Reporting on invasive lobular breast cancer in clinical drug trials : a systematic review

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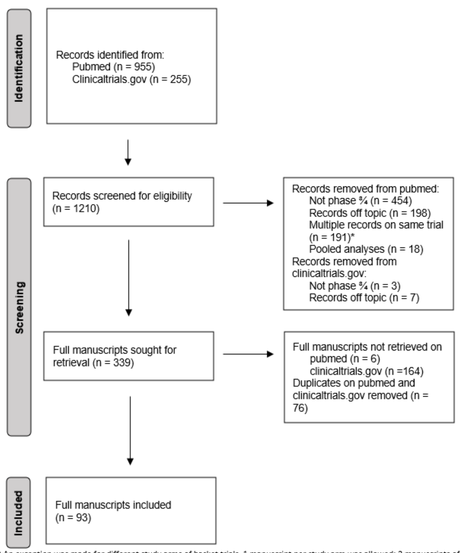
LAY ABSTRACT

Although previous studies demonstrated that differences between lobular breast cancer (ILC) and breast cancer of no special subtype (NST) exist, they are often treated the same. It is **unclear if treatments that were recently developed for breast cancer are as effective for ILC as for NST**. We looked into all manuscripts published on these recently developed treatments to see if they reported how many patients with ILC were involved in the trials. The aim was to **uncover the extent of the knowledge gap concerning ILC treatment**. In total 81 publications were found. **Only 13/93 (14.0%) reported how many patients with ILC they included.** The percentage of patients with ILC included, varied from 2.0 to 26.0% and only 3 of the studies did specific sub-analyses for the patients with ILC. We conclude that **ILC is greatly disregarded in clinical drug trials**. Patients with ILC deserve much more attention in clinical trials.

INTRODUCTION AND OBJECTIVES

- ILC represents 15% of all breast cancers[1]
- ILC needs to be seen as a separate entity as it differs from NST on a clinical, pathological and biological level[1]
- Differences in treatment response between ILC and NST have been described for chemotherapy[2]
- There is a lack of knowledge for treatment efficacy of novel breast cancer treatment in patients with ILC[1]
- Patients with ILC might be underrepresented in clinical trials, especially in case of stage IV disease[3]
- The unique growth pattern and metastatic pattern of ILC more often leads to non-measurable disease while RECIST criteria are commonly used as inclusion criteria for drug trials[1,3,4]

METHODS



* An exception was made for different study arms of basket trials, 1 manuscript per study arm was allowed: 2 manuscripts of 1 b (GeparQuinto, NCT00567554)[27,23] were included in this systematic review

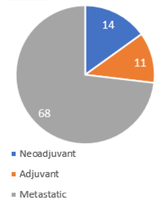
- Identification of phase 3/4 clinical trials for novel breast cancer treatments by use of keywords linked to treatment strategies and 'breast cancer'
- Inclusion of trials if a full manuscript was available on the 31st of July 2023
- Review of inclusion and exclusion criteria to see if patients with ILC or non-measurable disease were excluded
- Assessment of documentation on ILC: percentage included, central pathology and subgroup analyses

PRISMA-diagram of study selection of clinical drug trials

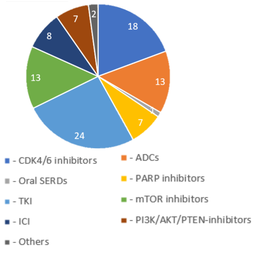
RESULTS

Features of clinical trials

Setting



Drug class



ILC documentation in clinical trials

In total 14% of the trials reported the percentage of patients with ILC included: 35,7% in neoadjuvant, 9,1% in adjuvant and 10,3% in metastatic setting

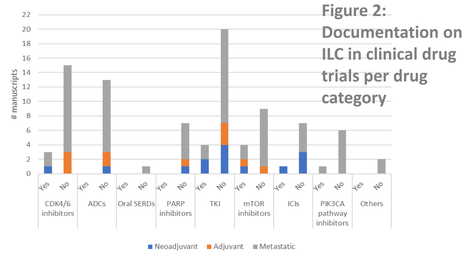
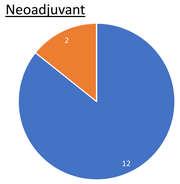


Figure 2: Documentation on ILC in clinical drug trials per drug category

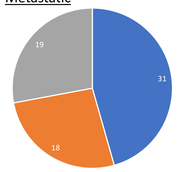
Inclusion and exclusion criteria in clinical trials

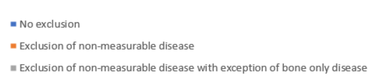
1/93 trials included exclusively patients with NST. Inclusion/exclusion based on measurable disease:

Neoadjuvant

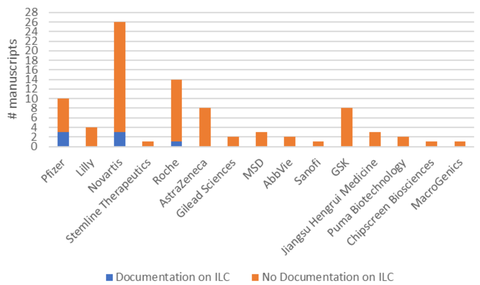


Metastatic





Documentation on ILC in clinical drug trials per pharmaceutical company



ILC representation in clinical trials

SETTING	TRIAL	DRUG	PATIENT POPULATION	% ILC INCLUDED	SUB-ANALYSIS
Neoadjuvant	SAFIA[31]	palbociclib (CDK4/6i)	HR+ HER2-	12.0	No
	IMpassion031[25]*	atezolizumab (ICI)	TNBC	2.0	No
	GeparQuinto Lapatinib[29]	lapatinib (TKI)	HR- HER2+ or HR+ HER2+ if cN+	2.8	Yes
	EPHOS B[32]	lapatinib (TKI)	HER2+	4.0	No
	GeparQuinto Everolimus[23]	everolimus (mTORi)	HR- HER2+ or HR+ HER2+ if cN+	10.8	Yes
Adjuvant	MAINtenance Afinitor[33]	everolimus (mTORi)	HR+ HER2-	16.3	No
Metastatic	PALOMA 2[27]**	palbociclib (CDK4/6i)	HR+ HER2-	14.7	No
	PALOMA 4[28]**	palbociclib (CDK4/6i)	HR+ HER2-	3.8	No
	NCT00281658[26]*	lapatinib (TKI)	HER2+	4.7	No
	DETECT III[34]	lapatinib (TKI)	HER2- with HER2+ CTCs	9.8	No
	BELLE-2[35]	buparlisib (PI3Ki)	HR+ HER2-	13.0	No
	INPRES[36]	everolimus (mTORi)	HR+ HER2-	26.0	Yes
	IMPROVE[30]	everolimus (mTORi)	HR+ HER2-	24.7	No

Race was evaluated in 6/13 (46,2%) of these trials ⇨ 3 of which differentiated only between Asian race and 'others'

CONCLUSIONS

ILC is greatly overlooked in the majority of clinical trial with

- poor documentation
- poor representation
- lack of specific sub-analyses
- lack of central pathology

Eligibility criteria and definitions of treatment response in clinical trials do not reflect the unique biology and clinical course of ILC.

Only few retrospective trials asses the use of novel breast cancer therapies for patients with ILC

ILC deserves much more attention from both clinical investigators and pharmaceutical industries.

ABBREVIATIONS

- ADC: antibody drug conjugate
- GEP: gene expression profile
- ICI: immune checkpoint inhibitors
- ILC: invasive lobular carcinoma
- MSP: molecular screening program
- NST: breast cancer of non-special type
- RECIST: response evaluation criteria in solid tumours
- SERD: selective oestrogen receptor degrader
- TKI: tyrosine kinase inhibitors

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ACKNOWLEDGEMENTS

The authors like to thank all contributors from the Lobular Breast Cancer Alliance (LBCA) and the European Lobular Breast Cancer Consortium (ELBCC) and Lobsterpot. This article/publication is based upon work from COST Action LOBSTERPOT CA19138, supported by COST (European Cooperation in Science and Technology, http://www.cost.eu/).

JVC is funded by the KU Leuven Fund Nadine de Beauffort.

KVB is funded by the KU Leuven Fund Nadine de Beauffort and a Conquer Cancer – Lobular Breast Cancer Alliance Young Investigator Award for Invasive Lobular Carcinoma Research, supported by Lobular Breast Cancer Alliance. Any opinions, findings, and conclusions expressed in this material are those of the author(s) and do not necessarily reflect those of the American Society of Clinical Oncology® or Conquer Cancer®, or Lobular Breast Cancer Alliance.

♥ We like to dedicate this work to Leigh Pate and Deborah Mueller, 2 amazing women who have meant so much for the ILC community and who will be greatly missed ♥