



# Optimizing choices and sequences in the diagnostic-therapeutic landscape of advanced triple-negative breast cancer: An Italian consensus paper and critical review

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## ABSTRACT

Triple-negative (TN) metastatic breast cancer (mBC) represents the most challenging scenario withing mBC framework, and it has been only slightly affected by the tremendous advancements in terms of drug availability and survival prolongation we have witnessed in the last years for advanced disease. However, although chemotherapy still represents the mainstay of TN mBC management, in the past years, several novel effective agents have been developed and made available in the clinical practice setting. Within this framework, a panel composed of a scientific board of 17 internationally recognized breast oncologists and 42 oncologists working within local spoke centers, addressed 26 high-priority statements, including grey areas, regarding the management of TN mBC. A structured methodology based on a modified Delphi approach to administer the survey and the Nominal Group Technique to capture perceptions and preferences on the management of TN mBC within the Italian Oncology community were adopted. The Panel produced a set of prioritized considerations/consensus statements reflecting the Panel position on diagnostic and staging approach, first-line and second-line treatments of PD-L1-positive/germline BRCA (gBRCA) wild-type, PD-L1-positive/gBRCA mutated, PD-L1-negative/gBRCA wild-type and PD-L1-negative/gBRCA mutated TN mBC. The Panel critically and comprehensively discussed the most relevant and/or unexpected results and put forward possible interpretations for statements not reaching the consensus threshold.

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## Background

Triple-negative (TN) breast cancer (BC) definition relies on immunohistochemistry (IHC) and in situ hybridization (ISH) assessment and refers to the absence of hormone receptor (HR) expression (estrogen receptor [ER] and progesterone receptor [PgR] expression  $< 1\%$  [1]) and HER2 protein overexpression or gene amplification [2]. In the setting of early-stage disease, TNBC is associated with the most unfavorable distant relapse-free survival rates among all BC subtypes, exhibiting a peculiar pattern of recurrence [3–5]. In particular, the increased risk for distant relapse of TNBC as compared to other BC subtypes is mostly attributable to an excess of visceral metastases (especially lung and brain), mainly in the first 2–3 years after diagnosis, reflecting a strong tendency to early metastatic dissemination with marked tropism for visceral sites [6,7]. Once metastatic, TNBC (TN mBC) is associated with dismal prognosis, with median overall survival (OS) from mBC diagnosis of approximately 15–20 months and 5-year survival rates of 11 %, clearly unsatisfactory in the contemporary landscape of mBC [8].

These considerations all contribute to outline TN mBC as the most challenging clinical scenario within mBC framework.

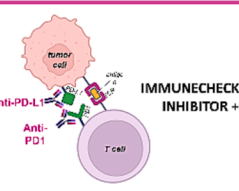

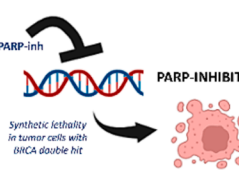
From a therapeutic point of view, chemotherapy still represents the mainstay of TN mBC management. However, in the past years, we have witnessed prominent advancements in the landscape of TN mBC with the development of novel agents with a demonstrated efficacy in terms of progression-free survival (PFS) and, in certain cases, also OS [9,10], as summarized in Fig. 1.

In detail, the randomized phase III IMpassion130 [11] and Keynote-355 [12] trials established immune-checkpoint inhibitor plus chemotherapy as the current standard of care for the first-line management of PD-L1-positive (PD-L1+) TN mBC patients. In particular, atezolizumab (+nab-paclitaxel) is EMA (European Medicines Agency)-approved and pembrolizumab (+chemotherapy: paclitaxel, nab-paclitaxel, carboplatin-gemcitabine) is both FDA (Food and Drug Administration)- and EMA-approved in this setting. In Italy, the atezolizumab-based treatment has been granted approval by the Italian Drug Agency (Agenzia Italiana del Farmaco [AIFA]), and is currently reimbursed by the Italian Health System, Fig. 1.

Beyond first-line treatment, the most compelling results have been observed within the phase III ASCENT trial, leading to FDA and EMA approval of the anti-TROP2 antibody drug conjugate (ADC), sacituzumab govitecan in TN mBC patients who have received two or more prior systemic therapies, at least one of them for advanced disease. In Italy, sacituzumab govitecan has been granted approval by AIFA and is currently reimbursed by the Italian Health System for TN mBC patients previously treated with at least 2 lines of treatments for mBC (or at least 1 prior line for early relapser, defined as patients exhibiting disease-free interval [DFI] from early BC treatment completion  $\leq 12$  months), Fig. 1.

Another compelling breakthrough within the treatment landscape of TN mBC regards the subgroup of patients harboring a germline BRCA1/2 mutation (gBRCA). Notably, the proportion of unselected BC patients with a germline mutation of these BC predisposition genes is approximately 5%, rising up to 20% when focusing on TNBC [13,14] (variable rates depending on personal/family history). In gBRCA mutation-carriers, the inhibition of the enzyme poly-ADP-ribose polymerase (PARP), which represents one of the main guarantors of the genomic integrity of BRCA-mutated tumor cells, has been proven to be an effective treatment strategy, capable of determining lethal consequences for tumor cells (BRCA homozygous cells), while sparing normal cells (BRCA-heterozygous cells), through the so-called synthetic lethality mechanism [15–18]. Based on the results from the phase III OlympiAD [19–21] and EMBRACA [22,23] trials, the PARP-inhibitors olaparib and talazoparib, respectively, received marketing authorization by FDA and EMA for patients with gBRCA1/2 mutations and HER2-negative locally-advanced/mBC. In Italy, both olaparib and talazoparib have been granted approval by AIFA with the same indication as EMA and FDA's, however, olaparib reimbursement by the Italian Health System has been granted only for patients with TN mBC already treated with taxane, anthracycline and carboplatin (not progressing while on this latter or within 12 months from its completion) and talazoparib reimbursement has been granted for HR+/HER2- patients already pre-treated also with a cyclin-dependent kinase (CDK) 4/6 inhibitor and TN patients pre-treated also with carboplatin (not progressing while on it or within 6 months from its completion), Fig. 1.

For patients exhausting or not eligible for these targeted treatment options, chemotherapy preferentially given as single agent or as

	Trial (n)	Experimental arm	Primary endpoint	Line of treatment	Significant results		Approval		
					PFS	OS	FDA	EMA	Italy
 <b>IMMUNE CHECKPOINT INHIBITOR + CT</b>	IMpassion 130 (902)	Atezolizumab+nab-paclitaxel	Co-primary endpoints: PFS and OS with hierarchical testing for OS: ITT → PD-L1+*	First-line (DFI $\geq 12$ months)	Yes in ITT and in PD-L1+	No in ITT → not tested in PD-L1+	Withdrawn	Yes	Yes
	Keynote-355 (847)	Pembrolizumab+chemotherapy (paclitaxel, nab-paclitaxel or carboplatin-gemcitabine)	PFS and OS in ITT and PD-L1+ with hierarchical testing: PD-L1+** CPS $\geq 10$ → PD-L1+** CPS $\geq 1$ → ITT	First-line (DFI $\geq 6$ months)	Yes in PD-L1+ CPS $\geq 10$ . No in PD-L1+ CPS $\geq 1$ → not tested in ITT	Yes in PD-L1+ CPS $\geq 10$ . No in PD-L1+ CPS $\geq 1$ → not tested in ITT	Yes	Yes	No
<small>*PD-L1 assessment: % of tumor-infiltrating immune cells staining for PD-L1 (as percentage of tumor area), Ventana SP342 assay (PD-L1+ <math>\geq 1\%</math>)  **PD-L1 assessment: CPS score, <math>\geq 23</math> pharmix</small>									
 <b>ANTIBODY DRUG CONJUGATE</b>	ASCENT (468)	Sacituzumab govitecan	PFS in patients without brain metastases	$> 2$ (neo/adjuvant treatment qualified as 1 prior line if DFI $< 12$ months)	Yes (patients without brain metastases)	Yes (patients without brain metastases)	Yes (2 prior lines at least 1 for MBC)	Yes (2 prior lines at least 1 for MBC)	Yes ( $> 2$ prior lines*)
<small>* neo/adjuvant treatment qualified as 1 prior line if DFI<math>&lt; 12</math> months</small>									
 <b>PARP-INHIBITOR</b> Synthetic lethality in tumor cells with BRCA double hit	OlympiAd (gBRCA+, 302)	Olaparib	PFS	$\leq 2$ (prior treatments required: anthracycline, taxane; no PD/DFI $\geq 12$ months from platinum)	Yes	No	Yes (prior chemotherapy)	Yes (prior anthracycline and taxane)	Yes (prior platinum required*)
	EMBRACA (gBRCA+, )	Talazoparib	PFS	$\leq 3$ (prior treatments required: anthracycline and/or taxane; no PD/DFI $\geq 6$ months from platinum)	Yes	No	Yes	Yes (prior anthracycline and/or taxane)	Yes (prior platinum required**)
<small>*no PD/DFI<math>\geq 12</math> months from platinum  **no PD/DFI<math>\geq 6</math> months from platinum</small>									

**Fig. 1.** Phase III trials and regulatory positioning of novel agents for TN mBC treatment. Abbreviations: PFS, progression-free survival; OS, overall survival; FDA, Food and Drug Administration; EMA, European Medicines Agency; CT, chemotherapy; ITT, intention-to-treat population; CPS, combined positive score; PARP-inh, PARP-inhibitor; DFI, disease-free interval; MBC, metastatic breast cancer; gBRCA, germline BRCA mutation; PD, disease progression.

polychemotherapy still represents an essential weapon of the TN mBC therapeutic armamentarium [2]. Several chemotherapeutic options are viable, based on prior exposures, patient conditions/comorbidities and preferences, with anthracycline, taxane and carboplatin-based regimens to be possibly prioritized.

The implementation of immune checkpoint and PARP inhibitors respectively for PD-L1 positive and gBRCA mutated patients, has revolutionized the traditional conception of TNBC as a theragnosticless entity [10], thus necessarily posing the need to properly select patients and to strategically sequence available therapeutic options. This consideration acquires crucial importance within the Italian regulatory scenario, where the National Health System, if on one hand grants the entire Italian population equal access to health services, on the other must necessarily ensure its own sustainability. The direct consequence of this balance is often represented by the application of rigid boundaries in drug reimbursement indications, as outlined in Fig. 1.

Within this framework, a Panel composed of internationally recognized Italian Oncologists (expert in BC) formulated several relevant statements regarding the management of TN mBC, to be addressed to a sample of local Italian oncologists in order to capture perceptions and preferences on the management of TN mBC within the Italian Oncology community.

## Methodology

A Scientific Board composed of 17 Italian oncologists, internationally recognized as expert in the field of BC (the Scientific Board), formulated relevant statements regarding TN mBC diagnostic and staging procedures, first- and second-line treatment (the process of generating and validating the statements took place between February 2022 and April 2022).

Subsequently, a sample of 42 Italian local oncologists (not necessarily completely dedicated to BC patients) were surveyed (between June 2022 and July 2022) by applying a modified Delphi method in order to capture the rate of agreement and disagreement with the proposed statements [24]. In detail, the Delphi method represents a survey approach aiming at quantifying the agreement/disagreement levels to develop a consensus.

For each statement, the voters were asked to express a preference among the following options:

- Completely disagree (contributing to the “disagreement”)
- Partially disagree (contributing to the “disagreement”)
- Partially agree (contributing to the “agreement”)
- Agree (contributing to the “agreement”)
- Completely agree (contributing to the “agreement”)

Agreement or disagreement were considered as reached in case of > 66.6 % of answers in either one of the two possible directions. In all other cases the consensus was not considered as reached.

The results of this survey were subsequently discussed in a meeting involving both the Scientific Board and the local Italian oncologists, by adopting the Nominal Group technique (NGT) (September 2022).

Descriptive statistics were applied to analyze data.

## Results

(Dis-)agreement levels for each answer option are shown in Supplementary Table 1. The aggregated agreement/disagreement levels (agreement level [%] = Partially agree + Agree + Completely agree; Disagreement level [%] = Completely disagree + Partially disagree) are shown below.

### a. Diagnosis, staging, and molecular biology

The only statement regarding the diagnostic and staging procedures

of TN mBC not reaching the consensus threshold regarded the value of TROP2 assessment.

- The inclusion of brain scan is recommended in the staging assessment of TN mBC.

Consensus reached (agreement level = 83.72 %).

- The majority of TN mBC patients should, at least once during mBC course, undergo metastatic tissue biopsy to phenotypically recharacterize the disease

Consensus reached (agreement level = 93.02 %).

- Germline BRCA1/2 test for therapeutic purposes should be offered at TN mBC diagnosis, if not already performed.

Consensus reached (agreement level = 97.68 %).

- PD-L1 status analysis should be carried out primarily on the primary tumor tissue, and, only in case of unavailability of the primary tumor tissue, on metastatic samples.

Consensus reached (agreement level = 97.68 %).

- PD-L1 expression should be evaluated/quantified before the start of first-line treatment, in compliance with indications provided in the drug label and according to chosen immunotherapeutic agent.

Consensus reached (agreement level = 100 %).

- The assessment of TROP2 expression levels by IHC is indicated in TN mBC

Consensus NOT reached (agreement level = 58.69 % vs disagreement level = 41.3 %).

- Patients with tumors exhibiting low levels of ER expression (1–9 %) should be considered as TN and should therefore be granted access to drugs developed/registered for TN mBC

Consensus reached (agreement level = 95.66 %).

### b. General considerations

All the statements regarding the role of polychemotherapy and the setting of patients with early relapse reached the consensus threshold.

- Polychemotherapy is to be preferred with respect to monochemotherapy as first-line treatment

Consensus reached (agreement level = 81.39 %).

- There is a standard treatment for early relapse TN mBC (DFI < 6 months from completion of [neo]adjuvant therapy)

Consensus reached (disagreement level = 72.09 %).

- Early relapse setting should be considered as a second-line setting by default

Consensus reached (agreement level = 83.72 %).

### c. First-line and second-line treatment of PD-L1+/gBRCA wild-type TN mBC

All the statements regarding PD-L1+ -gBRCA wild type subgroup reached the consensus threshold.

- The standard first-line treatment is atezolizumab + nab-paclitaxel or pembrolizumab + chemotherapy

Consensus reached (agreement level = 100 %).

- In second-line, sacituzumab govitecan is the optimal treatment choice in patients previously treated with first-line atezolizumab + nab-paclitaxel or pembrolizumab + chemotherapy and prior (neo) adjuvant systemic therapy

Consensus reached (agreement level = 97.67 %).

#### d. First-line and second-line treatment of PD-L1+/gBRCA mutated TN mBC

All the statements regarding PD-L1+ -gBRCA mutated subgroup reached the consensus threshold.

- The standard first-line treatment is atezolizumab + nab-paclitaxel or pembrolizumab + chemotherapy

Consensus reached (agreement level = 93.02 %).

- In second-line, a PARP-inhibitor is the optimal treatment choice in patients previously treated with first-line atezolizumab + nab-paclitaxel or pembrolizumab + chemotherapy

Consensus reached (agreement level = 100 %).

- In second-line, sacituzumab govitecan is the optimal treatment choice in patients previously treated with first-line PARP-inhibitor

Consensus reached (agreement level = 97.70 %).

#### e. First-line and second-line treatment of PD-L1-negative (PD-L1-)/gBRCA wild-type TN mBC

The only statement not reaching the consensus threshold regarded the role of chemotherapy regimens not including taxane, anthracycline and/or platinum in the first-line management of PD-L1- and gBRCA wild-type subgroup.

- There is NOT an optimal standard first-line treatment

Consensus reached (agreement level = 95.35 %).

- In first-line, platinum salt-based chemotherapy is the optimal treatment choice, even if already received

Consensus reached (agreement level = 67.09 %).

- In first-line, platinum salt-based chemotherapy is the optimal treatment choice, if not already received

Consensus reached (agreement level = 97.70 %).

- In first-line, anthracycline-based chemotherapy is the optimal treatment choice, if not already received

Consensus reached (agreement level = 74.41 %).

- In first-line, taxane-based chemotherapy is the optimal treatment choice, if the DFI from treatment completion for EBC is > 12 months

Consensus reached (agreement level = 93.02 %).

- In first-line, chemotherapy not including either taxane, platinum salts or anthracycline is the optimal treatment choice

Consensus NOT reached (agreement level = 44.18 % vs disagreement level = 55.82 %).

- In second-line, sacituzumab govitecan is the optimal treatment choice in patients previously treated with first-line chemotherapy and prior (neo)adjuvant systemic therapy

Consensus reached (agreement level = 97.67 %).

#### f. First-line and second-line treatment of PD-L1-/gBRCA mutated TN mBC

All statements on PD-L1- and gBRCA mutated subgroup reached the consensus threshold.

- In first-line, platinum salt-based chemotherapy is the optimal treatment choice, if NOT already received

Consensus reached (agreement level = 86.05 %).

- In first-line, a PARP-inhibitor is the optimal treatment choice, if NOT already received

Consensus reached (agreement level = 93.02 %).

- In second-line, platinum salt-based chemotherapy is the optimal treatment choice in patients previously treated with first-line PARP-inhibitor

Consensus reached (agreement level = 74.42 %).

- In second-line, sacituzumab govitecan is the optimal treatment choice in patients previously treated with first-line PARP-inhibitor and prior (neo)adjuvant systemic therapy

Consensus reached (agreement level = 100 %).

## Discussion

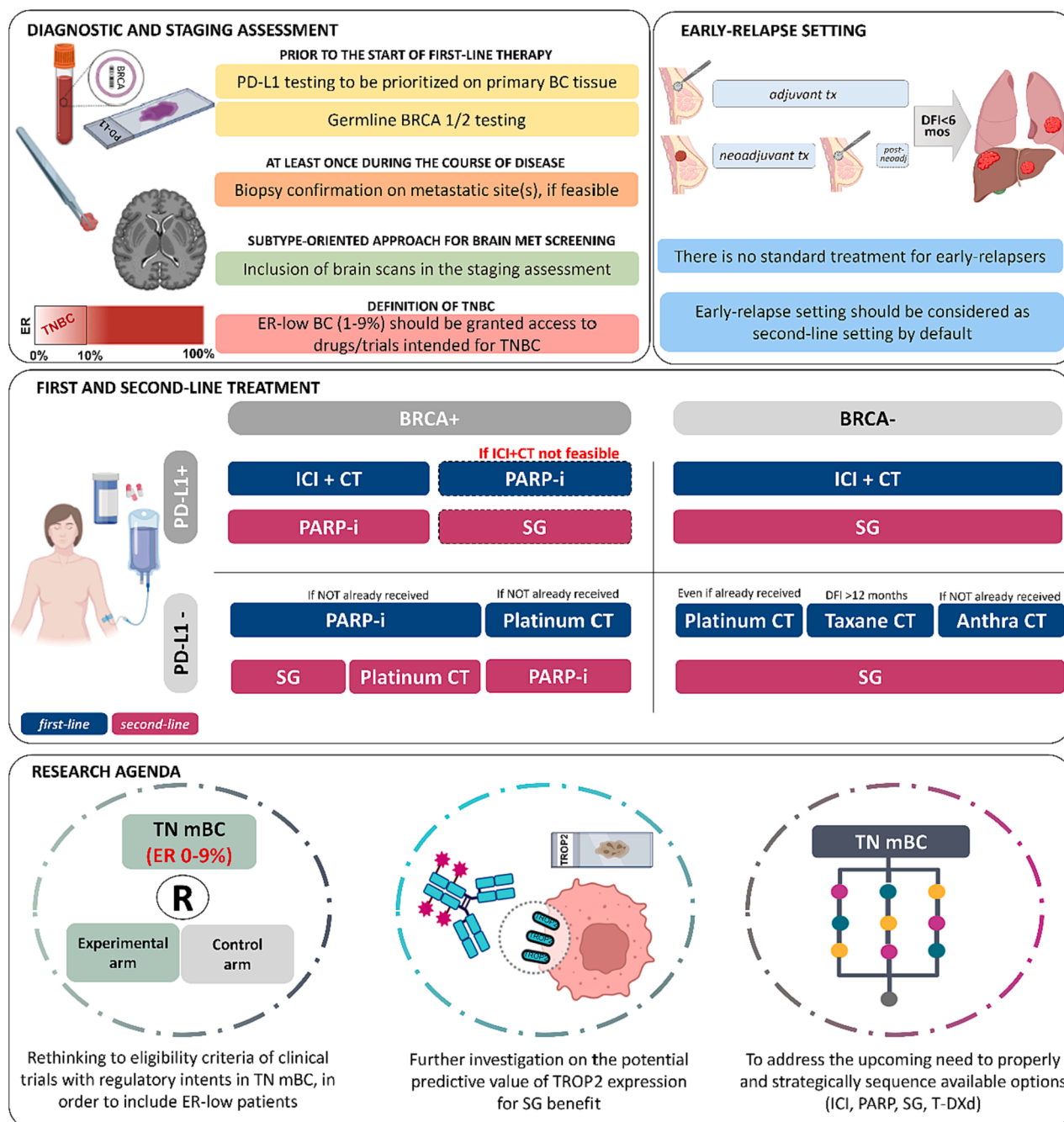
In the present study, highly relevant topics regarding the management of TN mBC were addressed by applying a modified Delphi approach to measure the agreement/disagreement levels across a Scientific Board (internationally recognized BC oncologists) and local Italian oncologists not necessarily completely focused on BC (collectively the "Panel"), with the ultimate aim of developing a consensus built on evidence-based expert opinion and common clinical practice.

Results from this survey overall highlight a substantial consensus among the involved oncologists, with statements reaching the agreement/disagreement threshold reasonably proxying the approach Italian oncologists adopt in everyday clinical practice when managing TN mBC.

Indeed, although results of the survey were in most cases expected, considerations raised during the discussion and debate process (NGT) are of high clinical/scientific interest and worthy of sharing (Fig. 2).

Regarding the initial diagnostic and staging approach of TN mBC, the key consideration is that within the contemporary Italian clinical practice, management of newly diagnosed patients include PD-L1 testing, to be prioritize on primary tumor tissue, and gBRCA testing, prior to the start of first-line treatment, as well as biopsy confirmation (when feasible) at least once during the course of disease, with an agreement level across the panelists of almost 100%. These results reflect the importance given, in common clinical practice, to a proper and





**Fig. 2.** Considerations of high clinical/scientific interest raised during the discussion and debate process. Abbreviations: PD-L1, programmed death-1 (PD-1) ligand 1; TNBC, triple-negative breast cancer; tx, therapy; DFI, disease-free interval; ICI, immune checkpoint inhibitor; CT, chemotherapy; PARP-I, poly ADP ribose polymerase inhibitor; SG, sacituzumab govitecan; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan.

comprehensive diagnostic/predictive assessment of TN mBC patients. A good level of consensus has also been reached regarding the value of brain imaging in TN mBC patients, even if asymptomatic. Indeed, the Panel endorses the adoption of a subtype-oriented approach when deciding to proactively scrutinize for brain metastases in asymptomatic mBC patients [2]. The Panel acknowledges the not negligible risk for TN mBC patients to present with brain metastasis at first relapse [3], thus warranting the ascertainment of brain metastasis presence in TN subtype. In this regard, it should be noted that approximately 16% of the panelists disagreed with this statement, thus possibly reflecting a degree of uncertainty regarding the lack of solid evidence supporting the clinical value of brain screening [25].

Another interesting point regards the statement on the optimal

threshold of ER level to define ER-negativity, representing one of the most debated issues within BC scientific community. Importantly, phase III trials for TN mBC conducted with regulatory intents systematically excluded patients with ER expression ranging from 1% to 9%, by complying with the cutoff of 1%, currently endorsed by the ASCO/CAP recommendations [1]. In the context of the present work, >95% of the panelists were in agreement with the inclusion of ER-low patients within the TNBC definition, with >32% polarized in the highest agreement position. This reflects that Italian oncologists consider available data in this regard [26–28] solid enough to potentially extend the indication of drugs formally intended for pure TNBC also to patients exhibiting low levels of ER. The Panel position, if from one hand makes it evident the direction this academic debate is going, on the other imposes the need to

rethink to eligibility criteria of clinical trials potentially leading to drug approval in TN mBC.

Conversely, one of the most unexpected results regards the value of TROP2 expression assessment in TN mBC. This statement did not reach the consensus, with approximately 40% of panelists disagreeing with the value of TROP2 evaluation in this context and the remaining showing a position in the opposite direction. Of course, the access to the anti-TROP2 ADC sacituzumab govitecan is granted irrespectively from TROP2 levels [29], however, an exploratory analysis of the ASCENT trial revealed that the magnitude of benefit from this agent may be enhanced in case of high or intermediate TROP2 levels [30], thus outlining a potential predictive role for TROP2 expression in TN mBC patients treated with sacituzumab govitecan. Within this framework, whilst TROP2 expression determination should not be considered a routine procedure with predictive purposes, the failure to reach a consensus makes this statement emerge as a possible issue to be prioritized in the research agenda.

Regarding the choice of the first line therapy in the subgroup of patients with PD-L1+ tumors, the consensus was widely reached, with agreement levels ranging from 93% to 100% in favor of immunotherapy + chemotherapy (atezolizumab + nab-paclitaxel or pembrolizumab + chemotherapy) as the standard of care. In Italy, only the atezolizumab + nab-paclitaxel combination is currently approved by AIFA and reimbursed by the National Health System in this setting.

Regarding the scenario of simultaneous presence of PD-L1+ tumor and gBRCA mutation, the ≈7% level of disagreement may reflect the possible uncertainty regarding the most strategical/biologically rational positioning of immunotherapy (+chemotherapy) with respect to PARP-inhibitors. In this context, in the absence of head-to-head comparisons, results from the translational analysis of the IMpassion130 trial revealing a preserved magnitude of benefit from immunotherapy in the subgroup of patients with germinal BRCA mutation [31], appear reassuring, thus well fitting in the current Italian regulatory scenario of immunotherapy + chemotherapy, which does not allow the positioning of this strategy in any different setting than the first-line.

For patients with a gBRCA mutation (PD-L1-), a consensus was reached for both carboplatin and PARP-inhibitors as optimal upfront strategies. This outlines that in common clinical practice, oncologists are prone to pharmacologically exploit the enhanced vulnerability of BRCA-related deficiency in DNA repairing mechanisms [32–34]. However, the higher agreement levels reached for first-line PARP-inhibitors as compared to first-line platinum may reflect two aspects: firstly, a possible concern of postponing the use of PARP-inhibitor in later lines should the patient progress on first-line carboplatin, given that both olaparib and talazoparib are currently indicated for TN mBC patients not showing features of “platinum-resistance/refractoriness”; secondly the value given to the OlympiAd subgroup analysis capturing a significant OS advantage in patients receiving olaparib as first-line therapy for mBC [20].

Intriguing remarks have been highlighted in the context of the choice of the first-line treatment for patients with no theragnostic markers (neither PD-L1 nor gBRCA mutation). In particular, a wide consensus was reached when outlining the lack of a standard approach in this setting and this consideration must be kept in mind in the interpretation of the following results. In particular, the fact that the statements defining either platinum salt, taxane (if DFI > 12 months) or anthracycline (if not already received) as optimal choices, all reached the agreement consensus, allows to define these treatment options as reasonable in this setting, as endorsed by international guidelines [2]. However, by dissecting the sublevels of agreement/disagreement, taxane and carboplatin stand out as the most solid and preferred first-line strategies. Indeed, the anthracycline statement appeared as the most divisive, with approximately 35% of panelists expressing some degree of disagreement. Consistently, the statement outlining different chemotherapeutic options other than taxane/platinum/anthracycline as the preferred first-line therapy failed to reach the consensus threshold,

further solidifying the clinical value of these 3 cytotoxic agents in the management of TN mBC. Another statement deserving to be commented regards the use of carboplatin as the optimal choice in the first line setting even if already received, reaching a wide agreement consensus. This result, if from one hand highlights the value that oncologists give to carboplatin in the management of TN mBC, on the other may underpin that in common clinical practice the notion of platinum sensitivity, albeit not formally recognized, may play a role. In this context, patients experiencing a DFI > 6–12 months from carboplatin exposure may possibly represent viable candidates for platinum re-challenge.

A final consideration regards the most unexpected results in the context of first-line treatment decision-making process. An agreement consensus was reached in favor of considering polychemotherapy to be preferred to monotherapy. Although it should be noted that the largest part of this agreement was built on moderate positions (<10% of “total” agreement), this is apparently in contrast with the position of international guidelines [2], which tend to consider the risk/benefit balance in favor of monotherapy as compared to polychemotherapy in most patients, with the exception of those at high risk of imminent organ failure or rapid visceral progression. When exploring the reasons underlying the panel position in this regard, two possible interpretations emerged. Firstly, the Panel contextualized this agreement consensus to the specific scenario of theragnosticless TN mBC and/or early-relapsing patients, where carboplatin-based combinations, as carboplatin + paclitaxel and carboplatin + gemcitabine, respectively, emerge as frequently adopted strategies in the first line setting. Secondly, it should be noted that the combination of chemotherapy plus the antiangiogenic agent bevacizumab is currently acknowledged by international guidelines as a viable therapeutic option in the first-line management of TN mBC [2] since it has been consistently demonstrated to provide a PFS benefit in mBC, with, however, no impact in terms of OS [35]. In Italy, the combination of bevacizumab with either paclitaxel or capecitabine (if taxane is not considered appropriate) is approved by AIFA as first-line treatment for mBC.

Turning to the setting of pre-treated patients, all the statements reached the consensus threshold and the most intriguing aspect regards the positioning of sacituzumab govitecan. In particular, the Panel components appear to be prone to consider sacituzumab govitecan after the exhaustion of targeted therapy options, thus outlining an ideal position of this agent in second-line in most cases with the exception of PD-L1+ /gBRCA-mutated subgroup, where the presence of both the therapeutically exploitable targets pushes sacituzumab govitecan as a valuable third line option. In particular, the Panel position is built on the EMA label, with sacituzumab govitecan being granted approval for TN mBC previously treated with 2 prior lines of systemic therapy, at least one of them for metastatic disease (reflecting wider eligibility criteria as compared to the ASCENT trial’s [29]). It should be noted that the voting process for the purposes of the present work took place before AIFA formally approved sacituzumab govitecan in Italy, with a reimbursed indication requiring 2 prior lines of therapy, with (neo)adjuvant treatment qualifying as one of the required two prior lines only in case of DFI < 12-months, consistently with the ASCENT inclusion criteria [29]. This disengagement between the drug Italian label and oncologists’ attitude may be considered a reliable proxy of TN mBC high level of clinical complexity, with effective strategies, demonstrated as capable of impacting on both PFS and OS, possibly deserving to be positioned in the earliest vacant regulatory seat, even at the cost of making the contextualization of trial eligibility criteria more flexible. This consideration may acquire a paramount importance also in the light of the – underestimated – phenomenon of patient attrition, referring to the proportion of patients not accessing a further line of treatment after progression (or, in general, treatment failure) to the previous one. Importantly, TN mBC is associated with an alarming patient attrition rate of 12–50 % across most contemporary randomized trials [36], imposing the urgent need to maximize the access to effective treatments early during TN mBC history.

In the same ground lies the issue of early relapse. Interestingly, although the Panel appeared fairly cohesive when outlining the lack of a standard treatment for patients exhibiting early relapse (DFI < 6 months from completion of neo/adjuvant treatments), an even higher agreement level was reached when stating that early-relapse setting should be considered as a second-line setting by default. The key of interpretation is that the Panel involved in the present consensus development acknowledges this particular scenario as one of the most challenging in the framework of TN mBC, where the short DFI underlies a marked treatment resistance and preludes to dismal prognosis, thus qualifying treatments for eBC as a full-fledged first-line therapy.

The present work has limitations. Firstly, the Panel addressed topics well-fitting within the Italian regulatory landscape, thus not necessarily being generalizable to different countries. Secondly, this work neglected trastuzumab-deruxtecan among possible treatment strategies for TN (HER2-low) mBC [37]. Indeed, HER2-low BC refers to tumors traditionally considered as HER2-negative but showing some degree of HER2 expression, and the currently accepted operational definition relies on IHC and ISH assessment, surrogating HER2-low tumors as those scored as 1+ or 2+ in the absence of gene amplification. Currently, trastuzumab deruxtecan is not approved by the Italian Health System for HER2-low/TN mBC and so it does not represent a viable option in the current Italian scenario. However, pending the scientific review process by the EMA's Committee for Medicinal Products for Human Use of trastuzumab-deruxtecan Type II Variation Application, this treatment strategy will likely be soon implemented in HER2-low mBC. Indeed, although the approval of this agent is expected to be prioritized in HR+/HER2-low mBC (the primary endpoint population of the Destiny-Breast04 trial [37]), it is likely that trastuzumab-deruxtecan indication will be soon extended also to HR-/HER2-low mBC. Within this upcoming landscape, the relative sequential positioning of sacituzumab govitecan and trastuzumab-deruxtecan for pre-treated TN-HER2-low mBC patients will become a high-priority issue. Thirdly, the Panel did not address access to PARP-inhibitors beyond gBRCA mutations. Notably, this issue is expected to gain increasing relevance based on the results of "TBCRC 048" [39] and "Talazoparib Beyond BRCA" [40] single arm phase II trials, reporting promising antitumor activity data with – respectively – olaparib and talazoparib in patients harboring germline PALB2 mutations, with also appealing results regarding olaparib activity in patients with somatic BRCA mutations [39]. Currently, although PARP inhibitors in this specific subset of mBC patients are considered as a possible option by ESMO guidelines [2], their use in patients not harboring gBRCA mutations is not allowed in Italy, thus making these considerations not lowerable into the Italian clinical practice landscape.

## Conclusions

TN mBC represents a challenging scenario, which has been only slightly affected by the tremendous advancements in terms of drug availability and survival prolongation we have witnessed in the last years for mBC. Within this framework, a panel composed of a scientific board of internationally recognized breast oncologists and oncologists working within local spoke centers, addressed high-priority issues, including grey areas, regarding the management of TN mBC. A structured methodology based on a modified Delphi approach was adopted to administer the survey and the NGT was applied to produce a set of prioritized considerations/consensus statements reflecting the Panel position. The most relevant findings were thoughtfully discussed and, for statements not reaching the consensus threshold, possible interpretations were put forward. The main focuses were diagnostic and staging approach in first instance. Secondly, the panel converged on the consensus regarding the first-line and second-line treatments, which were in agreement with the proposed therapeutic algorithms obtained from the multiple Bayesian network *meta*-analyses according to treatment line to establish an optimal therapeutic sequencing strategy in mTNBC [38]. A summary of main results and considerations is shown in

Fig. 2.

## CRedit authorship contribution statement

**F. Miglietta:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization. **A. Fabi:** Conceptualization, Methodology, Investigation, Writing – review & editing. **D. Generali:** Conceptualization, Methodology, Investigation, Writing – review & editing. **M.V. Dieci:** Conceptualization, Methodology, Investigation, Writing – review & editing. **G. Arpino:** Conceptualization, Methodology, Investigation, Writing – review & editing. **G. Bianchini:** Conceptualization, Methodology, Investigation, Writing – review & editing. **S. Cinieri:** Conceptualization, Methodology, Investigation, Writing – review & editing. **P.F. Conte:** Conceptualization, Methodology, Investigation, Writing – review & editing. **G. Curigliano:** Conceptualization, Methodology, Investigation, Writing – review & editing. **M. De Laurentis:** Conceptualization, Methodology, Investigation, Writing – review & editing. **L. Del Mastro:** Conceptualization, Methodology, Investigation, Writing – review & editing. **S. De Placido:** Conceptualization, Methodology, Investigation, Writing – review & editing. **A. Gennari:** Conceptualization, Methodology, Investigation, Writing – review & editing. **F. Puglisi:** Conceptualization, Methodology, Investigation, Writing – review & editing. **A. Zambelli:** Conceptualization, Methodology, Investigation, Writing – review & editing. **F. Perrone:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision. **V. Guarneri:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: FM reports personal fees from Gilead, Novartis, Roche; AF reports personal fees and non-financial supports for scientific consult, advisory board, lectures from Roche, Novartis, Lilly, Pfizer, MSD, Dompè, Pierre Fabre, Eisai, Sophos, Epionpharma, Gilead, Seagen, AstraZeneca, Exact Science; DG reports Honoraria from Novartis, Roche, Pfizer and Eli Lilly, Research Funding from Novartis and AstraZeneca; MVD reports personal fees from Eli Lilly, MSD, Exact Sciences, Novartis, Pfizer, Seagen; GB reports honoraria for Consultancy: Roche, AstraZeneca, MSD, Daiichi Sankyo, Gilead, Sanofi, Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Roche, AstraZeneca, Daiichi Sankyo, Lilly, MSD, Chugai, Eisai, Gilead, Seagen, Neopharm Israel, Support for attending meetings and/or travel: Roche, Pfizer, MSD, Chugai, Novartis, Advisory Board: Roche, Pfizer, AstraZeneca, Lilly, Novartis, Amgen, MSD, Chugai, Daiichi Sankyo, Eisai, Gilead, Seagen, Exact Science; GC reports Honoraria for speaker's engagement: Roche, Seattle Genetics, Novartis, Lilly, Pfizer, Foundation Medicine, NanoString, Samsung, Celltrion, BMS, MSD; Honoraria for providing consultancy: Roche, Seattle Genetics, NanoString; Honoraria for participating in Advisory Board: Roche, Lilly, Pfizer, Foundation Medicine, Samsung, Celltrion, Mylan; Honoraria for writing engagement: Novartis, BMS; Honoraria for participation in Ellipsis Scientific Affairs Group; Institutional research funding for conducting phase I and II clinical trials: Pfizer, Roche, Novartis, Sanofi, Celgene, Servier, Orion, AstraZeneca, Seattle Genetics, AbbVie, Tesaro, BMS, Merck Serono, Merck Sharp Dome, Janssen-Cilag, Philogen, Bayer, Medivation, Medimmune; FP reports Honoraria for advisory boards, activities as a speaker, travel grants, research grants Amgen - Astrazeneca - Daiichi Sankyo - Celgene - Eisai - Eli Lilly - Gilead - Ipsen - MSD - Novartis - Pierre Fabre - Pfizer - Roche - Seagen - Takeda - Viatrix Research funding Astrazeneca - Eisai - Roche; AZ reports personal fees and non-financial support from Novartis, AstraZeneca, Lilly, Pfizer, Daiichi Sankyo, MSD, Roche, Seagen, Exact Sciences, Gilaed, Istituto Gentili; VG reports personal fees for advisory board membership from Eisai, Eli Lilly, Exact



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## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctrv.2023.102511>.

## References

- [1] Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol* 2020;38:1346–66. <https://doi.org/10.1200/JCO.19.02309>.
- [2] Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol* 2021;32:1475–95. <https://doi.org/10.1016/j.annonc.2021.09.019>.
- [3] Dent R, Hanna WM, Trudeau M, Rawlinson E, Sun P, Narod SA. Pattern of metastatic spread in triple-negative breast cancer. *Breast Cancer Res Treat* 2009;115:423–8. <https://doi.org/10.1007/s10549-008-0086-2>.
- [4] Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-Negative Breast Cancer: Clinical Features and Patterns of Recurrence. *Clin Cancer Res* 2007;13:4429–34. <https://doi.org/10.1158/1078-0432.CCR-06-3045>.
- [5] Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, et al. Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer. *J Clin Oncol* 2008;26:1275–81. <https://doi.org/10.1200/JCO.2007.14.4147>.
- [6] Gerrata L, Davis AA, Polano M, Zhang Q, Shah AN, Lin C, et al. Understanding the organ tropism of metastatic breast cancer through the combination of liquid biopsy tools. *Eur J Cancer* 2021;143:147–57. <https://doi.org/10.1016/j.ejca.2020.11.005>.
- [7] Gerrata L, Fanotto V, Bonotto M, Bolzonello S, Minisini AM, Fasola G, et al. Pattern of metastasis and outcome in patients with breast cancer. *Clin Exp Metastasis* 2015;32:125–33. <https://doi.org/10.1007/s10585-015-9697-2>.
- [8] Grinda T, Antoine A, Jacot W, Blaye C, Cottu P-H, Diéras V, et al. Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008–2017 ESME cohort. *ESMO Open* 2021;6:100114. <https://doi.org/10.1016/j.esmoop.2021.100114>.
- [9] Miglietta F, Bottosso M, Griguolo G, Dieci MV, Guarneri V. Major advancements in metastatic breast cancer treatment: when expanding options means prolonging survival. *ESMO Open* 2022;7:100409. <https://doi.org/10.1016/j.esmoop.2022.100409>.
- [10] Bianchini G, Angelis CD, Licata L, Gianni L. Treatment landscape of triple-negative breast cancer — expanded options, evolving needs. *Nat Rev Clin Oncol* 2022;19:91–113. <https://doi.org/10.1038/s41571-021-00565-2>.
- [11] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med* 2018;379:2108–21. <https://doi.org/10.1056/NEJMoa1809615>.
- [12] Cortes J, Rugo HS, Cescon DW, Im SA, Yusuf MM, Gallardo C, Lipatov O, Barrios CH, Perez-Garcia J, Iwata H, Masuda N, Torregroza Otero M, Gokmen E, Loi S, Guo Z, Zhou X, Karantz V, Pan W, Schmid P, KEYNOTE-355 Investigators. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. *N Engl J Med*. 2022;387(3):217–26. <https://doi.org/10.1056/NEJMoa2202809>.
- [13] O'Shaughnessy J, Brezden-Masley C, Cazzaniga M, Dalvi T, Walker G, Bennett J, et al. Prevalence of germline BRCA mutations in HER2-negative metastatic breast cancer: global results from the real-world, observational BREAKOUT study. *Breast Cancer Res* 2020;22:114. <https://doi.org/10.1186/s13058-020-01349-9>.
- [14] S; Griguolo V, Zovato G, Agata S, Tognazzo S, Dieci MV, Matricardi L, Crivellari G, Miglietta F, Alducci E, Moserle L, Conte PF, Montagna M, Guarneri V. Role of BRCA1/2 pathogenic variants according to family and personal history of cancer in a large cohort of triple-negative breast cancer (TNBC) patients (pts) younger than 60 years of age. *Ann Oncol* 2021 32 Suppl5 S382-S406 101016annoncannonc686 n.d.
- [15] Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. *Target Oncol* 2021;16:255–82. <https://doi.org/10.1007/s11523-021-00796-4>.
- [16] Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: Clearing up the misunderstandings. *Mol Oncol* 2011;5:387–93. <https://doi.org/10.1016/j.molonc.2011.07.001>.
- [17] Javle M, Curtin NJ. The role of PARP in DNA repair and its therapeutic exploitation. *Br J Cancer* 2011;105:1114–22. <https://doi.org/10.1038/bjc.2011.382>.
- [18] Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. *Science* 2017;355:1152–8. <https://doi.org/10.1126/science.aam7344>.
- [19] Robson M, Im S-A, Senkus E, Xu B, Domchek S, Masuda N, et al. OlympiAD extended follow-up for overall survival and safety: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. 1011581538-7445SABCS19-PD4-03 Publ Febr 2020 n.d.
- [20] Robson ME, Tung N, Conte P, Im S-A, Senkus E, Xu B, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol* 2019;30:558–66. <https://doi.org/10.1093/annonc/mdz012>.
- [21] Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. *N Engl J Med* 2017;377:523–33. <https://doi.org/10.1056/NEJMoa1706450>.
- [22] Litton JK, Huvrutz SA, Mina LA, Rugo HS, Lee K-H, Gonçalves A, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. *Ann Oncol* 2020;31:1526–35. <https://doi.org/10.1016/j.annonc.2020.08.2098>.
- [23] Litton JK, Rugo HS, Ettl J, Huvrutz SA, Gonçalves A, Lee K-H, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med* 2018;379:753–63. <https://doi.org/10.1056/NEJMoa1802905>.
- [24] Milholland AV, Wheeler SG, Heieck JJ. Medical Assessment by a Delphi Group Opinion Technic. *N Engl J Med* 1973;288:1272–5. <https://doi.org/10.1056/NEJM197306142882405>.
- [25] Bonotto M, Gerrata L, Poletto E, Driol P, Giangreco M, Russo S, et al. Measures of Outcome in Metastatic Breast Cancer: Insights From a Real-World Scenario. *Oncologist* 2014;19:608–15. <https://doi.org/10.1634/theoncologist.2014-0002>.
- [26] Paakkola N-M, Karakatsanis A, Mauri D, Foukakis T, Valachis A. The prognostic and predictive impact of low estrogen receptor expression in early breast cancer: a systematic review and meta-analysis. *ESMO Open* 2021;6:100289. <https://doi.org/10.1016/j.esmoop.2021.100289>.
- [27] Dieci MV, Griguolo G, Bottosso M, Tsvetkova V, Giorgi CA, Vernaci G, et al. Impact of estrogen receptor levels on outcome in non-metastatic triple negative breast cancer patients treated with neoadjuvant/adjunct chemotherapy. *npj Breast Cancer* 2021;7:101. <https://doi.org/10.1038/s41523-021-00308-7>.
- [28] Villegas SL, Nekjudova V, Pfarr N, Engel J, Untch M, Schrodi S, et al. Therapy response and prognosis of patients with early breast cancer with low positivity for hormone receptors – An analysis of 2765 patients from neoadjuvant clinical trials. *Eur J Cancer* 2021;148:159–70. <https://doi.org/10.1016/j.ejca.2021.02.020>.
- [29] Bardia A, Messersmith WA, Kio EA, Berlin JD, Vahdat L, Masters GA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. *Ann Oncol Off J Eur Soc Med Oncol* 2021;32:746–56. <https://doi.org/10.1016/j.annonc.2021.03.005>.
- [30] Bardia A, Tolane SM, Punie K, Loirat D, Oliveira M, Kalinsky K, et al. Biomarker analyses in the phase III ASCENT study of sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer. *Ann Oncol* 2021;32:1148–56. <https://doi.org/10.1016/j.annonc.2021.06.002>.
- [31] Emens LA, Cruz C, Eder JP, Braithe F, Chung C, Tolane SM, et al. Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer. *JAMA Oncol* 2019;5:74. <https://doi.org/10.1001/jamaoncol.2018.4224>.
- [32] Rocha CRR, Silva MM, Quinet A, Cabral-Neto JB, Menck CFM. DNA repair pathways and cisplatin resistance: an intimate relationship. *Clinics* 2018;73:e478s. <https://doi.org/10.6061/clinics/2018/e478s>.
- [33] Turner N, Tutt A, Ashworth A. Hallmarks of “BRCAness” in sporadic cancers. *Nat Rev Cancer* 2004;4:814–9. <https://doi.org/10.1038/nrc1457>.
- [34] Farmer H, McCabe N, Lord CJ, Tutt ANJ, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005;434:917–21. <https://doi.org/10.1038/nature03445>.
- [35] Miles DW, Diéras V, Cortés J, Duenne A-A, Yi J, O'Shaughnessy J. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. *Ann Oncol* 2013;24:2773–80. <https://doi.org/10.1093/annonc/mdt276>.
- [36] Nuzzolese I, Montemurro F. Attrition in metastatic breast cancer: a metric to be reported in randomised clinical trials? *Lancet Oncol* 2020;21:21–4. [https://doi.org/10.1016/S1470-2045\(19\)30792-2](https://doi.org/10.1016/S1470-2045(19)30792-2).
- [37] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. *N Engl J Med* 2022;387:9–20. <https://doi.org/10.1056/NEJMoa2203690>.
- [38] Schettini F, Venturini F, Giuliano M, Lambertini M, Pinato DJ, Onesti CE, et al. Multiple Bayesian network meta-analyses to establish therapeutic algorithms for metastatic triple negative breast cancer. *Cancer Treat Rev* 2022;111:102468. <https://doi.org/10.1016/j.ctrv.2022.102468>.
- [39] Tung NM, Robson ME, Ventz S, Santa-Maria CA, Nanda R, Marcom PK, et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. *J Clin Oncol* 2020;38:4274–82. <https://doi.org/10.1200/JCO.20.02151>.
- [40] Gruber JJ, Afghahi A, Timms K, DeWees A, Gross W, Aushev VN, et al. A phase II study of talazoparib monotherapy in patients with wild-type BRCA1 and BRCA2 with a mutation in other homologous recombination genes. *Nat Cancer* 2022. <https://doi.org/10.1038/s43018-022-00439-1>.