic CEs, symptomatic CEs

and cardiac deaths in the entire population and by treatment arms (T; T+L). Secondary endpoints include: (1) the incidence of asymptomatic CEs, symptomatic CEs and cardiac deaths in the entire population and by treatment arms, (2) risk factors for the occurrence of any CEs (cardiac risk factors), (3) the time to development of CEs, (4) the recovery rate, (5) the association between cardiac risk factors and absence of acute recovery following a CE, (6) the time to recovery after CEs and (7) mean LVEF at screening and during anti-HER2 treatment by treatment arms, (8) anti-HER2 treatment completion rates and (9) reasons for anti-HER2 non-completion.
Logistic regressions were fitted to assess the odds of CEs, with treatment arms (T; T+L) as the only predictor for the univariate analysis, with other covariates included in the multivariate setting. The logistic regression was repeated for each risk factor. Odd ratios and 95% CI were reported for both univariate and multivariate analyses, with a p-value less than 0.05 considered statistically significant.
The incidence of CEs over time by treatment arms (T; T+L) and the number of risk factors was assessed using the cumulative incidence plot of CEs over time, based on competing risks. Time was considered from randomization. Mean LVEF over time and 95% CI, by treatment arms, were plotted for visual inspection.
All analyses were performed using SAS version 9.4.

Results

Patients' characteristics

With a median follow-up of 6.9 years (interquartile range [IQR] of 6.0 to 7.1), 2097 patients in T-arm and 2093 patients in T+L arms were included in this sub-analysis. Baseline characteristics were well distributed between treatment arms, except for diabetes mellitus (DM), with slightly more diabetic patients in T-arm (p = 0.024). Of note, the majority of patients were younger than 65 years old (90%), and few patients had any co-morbidity (28% in T-arm and 27% in T+L-arm). Most patients received an anthracycline-based chemotherapy regimen (95%). Table 1 summarizes baseline patients` characteristics according to treatment arm, focusing on features selected to be tested as cardiac risk factors.

Table 1 – ALTTO cardiac population:

Characteristic	T-arm (2097 patients) N (%)	T+L arm (2093 patients) N (%)	p-value
Age (years)			0.918
<65	1881 (90)	1879 (90)	
≥65	216 (10)	214 (10)	
Baseline LVEF			0.765
50-54%	98 (5)	102 (5)	
55% - 64%	1065 (51)	1053 (50)	
> 64%	934 (44)	937 (45)	
Missing	0	1 (<1)	
Any co-morbidity?			0.470
Yes	588 (28)	566 (27)	
No	1509 (72)	1527 (73)	
BMI (kg/m^2)			0.916
<25	999 (48)	989 (47)	
25-30	679 (32)	675 (32)	

>30	419 (20)	429 (21)	
Hypertension			0.293
Yes	471 (22)	442 (21)	
No	1626 (78)	1651 (79)	
Diabetes Mellitus			**0.024**
Yes	128 (6)	95 (5)	
No	1969 (94)	1998 (95)	
Hypercholesterolemia			0.290
Yes	179 (9)	160 (8)	
No	1918 (91)	1933 (92)	
Radiotherapy laterality*			0.165
Left	745 (50)	790 (53)	
Right	736 (50)	698 (47)	
Bilateral	5 (<1)	2 (<1)	
Chemotherapy regimen			0.902
Anthracycline followed by taxane	1985 (95)	1983 (95)	
Non-Anthracycline (docetaxel+carboplatin)	112 (5)	110 (5)	
Median doxorubicin cumulative dose	237.62 mg/m^2	237.84 mg/m^2	-
Median epirubicin cumulative dose	350.86 mg/m^2	349.75 mg/m^2	-
Median follow-up (IQR) in years	6.9 (6.0-7.1)	6.9 (6.0-7.1)	-

* Percentages derived using 1486 patients on T arm and 1490 patients on T+L arm that received radiotherapy as denominator.

Anti-HER2 treatment completion

Trastuzumab was discontinued before completion of 1 year of adjuvant treatment in 344 (16%) and 385 (18%) patients in T arm and T+L arm, respectively. Of those, reasons in T arm for discontinuation were: disease recurrence (15%), safety (36%) and other reasons (49%), whereas in T+L arm were disease recurrence (7%), safety (35%) and other reasons (58%).

Lapatinib was discontinued by 674 (32%) of patients in T+L arm. Of those, reasons for discontinuation were: disease recurrence (3%), other reasons (36%) and safety (60%). Of note, only 74 (11%) patients discontinued lapatinib due to cardiac safety, while 164 (22%) patients receiving trastuzumab had to discontinue it (table 2).

Table 2 – Summary of treatment discontinuation

	T (N = 2097) N (%)	T + L (N = 2093) N (%)
Trastuzumab completion status		
Completed trastuzumab	1753 (84)	1708 (82)
Discontinued trastuzumab	344 (16)	385 (18)
Reasons for trastuzumab discontinuation*		
Safety	123 (36)	135 (35)
Recurrence of disease	51 (15)	26 (7)
Other reasons	170 (49)	224 (58)
Safety reasons for trastuzumab discontinuation**		
Cardiac safety	86 (70)	78 (58)
Other safety	37 (30)	57 (42)
Lapatinib completion status		
Completed lapatinib	NA	1419 (68)
Discontinued lapatinib		674 (32)
Reasons for lapatinib discontinuation*		
Safety	NA	405 (60)
Recurrence of disease		23 (3)
Other reasons		246 (36)
Safety reasons for lapatinib discontinuation**		
Cardiac safety	NA	74 (18)
Other safety		331 (82)

* Discontinued trastuzumab/lapatinib used as denominator to derive percentages
** Safety used as denominator to derive percentages
Legends: NA = not available.

Cardiac Events and mean LVEF

Following ALTTO first report, an additional set of 103 CEs have occurred, for a total of 363 CEs in 4190 patients, representing a study incidence of 8.7%. One-hundred and sixty-six (7.9%) patients in T+L arm versus 197 (9.4%) patients in T arm experienced a CE, a non-significant absolute difference of -1.4% (HR of 0.85; 95% CI, 0.68-1.05; p= 0.139). Two-hundred and seventy CEs (6.4%) occurred during anti-HER2 treatment and only 93 (2.2%) during follow-up (FU), with a median time to onset of 6.6 months (interquartile range: 3.4 to 11.7 months). The incidence of CE over time per treatment arm tends to accumulate more from the 6th to the 12th month and to a lesser extent from the 12th to the 18th month from randomization, as depicted in figure 1.

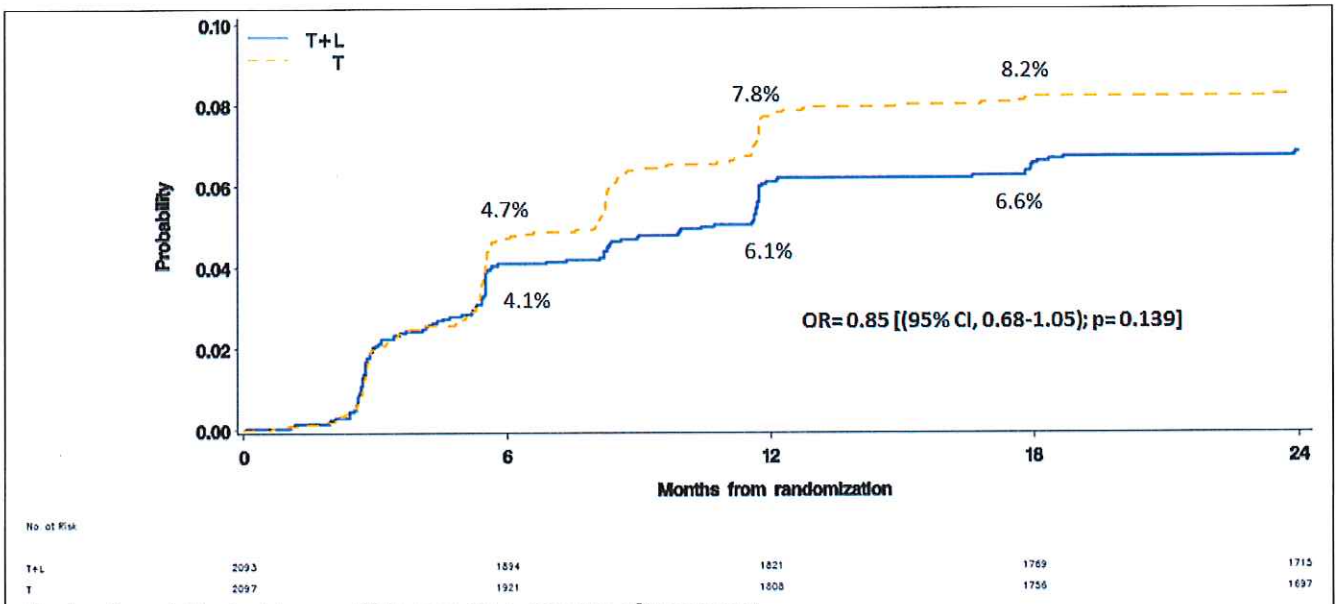

Fig. 1 – Cumulative incidence of CEs over time, per arm of treatment.
There is a non-statistical difference of -1.4% in the rate of CE on T+L arm (7.9%) vs T arm (9.3%), with a multivariate OR of 0.85 [(95% CI, 0.68-1.05); p= 0.139]. The rates of CEs at the 6th month are 4.1% and 4.7% on T+L arm and T arm, respectively, increasing to 6.1% and 7.8% at the 12th month, and to a lesser extent to 6.6% and 8.2% at the 18th month, respectively.

Asymptomatic CEs were the most frequent CE, with 265 events (6.3%), followed by 94 symptomatic events (2.2%) and 4 cardiac deaths (< 0.1%), as displayed in table 3.

Table 3 – Summary of cardiac events

CEs, subtype and timing	All pts (4190) N (%)	T arm (2097) N (%)	T+L arm (2093) N (%)
Cardiac events	363 (8.6)	197 (9.3)	166 (7.9)
CE during anti-HER2 therapy	270 (6.4)	153 (7.2)	117 (5.6)
CE during follow-up phase	93 (2.2)	44 (2.1)	49 (2.3)
Asymptomatic CE	265 (6.3)	155 (7.4)	110 (5.3)
Symptomatic CE	94 (2.2)	40 (1.9)	54 (2.6)
Cardiac deaths	4 (<0.1)	2 (<0.1)	2 (<0.1)
Median time in months to develop a CE (range)	6.6 (3.4-11.7)	6.4 (3.6-11.7)	7.1 (2.9-16.6)

Figure 2 shows a similar yet small decrease of cardiac function in both arms, from screening to week 13 after randomization, which stabilizes until the end of treatment.

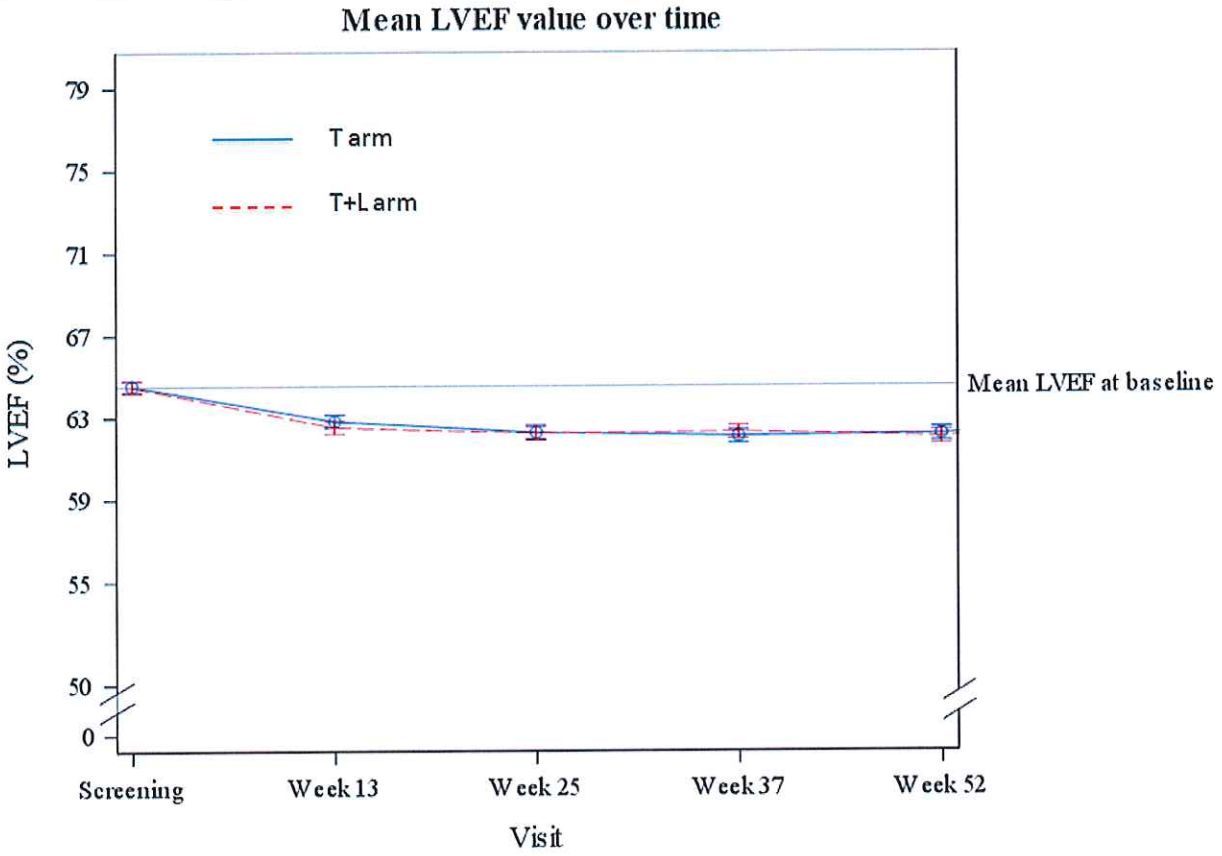

Figure 2 – mean left ventricular ejection fraction (mLVEF) over time according to treatment arm.
After a minor decrement from screening to week 13 (T+L arm: 64.5% to 62.5%, T arm: 64.5% to 62.8%, respectively), mLVEF becomes stable in both treatment arms until the end of treatment (T+L arm: 62.0%, T arm: 62.2%).

Cardiac Recovery and second LVEF drop

Excluding 2 cardiac deaths in each treatment arm, 163 (83.6%) patients recovered from a CE in T arm and 138 (84.1%) recovered in T+L arm, with a median time to recovery of 3.3 (range 0.0 to 79.0) and 3.5 months (range 0.1 to 23.9), respectively. Anti-HER2 treatment re-exposure was done in 58 and 32 patients in T and T+L arms, respectively, following acute recovery. In these patients, a second LVEF drop to < 50% was experienced by 15 patients (25.9%) in T arm and 12 patients (37.5%) in T+L arm.

Cardiac Risk Factors and incidence of CEs according to cumulative number of risk factors

The following baseline characteristics were positively associated with CEs (hereafter cardiac risk factors) for the entire population, after adjusting for confounding variable in the multivariate analysis: pre anti-HER2 treatment LVEF < 55% (vs > 64%, OR 3.1), diabetes mellitus (OR 1.85), BMI >30kg/m^2 (vs < 25mg/kg^2, OR 2.21), cumulative dose of doxorubicin ≥ 240mg/m^2 (OR 1.36) and cumulative dose of epirubicin ≥ 480mg/m^2 (OR 2.33). No impact on CEs incidence was demonstrated for hypercholesterolemia (p =0.629), hypertension (p =0.402), radiotherapy (p =0.709), left side radiotherapy (p =0.509) and dual HER2 blockade (p =0.139) (table 4).

Table 4 – Cardiac risk factors

Baseline Characteristic	Cardiac Events (%)	N	Univariate OR (95%CI)	Univariate P-value	Multivariate OR (95%CI)	Multivariate P-value
Pre anti-HER2 LVEF	363 (8.67)	4189				
> 64%	102 (4.82)	2118	-	-	-	-
55% - 64%	225 (12.03)	1871	2.70 (2.12 to 3.44)	**<0.001**	2.32 (1.61 to 3.35)	**<0.001**
< 55%	36 (18.00)	200	4.34 (2.87 to 6.55)	**<0.001**	3.10 (1.54 to 6.25)	**0.002**
Diabetes Mellitus	363 (8.66)	4190				
No	330 (8.32)	3967	-	-	-	-
Yes	33 (14.80)	223	1.91 (1.30 to 2.82)	**<0.001**	1.85 (1.25 to 2.75)	**0.002**
Doxorubicin cumulative dose	205 (10.90)	1880				
< 240mg/m2	109 (9.62)	1133	-	-	-	-
≥240mg/m2	96 (12.85)	747	1.39 (1.04 to 1.85)	**0.028**	1.36 (1.01 to 1.82)	**0.039**
Epirubicin cumulative dose	142 (6.79)	2092				
< 480mg/m2	107 (5.88)	1819	-	-	-	-
≥480mg/m2	35 (12.82)	273	2.35 (1.57 to 3.53)	**<0.001**	2.33 (1.55 to 3.51)	**<0.001**
BMI CATEGORY	363 (8.66)	4190				
<25	146 (7.34)	1988	-	-	-	-
25-30	125 (9.23)	1354	1.28 (1.00 to 1.65)	**0.050**	1.65 (1.11 to 2.46)	**0.014**
>30	92 (10.85)	848	1.54 (1.17 to 2.02)	**0.002**	2.21 (1.40 to 3.49)	**<0.001**
Age dichotomized at 65	363 (8.66)	4190				
<65	314	3760	-	-	-	-

	(8.35)					
≥65	49 (11.40)	430	1.41 (1.03 to 1.94)	**0.034**	1.36 (0.98 to 1.88)	0.064
Hypertension	363 (8.66)	4190				
No	279 (8.51)	3277	-	-	-	-
Yes	84 (9.20)	913	1.09 (0.84 to 1.41)	0.514	0.89 (0.67 to 1.17)	0.402
Hypercholesterolemia	363 (8.66)	4190				
No	334 (8.67)	3851	-	-	-	-
Yes	29 (8.55)	339	0.99 (0.66 to 1.46)	0.941	0.90 (0.60 to 1.36)	0.629
Radiotherapy	363 (8.66)	4190				
No	111 (9.14)	1214	-	-	-	-
Yes	252 (8.47)	2976	0.92 (0.73 to 1.16)	0.481	0.96 (0.75 to 1.21)	0.709
Radiotherapy laterality	252 (8.49)	2969				
Right	127 (8.86)	1434	-	-	-	-
Left	125 (8.14)	1535	0.91 (0.70 to 1.18)	0.486	0.92 (0.71 to 1.19)	0.509
Anti-HER2 arm	363 (8.66)	4190				
T	197 (9.39)	2097	-	-	-	-
T + L	166 (7.93)	2093	0.83 (0.67 to 1.03)	0.093	0.85 (0.68 to 1.05)	0.139

Legends: BMI= body mass index; CI= confidence interval; N= number; OR= odds ratio.

As shown in figure 3, CE rates increased from 1.3% to 2.1% at 6 and 12 months of anti-HER2 treatment in the lowest cumulative risk category (0-1 cardiac risk factors). CEs increased from 9.2% to 14% at 6 and 12 months, respectively, in the highest cumulative risk category (4 risk factors).

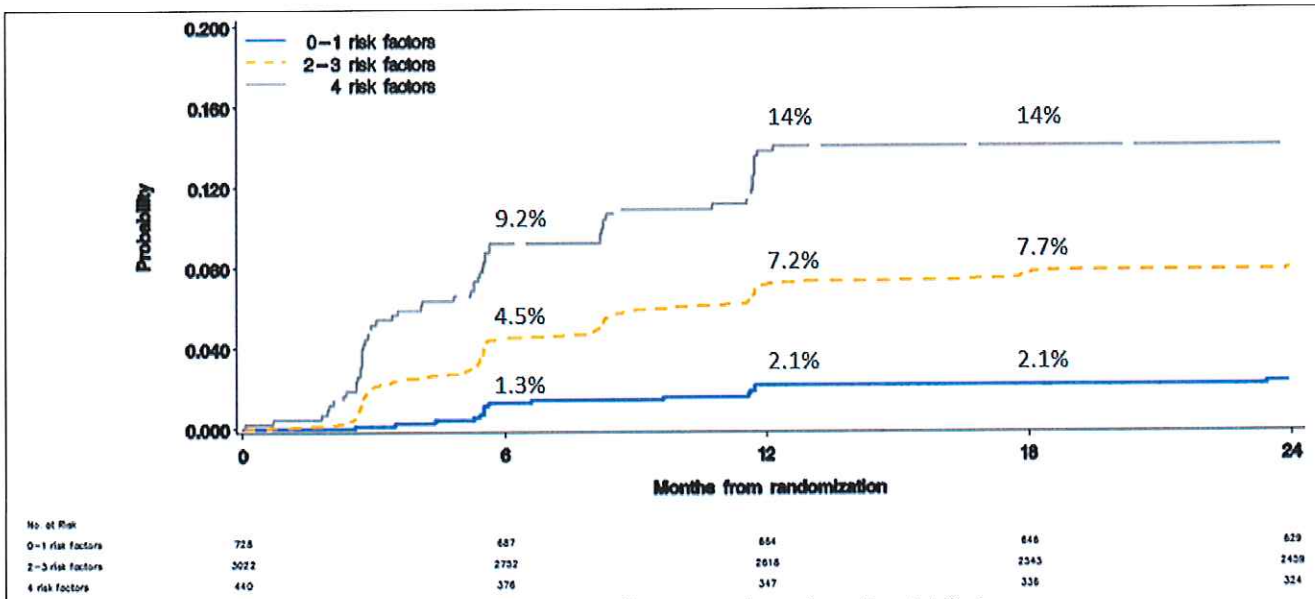

Figure 3 – Cumulative incidence of CEs over time, according to number of cardiac risk factors.
At 6, 12 and 18 months from randomization, patients with 0-1 risk factors have an incidence of CE of 1.3%, 2.1% and 2.1%, respectively. Patients with 2-3 risk factors, at the same time-points, have an incidence of CE of 4.5%, 7.2% and 7.7%, respectively. For those with 4 risk factors, the incidences are 9.2%, 14.0% and 14.0%, respectively.

Conclusion

Dual HER2 blockade with T+L is a safe regimen from a cardiac stand-point. Most CEs are asymptomatic, occurs during anti-HER2 treatment and accumulate from the 6th to the 12th month of treatment, hence cardiac monitoring in this period should be followed according to guidelines, especially for patients with one or more of the following risk factors: pre-treatment LVEF< 55%, BMI> 30kg/m^2, high cumulative anthracycline exposure and DM. Future trials could test whether a low cardiac risk population could be safely monitored with a less intense LVEF schedule of assessment, thus helping to reduce financial costs associated with anti-HER2 treatment.

List of presentations / publications resulting from the fellowship

1- Eiger D, Pondé NF, Azambuja E de. Pertuzumab in HER2-positive early breast cancer: current use and perspectives. Futur Oncol [Internet]. 2019 Apr 2 [cited 2019 Apr 10];fon-2018-0896. Available from: http://www.ncbi.nlm.nih.gov/pubmed/309385422

2- Eiger D, Ponde NF, Agbor-Tarh D, Korde LA, Moreno Aspitia A, Rodeheffer RJ, et al. 199OLong-term cardiac outcomes of HER2+ breast cancer patients treated in the ALTTO trial. Ann Oncol [Internet]. 2019 May 1 [cited 2019 Jul 5];30(Supplement_3). Available from: https://academic.oup.com/annonc/article/doi/10.1093/annonc/mdz101/5488368

3- Maurer C, Eiger D, Velghe C, Aftimos PG, Maetens M, Gaye J, et al. 195TiPSYNERGY: Phase I and randomized phase II trial to investigate the addition of the anti-CD73 antibody oleclumab to durvalumab, paclitaxel and carboplatin for previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC). Ann Oncol [Internet]. 2019 May 1 [cited 2019 Jul 5];30(Supplement_3). Available from: https://academic.oup.com/annonc/article/doi/10.1093/annonc/mdz100.046/5488340

Submitted, waiting peer-review:

4- "Biomarkers of response and resistance to PI3K inhibitors in HR-positive breast cancer patients and

combination therapies involving PI3K inhibitors" at Annals of Oncology
5- "Same story with different endings in HER2-positive breast cancer: why is the benefit of pertuzumab robust in the metastatic scenario and modest in the adjuvant setting?" at the Journal of Clinical Oncology
6- Abstract #3058 - "Meta-analysis of anti-PD1 vs. chemotherapy in patients with advanced melanoma after failure to anti-CTLA4" at ESMO 2019 Congress
7- Abstract 19-A-1034-SABCS – "Characteristics and survival outcomes of HIV-positive breast cancer patients: a systematic review and meta-analysis" at SABCS 2019

Waiting co-authors` review before submitting to British Journal of Cancer:

8- ALTTO Cardiac manuscript

Future work and work-in-progress:

9- Brain metastases project in triple negative breast cancer
10- APHINITY cardiac sub-analysis
11- Cardiac risk calculator
12- Correspondence to Lancet regarding anthracycline use as adjuvant treatment in HER2-positive breast cancer

Acknowledgements / personal statement

I acknowledge this unique opportunity of pursuing this fellowship abroad in an European centre of excellence, thanks to ESMO`s irreplaceable effort in improving clinical research and cancer care, regardless of continental borders, and to Novartis educational grant.
My special gratitude to my mentor, and now friend, Evandro de Azambuja, whose guidance was paramount to accomplish this project and other more to come; to my dear friend Noam Falbel Pondé, who trusted me capable of pursuing this fellowship; the new friends made along the way here at Institut Jules Bordet; and to my wife Melanie S.N. Eiger, for accompanying and supporting me in this endeavour.

References

1. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev [Internet]. 2012 Apr 18 [cited 2019 Apr 24];(4). Available from: http://doi.wiley.com/10.1002/14651858.CD006243.pub2
2. Pondé NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. ESMO Open [Internet]. 2016 Jul 21 [cited 2019 Feb 14];1(4):e000073. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27843627
3. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med [Internet]. 2017 Jul 13 [cited 2019 Feb 14];377(2):122–31. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1703643
4. Swain SM, Baselga J, Kim S-B, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer. N Engl J Med [Internet]. 2015 Feb 19 [cited 2019 Feb 14];372(8):724–34. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1413513
5. Piccart-Gebhart M, Holmes E, Baselga J, de Azambuja E, Dueck AC, Viale G, et al. Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial. J Clin Oncol [Internet]. 2016 Apr 1 [cited 2019 Feb 14];34(10):1034–42. Available

from: http://ascopubs.org/doi/10.1200/JCO.2015.62.1797

6. Zhou Y, Li S, Hu YP, Wang J, Hauser J, Conway AN, et al. Blockade of EGFR and ErbB2 by the Novel Dual EGFR and ErbB2 Tyrosine Kinase Inhibitor GW572016 Sensitizes Human Colon Carcinoma GEO Cells to Apoptosis. Cancer Res [Internet]. 2006 Jan 1 [cited 2019 May 6];66(1):404–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16397255
7. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol [Internet]. 2018 Aug 1 [cited 2019 Feb 14];29(8):1634–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30032243
8. Giordano SH, Temin S, Chandarlapaty S, Crews JR, Esteva FJ, Kirshner JJ, et al. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol [Internet]. 2018 Sep 10 [cited 2019 Feb 14];36(26):2736–40. Available from: http://ascopubs.org/doi/10.1200/JCO.2018.79.2697

SIGNATURE	
Award Recipient full name	***Signature and Date***
Daniel Eiger	Daniel Eiger 9/07/19

The ESMO Clinical Research Fellowship is supported by an Educational Grant from Novartis.

NOVARTIS
ONCOLOGY