REVIEW

Current and future diagnostic and treatment strategies for patients with invasive lobular breast cancer

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Background: Invasive lobular breast cancer (ILC) is the second most common type of breast cancer after invasive breast cancer of no special type (NST), representing up to 15% of all breast cancers.

Design: Latest data on ILC are presented, focusing on diagnosis, molecular make-up according to the European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets (ESCAT) guidelines, treatment in the early and metastatic setting and ILC-focused clinical trials.

Results: At the imaging level, magnetic resonance imaging-based and novel positron emission tomography/computed tomography-based techniques can overcome the limitations of currently used imaging techniques for diagnosing ILC. At the pathology level, E-cadherin immunohistochemistry could help improving inter-pathologist agreement. The majority of patients with ILC do not seem to benefit as much from (neo-)adjuvant chemotherapy as patients with NST, although chemotherapy might be required in a subset of high-risk patients. No differences in treatment efficacy are seen for anti-human epidermal growth factor receptor 2 (HER2) therapies in the adjuvant setting and cyclin-dependent kinases 4 and 6 inhibitors in the metastatic setting. The clinical utility of the commercially available prognostic gene expression-based tests is unclear for patients with ILC. Several ESCAT alterations differ in frequency between ILC and NST. Germline *BRCA1* and *PALB2* alterations are less frequent in patients with ILC, while germline *CDH1* (gene coding for E-cadherin) alterations are more frequent in patients with ILC. Somatic *HER2* mutations are more frequent in ILC, especially in metastases (15% ILC versus 5% NST). A high tumour mutational burden, relevant for immune checkpoint inhibition, is more frequent in ILC metastases (16%) than in NST metastases (5%). Tumours with somatic inactivating *CDH1* mutations may be vulnerable for treatment with *ROS1* inhibitors, a concept currently investigated in early and metastatic ILC.

Conclusion: ILC is a unique malignancy based on its pathological and biological features leading to differences in diagnosis as well as in treatment response, resistance and targets as compared to NST.

Key words: invasive lobular breast cancer, treatment strategies, clinical management, imaging, ESCAT alterations, ongoing trials

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INTRODUCTION

Invasive lobular breast cancer (ILC) is the second most commonly diagnosed type of breast cancer in women, after invasive breast cancer of no special type (NST). ILC accounts for up to 15% of all invasive breast cancers in women.[1,2] An increase in ILC incidence was seen in the past two decades and can be partially explained by the advances in the diagnosis of ILC[3] and the increased use of hormone

replacement therapy (HRT) in postmenopausal women.[3-7] While ILC differs from NST on a clinical, histological and molecular level, in current clinical practice the histological type is barely considered when systemic treatment decisions are made. In this review, we discuss the pathological, clinical and biological differences between ILC and NST and the subsequent challenges and opportunities in ILC management.

CLINICAL PRESENTATION

In general, at diagnosis, women with ILC are slightly older than women with NST (mean age 63.4 versus 59.5 years, respectively).[8,9] ILC is more difficult to detect through standard screening programs and presents more often as a larger tumour[9] and with nodal involvement,[10] as compared to NST. Additionally, ILC is more often multifocal.[11] ILC is thought to come with increased rates of bilateral disease as well[12]; however, controversy exists as Pestalozzi et al. found similar rates of bilateral disease for NST and ILC.[9] In some series, the long-term risk of developing metastatic disease is higher for ILC in comparison to NST, even when estrogen receptor (ER)-positive ILC is compared to ER-positive NST.[9,13] Other series, like the one from Timbres et al., found similar long-term survival rates for patients with NST and ILC.[14] Late relapses are more frequently seen in patients with ILC than in patients with NST, with relapses of ILC frequently occurring >10 years after primary diagnosis.[9] ILC has a distinct metastatic pattern with a wider metastatic spread,[15,16] favouring serosa and including metastases in the gastrointestinal and reproductive tract. In patients with ER-positive ILC, metastases are less frequently seen in the lung, central nervous system (with the exclusion of leptomeningeal disease which is more frequent in ILC) and distant lymph nodes as compared to NST.[9,17-21]

RISK FACTORS FOR DEVELOPING ILC

Early menarche, use of progesterone-based HRT, late age at first live birth[4] and alcohol consumption[22] are more strongly associated with the risk of developing ILC as compared to NST. Obesity in postmenopausal women does not seem to affect the risk of developing ILC over NST[4,23] (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.05.006). Several studies have reported that germline BRCA2 and CDH1 (the gene coding for E-cadherin) mutations are associated with a high risk of developing ILC, and germline ATM, CHEK2 and PALB2 mutations are associated with a moderate risk of developing ILC.[24-26] Germline BRCA1 mutations are not associated with a clinically relevant risk of developing ILC.[25,26] Yadav et al. also reported germline BRCA1 and PALB2 mutations to be significantly less frequent in patients with ILC and germline CDH1 mutations, which also predispose to diffuse type gastric cancer, to be significantly more frequent (Table 1). While germline CDH1 mutations are rare in patients with ILC (<1%), they appear to be more common (8%) in women with bilateral ILC.[27] In a study investigating 1434 women with ILC, 11% of women younger than 40 years of age had a

germline mutation associated with increased breast cancer risk.[24] There is also evidence that low penetrance breast cancer predisposition single nucleotide polymorphisms (SNPs) have differential effects on the development of ILC and NST, with one specific SNP for ILC at 7q34.[28]

PATHOLOGICAL DIAGNOSIS AND CHARACTERIZATION OF ILC

According to the fifth edition of the World Health Organization's (WHO) Classification of Breast Tumours,[29] recognizing the non-cohesive nature, single file or targetoid pattern, observed on routine histology is essential for the pathological diagnosis of ILC. Supporting techniques such as immunohistochemistry (IHC) or DNA sequencing are, according to WHO, not required for diagnosis. However, a recent worldwide survey of pathologists highlighted that the vast majority uses IHC systematically to confirm ILC diagnosis.[30] Loss or aberrant expression of the cell-to-cell adhesion molecule E-cadherin supports the diagnosis of ILC.[30] Lack of E-cadherin protein expression, observed in the majority of ILC (>85% of the cases),[31,32] is predominantly caused by somatic mutations and loss of heterozygosity, although promoter methylation of CDH1 has also been reported in rare cases.[31,33] Mutational loss of E-cadherin causes cytosolic translocation of p120-catenin (p120), a multifaceted protein that plays crucial roles in the pathobiology of ILC.[34-36] Besides classic ILC that represents more than half of the ILC cases (~55%), special ILC subtypes exist.[29,37,38] These ILC subtypes differ in the underlying molecular alterations, possibly impacting treatment targets and efficacy.[31] Of note, multivariate analyses of a large series of ILC suggested that patients with pure classical patterns had the best outcome and patients with the solid and mixed non-classic types of ILC had worse outcomes.[37] Pathological diagnosis of ILC (versus NST) remains a point of concern as a retrospective analysis of two trials showed that only 60%-66% of the tumours diagnosed as ILC by local pathology were confirmed to be ILC by central pathology.[39,40] In this context, a recent study has demonstrated that the inter-pathologist concordance can be significantly improved by using E-cadherin IHC for diagnosing ILC.[41]

More than 90% of primary ILCs express ER and progesterone receptors (PRs),[32] although low ER and PR expression has been reported in the metastases of 11% and 38% of the patients, respectively.[42] Human epidermal growth factor receptor 2 (HER2) amplification/overexpression is generally only present in 3%-13% of cases.[29,38] Furthermore, most ILC cases have a low or intermediate proliferation grade.[2,33] Triple-negative ILC represents only 2%-9% of all ILCs.[38] A vast majority of triple-negative ILCs express the androgen receptor (AR), implying that this rare subtype has a different biology compared to triple-negative NST.[38,43,44] Controversy exists about the so-called 'HER2-low' tumours, HER2 not amplified tumours with a 1+ or 2+ IHC score which could potentially benefit from novel anti-HER2 therapies.[45] Some studies reported that these 'HER2-low' tumours are less frequent in HER2-non-amplified ILC (33%)

Table 1. Actionability of the genomic alterations in primary and metastatic ILC as per ESCAT[53,206]

	Readiness of use in clinical practice	ESCAT alterations in breast cancer	% Primary ILC (% primary NST)	% Metastatic ILC (% metastatic NST)
Tier I	Targets ready for implementation in routine clinical decisions	ERBB2/HER2 amplification	7.4 (20.6)[25]	6.8 (11.4)[55]
		Germline BRCA1 mutations	0.3 (2.3)[25,55]	
		Germline BRCA2 mutations	2.2 (2.4)[25]	
		NTRK1-3 fusions	0 (0)	0.6 (0)[33]
		PIK3CA mutations	43-48 (33.5)[31]	38-47.2 (33.1)[42,55]
		MSI	NA	NA
		High TMB (>10 mutations/Mb)	4.7 (NA)[54]	16 (5)[58]
Tier II	Investigational targets likely to define patients who benefit from a targeted drug, but additional data needed	AKT1 mutations	1.6-4 (3.1)[31,33]	7.5-10 (6.4)[42,55]
		ERBB2/HER2 mutations	3.9-5 (1.4)[31,33]	14.3-15 (4.6)[42,55]
		ESR1 mutations	0-0.8 (0.8)[31,33]	15.5-18 (15.3)[42,55]
		PTEN loss	13.4 (11.2)[33]	14.3-15 (8.4)[42]
Tier III	Clinical benefit previously demonstrated in other tumour type or for similar molecular targets	Somatic BRCA1 mutations	0 (2.9)[31,33]	1.2 (1.9)[55]
		Somatic BRCA2 mutations	0.8-2 (2.5)[31,33]	6.2 (3.5)[55]
		MDM2 amplifications	2-2.4 (4.7)[31,33]	2-6.2 (4.2)[42,55]
		NF1 mutations	1-3.9 (2.9)[31,33]	7-7.5 (5.8)[42,55]
		ERBB3/HER3 mutations	0.8-4 (2.3)[31]	0-2.5 (1.9)[42,55]
Tier IV	Preclinical evidence of actionability	ARID1A mutations	5.5-6.3 (3.7)[31]	8.7-15 (6.1)[42,55]
		ARID1B mutations	0.2-0.8 (2.1)[31,33]	2.5 (2.8)[55]
		Germline ATR mutations	NA	
		Germline ATM mutations	1.03 (1.1)[25]	
		Germline PALB2 mutations	0.37 (1.5)[25]	
		CDH1 mutations	63-65 (2)[31,33]	69-75.8 (2.1)[42,55]
		Germline CDH1 mutations	0.54 (0.04)[25]	
		IGF1R mutations	0-1.6 (0.8)[31,33]	0-13 (2.1)[42,55]
		INPP4B loss	0.8 (0.8)[33]	0.6 (0.3)
		MAP3K1 mutations	5.3-5.5 (8.2)[31,33]	7.5-17 (7)[42,55]
		MAP2K4 mutations	1.2-1.4 (4.9)[31,33]	2-4.3 (3.7)[42,55]
		MT4 mutations	NA	
		MYC amplifications	4.7-6.3 (26.8)[31,33]	3.7-15 (11.6)[42,55]
		PIK3R1 mutations	0-1 (1.8)[33]	1.9 (2.7)[55]
		RUNX1 mutations/deletions	4-10.2 (2.5)[33]	5 (2.7)[55]
		CBFB mutations/deletions	3.2 (3.3)[33]	4.3 (3.5)[55]
		SF3B1 mutations	1.5-3.1 (2.5)[33]	3.1 (1.7)[55]
		TP53 mutations	7.3-7.9 (44)[31,33]	12-19.9 (42.9)[42,55]
Tier X	Lack of evidence of actionability	FGFR1 amplification	9.4-25 (13.9)[31,33]	14.3-15 (14.6)[42,55]
		CCND1 amplification	17.3-38 (16.2)[31,33]	19.9-24 (22.7)[42,55]
		ESR1 amplification	0.8-10 (3.5)[33,207]	1.0 (3.2)[55]
		FGFR4 mutations	0 (0.2)[33]	2.5 (1.0)[55]

All alterations in the table are somatic unless otherwise specified. Red and darkgreen, respectively, denote the alterations that were found to be statistically significantly more and less prevalent in ILC versus IDC tumours, respectively. When referring to Desmedt et al.[30] and Richard et al.,[43] alterations were coloured when significantly different in the multivariate analyses comparing ER-positive/HER2-negative ILC versus NST tumours. HER2 amplification status on the metastases was retrieved from the copy number data from Razavi et al.[55]

ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ILC, invasive lobular breast cancer; MSI, microsatellite instability; NA, not available; TMB, tumour mutational burden.

as compared to HER2-non-amplified NST (53%),[46] while others reported similar rates.[47] With regard to stromal tumour-infiltrating lymphocytes (sTILs), studies have consistently shown lower levels in ER-positive/HER2-negative primary ILC versus NST.[42,48,49] These studies also suggest that higher levels of sTIL could be associated with a worse prognosis in ER-positive breast cancer (regardless of histology). Finally, the expression of programmed death-ligand 1 (PD-L1) seems to be lower in ILC versus NST in primary treatment-naive samples.[50]

MOLECULAR FEATURES OF ILC

ILC presents several differences in its somatic mutational landscape as compared to NST, both at the primary[31,33,51] and metastatic[42,52] levels. Some of the genes that are differentially altered between ILC and NST harbour (potential) clinical relevance. This is shown in Table 1, where the alterations are displayed according to the European Society for Medical Oncology (ESMO) Scale for Clinical

Actionability of molecular Targets (ESCAT).[53] The extracted mutational frequencies reported in Table 1 should be taken with caution since the cohorts differ in terms of clinical and pathological characteristics.[54] Also, some studies report only ILC confirmed by central pathology,[31,33,42] while others do not.[55] As reported in Table 1, the proportion of metastases with a high tumour mutational burden (TMB, >10 mutations per megabase) is significantly higher in ILC as compared to NST,[52,56-58] suggesting that for a subset of patients with ILC, immune checkpoint inhibitors (ICIs) might be a valid treatment option, an hypothesis being tested in the Assessing Efficacy of Carboplatin and Atezolizumab in Metastatic Lobular Breast Cancer (GELATO) trial.[59] A significantly higher number of HER2 mutations have also been reported in ILC versus NST, especially in grade 3 ILC and in the metastatic setting,[60] of relevance for treatment with second-generation HER2 tyrosine kinase inhibitors.[61] While alterations in the HER2 and phosphoinositide 3-kinase (PI3K) pathway are frequently observed in ILC, Teo

et al. demonstrated increased responsiveness of the growth factor receptor-dependent activation of the PI3K/Akt pathway in experimental ILC models, highlighting a potential for drugs targeting the PI3K/Akt axis in ILC irrespective of mutations in the pathway.[62] Several studies also documented the distinct regulation of ER signalling in ILC as compared to NST,[63-65] identifying, for instance, lower levels of ER at the messenger RNA and protein level in ER-positive ILC versus ER-positive NST and a distinct regulation of ER signalling by selective ER downregulators in ILC versus NST cell lines. Finally, Nagle et al. reported an enhanced insulin-like growth factor-1 receptor (IGF-1R) pathway activity in ILC, which could potentially be targetable with IGF-1R/insulin receptor therapy.[66] Altogether, the molecular features of ILC are being slowly uncovered during the past decade, mainly thanks to the increasing number of human ILC samples and models that are becoming available.[67]

CLINICAL IMAGING

Screening, diagnosis and pre-operative assessment

Mammography has some well-known limitations in detecting ILC,[68] because the peculiar growth patterns of ILC make it harder to distinguish it from normal mammary tissue (sensitivity 34%-83%, Table 2).[69] The sensitivity is further reduced to ~10% in women with dense breasts (American College of Radiology—ACR 4).[70] The accuracy of two-dimensional mammography can be improved by the use of digital breast tomosynthesis (DBT)[71,72] or contrast-enhanced digital mammography.[73]

Over the past decades, ultrasound techniques have improved, with an increase of overall sensitivity for the detection of ILC from 68% to 88%-98%.[74-76] Although ultrasound is almost always used for diagnosis, it is not commonly used in population breast cancer screening. It has been suggested by some as an additional imaging technique in women with dense breasts and in women with a higher risk of developing ILC.[77,78]

Magnetic resonance imaging (MRI) is the modality with the highest sensitivity for ILC, being 93%-100%.[79] High sensitivity comes at the cost of a low specificity and overestimation of the size of the lesions in 20% of the patients (mainly because of the presence of lobular carcinoma in situ).[69,80] Synchronous lesions are solely detected on MRI in 32% and 7% of patients in the ipsilateral and contralateral breast, respectively, with an accuracy of 80%-90%,[81] impacting the surgical treatment approach of the patient.[82,83]

Breast surveillance

Once a patient is treated for primary ILC, it is questioned which examination is most suitable to detect locoregional relapses. Routinely, a yearly mammogram is carried out, complemented with ultrasound if needed.[84] Regular MRI of the breast could be useful in certain subgroups of patients (e.g. women with dense breast tissue), although there is no available evidence addressing the impact on survival.[85]

Metastatic disease assessment

Computer tomography (CT), bone scan and [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}F-FDG)—positron emission tomography (PET)/CT are commonly used for the detection and monitoring of metastatic spread in breast cancer.[86] However, the probability that ^{18}F-FDG—PET/CT detects metastases is 2.82 times lower in patients with locally advanced ILC compared to NST.[87] This is due to the lower metabolic activity of ILC and the tendency to form sclerotic bone lesions.

Other PET/CT modalities show promising results in ILC. In a small cohort, a higher uptake of ^{18}F-fluciclovine (a synthetic amino acid) than ^{18}F-FDG was seen for ILC.[88] It is hypothesized that the metabolism of ILC might depend more on amino acids than on glucose.[88] ^{18}F-fluoroestradiol (^{18}F-FES) may be superior in the detection of ILC metastases given the high rate of ER expression and its use is currently investigated in an ILC-specific phase II trial (NCT04252859).[89-91] The potential clinical benefit of ^{18}F-FES—PET/CT may lie in the detection of metastases in patients with false-negative ^{18}F-FDG—PET/CT, the distinction between oligometastatic and diffuse metastatic disease, the

Table 2. Overview of imaging techniques for ILC in the pre-operative setting

Technique	Sensitivity ILC (%)	Imaging features ILC	Benefit of imaging technique as compared to mammography	Disadvantages of imaging technique as compared to mammography
Mammography	34-83[69]	- Asymmetric density - Mass with poorly defined margins		
DBT	83.3[208]	- Small spiculated lesions - Stellar distortion - Non-calcified masses	- Increased detection rate (doubling of ILCs detected)[87,88]	
CEDM	100 (small sample sizes)[209,210]	- Asymmetric density	- Accuracy of 85%[90,91]	
Ultrasound	88-98[74,75]	- Less 'taller than wide' lesions	- Better estimation of tumour size[97,98] - Improved detection of multifocality[97,98]	- Higher rate of false-positive findings
MRI	93-100[79]	- Irregular mass with heterogeneous type 2 enhancement	- Improved detection of multifocality and bilateral disease[100,102]	- Higher rate of false-positive findings - Overestimation of tumour size

CEDM, contrast-enhanced digital mammography; DBT, digital breast tomosynthesis; ILC, invasive lobular breast cancer; MRI, magnetic resonance imaging.

detection of lesions that can be reached for biopsy and the prediction of endocrine treatment response.

Whole-body diffusion-weighted MRI (WB-DWI/MRI) appears to have the potential to detect distant metastases in patients with ILC earlier than CT and ^{18}F-FDG—PET/CT.[92] For peritoneal lesions, which are common in ILC, WB-DWI/MRI is superior to CT and ^{18}F-FDG—PET/CT.[92]

TREATMENT IN THE EARLY SETTING

Neoadjuvant therapy

Patients with ILC seem to benefit less from neoadjuvant chemotherapy (NACT) in terms of downstaging and facilitating breast-conserving surgery (BCS) than patients with NST.[93] The low proliferation rate and high ER expression make ILC less sensitive to chemotherapy, as reflected by low pathological complete response (pCR) rates.[94-96] Conflicting results exist as to whether these low pCR rates can be attributed to differences in ER expression. Lips et al. investigated the influence of histology when adjusting for clinicopathological features and did not find differences in the responsiveness to chemotherapy between ILC and NST.[97] However, other trials have shown that when comparing ILC and NST with a similar receptor status, pCR rate is still lower for patients with ILC.[14] Although pCR is seen as a good prognostic factor for most breast cancers, it seems that this might not hold true for ILC, since lower pCR rates do not seem to lead to significantly worse outcomes in patients with ILC versus NST.[95] The majority of patients with ILC still require a mastectomy after their NACT.[95,98,99]

Since the majority of ILCs have high ER/PR expression, it is hypothesized that neoadjuvant endocrine treatment (NET) could be considered for treating ILC.[100] However, data are scarce, since patients with ILC were often not analysed separately.[101] A retrospective study of 61 patients with ILC reported that after a treatment of ∼9 months, the tumours of 40/61 patients were eligible for resection.[102] No significant difference in survival rate (after adjustment for covariates) was seen for NET versus NACT for patients with node-positive ILC.[103]

Recently, trials have looked into the effect of NET in combination with CDK4/6 inhibitors.[104-106] In these trials, ∼15% of the included patients had ILC, but the efficacy in ILC specifically was not reported.[105,106] The addition of ICIs to NACT shows promising results especially in triple-negative breast cancer but separate results for ILC are currently lacking.[107]

Surgery

Given the larger tumour size at diagnosis, the higher rates of multifocality and the difficulties estimating the actual size of ILC pre-operatively, mastectomy is more often carried out in patients with ILC than NST.[108,109] Recent trials report mastectomy rates ranging from 22% to 52% in patients with ILC (compared to 14%-46% in patients with NST).[32] A 17%-65% chance of having positive resection margins in patients with ILC undergoing BCS has been reported.[32] Similar to

NST, there is no benefit seen regarding long-term survival for mastectomy in patients with ILC in comparison to BCS with clear margins and in combination with radiotherapy.[110]

Several studies report a higher nodal stage at diagnosis and a higher number of positive lymph nodes at the time of surgery in ILC compared to NST, resulting in a higher rate of axillary lymph node dissection.[9,10,111] This might be attributable to the larger tumour sizes and other confounding factors, as this was no longer seen in multivariate analysis.[112] Following sentinel lymph node biopsy, there is a 38% rate of nodal positivity in clinically node-negative patients, highlighting the challenges of clinical nodal assessment in ILC.[113]

Adjuvant radiotherapy

Local control rates for BCS (with clear margins) followed by whole-breast radiotherapy are similar for ILC and NST.[114] Since ILC is often multifocal, ILC has been an exclusion factor in partial breast irradiation (PBI) trials and therefore the technique is not recommended in ILC.[84] Concerns regarding PBI in ILC are supported by a single-institution retrospective review of accelerated PBI, which showed an increase in ipsilateral breast cancer recurrence in patients with ILC.[115]

ILC represented 10%-15% of the cases enrolled into the large hypofractionated radiotherapy trials in breast cancer [The UK Standardisation of Breast Radiotherapy (START)[116] and Fastforward (NCT04148586)[117]] but the local relapse rates were not reported separately per histological type. Post-mastectomy radiation in patients with ILC appears to be as effective as it is in NST resulting in improved local control and survival.[118]

Adjuvant endocrine treatment

Metzger et al. reported a significant benefit of 5 years of the aromatase inhibitor (AI) letrozole over 5 years of tamoxifen for postmenopausal women in the Breast International Group (BIG) 1-98 trial, an effect that was more pronounced in ILC as compared to NST.[119] The TEAM trial (Tamoxifen and Exemestane Adjuvant Multinational, NCT00279448, NCT00036270) comparing 5 years of exemestane versus 2.5 years of tamoxifen followed by 2.5 years of exemestane[120] reported no statistically significant differences in recurrence-free survival in patients with ILC or NST. However, follow-up was limited to 5 years, while recurrences in ILC might occur later.[9] In a recent meta-analysis presented at San Antonio Breast Cancer Symposium 2021 including 7415 patients from TEAM, BIG 1-98 and Arimidex, Tamoxifen, Alone or in Combination (ATAC) trials, the differential effect for AI versus tamoxifen in ILC versus NST was not confirmed.[121] Although AI is superior to tamoxifen for ILC, this meta-analysis did not support a more pronounced effect for ILC compared to NST. The addition of ovarian function suppression (OFS) in women with premenopausal diagnosis of ILC has not yet been analysed, which might be partially explained by the low incidence rate of ILC in young women. It is known from the Suppression of Ovarian

Function Trial (SOFT) (NCT00066690) and Tamoxifen and Exemestane Trial (TEXT) (NCT00066703) that in premenopausal patients with clinically high-risk tumours OFS can be beneficial.[122] Furthermore, extended endocrine treatment with preference for AI needs to be considered in all patients with clinically high-risk ILC, similarly to patients with high-risk NST.[84] The addition of CDK4/6 inhibitors to adjuvant endocrine treatment needs further exploration since conflicting results of additional benefit were seen in monarchE[123] versus Palbociclib Collaborative Adjuvant Study (PALLAS)[124] and Penelope-B,[125] and to our knowledge, no separate conclusions were made about the effect in patients with ILC.[126]

Adjuvant chemotherapy

Trapani et al. recently conducted a meta-analysis of eight retrospective trials consisting of 38 387 patients with ILC.[127] They did not identify a beneficial role for adjuvant chemotherapy with regard to overall survival (OS), in line with other literature.[37,128-131] Most of the studies included in this meta-analysis did, however, not correct for ER, PR and HER2 and had a relatively short follow-up. A more recent US registry study that evaluated 17 789 patients with stage I-III ILC observed a similar OS after 5 years between patients receiving endocrine therapy alone and those receiving the combination of chemotherapy and endocrine therapy, after adjusting for age, stage, lymph node involvement, histology and radiotherapy.[132] When comparing ILC with NST, a recent Oxford meta-analysis (37 298 patients) did not find significant differences in the magnitude of benefit between ILC and NST when dose-dense chemotherapy regimens were used.[133] de Nonneville et al. described a survival advantage of adjuvant chemotherapy in high-risk, ER-positive, HER2-negative ILC (defined as having either macroscopic lymph node involvement, or a tumour size >20 mm and lymphovascular invasion), but not in low-risk ILC, findings that were confirmed by Tamirisa et al.[134,135] Recently, it was stated that anthracycline-free regimens containing only cyclophosphamide and taxanes had non-inferior efficacy to anthracycline-containing regimens in HER2-negative breast cancer patients while tolerability was significantly improved.[136,137] de Gregorio et al. confirmed this observation for the global breast cancer population; however, patients with ILC, especially in case of pN2 and pN3, did seem to benefit more from anthracycline-containing than anthracycline-free regimens.[138] Overall, this suggests that although the majority of ILCs are not chemo-sensitive, there is a subset of patients with high-risk ILC who could benefit from chemotherapy.

Adjuvant anti-HER2 therapy

Results from the HERceptin Adjuvant (HERA) trial (NCT00045032) suggest that ILC patients benefit equally from adjuvant trastuzumab in comparison to NST patients.[139] Further research is necessary to analyse the efficacy of HER2-targeted treatments in the early setting for patients with *HER2*-mutated ILC.

Gene expression-based prognostic tests

Commercially available prognostic tests based on the assessment of the expression of predefined genes, such as Oncotype DX Breast Recurrence Score (RS)®, MammaPrint®, Prosigna-PAM50 risk of recurrence (ROR) score and EPClin, have a great potential in determining which patients with ER-positive/HER2-negative breast cancer benefit from adjuvant chemotherapy. However, most of these tests have been developed without considering the specific aetiology and histology of ILC. Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.05.006, summarizes the main features, characteristics and findings of the studies that evaluated these tests for patients with ILC. Of note, while the RS®[39,128,131,140-148] and MammaPrint®[40,149-151] have been evaluated in multiple studies (12 and 4, respectively), only a single study was reported for the other tests. A formal comparison of all tests cannot be done because they were all investigated in different patient cohorts, with important differences with regard to ILC definition (based on local versus central pathology), treatment and the duration of follow-up. Several messages can however be drawn from these studies. Firstly, the proportion of patients classified as 'high risk' varies significantly according to the test used, ranging between 1% and 2% for the RS® using the RS >30 cut-off (or ∼8% when considering the RS >25 cut-off),[39,128,131,140-148] 11% and 28% for MammaPrint®,[40,149-151] 31% for the Prosigna-PAM50 ROR score,[152] 37% for EPClin[153] and 46% for The Breast Cancer Index (BCI) Risk of Recurrence.[154] A higher proportion of 'high-risk' patients were consistently identified in non-classic ILC compared to classic ILC, both when considering the RS®[39] and MammaPrint®.[40] Secondly, all the tests were shown to carry independent prognostic value in multivariate analyses. Finally, it is currently still unclear whether the classifiers are only of prognostic value or whether they can also be used to tailor adjuvant treatment for patients with ILC.

Next to the commercial tests reported above, the Genomic Grade Index (GGI) identified 17% of the investigated ILC tumours as 'high risk' and recognized an independent prognostic value of the GGI.[155] LobSig is the only gene expression signature that was designed specifically for patients with ILC but additional validation is needed.[156]

TREATMENT IN THE METASTATIC SETTING

Endocrine-based treatment

The pillar in treating metastatic ER-positive ILC consists of endocrine treatment. Recently, the addition of CDK4/6 inhibitors to endocrine treatment has become the standard of care in first-line treatment of ER-positive metastatic breast cancer as four out of seven phase III trials demonstrated a clear survival benefit over endocrine treatment alone.[157-164] Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.05.006, gives an overview of these trials within the context of ILC. Of these trials, only PALOMA-2 reported data for ILC specifically with a clear improvement of progression-free survival (PFS) upon the

addition of palbociclib to letrozole.[159] A large, pooled analysis of all seven trials, carried out by the United States Food and Drug Administration, demonstrated that CDK4/6 inhibitors significantly improved PFS in patients with ILC.[165] More recently, a pooled analysis of OS in three trials exploring CDK4/6 inhibition combined with fulvestrant demonstrated a numerical survival benefit in patients with ILC.[166]

Chemotherapy

Only a few trials comparing chemotherapy regimens in metastatic ILC versus NST exist. Pérez-Garcia et al. carried out retrospective analyses on three trials where eribulin was administered after prior use of anthracyclines and taxanes.[167] No difference was found between the efficacy in patients with ILC compared to NST. Furthermore, limited evidence exists that capecitabine results in similar disease-free survival in patients with metastatic ILC compared to NST.[168] In clinical practice, chemotherapy can be considered in patients with ILC in case of endocrine resistance or a visceral crisis.

Targeted therapy and immune checkpoint inhibitors

Although no specific studies have been carried out about the benefit of HER2-targeted therapies and the HER2-targeting antibody-drug conjugates (ADCs) for ILC, it is currently assumed that the benefit is similar for ILC versus NST. Approximately 15% of metastatic ILCs have underlying
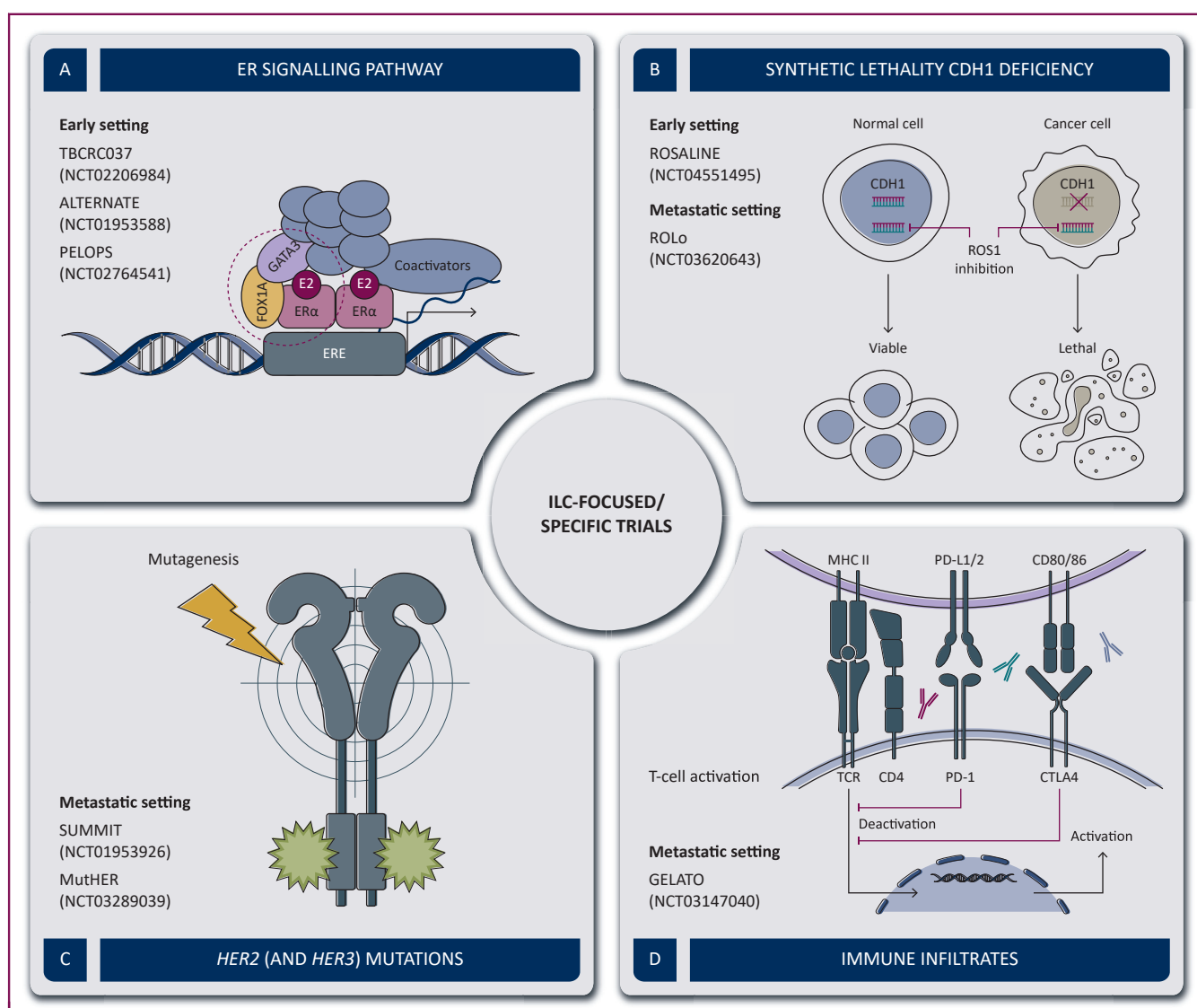

Figure 1. Overview of ILC-focused/specific ongoing trials investigating systemic treatment options.
(A) A schematic overview of the ER signalling pathway with the targets of the ongoing trials is shown. (B) This figure visualizes that when ROS inhibitors are administered in cells with CDH1 deficiency the cells are no longer viable whereas normal cells are not affected. (C) The effect of second-generation HER2 blockade (visualized in green) which forms irreversible covalent bonds to inhibit signal transduction is shown. (D) The mechanism behind PD-1 and PD-L1 inhibition, inhibiting the T-cell deactivation by the tumour cells, is shown (created with BioRender.com).
CTLA4, cytotoxic T-lymphocyte-associated antigen 4; ER, estrogen receptor; FOXA1, forkhead box protein A1; HER2, human epidermal growth factor receptor 2; ILC, invasive lobular breast cancer; MHC II, major histocompatibility complex II; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; ROS, reactive oxygen species; TCR, T-cell receptor.
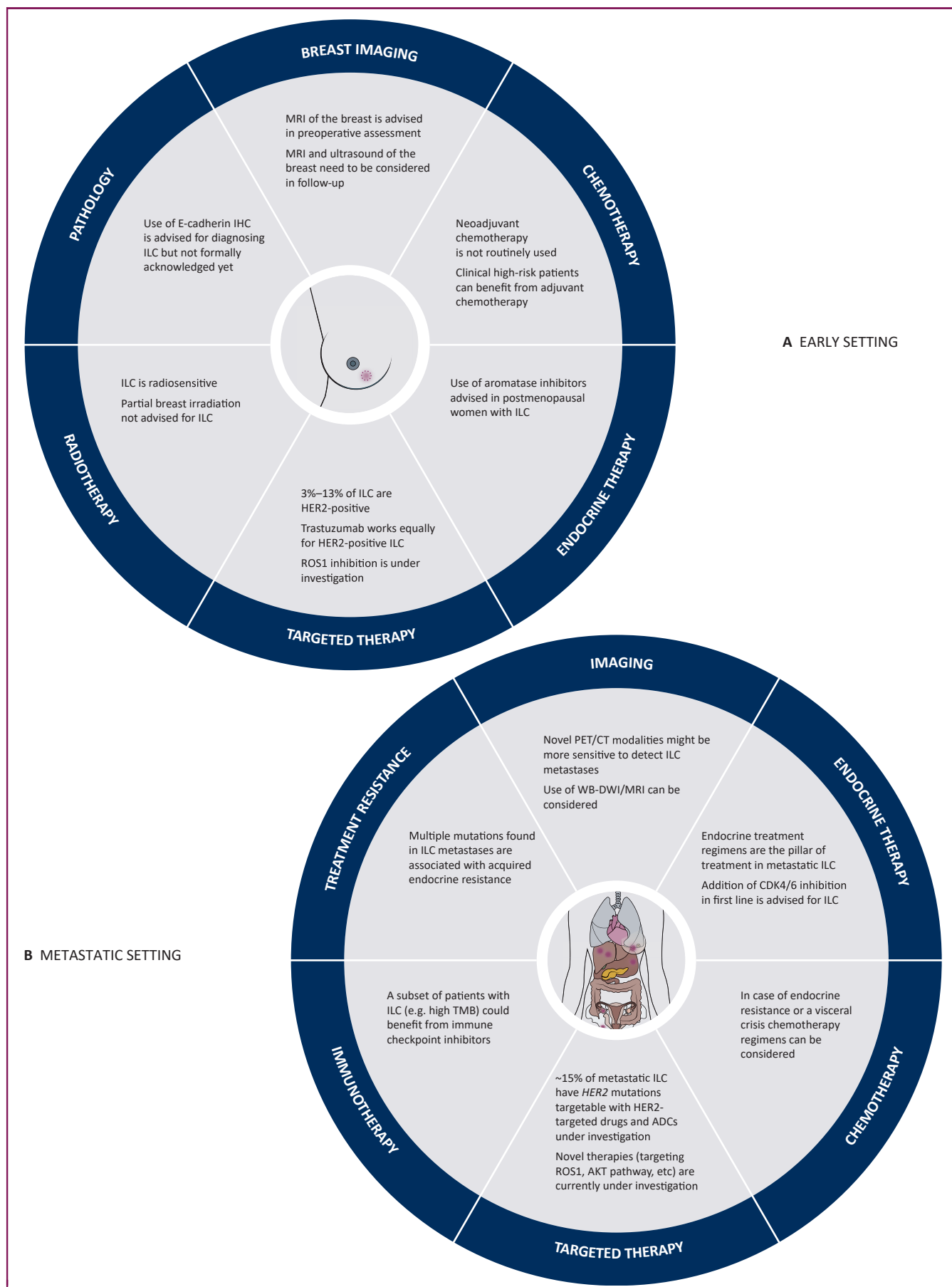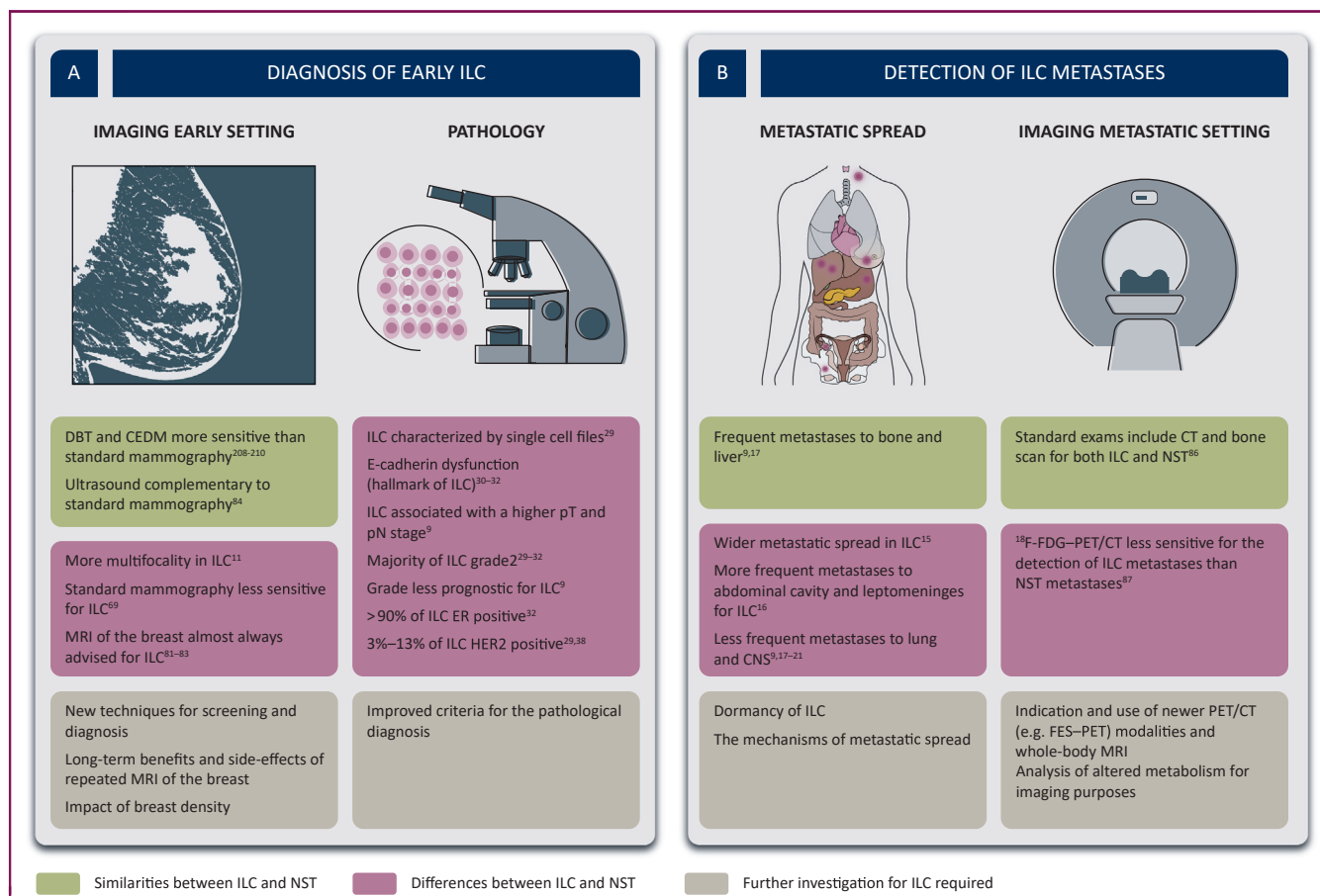
Figure 2. Overview of the key concepts of ILC.

Figure 3. Diagnostic similarities and differences between patients with ILC and those with NST.
This figure shows the similarities between ILC and NST, the differences between ILC and NST and the aspects that require further investigation. (A) Diagnosis in the early setting. (B) Detection of metastases.
^{18}F-FDG—PET/CT, [^{18}F]2-fluoro-2-deoxy-D-glucosepositron emission tomography/computed tomography; CEDM, contrast-enhanced digital mammography; CNS, central nervous system; CT, computed tomography; DBT, digital breast tomosynthesis; ER, estrogen receptor; FES, ^{18}F-fluoroestradiol; HER2, human epidermal growth factor receptor 2; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; NST, non-special type; pN, pathological nodal stage; pT, pathological tumour size (created with BioRender.com).

HER2 mutations.[42] Preliminary results of prospective trials (SUMMIT—NCT01953926, MutHER trial, part 2—NCT03289039) targeting these mutations by second-generation HER2 tyrosine kinase inhibitors such as neratinib in combination with endocrine treatment show higher response in ILC than in NST (Figure 1, Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.05.006).[61,169]

While in *HER2*-mutated non-small-cell lung cancer impressive response rates to the HER2-targeting ADC trastuzumab-deruxtecan were observed,[170] no data are available yet on HER2-targeting ADCs in *HER2*-non-amplified ILC. An increased frequency of *HER3* (*ERBB3*) mutations was reported in ILC as compared to NST; however, it is unknown

whether these *HER3*-mutated tumours could benefit from second-generation HER2 tyrosine kinase inhibitors or ADCs targeting HER3.[31,171]

To our knowledge, clinical data on the effectiveness of ICIs in ILC are limited. In the small KEYNOTE-28 study that evaluated pembrolizumab in heavily pre-treated ER-positive metastatic breast cancer, two out of the three responders were of ILC origin.[172] In the GELATO trial (NCT03147040), patients with metastatic ILC are treated with carboplatin as immune induction for 12 weeks, followed by atezolizumab (anti-PD-L1), thereby inducing potential synergy between these agents and enhancement of the anticancer immune response. So far, 23 patients have received at least one cycle of atezolizumab (18 ER positive, 5 triple negative).

(A) Key concepts of ILC in the early setting; surgery was not included in this figure since it depends more on tumour and patient characteristics than on histological subtype. (B) Key concepts of ILC in the metastatic setting. Use of the combination of other drugs with endocrine treatment was not included in this figure but can be considered after first-line progression (e.g. alpilisib, everolimus). Additionally, PARP inhibition can be considered for patients with germline BRCA mutation. Additional novel agents can be considered in triple-negative metastatic ILC; however, since this is a minor subgroup of ILC, these were not included in the figure.
ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; PARP, poly(ADP-ribose) polymerase; PET/CT, positron emission tomography/computed tomography; TMB, tumour mutational burden; TNBC, triple-negative breast cancer; WB-DWI/MRI, whole-body diffusion-weighted MRI (created with BioRender.com).
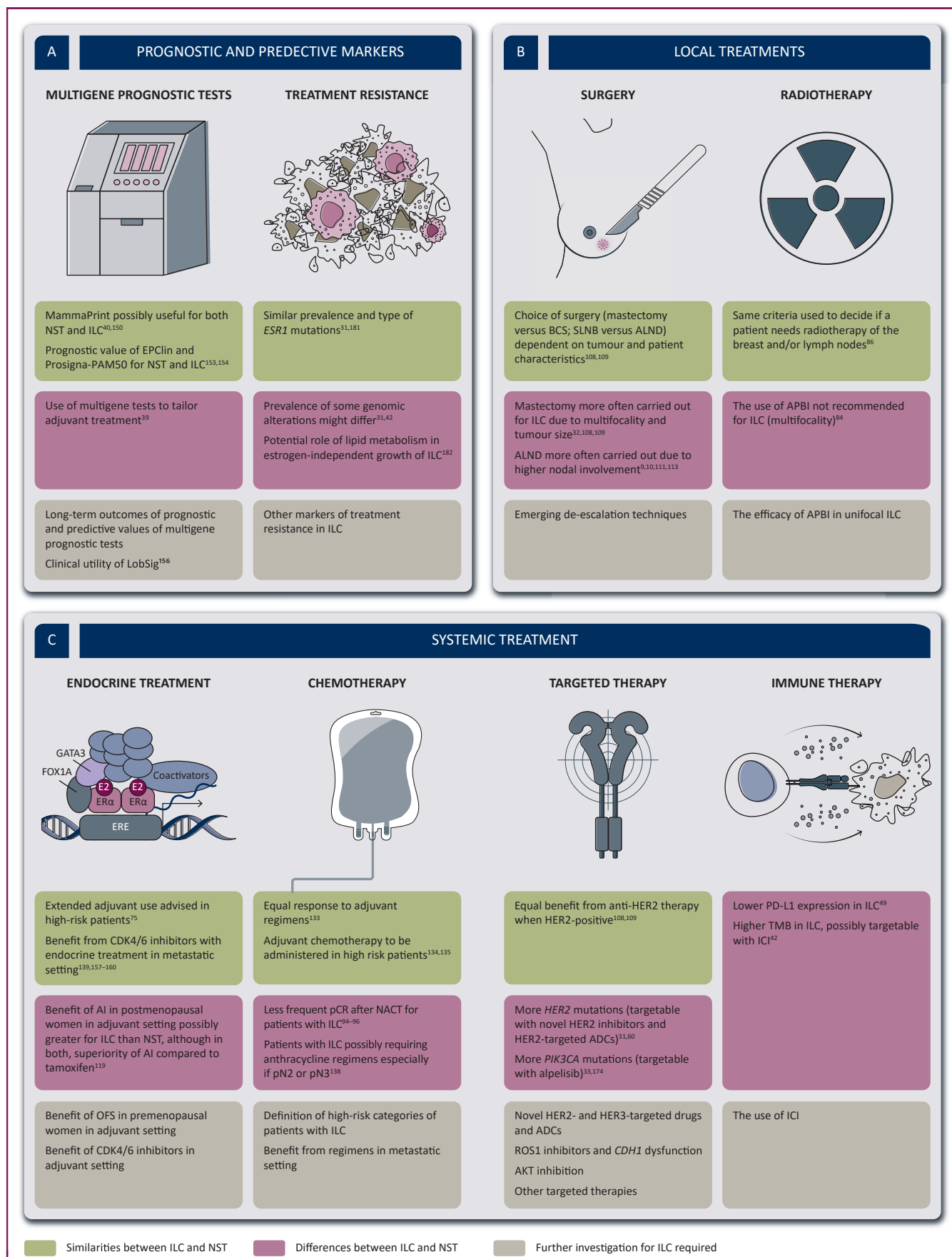
Figure 4. Similarities and differences concerning treatment and treatment markers between patients with ILC and those with NST.

Preliminary results are promising but response is mainly limited to triple-negative ILC.[173]

Other treatment options include the targeting of the PI3K—AKT signalling pathway, since this is often activated in ILC.[33,62] *PIK3CA* mutations form, after *CDH1* mutations, the second most common alterations in metastatic ILC, suggesting the possible utility of the PI3K inhibitor alpelisib.[33,174] In the SOLAR-1 trial, it was shown that alpelisib combined with fulvestrant prolonged PFS in *PIK3CA*-mutated ER-positive breast cancer, but both the proportion of ILC patients and the efficacy in that group were not reported.[175] Similarly, the efficacy in ILC specifically has also not been reported in the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2), in which inhibition of mammalian target of rapamycin (mTOR) by everolimus, in combination with exemestane, has been shown to improve PFS but not OS in ER-positive breast cancer.[176,177] Patients with ILC harbouring a germline *BRCA1/2* mutation might benefit from poly(ADP-ribose) polymerase inhibitors, although no specific subgroup analyses for ILC have been carried out to our knowledge.[178] An additional treatment option for metastatic triple-negative ILC is sacituzumab govitecan which targets trophoblast cell surface antigen 2, but it is not reported as to how many patients with ILC were included in the ASCENT trial.[179]

MARKERS OF TREATMENT RESISTANCE IN THE METASTATIC SETTING

Exposure to endocrine treatment can lead to acquired endocrine resistance, which complicates treatment of metastatic ILC. The best-known mutation linked to endocrine resistance is the *ESR1* mutation.[180] Desmedt et al. did not see a difference in prevalence and type of *ESR1* mutations between ILC and NST.[181] *NF1* mutations, which seem to occur more frequently in metastatic ILC, are mutually exclusive with *ESR1* mutations, and might be associated with endocrine resistance.[52] *FOXA1* mutations, which are also associated with endocrine resistance, are more prevalent in ILC than in NST.[31] Genomic analyses by Richard et al. comparing matched primary and metastatic ILC lesions have identified genomic alterations associated with endocrine resistance only present in metastatic but not the primary lesions, possibly suggestive of acquired resistance.[42] Additionally, experimental data suggested that lipid metabolism may play a role in the estrogen-independent growth of ILC,[182] and that fibroblast growth factor receptor 4 *(FGFR4)* overexpression/mutations[183] and WNT4 signalling[184] could act as mediator of endocrine resistance. With regard to CDK4/6 inhibitors, mechanisms of resistance are now also increasingly being described.[185,186] The acquired loss of *RB* and *PTEN* and alterations in *CCND1* seem to be associated with resistance to ribociclib.[185,186] *PTEN* loss, numerically

slightly more prevalent in ILC as in NST (Table 1), is also linked to resistance to PI3K inhibitors like alpelisib.[185]

Metastases are often difficult to biopsy; therefore, treatment resistance in patients with ILC is difficult to study. Analysis of circulating tumour DNA (ctDNA) may present a potential solution to overcome these issues. ctDNA has recently been investigated successfully in plasma or cerebrospinal fluid from patients with ILC.[187] To further investigate disease progression and treatment resistance, an autopsy programme called UPTIDER (NCT04531696) with a specific substudy focusing on ILC has been set up at the University Hospitals of Leuven.

ONGOING TRIALS AND FUTURE PERSPECTIVES

With the growing knowledge that ILC is an entity in many ways distinct from NST, new trials focusing more specifically on the treatment of patients with ILC slowly arise (Figure 1, Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.05.006).[188] This is much needed since recently it became evident that patients with ILC are often excluded from clinical trials in the metastatic setting.[189]

Since most ILCs are ER positive, the ER signalling pathway represents a target of great interest, mainly in the early setting. Within the window of opportunity trial TBCRC037 (NCT02206984), the anti-proliferative effect of different endocrine treatments (tamoxifen versus anastrozole versus fulvestrant) administered in the window between diagnosis and primary surgery is evaluated. In the ALTERNATE trial (NCT01953588), anastrozole is compared to fulvestrant alone and to the combination of anastrozole with fulvestrant for both ILC and NST patients in the neoadjuvant setting. Preliminary results did not show any significant difference in intrinsic sensitivity to the different regimens.[190] The Palbociclib and Endocrine Therapy for Lobular Breast Cancer Preoperative Study (PELOPS) (NCT02764541) including both ILC and NST patients will look into the differences in response rates to tamoxifen plus CDK4/6 inhibition versus letrozole plus CDK4/6 inhibition.

Central to future clinical management may be interventions that target molecules or pathways downstream of E-cadherin.[191,192] Because E-cadherin loss in ILC predisposes cancer cells towards growth factor receptor sensitivity,[62,66,193] the small-molecule MET/ALK/ROS1 inhibitors such as crizotinib and entrectinib are currently being studied as synthetic lethal drugs in both the early and metastatic settings. Entrectinib in combination with letrozole is being investigated in patients with ILC in the neoadjuvant multicentre trial ROSALINE (NCT04551495), the primary endpoint being residual cancer burden at surgery. In the metastatic setting, crizotinib is investigated in the ROLo trial (NCT03620643), either in combination with fulvestrant in patients with ILC or as a single agent in patients

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This figure shows the similarities between ILC and NST, the differences between ILC and NST and the aspects that require further investigation. (A) Prognostic and predictive markers guiding treatment. (B) Local treatment. (C) Systemic treatment (created with BioRender.com).

ADCs, antibody-drug conjugates; AI, aromatase inhibitor; ALND, axillary lymph node dissection; APBI, accelerated partial breast irradiation; BCS, breast-conserving surgery; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitors; ILC, invasive lobular carcinoma; NACT, neoadjuvant chemotherapy; NST, non-special type; OFS, ovarian function suppression; pCR, pathological complete remission; PD-L1, programmed death-ligand 1; SLNB, sentinel lymph node biopsy; TMB, tumour mutational burden.

with *CDH1*-mutated triple-negative breast cancer or diffuse gastric cancer.

Other possible treatment opportunities lie in the *HER2* and *HER3* mutations that are more often present in ILC than in NST, and in the investigation of ICI in patients with tumours presenting a high TMB or immune-rich characteristics, as described above.

Emerging explorative trials on ILC are setting the basis for future treatment strategies by uncovering new potential targets.[188] A number of preclinical studies have utilized models of *CDH1*-defective breast cancer to identify new vulnerabilities/targets that could be therapeutically applied to treat ILC. Genetic perturbation (RNA interference) screens have identified G protein-coupled receptors, ion channels, proteasomal subunits, BH3-only proteins, ubiquitinylating enzymes and proteins such as Rock1 that control actomyosin contraction as synthetic lethal targets in *CDH1*-defective cells, when compared to *CDH1*-wild-type cells.[36,193-195] Interestingly, insertional mutagenesis of genes such as *MYPT1*, *MYPT2*, *ASPP2* and *MYH9* that control actomyosin relaxation enhances ILC tumour formation in mice with a conditional *CDH1* mutation (*Wcre;Cdh1^{F/F};mTmG* mice).[196] Taken together with the *CDH1* synthetic lethality data, this suggests that modulation of actomyosin may underlie the development and progression of ILC and as such be a potentially rich source of therapeutic targets in this disease. It is also hypothesized that when patients with ILC develop endocrine resistance, new possible treatment strategies may involve the inhibition of bromodomain and extraterminal proteins and *FGFR1*.[65,197,198] Additionally, mTOR, PI3K/AKT inhibition and IGF-1 inhibition have all been suggested as potential targets in ILC.[66,199-202] Finally, since AR is often enriched in ILC, this pathway may also be of interest, especially in triple-negative ILC.[44,203,204]

CONCLUSIONS AND PERSPECTIVES

ILC research and treatment faces many difficulties. ILC usually represents a small subgroup within clinical trials that is rarely separately analysed. Moreover, there is a concerning suboptimal degree of concordance between local and central pathology to define ILC, which is currently being further investigated by the pathology working group of the European Lobular Breast Cancer Consortium (ELBCC; www. elbcc.org).

The ILC subtype warrants differences in diagnostic and treatment strategies summarized in Figures 2-4. The preoperative assessment of ILC comes with many challenges and requires the use of different complementary imaging techniques, like MRI and DBT of the breast in addition to the standard mammogram and ultrasound. Screening for metastases can be challenging, although new PET/CT techniques are emerging and expertise in WB-DWI/MRI is growing.

Treatment decisions in the early setting need to be made based on additional clinicopathological features. A significant benefit for the use of aromatase inhibition in postmenopausal women was already proven for ILC in the past, although recent trials suggest similar findings for NST. The role of multigene prognostic tests in guiding adjuvant treatment in patients with ILC needs to be further evaluated. Although some multigene tests have prognostic potential in ILC, a predictive value to further guide treatment decisions is currently unknown. Chemotherapy seems to have less effect in ILC, although subgroups of patients with ILC, which need to be further defined, might still benefit from the addition of chemotherapy. In the future, a combination of molecular and biochemical/histological profiling may be the best way to classify ILC instead of their histological appearance only.

For most patients with metastatic ILC, endocrine treatment remains the most important pillar, in first line now with the addition of CDK4/6 inhibition. Key mechanisms underlying the disease aetiology and treatment resistance are currently being discovered but more research is needed. Liquid biopsies seem to hold a prognostic value towards ILC and their use in guiding treatment needs to be further evaluated. Furthermore, more insights arise regarding dormancy of ILC cells, which might reveal new treatment options in the future. Clinical trials focusing on ILC are emerging and collaborative efforts between clinicians, researchers and patient advocates are increasing,[205] which hopefully enables more prospective clinical and translational research to provide the optimal treatment strategies for patients with ILC.

DISCLOSURE

The authors have declared no conflicts of interest.

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