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# HER2 positive lobular vs ductal carcinoma of the breast: pattern of first recurrence and molecular insights

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**Running title**: HER2 positive lobular breast cancer.

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## ABSTRACT

*Background*: Infiltrating lobular carcinoma (ILC) represents about 10% of breast cancer, and rarely shows overexpression of human epidermal growth factor receptor 2 (HER2). In this study we compared biological and clinical characteristics of HER2 positive ILC versus HER2 positive Infiltrating ductal carcinoma (IDC).
*Methods*: We retrospectively analyzed 328 patients with HER2 positive, pure ductal or lobular breast carcinoma, comparing clinical and biological data at diagnosis, and the outcome between two histologies. The analysis of gene mutations has been performed in a subset of patients.
*Results*: Two hundred ninety-one patients (88.7%) had IDC and 37 patients (11.3%) ILC. ILC resulted more frequently multicentric (24.3% vs 6.5%, $p<0.0001$), node positive (54.1% vs 45%, $p=0.013$), with lower proliferative activity (Mib1<20%: 51.4% vs 22.3%, $p<0.0001$) and lower histological grade (G3: 32.4% vs 57.4%, $p=0.038$). Disease recurrence occurred in 57 patients (17.4%), involving the bone in 40% of ILC patients (vs 17% of IDC patients), and the viscera in 30% of ILC patients (vs 59.6% of IDC patients). No difference in recurrence rate between the two histologies has been observed in patients treated with adjuvant trastuzumab (12.5% of ILC patients and 8.3% of IDC patients). Exploratory molecular analysis revealed higher frequency of mutations in ILC, with more cases showing multiple mutations.
*Conclusions*: HER2 positive ILC shows different biological behaviour than IDC, with possible higher mutational load. Despite lower proliferation activity and ER expression of ILC breast cancer, trastuzumab is clearly effective also in this histological subtype.


## MICROABSTRACT

Adjuvant trastuzumab benefit in HER2 positive lobular breast carcinoma compared to HER2 positive ductal carcinoma has been evaluated. A higher recurrence rate in lobular than in ductal patients in pre-trastuzumab era was observed, but no difference regarding histology in patients treated with adjuvant trastuzumab. In an exploratory molecular analysis, high mutational load in lobular carcinoma has been found.

***Keywords***: Lobular Breast Cancer, HER2 Positive, mutational load.

## INTRODUCTION

Infiltrating ductal carcinoma (IDC) and infiltrating lobular carcinoma (ILC) are the most common histologic types of invasive breast cancer, occurring in approximately three fourths and one tenth of breast cancer patients, respectively[1,2].
ILC presents relevant differences in transcriptomic profiles, metastatic pattern and clinical behaviour compared to IDC and warrants its separation as specific entity[3-5]. ILC is less sensitive to chemotherapy, more frequently bilateral and more prone to form gastrointestinal, peritoneal and ovarian metastases than IDC[6-8]. Recent reports conducted on a large number of patients indicate that ILC carries a poorer prognosis if compared to IDC[1,9].
Histologically, ILC is defined as an invasive carcinoma comprising non-cohesive cells dispersed individually in a single-file linear pattern in a fibrous stroma[10,11]. In most cases ILC have a low or intermediate histologic grade, a positivity for estrogen receptor (ER) and are negative for human epidermal growth factor receptor 2 (HER2)[7,12-14].
Amplification of the HER2/neu proto-oncogene,has been reported to occur in 10% to 34% of all invasive breast carcinoma[15]. HER2 overexpression is less frequently in ILC than in IDC (4-13% vs 18-25%), otherwise maintaining its adverse prognostic significance[16-19]. However, limited information regarding the degree of trastuzumab benefit in HER2 positive ILC patients are available in literature[20,21].
The present analysis aims to describe the clinical behaviour of HER2 positive ILC, focusing on the differences in clinico-pathological characteristics at diagnosis, site and time of first relapse, and effect of adjuvant trastuzumab, in respect with IDC.

## MATERIAL AND METHODS

We retrospectively performed an observational mono-institutional study collecting data regarding 328 patients with early-stage (IA-IIIC), HER2 positive pure ILC or IDC breast cancer diagnosed and treated between January 2001 and December 2013 at the Oncology Unit of Ferrara S. Anna University Hospital. Patients with metastatic disease at time of breast cancer diagnosis, patients that received neoadjuvant chemotherapy or with unknown estrogen- (ER), progesterone- (PR) and HER2 receptor status were excluded.
For each patient, we collected information about age and menopausal status at breast cancer diagnosis, tumor size, number of metastatic lymph nodes, pathological stage (according to the Tumour, Nodes, and Metastases [TNM] staging system, seventh edition), tumor grading, tumor histology, ER, PR and HER2 status, proliferative index (Ki67), adjuvant treatment performed, date of recurrence, site of first distance recurrence, of local recurrence and date of death.
Biological parameters were recorded both as continuous variable and as dichotomic variables. ER and PR positivity were defined by immunohistochemistry as any positive nuclear staining (ie, ≥ 1%), and HER2 positive cases were defined as immunohistochemistry (IHC) 3+ score or immunohistochemistry 2+ score plus in situ hybridization with gene amplification (gene to chromosome ratio ≥ 2.0). Ki67 was considered high when the intensity of immunohistochemical staining was ≥ 20%.
Statistical analysis was performed with SPSS 18.0 for Windows. Data were expressed in absolute values as frequencies or medians (range). Differences between the characteristic of ILC and IDC groups were compared using contingency tables and chi-square tests. Distant-Disease Free Survival (D-DFS) was calculated and first recurrence or death, using the Kaplan-Meier method. Patients without events were censored at the time of last follow-up. We also evaluated patients who developed a local recurrence, considering relapse of the breast, chest wall skin after mastectomy and regional lymphnodes.
In a subgroup of patients with available archive tissue (9 patients) (6 IDC and 3 ILC) an exploratory gene mutation analysis was performed by sequencing hot-spot regions of fifty genes, frequently involved in cancer. Sequencing was performed by Ion Torrent Personal Genome Machine (PGM) using Ion AmpliSeq™ Cancer Hotspot Panel v2 (Thermo Fisher) (see https://www.ampliseq.com for complete list of genes), following Ion Ampliseq Library kit 2.0 protocol (Thermo Fisher). Sequencing data analysis was conducted by using Torrent Suite software v.3.4 (Thermo Fisher). Low-quality reads were removed, adapter sequences trimmed and alignment against a reference human genome (hg19) performed by Torrent Mapping Alignment Program. Variants were identified using Variant Caller plugin. Only non-synonymous alterations in exonic or splicing regions, having a frequency higher than 10% and coverage higher than 50x were considered. Annovar algorithm was used to predict pathogenicity of mutations: variations having Polyphen score = 0 were excluded.

## RESULTS

Three hundred twenty eight HER2 positive breast cancer patients with pure lobular or ductal histology (according to World Health Organization (WHO) classification[10]) were selected for this analysis. 291 patients (88.7%) had an IDC and 37 patients (11.3%) an ILC. Due tolittle literature data being available on lobular HER2+ breast cancer patients, we report here also statistically non-significant data, that can be useful to describe the clinical picture of the disease.

The baseline clinico-pathological characteristics and treatment modalities according to histological types are reported in Table 1. Median age at diagnosis was 59 years, without significant differences between the 2 groups (58 and 61 years for IDC and ILC respectively) (p=0.416). ILC resulted significantly more frequently diagnosed in postmenopause (86.5% vs 67.7%, p=0.019), to be multicentric or multifocal (24.3% vs 6.5%, p<0.0001), more prone to metastasise to axillary nodes (54.1 vs 45%, p=0.013) and to massive axillary involvement (N3: 21.6% vs 6.2%), more frequently slow proliferating (Mib1≥20%: 48.6% vs 77.7%, p<0.0001) and with low histological grade (G3: 32.4% vs 57.4%, p=0.038). Considering tumor size at diagnosis, ILC were more frequently observed at ≥ 2 cm (42.2% vs 38.1%) but this difference was not statistically significant (p=0.826).

No significant difference between ILC and IDC patients has been recorded in hormone receptor status (ER+: 78.4% in ILCs vs 72.2% in IDCs, p=0.423; PR+ 78.4% in ILCs vs 62.5% in IDCs, p=0.058). Among ILC patients, we observed a greater number of HER2 IHC 2+/ SISH amplified than in IDC pts (13.5% vs 2.7%, p=0.002).

One hundred fifty patients (46%) were diagnosed in pre-trastuzumab era and did not receive trastuzumab in the adjuvant setting. After clinical availability of trastuzumab, 178 patients (54%) were diagnosed [156 IDCs (87.6%) and 22 ILCs (12.4%)] and 41 patients (23%) (35 IDCs and 6 ILCs) of these did not receive adjuvant trastuzumab due to several reasons (cardiac comorbidity, chemotherapy contraindications, age, patients choice, pT < 1 cm without nodal involvement).

At a median follow-up of 84.9 months (range 3.2-182.3) 75.6% patients are alive, 70.3% in ILC subgroup and 76.3% in the IDC one (p=0.422) [Fig.1a], and 71.6% patients are free of distant metastases (64.9% in the ILC and 72.5% in the IDC subgroup) (p=0.331) [Fig.1b].

Fifty-seven patients (17.4% - 10 ILC and 47 IDC) recurred at distant sites (median 30.8 months, 2.6-123.3). In both groups, the relapse occurred mostly in patients who did not receive trastuzumab (80% and 78.7%, respectively). A significant gain from adjuvant trastuzumab on OS and D-DFS occurred both in the ILC and IDC patients [Fig. 2a-b and Fig.3a-b].

Considering the first site of distance recurrence, ILC pts developed more frequently bone metastases as the only metastatic site (40% vs 17% of IDCs) whereas visceral involvement occurred in 30% of ILC patients, vs 59.6% of IDCs. Simultaneous multiple sites of first distance recurrence have been observed in 30% of ILC patients and 42.6% of IDC patients [Table 2].

Considering regional recurrence, defined as relapse in the breast, chest wall skin after mastectomy or regional lymph nodes, we observed a significant higher incidence in ILC pts (p=0.046). While the percentage of regional recurrence in IDC pts has not changed with respect to adjuvant trastuzumab (8.2% without trastuzumab vs 8.3% with trastuzumab), we observed a local relapse reduction among ILC pts treated with trastuzumab (28.6% without trastuzumab vs 12.5% with trastuzumab, p=0.086) [Table 2].

Among patients that did not receive adjuvant trastuzumab, we found a higher, but statistically non-significant (p=0.114), recurrence rate in ILC than in IDC patients (38.1% vs 21.8% respectively),whereas considering patients treated with adjuvant trastuzumab we observed a smaller difference in terms of recurrence rate in both groups (12.5% of ILCs and 8.3% of IDCs, respectively).

All nine patients in which we performed gene mutation analysis had a triple positive phenotype. Among these, 3 were ILC and 6 were IDC. Mutations are listed in [Table3]. All three ILC displayed mutation in at least one gene. Among the six IDC, only three patients displayed mutation in at least one gene of the panel.

## DISCUSSION

Our analysis demonstrated that HER2 positive ILC has different clinical and biologic characteristics compared with HER2 positive IDC. Several studies have reported differences between ILC and IDC but data comparison between these two histologies only in HER2 positive cases are lacking in literature. We focused in this analysis on tumours with pure lobular or ductal histology, without considering mixed ductal and lobular histology to have more homogeneous groups. However, it would be useful to evaluate also mixed histologies, to assess whether their behaviour is more similar to the ductal or the lobular cancers. We decided to report and comment also statistically non-significant findings, considering the lack of data on this topics.

We observed that clinicopathologic characteristics at diagnosis are different: HER2 positive lobular carcinomas are more frequently multicentric or multifocal, with axillary lymph nodes involvement, lower proliferative activity and histological grade. In contrast to previous observations that ILC patients are on average older[12,13,22], our analysis in HER2 positive cases does not show significant differences in age at

diagnosis, nor in tumour size. However, despite conflicting reports regarding the lymph node status[13,23], we found that axillary lymph nodes involvement was more common in ILC patients (54.1% of ILCs vs 45% of IDCs, p=0.013), especially in case of massive nodal involvement (N3: 21.6% of ILCs and 6.2% in IDCs).
Multicentric or multifocal involvement was significantly more frequent in ILC patients, according to literature data[4,5,24], in our dataset in HER2 positive ILCs, this characteristic was up to four times higher than in IDCs (24.3% of ILCs vs 6.2% of IDCs, p<0.0001).
Some previous reports have demonstrated higher rates of steroid receptor positivity in ILCs[12,13,20]. In our patients, we observed a higher percentage (not statistically significant) of ER and PgR expression in ILC patients than in IDC (ER positive: 78.4% vs 72.2%, p=0.423 and PgR positive: 78.4% vs 62.5%, p=0.058). This data is partially different from literature, in which, beside the Metzer-Filho study[20], the analyses comprise both positive and negative HER2 ILC.
A different metastatic spread was observed in HER2 positive ILC and IDC patients[7]. Probably the microenvironment of the involved organ or physical properties including cell size or shape and loss of expression of cell-cell adhesion molecule E-cadherin could influence metastatic pattern[12,13].
In our analysis, as in the previous studies, the rate of bone metastasis was higher in HER2 positive ILC patients compared to HER2 positive IDC patients, whereas in IDC patients was higher the percentage of lung and liver metastases. With the limit of the small number of patients included in our study, we did not observe any peritoneal, ovarian or gastrointestinal tract relapse in HER2 positive ILC patients. This feature was also reported by Metzer-Filho in his analysis of ILC patients included in the HERA trial[20] and could suggest a different pattern of metastasis between HER2 positive and negative ILC patients. We also observed a significantly higher incidence of local recurrence in ILC patients, with a lower percentage in patients treated with adjuvant trastuzumab.
All trials that evaluated trastuzumab efficacy in the adjuvant setting have reported a statistically significant benefit[25-27],but to what extent specific histologic features within HER2 positive patients may predict response to anti-HER2 therapies remains an unanswered question. To our knowledge, the Metzer-Filho study is the only one that tried to analyze the trastuzumab therapy benefit in patients with lobular histology compared with ductal histology, demonstrating a benefit of a similar magnitude between the two groups[20]. The present analysis confirmed no difference in the trastuzumab benefit in ILC vs IDC patients. A higher recurrence rate (although not statistically significant) was observed in ILCs comparing with IDCs in the pre-trastuzumab era, but the introduction of trastuzumab has overcome this phenomenon in most recent time.
Molecular analysis, although exploratory, considering the small number of samples tested, seems to indicate that ILC patients have higher mutational load than IDC (100% vs 50% respectively). In one case, we also observed the co-existence of TP53 and PIK3CA mutations. The limited number of cases, however, does not allow for any firm conclusion. The meaning of PIK3CA mutation in breast cancer is still debated, particularly for HER2 positive tumors. Several studies found a significant association of PIK3CA mutations and longer relapse-free survival, especially in luminal subtypes[28], whereas others suggest that PIK3CA-mutated tumors could be resistant to trastuzumab therapy[29], demonstrating that tumors with PI3K/AKT pathway activation including PTEN loss or PIK3CA mutation or both are less sensitive to trastuzumab treatment[30]. There are even less data about the meaning of PIK3CA mutations between different breast cancer histologies. A recent study performed a comprehensive analysis of somatic mutations in ILC compared to IDC, finding a significantly higher percentage of PIK3CA mutations in ILC (48% vs 33%)[31]. Even Buttitta et. al. found more frequent PIK3CA mutations in ILC (46%) vs IDC (22%), especially considering mutations in exon 9 (30% of ILC cases vs less than 5% of other histology cases)[32]. Considering TP53, this mutation predicts poor prognosis in early breast cancer pts with luminal and triple negative tumors, while immunopositivity for p53 protein may be predictive for adjuvant trastuzumab benefit[33].

**Study limitations.** The main limitations of the study are related to its retrospective design and to the effects of the small number of patients from a single center on the results of the statistical analyses, non-significant in many cases. The molecular analyses has been also evaluated in a small sample of patients and should be considered preliminary. However, due to the limited literature available on this breast cancer subtype, these data might be useful for further discussions and to eventually design prospective studies.

## CONCLUSIONS

Despite of some limitations of our study, we confirmed that HER2 positive ILC and IDC are different entities with different clinical course and different biology, with higher mutational load. We also observed that, despite lower proliferation activity, trastuzumab is clearly effective in HER2 positive ILC, confirming the indication to use adjuvant trastuzumab with the backbone chemotherapy also in this histological subtype.

## CLINICAL PRACTICE POINTS

- Infiltrating lobular breast carcinoma is the second common histologic types of invasive breast cancer, with peculiar features compared to ductal carcinoma;
- HER2 overexpression is less frequently in lobular than in ductal carcinoma (4-13% vs 18-25%), with limited information regarding the degree of adjuvant trastuzumab benefit;
- This study evaluated adjuvant trastuzumab benefit in lobular HER2 positive breast cancer, demonstrating a high efficacy even in this patients subset, despite a lower proliferation activity;
- We observed a higher mutational load in HER2 positive lobular breast cancer compared to HER2 positive ductal breast cancer.

**Conflict of interest** The authors declare that they have no conflicts of interest.

**FIGURE LEGEND**

**Figure 1.** a) OS according to histology; b) D-DFS according to histology.
**Figure 2.** a) OS according to trastuzumab treatment in IDC histology subgroup; b) OS according to trastuzumab treatment in ILC histology subgroup.
**Figure 3.** a) D-DFS according to trastuzumab treatment in IDC histology subgroup; b) D-DFS according to trastuzumab treatment in ILC histology subgroup.

**TABLE LEGEND**

**Table 1.** Baseline clinical and pathological characteristics.
**Table 2.** Site of first distance recurrence and local recurrence according to histology and adjuvant trastuzumab therapy.
**Table 3.** Mutations in investigated samples.

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**Table 1.** Baseline clinical and pathological characteristics.

| *Characteristics* | *Ductal* (n = 291) No. | % | *Lobular* (n = 37) No. | % | *Signific* |
|---|---|---|---|---|---|
| Age at diagnosis, years | | | | | |
| Median | 58 | | 61 | | p=0.416 |
| Range | 27-91 | | 36-79 | | |
| Menopausal status | | | | | |
| Premenopausal | 94 | 32.3 | 5 | 13.5 | p=0.019 |
| Postmenopausal | 197 | 67.7 | 32 | 86.5 | |
| Multicentric/Multifocal | | | | | |
| No | 272 | 93.5 | 28 | 75.7 | p<0.0001 |
| Yes | 19 | 6.5 | 9 | 24.3 | |
| Tumor stage* | | | | | |
| T1 | 180 | 61.9 | 21 | 56.8 | |
| T2 | 91 | 31.3 | 12 | 32.4 | p=0.826 |
| T3 | 11 | 3.8 | 2 | 5.4 | |
| T4 | 9 | 3.1 | 2 | 5.4 | |
| Node stage* | | | | | |
| N0 | 160 | 55.0 | 17 | 45.9 | |
| N1 | 79 | 27.1 | 8 | 21.6 | p=0.013 |
| N2 | 34 | 11.7 | 4 | 10.8 | |
| N3 | 18 | 6.2 | 8 | 21.6 | |
| Histological grade | | | | | |
| G1 | 12 | 4.1 | 2 | 5.4 | |
| G2 | 106 | 36.4 | 22 | 59.5 | p=0.038 |
| G3 | 167 | 57.4 | 12 | 32.4 | |
| Not assessed | 6 | 2.1 | 1 | 2.7 | |
| Proliferative activity | | | | | |
| Mib1 < 20% | 65 | 22.3 | 19 | 51.4 | p<0.0001 |
| Mib1 ≥ 20% | 226 | 77.7 | 18 | 48.6 | |
| ER Expression | | | | | |
| Positive (≥1%) | 210 | 72.2 | 29 | 78.4 | p=0.423 |
| Negative | 81 | 27.8 | 8 | 21.6 | |
| PgR Expression | | | | | |
| Positive (≥1%) | 182 | 62.5 | 29 | 78.4 | p=0.058 |
| Negative | 109 | 37.5 | 8 | 21.6 | |
| HER2 | | | | | |
| IHC 3+ | 283 | 97.3 | 32 | 86.5 | p=0.002 |
| IHC 2+ - SISH amplified | 8 | 2.7 | 5 | 13.5 | |
| Adjuvant Chemotherapy | | | | | |
| Yes | 205 | 70.4 | 26 | 70.3 | p=0.002 |
| No | 84 | 28.9 | 8 | 21.6 | |
| NA | 2 | 0.7 | 3 | 8.1 | |
| Adjuvant Trastuzumab | | | | | |
| Yes | 121 | 41.6 | 16 | 43.2 | p=0.847 |
| No | 170 | 58.4 | 21 | 56.8 | |

*According to American Joint Committee on Cancer, Seventh Edition, 2009.
Abbreviations: NA, Not Available; ER, estrogen receptor; PgR, progesterone receptor; IHC, immunohistochemistry.

**Table 2.** Site of first distance recurrence and local recurrence according to histology and adjuvant trastuzumab therapy.

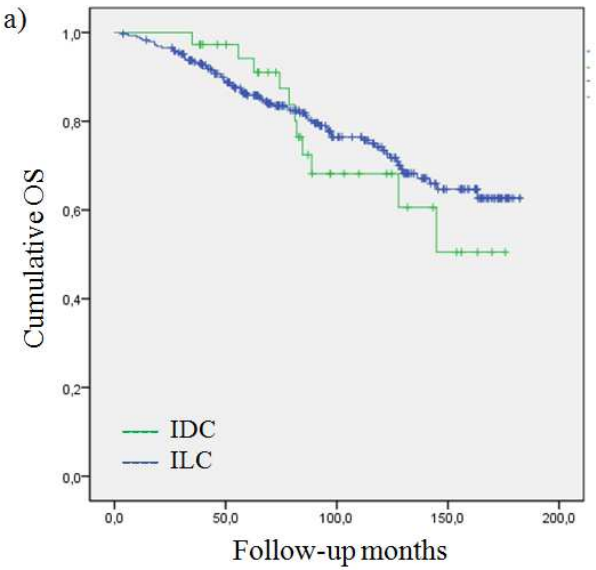
| | *No Adjuvant Trastuzumab* | | | | *Adjuvant Trastuzumab* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Ductal* (n = 170) | | *Lobular* (n = 21) | | *Ductal* (n = 121) | | *Lobular* (n = 16) | |
| | No. | % | No. | % | No. | % | No. | % |
| *D-DFS Event* | | | | | | | | |
| Patients with an event | 37 | 21.8 | 8 | 38.1 | 10 | 8.3 | 2 | 12.5 |
| Bone | 15 | 40.5 | 5 | 62.5 | 3 | 30.0 | 1 | 50.0 |
| Lung | 8 | 21.6 | 1 | 12.5 | 3 | 30.0 | 0 | 0.0 |
| Liver | 14 | 37.8 | 0 | 0.0 | 4 | 40.0 | 0 | 0.0 |
| Skin or lymph nodes | 12 | 32.4 | 3 | 37.5 | 8 | 80.0 | 2 | 100.0 |
| CNS | 6 | 16.2 | 2 | 25.0 | 2 | 20.0 | 0 | 0.0 |
| Other | 4 | 10.8 | 0 | 0.0 | 0 | 0.0 | 1 | 50.0 |
| *Local Recurrence* | | | | | | | | |
| Patients with an event | 14 | 8.2 | 6 | 28.6 | 10 | 8.3 | 2 | 12.5 |
| Breast | 7 | 4.1 | 4 | 19 | 6 | 4.9 | 1 | 6.2 |
| Regional lymph nodes | 3 | 1.8 | 1 | 4.7 | 4 | 3.3 | 1 | 6.2 |
| Chest wall skin | 4 | 2.4 | 1 | 4.7 | 0 | 0.0 | 0 | 0.0 |

Note: patients may be listed multiple times in case of simultaneous multiple sites of distance recurrence.

**Table 3.** Mutations in investigated samples.

| Sample | Histotype | ER | PR | HER2 | Mutations |
|---|---|---|---|---|---|
| 1 | ILC | +++ | +++ | +++ | TP53 (c.206C>T; p. A69V); PIK3CA (c.3140A>G; p.H1047R); CDKN2A (c.242C>T; p.P81L) |
| 2 | ILC | +++ | +++ | +++ | TP53 (c.536A>T; p.H179L) |
| 3 | ILC | +++ | +++ | +++ | ABL1 (c.740A>G; p.K247R) |
| 4 | IDC | +++ | +++ | +++ | ERBB2 (c.2305G>T; p.D769Y) |
| 5 | IDC | +++ | +++ | +++ | MET (c.504G>T; p.E168D) |
| 6 | IDC | +++ | +++ | +++ | PIK3CA (c.1357G>A; p.E453K) |
| 7 | IDC | +++ | +++ | +++ | None |
| 8 | IDC | +++ | +++ | +++ | None |
| 9 | IDC | +++ | +++ | +++ | None |

a)


Cumulative OS
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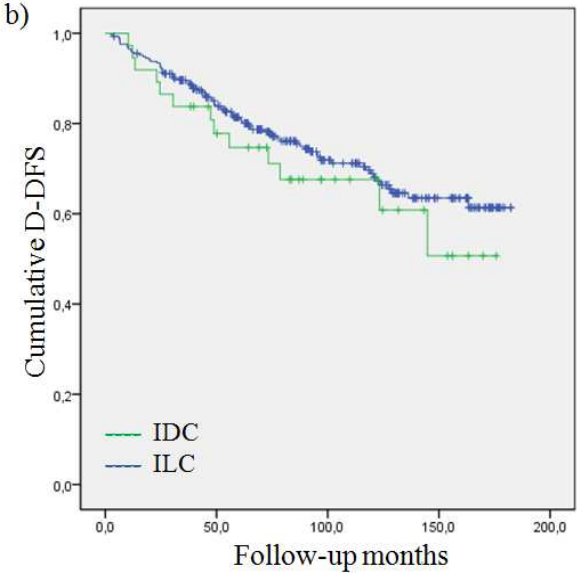
0,6
0,4
0,2
0,0
IDC
ILC
0,0
50,0
100,0
150,0
200,0
Follow-up months

b)


Cumulative D-DFS
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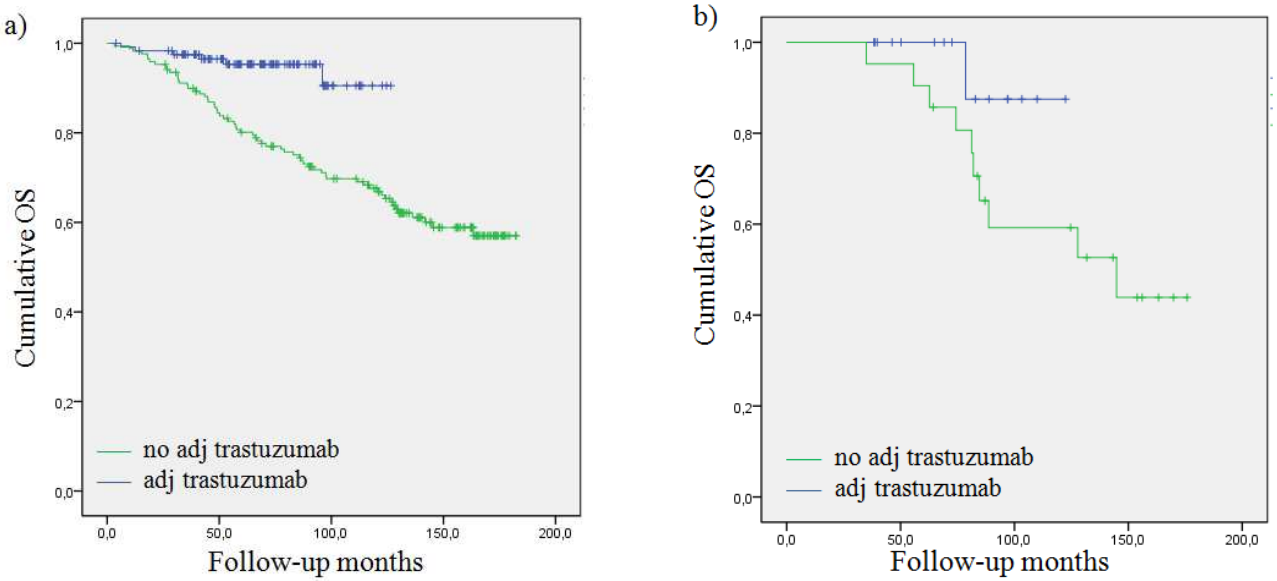
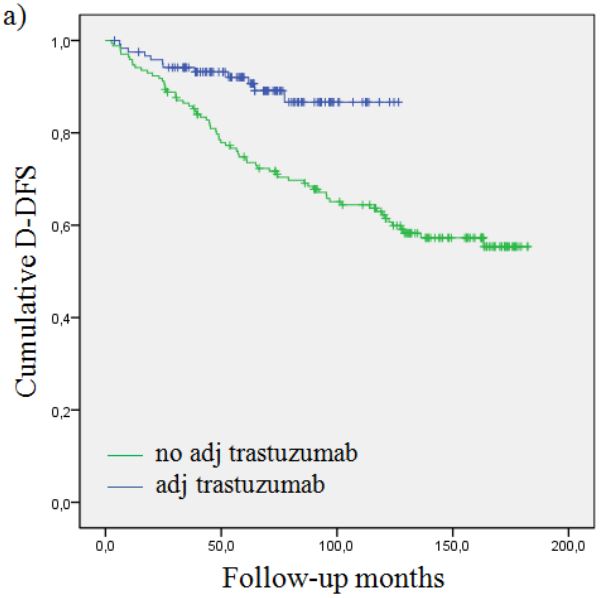
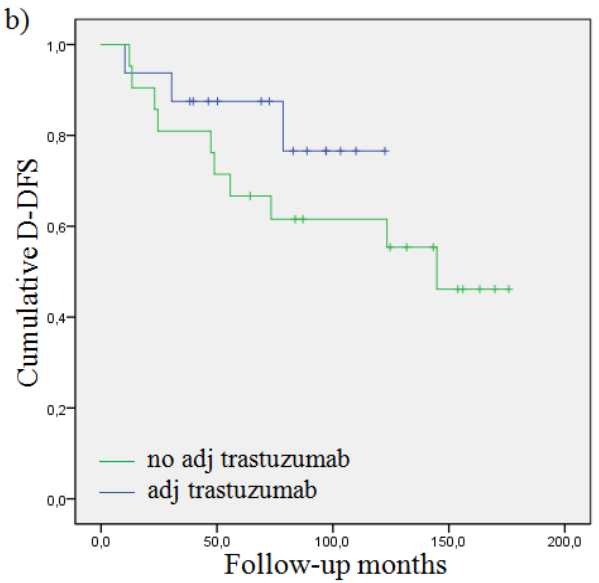
0,8
0,6
0,4
0,2
0,0
IDC
ILC
0,0
50,0
100,0
150,0
200,0
Follow-up months


a)
Cumulative OS
1,0
0,8
0,6
0,4
0,2
0,0
0,0
50,0
100,0
150,0
200,0
Follow-up months
no adj trastuzumab
adj trastuzumab
b)
Cumulative OS
1,0
0,8
0,6
0,4
0,2
0,0
0,0
50,0
100,0
150,0
200,0
Follow-up months
no adj trastuzumab
adj trastuzumab

a)


Cumulative D-DFS
1,0
0,8
0,6
0,4
0,2
0,0
no adj trastuzumab
adj trastuzumab
0,0
50,0
100,0
150,0
200,0
Follow-up months

b)


Cumulative D-DFS
1,0
0,8
0,6
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0,0
no adj trastuzumab
adj trastuzumab
0,0
50,0
100,0
150,0
200,0
Follow-up months