Cancer Treatment Reviews 128 (2024) 102762

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Anti-tumour Treatment

Navigating practical challenges in immunotherapy for metastatic triple negative breast cancer

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A B S T R A C T

Immunotherapy has revolutionized cancer therapy and now represents a standard of care for many tumor types, including triple-negative breast cancer. Despite the positive results that have led to the approval of immunotherapy in both early- and advanced-stage triple-negative breast cancer, pivotal clinical trials cannot address the myriad questions arising in everyday clinical practice, often falling short in delivering all the information that clinicians require. In this manuscript, we aim to address some of these practical questions, with the purpose of providing clinicians with a guide for optimizing the use of immune checkpoint inhibitors in the management of breast cancer patients and identifying opportunities for future research to clarify unresolved questions.

Introduction

Immunotherapy is a standard of care for various tumor types, including triple negative breast cancer (TNBC) [1,2]. The anti-PD-L1 atezolizumab and the anti-PD-1 pembrolizumab have gained approval for use in combination with chemotherapy as first-line therapy for PD-L1-positive (PD-L1 +) advanced-stage TNBC, based on the results of the IMpassion130 [3,4] and KEYNOTE-355 [5,6] trials, respectively. In IMpassion130, patients were randomly assigned in a 1:1 ratio to receive atezolizumab plus nab- paclitaxel or placebo plus nab-paclitaxel [3,4]. KEYNOTE-355 randomly assigned patients in a 2:1 ratio to receive pembrolizumab plus the investigator's choice of chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine–carboplatin) or placebo plus chemotherapy [5,6]. Both trials demonstrated substantial benefits in objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) with the addition of immunotherapy to chemotherapy for the PD-L1 + population −although significance for OS in IMpassion130 was not formally tested due to the trial's hierarchical statistical design and the lack of significance in the intention-to-treat population. Based on these results, atezolizumab was granted accelerated approval by the FDA in March 2019 and approval by the EMA in June 2019, while pembrolizumab received full approval from both the FDA and EMA in July 2021 and May 2022, respectively. However, the IMpassion131 trial, which enrolled a similar population to that of

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https://doi.org/10.1016/j.ctrv.2024.102762
Received 8 February 2024; Received in revised form 5 May 2024; Accepted 15 May 2024
Available online 16 May 2024
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IMpassion130 but used paclitaxel instead of nab-paclitaxel as the chemotherapy backbone, did not show any efficacy improvements from the addition of atezolizumab to chemotherapy [7,8]. Consequently, Roche, in consultation with the US FDA, chose to voluntarily withdraw the accelerated approval for atezolizumab in the USA in August 2021 [8]. This decision had no impact on atezolizumab's approval status in Europe, where the drug remains authorized.

Moreover, pembrolizumab has been approved for stage II-III TNBC treatment, based on the positive results of the KEYNOTE-522 trial, which showed that the addition of pembrolizumab to neoadjuvant chemotherapy followed by single-agent adjuvant pembrolizumab for up to nine cycles led to a statistically significant and clinically meaningful improvement in event-free survival [9].

In this evolving therapeutic landscape, novel challenging questions continue to emerge. Data from clinical trials often fall short in delivering all the information that clinicians require to navigate the diverse challenges they face in their daily practice. To support the oncology community and provide evidence-based recommendations, the Society for Immunotherapy of Cancer (SITC) has developed clinical practice guidelines covering various topics related to immunotherapy in breast cancer [10]. In this manuscript, we aim to address practical questions regarding the management of patients with metastatic triple negative breast cancer, with the purpose of providing clinicians with a guide for optimizing the use of immune checkpoint inhibitors (ICIs) and identify opportunities for future research to clarify unresolved questions.

Questions and statements development

Between June and November 2023, a group of breast cancer experts convened in three virtual meetings to identify and discuss some of the most contentious issues regarding the management of immunotherapy in patients with metastatic triple-negative breast cancer. The group of experts is the same of the authors. After open communication and scientific debate during the first two meetings, statements were formulated in the final meeting, each in response to a specific question, to represent the shared opinion of the experts.

Question 1. Can the PD-L1 diagnostic assays for atezolizumab and pembrolizumab be used interchangeably?

The Dako PD-L1 22C3 and the Ventana PD-L1 SP142 assays cannot be used interchangeably due to a high discordance rate, affecting approximately 1 out of 4 patients. Therefore, it is recommended that patients undergo both tests if both atezolizumab and pembrolizumab are possible treatment options.

The assessment of PD-L1 expression in tumors through immunohistochemistry (IHC) assays is the most extensively studied and applied biomarker for selecting patients to receive ICIs [11]. Multiple IHC assays have been employed to detect PD-L1 expression in tumor samples. Each of these use different antibodies and scoring systems resulting in distinct sensitivities and specificities for antigen detection and prediction of clinical benefit from ICI therapy [12]. Pembrolizumab has been co-developed with the Dako PD-L1 22C3 assay [13], while atezolizumab has been co-developed with the Ventana PD-L1 SP142 and SP263 assays, with only the former being used in the case of breast cancer [14,15]. Important differences exist between these two assays. The Ventana PD-L1 SP142 is used to generate the Immune Cell (IC) score, which represents the proportion of tumor area that is occupied by PD-L1-expressing immune cells. The Dako system provides the Combined Positive Score (CPS), defined as the percentage of PD-L1-expressing tumor and immune cells relative to all viable tumor cells. The cutoffs used to define positivity also differ: for atezolizumab eligibility, patients with metastatic TNBC should have an IC $\geq$ 1 %, while for pembrolizumab eligibility, they should have a CPS $\geq$ 10. Consequently, the concordance between the two assays is modest. Moreover, the CPS threshold for positivity varies depending on tumor type. In IMpassion130, only 73 % of patients tested with both the Ventana SP142 and Dako 22C3 assays showed concordant results (36 % with IC $\geq$ 1 % and CPS $\geq$ 10; 37 % with IC $<$ 1 % and CPS $<$ 10) [16]. In the subgroup of patients with PD-L1 + tumors defined as CPS $\geq$ 10 but having IC $<$ 1 %, atezolizumab conferred no significant benefit in terms of either PFS or OS [16]. Of note, the European label indications for both pembrolizumab and atezolizumab do not explicitly specify which companion diagnostic should be used for PD-L1 evaluation. We recommend that, if available, both assays should be performed to tailor the most appropriate therapy and to avoid missing potential candidates for ICIs therapy (Fig. 1). Patients with PD-L1 IC $<$ 1 % and CPS $<$ 10 should not receive ICIs; tumors with IC $\geq$ 1 % and CPS $<$ 10 should be treated with the combination of nab-paclitaxel and atezolizumab (where approved); tumors with CPS $\geq$ 10 and IC $<$ 1 should be treated with the combination of chemotherapy and pembrolizumab. Patients who are positive with both assays have the choice between both ICIs and selection could be based on costs, schedule, and preference for chemotherapy partner (pembrolizumab may be combined with either paclitaxel, nab-paclitaxel, or carboplatin/gemcitabine).

Question 2. If the primary tumor is PD-L1 negative, should we consider retesting the metastatic sites?

Although PD-L1 positivity is usually higher in primary tumor samples than in metastatic sites, the spatial and temporal heterogeneity of PD-L1 expression justifies retesting the metastatic site to increase the likelihood of eligibility for immunotherapy.

Apart from the agnostic use of immunotherapy in tumors with high tumor mutational burden or microsatellite instability, the evaluation of PD-L1 in tumor samples is the sole biomarker employed to guide decisions regarding immunotherapy in TNBC. However, the broad acceptance of PD-L1 as an ideal predictive biomarker for the response to ICIs is not yet firmly established [17]. Several technical and biological variables that may hamper an unequivocal interpretation of the employed assays should be taken into account. Tumors and their immune microenvironments naturally evolve and are heterogeneous, both spatially and temporally. Several studies have demonstrated that this heterogeneity is also evident in PD-L1 expression [11]. For example, older specimens seem to be less dependable as sources of material for assessing PD-L1, as they may no longer accurately reflect the immunological status of a patient's tumour [18]. In TNBC, PD-L1 expression is markedly reduced in metastases compared with primary tumor samples. Within different metastatic sites, liver metastases usually present a more immunodepleted state, with lower TILs and a higher likelihood of PD-L1 negativity, while the opposite is observed in lymph nodes [19,20].

Spatial heterogeneity of PD-L1 expression may also be evident intratumorally, resulting from subclonal genomic and transcriptomic evolution that can confound the determination of PD-L1 expression in small biopsy samples [21]. Pharmacodynamic modulation of PD-L1 expression should also be taken into account, as different treatments may affect this dynamic in different ways [22]. In general, clinical trials evaluating ICIs did not require the utilization of a biopsy sample obtained specifically from a primary lesion or a metastatic one. Both the IMpassion130 and KEYNOTE-355 trials allowed for archival or newly obtained formalin-fixed tumor samples for baseline PD-L1 expression assessment at a central laboratory. In IMpassion130, PD-L1 positivity appeared to be equally informative for atezolizumab benefit regardless of the sample collection time and site [20]. Therefore, to increase the likelihood of eligibility for immunotherapy, PD-L1 assessment in a metastatic site in case of PD-L1 negativity of the primary tumor is advisable, if it can be safely performed. If multiple metastatic sites are available for biopsy, clinicians should prefer those with a predicted higher chance of PD-L1 positivity, such as lymph nodes or lung lesions (Fig. 1).

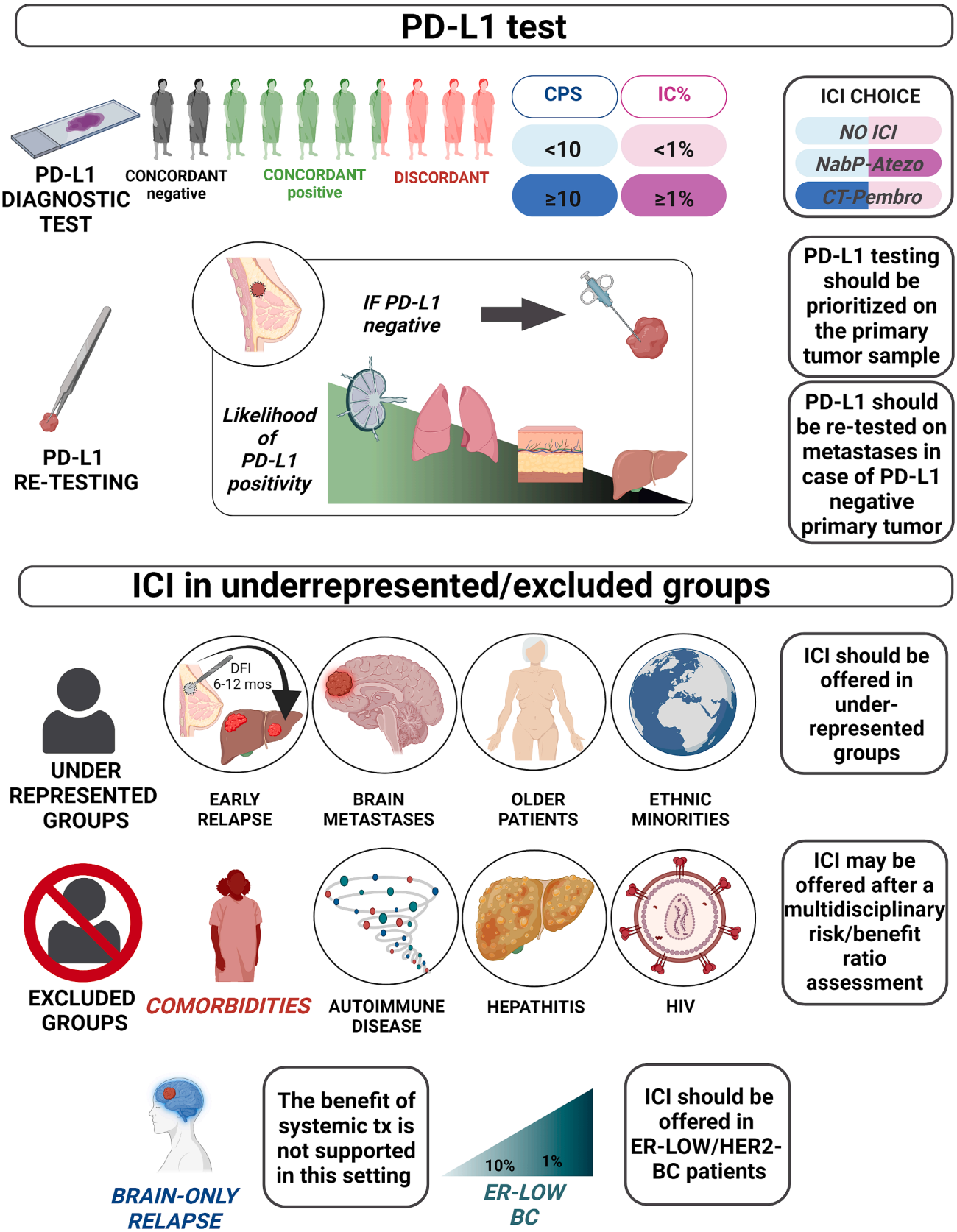

Fig. 1. Practical challenges in immunotherapy for metastatic triple negative breast cancer: differences between the PD-L1 diagnostic assays and patient's populations underrepresented or excluded from clinical trials.

Question 3. Are there any subgroup of patients under-represented in clinical trials?

Patients with early relapse, those with brain metastases, as well as older patients and ethnic minorities, are underrepresented in the pivotal clinical trials. While additional data should be collected in these populations, treatment should also be offered to these subgroups at present.

In the context of the registration trials for ICIs in metastatic TNBC, several subgroups defined by disease- and patient-related characteristics were underrepresented (Fig. 1). Patients with a disease-free interval (DFI) of less than 12 months were excluded from IMpassion130, while KEYNOTE-355 permitted the enrollment of patients with a DFI of 6–12 months (about 20 % of the overall population). Given the overall positive results of the KEYNOTE-355 trial, patients with a DFI of 6–12 months are eligible for treatment with pembrolizumab and chemotherapy. However, in exploratory subgroup analysis, a clear benefit from the addition of pembrolizumab to chemotherapy was not seen for these patients (in patients with CPS $\geq$ 10, median OS was 17.1 months in the pembrolizumab group and 19.7 months in the placebo group; HR 1.44, 95 % CI 0.73–2.82) [6]. Furthermore, both IMpassion130 and KEYNOTE-355 permitted the enrollment of patients with non-active brain metastases, but this population constituted less than 7 % of patients in IMpassion130 (n = 26 in the IC $\geq$ 1 % population) and only 3 % of patients in KEYNOTE-355 (n = 11 in the CPS $\geq$ 10 population). In addition, neither of the two studies can provide information on patients with unmeasurable disease, nor on patients previously exposed to immunotherapy in the early setting [3,6].

Regarding patient-related characteristics, both IMpassion130 and KEYNOTE-355 enrolled mainly young and white patients. Patients $\geq$ 65 years were about 24 % in IMpassion130 (n = 86 in the IC $\geq$ 1 % population) and about 21 % in KEYNOTE-355 (n = 66 in the CPS $\geq$ 10 population). Racial and ethnic disparities in cancer research and the resulting underrepresentation of specific populations in clinical trials have been well documented [23]. In the IMpassion130 trial, Black patients accounted for approximately 6 % of the population (n = 23 in the IC $\geq$ 1 % population), and in the KEYNOTE-355 trial, they represented about 4 % (n = 15 in the CPS $\geq$ 10 population). Asian patients were significantly more represented in both trials, comprising around 18 % in IMpassion130 and approximately 20 % in KEYNOTE-355 [3,6]. Given that real-world data have documented age- and race-specific differences in both efficacy and toxicity [24,25], conducting thorough assessments of outcomes among under-represented subgroups such as elderly patients and ethnic minorities undergoing immunotherapy is crucial. This underscores the need for enhanced scrutiny in the drug development process with the ultimate aim to better inform clinical practice.

Question 4. Should patients with autoimmune diseases, hepatitis and HIV be considered for immunotherapy in clinical practice?

Patients with pre-existing autoimmune disease (AD), hepatitis, or HIV may be considered for immunotherapy treatment through a case-by-case evaluation. In this context, a multidisciplinary approach considering both the clinical status of the pre-existing disease on one hand, and cancer prognosis as well as alternative treatment options on the other, along with joint decision making that takes into account patient's risk tolerance, are needed for optimal treatment decision.

With the exceptions of well-controlled autoimmune-related hypothyroidism and type 1 diabetes mellitus on stable replacement therapy, patients with ADs have been usually excluded from clinical trials investigating immunotherapy, due to concerns about the development of severe adverse events resulting from exacerbation of their preexisting disease. Nevertheless, a mounting body of real-world evidence suggest that ICIs may be safe and effective in a substantial proportion of these patients. Collectively, retrospective studies showed that patients with preexisting ADs derive a benefit from ICIs comparable to that observed in the general population, but they also face an increased risk of immune-related adverse events (irAEs) [26–28]. Patients with a history of AD who are no longer on immunosuppressive treatment may undergo ICIs, but approximately 30 % may experience exacerbation of their underlying AD. Patients with active and on-treatment AD may require a tapering of steroids or a switch to a biological disease-modifying antirheumatic drug [28].

ICI appears to be safe in patients with concurrent B or C hepatitis. Thus, HBV and HCV infection should not represent an absolute contraindication to ICI treatment. While the risk of virus reactivation and virus-related hepatotoxicity appears to be low, it is recommended that patients with chronic HBV or HCV should be routinely monitored and treated with antiviral agents if indicated [29–31]. Consideration of antiviral prophylaxis to prevent reactivation may be warranted, but further studies are needed to better define its indication.

Patients with a history of HIV infection have been excluded from most ICIs clinical trials due to their dysfunctional immune systems and the resulting safety and efficacy concerns associated with immunotherapy. Nevertheless, sparse retrospective data suggest that ICIs are active and may be safely administered for patients with HIV [32]. A recent large real-world study involving 390 patients undergoing ICI treatment for diverse cancer types confirmed these findings providing support for the utilization of ICIs in patients with HIV and advocates for their inclusion in clinical studies [33]. It is highly advisable that all these patient categories undergo treatment with ICIs with close monitoring for toxicities and only after receiving a thorough multidisciplinary assessment of their risks/benefit ratio and adequate awareness of the possible treatment complications (Fig. 1). In this scenario, the presence of subspecialty colleagues proficient in managing complex immunotherapy-related toxicities, and their early involvement in addressing significant toxicity events, would be highly beneficial.

Question 5. Can we rechallenge immunotherapy in the first-line metastatic setting after (neo)adjuvant chemo-immunotherapy?

There is currently no evidence demonstrating a benefit from immunotherapy rechallenge, and these patients should be prioritized for enrollment in clinical trials. However, if rechallenge is being considered, it might be reasonable to opt for a different ICI than the one used in the early setting, if this option is available.

In recent years, there has been a growing interest in ICI rechallenge after discontinuation of treatment due to disease progression. The outcomes of ICI rechallenge have been primarily reported in patients with melanoma [34] and non-small cell lung cancer [35], and limited data are also available for patients with renal cell carcinoma [36] and urothelial carcinoma [37]. Taken together, these data suggest that rechallenge with ICIs may represent a feasible and effective strategy [38]. Nevertheless, given the distinctive immunological microenvironment inherent in certain tumor types like lung cancer or melanoma, extrapolating data from these conditions and applying them to breast carcinoma warrants caution. Even though rechallenge outcomes are often positively correlated with the efficacy of the prior ICI, responses have been observed in patients receiving rechallenge after disease progression as the best response. Switching from one class of ICIs to another may be a reasonable strategy for some patients [39,40] (Fig. 2), but the most promising approach for ICI rechallenge lies in novel immunotherapy combinations designed to overcome treatment resistance [41–43]. In this context, the combinations of ICIs with anti-angiogenic compounds or antibody-drug conjugates (ADCs) seem particularly intriguing. In the multicohort phase 2 LEAP-005 study, the combination of pembrolizumab and the antiangiogenic multiple receptor tyrosine kinase inhibitor lenvatinib in patients with heavily pretreated metastatic TNBC led to an objective response rate (ORR) of 29 % and prolonged disease control [44].

In the first-line setting, the results from the BEGONIA and ATRACTIB trials are highly promising. In the phase Ib/II BEGONIA trial, 62 patients treated with the combination of durvalumab and the anti-TROP2 ADC

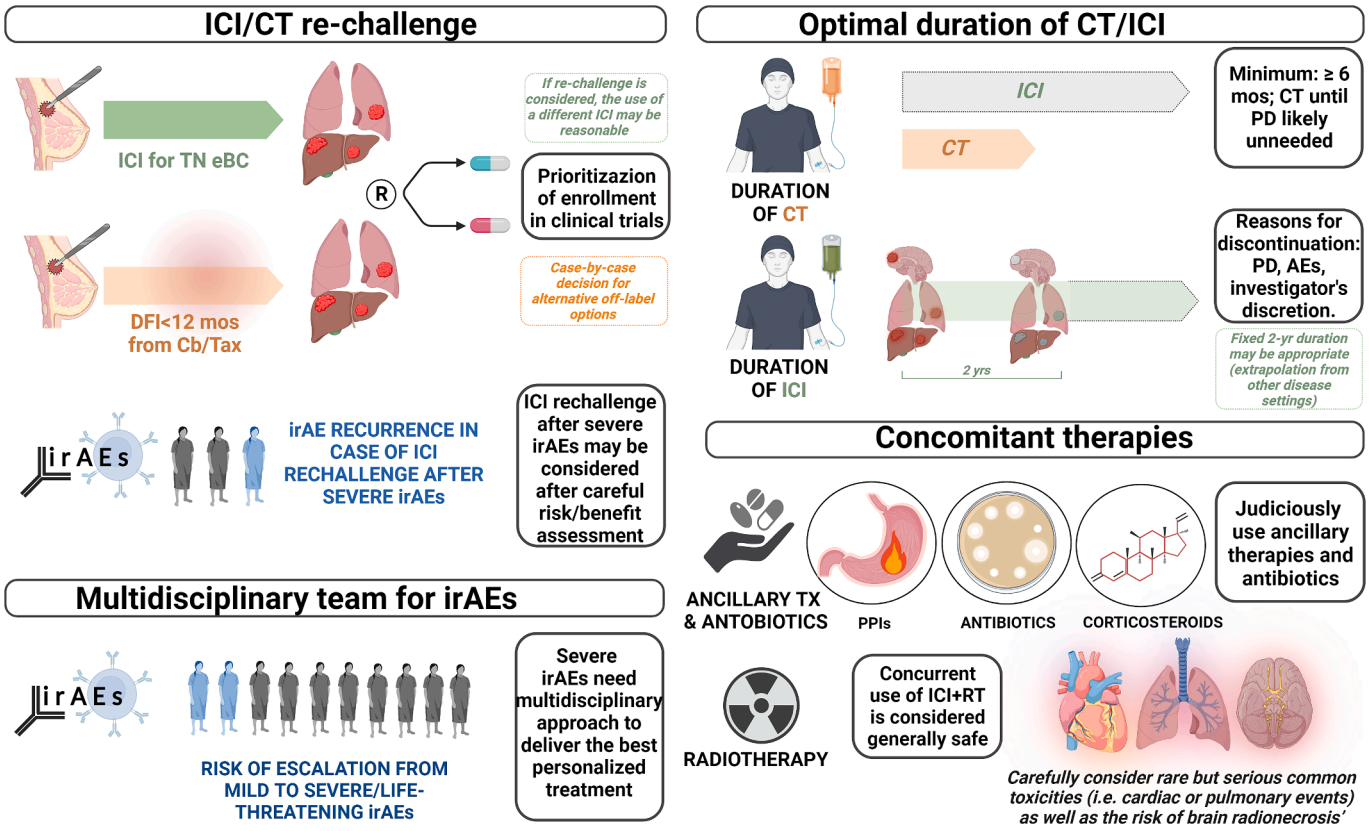

Fig. 2. Practical challenges in immunotherapy for metastatic triple negative breast cancer: immunotherapy rechallenge, concomitant therapies, the ideal chemotherapy backbone, the optimal treatment duration and the management of immune-related adverse events.

datopotamab deruxtecan achieved an ORR of 79 %, with a median duration of response of 15.5 months and a median PFS of 13.8 months [31]. In the phase II ATRACTIB, 100 patients receiving the combination of atezolizumab, paclitaxel and bevacizumab demonstrated an ORR of 55 %, a median duration of response of 10.0 months and a median PFS of 11.0 months [45]. Although both trials did not include patients previously exposed to ICIs, the responses observed regardless of tumor PD-L1 expression level are encouraging and raise hope that these combinations might be potentially effective even in patients previously exposed to neoadjuvant ICI. Finally, ongoing investigations are exploring several combinations involving additional ICIs like anti-CTLA4, anti-LAG3, or anti-TIGIT, as well as immunotherapies beyond ICIs, such as T cell-targeted immunomodulators, vaccines, oncolytic viruses, and various other immunomodulatory agents. These emerging approaches hold promise and merit further investigation in this context.

Question 6. Should patients with ER-low/HER2-negative disease be offered Immunotherapy?

Given the biology and clinical behavior of HER2-negative breast cancer with low ER expression (ER 1–10 %), offering immunotherapy to these patients should be considered.

Estrogen receptor low-positive (ER-low) breast cancers, defined as tumors with ER expression between 1 and 10 % [46], represent approximately 2–5 % of HER2-negative breast cancers [47]. Several studies have demonstrated that ER-low/HER2-negative tumors exhibit biological features similar to TNBC and are primarily classified as basal-like by PAM50 intrinsic subtyping [48,49]. Furthermore, it has been reported that patients with ER-low/HER2-negative breast cancer experience outcomes similar to those with TNBC [50–52]. Accordingly, the 2020 ASCO/CAP Guideline emphasizes that, while patients with ER-low breast cancer should be considered eligible for endocrine treatment, clinicians should be capable of discussing with patients the limited data regarding the overall benefit of endocrine therapies for this group [46]. More recently, it has also been demonstrated that the immune landscape of ER-low/HER2-negative tumors is similar to TNBC in terms of TILs presence, PD-L1 expression and expression of immune-related gene sets [53,54]. Additionally, data from prospective trials suggest that ER-low breast cancer may benefit from immunotherapy. In the metastatic setting, estrogen signaling was negatively associated with the response to pembrolizumab and eribulin in patients with ER+/HER2- breast cancer [55]. In two trials from the I-SPY2 program, both the addition of pembrolizumab and the addition of durvalumab/olaparib to neoadjuvant chemotherapy significantly improved pCR rate in ER+/HER2- breast cancers with an ultrahigh MammaPrint signature, which correlated with low ESR1 expression and high proliferation [56,57].

More recently, both the KEYNOTE-756 and the CheckMate 7FL trials, investigating the addition of pembrolizumab and nivolumab, respectively, to neoadjuvant chemotherapy for ER+/HER2-negative breast cancer patients, showed that the small subgroup of ER-low tumors (5.4 % in KEYNOTE-756 and 7.0 % in CheckMate 7FL) derive a much larger benefit in terms of pCR rates increase than tumors with ER > 10 % [58,59], and pCR rates in ER-low tumors were similar to that observed in ER-negative tumors with neoadjuvant pembrolizumab plus carboplatin and docetaxel in the NeoPACT trial [60]. These and other data highlight that using the traditional restrictive threshold of ER < 1 % might not be optimal for ICIs treatment. Pragmatically, patients with ER-low/HER2-negative breast cancer should be considered as patients with TNBC for clinical trials enrollment (Fig. 1), as has already been done in some cases [61–63].

Question 7. Which chemotherapy backbone should be used in patients with a Treatment-Free interval (TFI) < 12 months and prior exposure to carboplatin and taxanes?

None of the available chemotherapy options are ideal for this group, and these patients should be prioritized for inclusion in clinical trials. Antibody-drug conjugates are emerging as promising therapies but currently a case-by-case decisions could consider alternative off-label options.

Patients with TNBC who experience relapse within 1 year after completing (neo)adjuvant therapy represent a clinically defined subgroup characterized by an aggressive metastatic disease course, rapid progression, and significant treatment resistance [64]. IMpassion130 excluded patients with a TFI < 12 months, and, as a result, they cannot be considered for first-line atezolizumab plus nab-paclitaxel. KEYNOTE-355 allowed the enrollment of patients with a DFI of 6–12 months, but an exploratory subgroup analysis failed to demonstrate a clear benefit from adding pembrolizumab to chemotherapy in this population, although the 95 % confidence interval is broad and does not exclude the possibility of benefit. Furthermore, with an anticipated increase in the number of early-stage TNBC patients receiving both taxanes and carboplatin due to the growing use of the KEYNOTE-522 regimen, alternative combinations with immunotherapy are needed for these patients.

The ongoing phase III IMpassion132 trial (NCT03371017), evaluating atezolizumab plus capecitabine (mandatory in platinum-pretreated patients) or carboplatin/gemcitabine for early relapsed metastatic TNBC, will provide additional data in this setting. Apart from chemotherapy combinations, one of the most promising therapeutic strategies for patients with early relapsed metastatic TNBC who may be eligible for immunotherapy is the combination of ICIs with ADCs. In this context, the TROPION-Breast05 and the ASCENT-04 trials, comparing pembrolizumab plus chemotherapy with datopotamab deruxtecan with or without durvalumab or sacituzumab govitecan plus pembrolizumab, respectively, will hopefully provide additional insights for the optimal management of these patients. However, both trials excluded patients with a TFI < 6 months. To date, early relapsed metastatic TNBC remains a major unmet medical need for which increased research efforts and dedicated clinical trials are urgently required **(**Fig. 2**)**.

Question 8. Should immunotherapy be considered for brain-only metastatic relapse?

According to current guidelines, these patients should undergo local therapy without any systemic treatment, given the lack of evidence demonstrating the benefit of any type of systemic therapy in this setting.

The incidence of brain metastases (BMs) from breast cancer has increased in recent years due to enhanced imaging modalities and, more importantly, the increasing therapeutic options that have led to improved survival rates for patients with metastatic disease [65,66]. Local therapies remain the mainstay treatment of BMs and, apart few exceptions, should not be deferred even in patients with asymptomatic brain metastases [67,68]. While systemic therapy may play an important role in the control of intracranial disease in patients with certain cancer types, such as HER2-positive breast cancer, the role of immunotherapy in this context remains largely unknown **(**Fig. 1**)**. As noted above, the registration trials in metastatic TNBC provide insufficient information on the efficacy of ICIs in patients with BMs, as these patients were significantly underrepresented in both trials [3,6]. Nevertheless, clinical evidence in other disease settings has demonstrated promising findings. Studies in patients with melanoma and BMs demonstrated that single-agent ipilimumab or pembrolizumab led to an intracranial ORR of 24 % and 26 %, respectively [69,70]. In the CheckMate 204 trial, which investigated the use of nivolumab plus ipilimumab for four cycles followed by nivolumab for up to 2 years until disease progression or unacceptable toxicity in both asymptomatic and symptomatic patients with melanoma BMs, asymptomatic patients achieved an intracranial ORR of 54 %, a median duration of response of 33 months and a 36-month OS of 72 % [71].

In patients with PD-L1 + NSCLC, pembrolizumab monotherapy induced an intracranial ORR of 29.4 % [72]. An exploratory analysis of the OAK study showed that atezolizumab monotherapy led to a prolonged time to radiographic identification of new symptomatic BMs compared with docetaxel [73]. The single-arm phase II ATEZO-BRAIN trial, evaluating atezolizumab plus chemotherapy in treatment-naïve patients with NSCLC and untreated BMs, showed an intracranial ORR of 40 % and a median intracranial PFS of 6.9 months [74]. Collectively, these data show that immunotherapy may be effective also in patients with BMs.

Question 9. Should ancillary therapies and antibiotics be used with caution for the potential detrimental effect on immunotherapy efficacy?

Current evidence suggests that the use of antibiotics, proton pump inhibitors (PPIs), and corticosteroids may have a detrimental impact on the efficacy of ICIs. Therefore, it is advisable to use them judiciously.

Preclinical evidence suggests that the composition of the gut microbiota may affects tumor responses to anticancer immunotherapies, potentially serving as a novel biomarker of response [75,76]. Factors influencing microbiota homeostasis may play a role in determining the sensitivity to ICIs. The potential impact of antibiotics and PPIs that may alter gut microbiota has been explored in retrospective studies. The use of antibiotics before or during ICIs treatment is linked to unfavorable clinical outcomes in several cancer types [77,78]. These studies are intriguing but remain inconclusive since patients with compromised performance status and more advanced disease require antibiotics more frequently, however multivariate analyses suggested that antibiotics use was independently associated with worse outcome [79,80]. PPIs administration at the beginning or during treatment with ICIs has been associated with worse outcomes, especially in patients receiving anti-PD-L1 agents [81–83]. A retrospective study evaluating the impact of concomitant medications on ICIs efficacy showed that PPIs use was correlated with a significantly higher risk of disease progression [84]. More recently, a large *meta*-analysis conducted on more than 20,000 patients with different tumors types concluded that PFS and OS were negatively associated with the use of PPIs [85]. All these studies suffer the well-known limitations of retrospective analyses and are further compounded by the fact that antibiotics and PPIs are administered to treat potentially serious co-morbid illnesses.

Due to their immunosuppressive properties, steroids are among the medications most studied for their potential to interfere with immunotherapy efficacy. Indeed, the use of steroids has been associated with worse clinical outcomes in patients receiving ICIs [86]. However, it is important to note that specific timing and indications for steroids can have varying effects on immunotherapy efficacy. Worse outcomes have been demonstrated when steroids are used for cancer-related symptoms before or shortly after starting ICIs, while there is no evidence of a detrimental effect when steroid are used for the management of irAEs, as short-term prophylactic antiemetics or later on, after the immune-response is supposed to be established [87].

Until additional prospective data becomes available, clinicians should assess the risk benefit ratio of using antibiotics, PPIs, and palliative steroid therapy for patients undergoing immunotherapy **(**Fig. 2**)**. However, these drugs should not be withheld to treat serious infections or severe symptoms that compromise quality of life.

Question 10. What is the optimal duration of chemotherapy in combination with immunotherapy in metastatic breast cancer?

The optimal duration of chemotherapy in combination with immunotherapy is not established in metastatic breast cancer. While a minimum recommendation of at least 6 months of chemotherapy or until best response is achieved may be considered, the pivotal breast cancer trials have continued concurrent chemotherapy and ICI therapy until progression.

As per the protocols of the IMpassion130 and KEYNOTE-355 trials, the study treatment was intended to continue until disease progression, unacceptable toxicity, or at the investigator's discretion [3,6]. In IMpassion130, nab-paclitaxel should have been administered for a target of at least 6 cycles. In that trial, the median duration of atezolizumab and nab-paclitaxel in the experimental arm was 24.1 weeks and 22.1 weeks, respectively. However, this study does not provide data regarding the optimal chemotherapy duration. An exploratory analysis of the KEYNOTE-355 trial aimed to assess efficacy outcomes in patients who achieved disease control and discontinued chemotherapy but continued with pembrolizumab [88]. Among the 143 patients with PD-L1 + tumors who achieved disease control with pembrolizumab plus chemotherapy, 46 of them discontinued chemotherapy before pembrolizumab. For these patients, the median durations of pembrolizumab and chemotherapy administration were 20.8 and 6.8 months, respectively. In this cohort, the median PFS was 36.7 months, and the median OS was not reached. Despite limited by the small sample size and the exploratory nature of the analysis, these data suggest that there may be no detrimental effect on outcomes when chemotherapy is discontinued before immunotherapy in patients who are benefiting from the combination and may have achieved their best objective response **(**Fig. 2**)**. However, discontinuing chemotherapy before progression cannot be considered standard of care, and it should be carefully justified and discussed with a patient before implementing it. Studies exploring scheduling of ICIs and chemotherapy, as well as shorter versus longer chemotherapy durations are warranted.

Question 11. Should immunotherapy be continued until progression in metastatic breast cancer that is responding to therapy?

The Impassion130 and KEYNOTE-355 trials recommend continuing the immune checkpoint inhibitor until disease progression, unacceptable toxicity, or at the investigator's discretion, representing the current clinical practice. However, data from other diseases suggest that a fixed 2-year duration of immunotherapy might be enough, prompting the question of the optimal duration of ICI in breast cancer.

Most of the approved indications for atezolizumab in patients with advanced solid tumors recommend a treatment duration until disease progression or unacceptable toxicity [89]. In contrast, the US FDA label for pembrolizumab indicates a maximum treatment duration for up to 24 months in the absence of progression, as this duration was arbitrarily set in pivotal pembrolizumab trials [90].

However, considerable hesitation exists around ICI discontinuation, and in other diseases many patients continue pembrolizumab beyond the recommended 2-year period. The results of the Checkmate-153 study provided arguments in favor of continuing immunotherapy indefinitely [91]. In this study, patients with previously treated NSCLC who exhibited no evidence of disease progression with nivolumab and were assigned to a 1-year fixed duration of treatment had significantly shorter PFS and OS than patients treated with indefinite-duration ICI therapy. However, these results were obtained in a second-line setting and assessed a shorter fixed duration of ICI than 2 years. Long duration ICI therapy carries inherent drawbacks including continued risk of immune related adverse events and large financial burden [92]. Data from long-term follow-up of randomized clinical trials in other cancer types and from large cohort studies suggest sustained responses even after discontinuation of ICI therapy in patients who responded to therapy, however the optimal duration of therapy remains unknown [93,94]. To what extent these findings apply to metastatic breast cancer is also unknown, therefore discontinuing ICI therapy before two years of duration in responding patients should be carefully discussed **(**Fig. 2**)**.

Question 12. Who should manage immunotherapy-related adverse events (irAE) and when to include a multidisciplinary team?

While the majority of irAEs are mild to moderate and can be effectively addressed in outpatient settings by an experienced oncology team, some cases can escalate to severe, even life-threatening conditions. These cases necessitate a multidisciplinary approach involving various medical specialties to ensure the delivery of the best-personalized treatment.

Immune-related adverse events tend to occur more frequently in organs presumed to have pre-existing or smoldering autoimmunity, like the thyroid and joints, or in those with extensive environmental interfaces, such as the skin, lungs, liver, and gastrointestinal tract [95]. However, irAEs can manifest in virtually any organ system, including but not limited to the brain, heart, bone marrow, kidneys, bones and any endocrine organs. Therefore, the optimal management of irAEs involves conducting a thorough diagnostic work-up to rule out non-immune related causes and choosing the most appropriate therapeutic strategy [96]. These processes often necessitate a multidisciplinary approach. Generally, asymptomatic or mildly symptomatic lower grades irAEs can be effectively handled through ambulatory care. However, noteworthy exceptions include cardiovascular and neurological events, which typically demand inpatient management and the engagement of a multidisciplinary team (MDT), even in instances of low-grade events. For grade $\geq$ 3 irAEs, consultation with a specialist is recommended. Severe irAEs that do not respond to steroids within 48–72 h necessitate the initiation of an additional immunosuppressant agent and management within the framework of a MDT [96]. Therefore, although it is not mandatory to administer immunotherapy solely in centers with a MDT, it is strongly recommended that all patients receiving ICIs be managed by oncologists who can easily access consultations with other specialists with whom they collaborate closely **(**Fig. 2**)**.

Question 13. Is it possible to resume immunotherapy after severe irAEs?

Approximately 1 out of 3 patients who are rechallenged with an ICI after its discontinuation for an irAE may experience a recurrence of the same irAE. Therefore, ICI resumption can be considered appropriate only after a proper assessment of the individual risks/benefit ratio. If rechallenge is undertaken, a strict monitoring for treatment-related toxicity recurrence is mandatory.

Use of ICIs has been associated with irAEs that are potentially severe or even fatal [97,98]. However, most irAEs resolve after holding ICIs and instituting appropriate treatment. ICI rechallenge after temporary discontinuation of treatment for toxicity management can be appropriate, particularly after grade 1 and 2 adverse events. The decision to resume ICIs after resolution of toxicity is challenging and requires a careful assessment of the risks and the benefit expected from the rechallenge as well as its actual medical need **(**Fig. 2**)**. Clinicians should consider the type and severity of the toxicity, the time needed for its resolution, the duration of ICI treatment, the tumor response at the time of its discontinuation, the availability of alternate therapies and the patient conditions. Responding patients, especially after a long treatment course, may not require a treatment resumption, since response and stable disease may persist after ICIs discontinuation [93]. In contrast, patients who have not yet responded and have limited or no alternative therapeutic options, may be considered for an ICIs rechallenge after resolution of toxicity.

Large retrospective studies indicate that ICI rechallenge is associated with a 25–50 % risk of recurrent irAEs [99,100]. Recurrences of irAEs are more frequent with anti-CTLA-4 than with anti-PD-1/PD-L1 and the risk appears higher for colitis, hepatitis and pneumonitis compared with other irAEs [100]. Current guidelines recommend permanent discontinuation of ICIs in most cases of grade 4 toxicities. However, there are few exceptions. For example, ICI resumption can be considered after resolution of grade 4 skin rash and after patient stabilization with replacement hormone in case of grade 4 hypothyroidism, primary adrenal insufficiency, hypophysitis and type 1 diabetes [96,101]. ICI therapy should be permanently discontinued after grade $\geq$ 3 neurological toxicities such as myasthenia gravis, Guillain-Barre´ syndrome or peripheral neuropathy, as well as in case of grade $\geq$ 2 cardiovascular toxicities such as myocarditis, pericarditis or arrhythmias [96,101].

Question 14. Can we consider the concurrent use of immunotherapy with radiotherapy (RT) safe?

The concurrent use of immunotherapy with RT appears to be generally safe. Nevertheless, rare but potentially serious common toxicities such as cardiac or pulmonary events, as well as the risk of brain radionecrosis need to be carefully considered when concurrent radiation is administered.

Preclinical evidence indicates that tumor irradiation initiates immunostimulatory processes in the tumor microenvironment that can augment systemic antitumor effects of immunotherapy [102]. Despite the strong biological rationale, clinical studies investigating the concurrent use of ICIs and RT have generated conflicting results in terms of efficacy [103]. These studies also showed that the combination of ICI and RT is generally safe (Fig. 2). A pooled analysis of 68 prospective trials including more than 16,000 patients evaluated the safety of RT administered within the 90 days prior to starting ICIs. The analysis showed no meaningful increase in serious AEs in patients receiving an ICI following RT than those who had not received prior RT [104]. However, patients who undergone RT had a slightly higher incidence of pneumonitis, endocrinopathies, and fatigue, and they were more likely to discontinue treatment due to pneumonitis [104]. In addition to pulmonary toxicities, cardiac events represent another potential common toxicity of ICIs and RT. ICI-related myocarditis is infrequent but is associated with fatality rates of 40–50 % [105]. Therefore, this complication should be taken into account in patients treated with ICIs who undergoing RT that could involve cardiac tissues. Patients receiving ICIs and brain-directed RT may be at higher risk of developing brain radionecrosis. In a retrospective study involving 480 patients with various cancer types who received SRS for BMs, those who received concurrent ICIs had higher rates of symptomatic radionecrosis than those who received SRS alone (20 % vs. 7 %, HR 2.56, P = 0.004) [106]. However, other studies did not confirm such an increased risk, and overall, the safety profile of concurrent ICI and SBS appears tolerable [107]. In KEYNOTE-522 concurrent ICI plus locoregional radiation was allowed and no new safety signals were noted.

Future directions and major unmet needs for immunotherapy in this setting

Immunotherapy has changed the therapeutic landscape of both early- and advanced-stage TNBC. Despite their therapeutic successes, pivotal clinical trials cannot address the myriad questions arising in everyday clinical practice (Fig. 3). For instance, the optimal backbone for ICIs, if one exists, is yet to be defined, particularly in patients who have previously undergone standard neoadjuvant/adjuvant chemotherapy for early-stage disease. Additionally, the role of immunotherapy retreatment of metastatic patients who previously received ICIs in the early-stage setting remains unclear. Determining the most appropriate duration of ICI treatment in patients experiencing prolonged stable disease while on treatment is also an important unmet need. Real-world data and prospective registries could significantly contribute to fine tuning administration of ICI therapies and help clarifying its role and efficacy in populations underrepresented or excluded in landmark clinical trials, for examples patients with ER-low/HER2-negative tumors or those with preexisting autoimmune diseases. Conducting comprehensive translational research and identifying predictive biomarkers will enable clinicians to refine patient selection, ultimately guiding individual patients toward the most suitable treatments. Addressing the challenge of understanding the risks and mitigating ICIs toxicity also remains an unmet need.

Disclosures

LL has received consulting fee from Exact Sciences, Helsinn, EISAI, Daiichi Sankyo; honoraria for speakers' bureaus from Gilead, Exact Sciences, Helsinn, Lilly; support for attending meetings from Lilly, Gilead, Accord; and has served on Advisory Board for Lilly, Exact Sciences, AstraZeneca, Italfarmaco, Daiichi Sankyo, Accord, Seagen.

MVD received personal fees for consultancy/advisory role from: Eli Lilly, Pfizer, Novartis, Seagen, Gilead, **MSD**, Exact Sciences, AstraZeneca, Roche, Daiichi Sankyo, Roche.

CDA reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Daicii-Sankyo, Gilead, and GSK and speaker honoraria from Roche, Lilly, Novartis, Pfizer, Seagen, GSK, GILEAD, and Daiichi-Sankyo. Travel Grants from Gilead and research support (to the Institution) from Novartis, GILEAD, and Daiichi-Sankyo outside the submitted work.

CM reports personal consultancy fees from Roche, Astrazeneca, Bayer, Novartis, Daiichi Sankyo.

FM reports personal fees from Roche, Novartis, Seagen, AstraZeneca, Pfizer, Menarini, Gilead.

LC reports speaker honoraria from Astra Zeneca, Pfizer, Novartis, Gilead, MSD and advisory role for Astra Zeneca, Pfizer, MSD, Amgen.

AF reports advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Daicii-Sankyo, Gilead, Seagen; speaker honoraria from Astra Zeneca, Roche, Lilly, Novartis, Pfizer, Seagen, GILEAD, Daiichi-Sankyo. Research support (to the Institution) from Roche, Astra Zeneca, Daicii-Sankyo.

PS reports institutional research funding from Astellas, AstraZeneca, Genentech, Novartis, Oncogenex, Roche and Medivation; consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Pfizer, Puma, Roche, Eisai and Celgene; and spouse's employment at Roche.

JC reports consulting/advisor from: Roche, AstraZeneca, Seattle Genetics, Daiichi Sankyo, Lilly, M erckSharp&Dohme, Leuko, Bioasis,

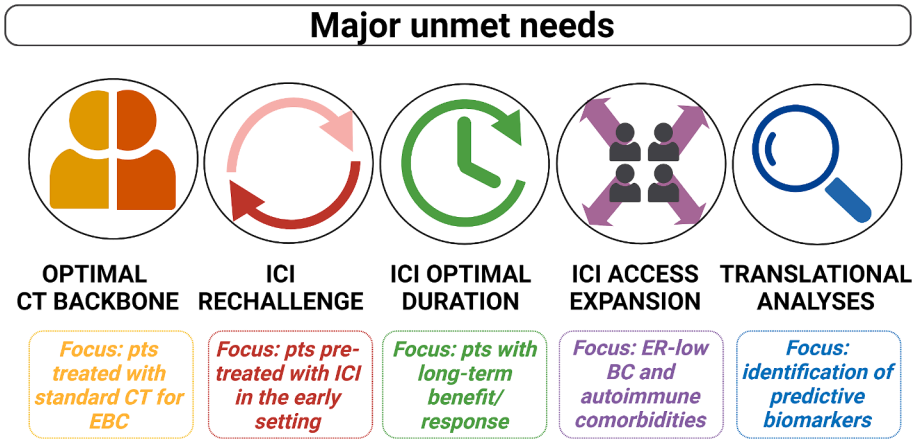

Fig. 3. Future directions and major unmet needs for immunotherapy in metastatic triple negative breast cancer.

Clovis Oncology, Boehringer Ingelheim, Ellipses, Hibercell, BioInvent, Gemoab, Gilead, Menarini, Zymeworks, Reveal Genomics, Scorpion Therapeutics, Expres2ion Biotechnologies, Jazz Pharmaceuticals, Abbvie, Bridgebio, Biontech; honoraria from: Roche, Novartis, Eisai, Pfizer, Lilly, Merck Sharp&Dohme, Daiichi Sankyo, Astrazeneca, Gilead, Steamline Therapeutics; research funding to the Institution: Roche, Ariad pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer healthcare, Eisai, F.Hoffman-La Roche, Guardanth health, Merck Sharp&Dohme, Pfizer, Piqur Therapeutics, Iqvia, Queen Mary University of London. Stock: MAJ3 Capital, Leuko (relative); travel, accommodation, expenses from: Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, Astrazeneca, Gilead, Merck Sharp&Dhome, Steamline Therapeutics. Patents: Pharmaceutical Combinations of A Pi3k Inhibitor And A Microtubule Destabilizing Agent. Javier Cortés Castán, Alejandro Piris Giménez, Violeta Serra Elizalde. WO 2014/199294 A. ISSUED Her2 as a predictor of response to dual HER2 blockade in the absence of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/0,338,368 A1. LICENSED.

LP has received consulting fees and honoraria for advisory board participation from Pfizer, Astra Zeneca, Merck, Novartis, Bristol-Myers Squibb, Stemline-Menarini, GlaxoSmithKline, Genentech/Roche, Personalis, Daiichi, Natera, Exact Sciences and institutional research funding from Seagen, GlaxoSmithKline, AstraZeneca, Merck, Pfizer and Bristol Myers Squibb.

GC reports consulting fees from Roche, Novartis, Lilly, Pfizer, Astra Zeneca, Daichii Sankyo, Ellipsis, Veracyte, Exact Science, Celcuity, Merck, BMS, Gilead, Sanofi, Menarini; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events by Lilly, Pfizer, Relay, Gilead, Novartis and support for attending meetings and/or travel from Daichii Sankyo.

GB has received consulting fee from Roche, AstraZeneca, Novartis, MSD, Sanofi, Daiichi Sankyo, and Exact Sciences; honoraria for speakers' bureaus from Roche, Pfizer, Astra- Zeneca, Lilly, Novartis, Neopharm Israel, MSD, Chugai, Daiichi Sankyo, EISAI, and Exact Sciences; support for travel, accommodations, expenses from Roche, Pfizer, and AstraZeneca; is co-inventor of 'European patent Application N. 12195182.6 and 12196177.5 titled "PDL-1 expression in anti-HER2 therapy" –Roche- Issued (no compensation provided); has served on the advisory boards for Pfizer, Roche, Daiichi Sankyo, Lilly, MSD, Novartis, AstraZeneca, Genomic Health, EISAI, Gilead, Seagen.

Editorial assistance was provided by Editamed srl.

This work was supported by an unrestricted grant from Roche S.p.A.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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