Clinical management of first-line advanced triple-negative breast cancer patients

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SUMMARY

Chemotherapy has represented the main treatment option for patients with advanced triple-negative breast cancer for a long time. However, due to our better understanding of tumour biology, recent clinical trials led to a change in the treatment paradigm of this disease, identifying clinically relevant subgroups with different therapeutic options. Both clinical and biological factors have become relevant and need to be considered in the treatment decision algorithm of this heterogeneous disease.

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INTRODUCTION

Triple-negative breast cancer (TNBC), defined by the absence of human epidermal growth factor receptor 2 (HER2) overexpression/amplification and the lack of oestrogen and progesterone receptor expression, accounts for 10-20% of all breast cancer (BC) cases.[1]

TNBC represents an aggressive and heterogeneous disease, including different histological and molecular subtypes, as described by several studies.[2,3] However, there are currently no recommendations for treatment personalisation according to TNBC molecular subtypes.[4] Indeed, chemotherapy has been the only therapeutic option in advanced TNBC for decades. Only recent clinical trials have offered novel therapeutic opportunities for subgroups of TNBC patients based on predictive biomarkers, namely programmed death receptor ligand 1 (PD-L1) and germline mutations in the BReast CAncer 1 and 2 genes (*BRCA1/2*).

Herein, we propose a treatment algorithm (*Figure 1*) for the management of advanced TNBC patients in the first-line setting. Participation in clinical trials should be considered for all suitable advanced TNBC patients, as this approach allows to receive innovative treatments and, potentially, to improve their clinical outcome. Standard clinical management, guided by patient characteristics and clinical factors, should include the evaluation of PD-L1 expression and genetic counselling for germline *BRCA* mutations testing. Biopsy of a metastatic lesion should always be performed, in the absence of contraindications.

PATIENTS WITH PD-L1-POSITIVE TNBC, GERMLINE *BRCA1/2* WILD-TYPE

In patients suitable for standard treatment, PD-L1 testing should be performed in order to identify candidates to receive immunotherapy, based on the results of the IMpassion130 study.[5] The IMpassion130 phase III trial evaluated the combination of the anti-PD-L1 antibody atezolizumab with nab-paclitaxel compared to nab-paclitaxel plus placebo in advanced TNBC untreated for advanced disease. Previous chemotherapy (including taxanes) in the context of curative treatment was allowed if completed ≥12 months before randomisation. PD-L1 positivity was defined as PD-L1 expression on tumour-infiltrating immune cells ≥1% of the tumour area with the SP142 PD-L1 immunohistochemical assay (Ventana Medical Systems). In the intention-to-treat analysis (PD-L1 positive and negative tumours), the combination of atezolizumab with nab-paclitaxel significantly improved progression-free survival (PFS, 7.2 *vs.* 5.5 months; hazard ratio [HR] 0.80; 95% confidence interval [CI] 0.69-0.92; p= 0.002); nonetheless, the benefit in overall survival (OS) was not significant (21.3 *vs.* 17.6 months; HR[95%CI]: 0.84[0.69-1.02], p= 0.08). In the PD-L1 positive cohort, the median PFS was significantly increased in the atezolizumab plus nab-paclitaxel arm (7.5 *vs.* 5.0 months; HR[95%CI]: 0.62[0.49-0.79], p< 0.001). In the first *interim* analysis, the median OS was also improved in the PD-L1-positive cohort (25.0 *vs.* 15.5 months; HR[95%CI]: 0.62[0.45-0.86]), a benefit confirmed, but less pronounced in the second *interim* analysis (difference of seven months).[6] However, the OS result could not be formally tested due to the pre-specified statistical testing hierarchy and has to be considered exploratory. Adverse events were consistent with the known safety profile of each agent. These results led to the approval of atezolizumab in combination with nab-paclitaxel in PD-L1-positive advanced TNBC by the Food and Drug Administration and the European Medicines Agency.

Despite the results of IMpassion130, important clinical questions remain to be addressed in this patient population. Firstly, IMpassion130 did not allow the enrolment of patients presenting a disease-free interval (DFI) <12 months after curative treatment. Furthermore, approximately 37% of the patients enrolled in the IMpassion130 trial were treatment-naïve and did not receive any (neo-)adjuvant therapy, while about 75% had 0-3 metastatic sites involved. Subgroup analyses suggest an increased benefit for these subpopulations and, therefore, a potential higher efficacy in low-burden and/or *de novo* metastatic TNBC patients, highlighting the need for confirmatory data. Nab-paclitaxel allows to limit the use of corticosteroids compared to other taxanes, avoiding their potential immunosuppressive effect. However, recent data showed that premedication with steroids may be safely omitted if no severe allergic reaction occurred after two paclitaxel administrations.[7] Of interest, several clinical trials are evaluating other cytotoxic drugs, including paclitaxel, in association to immunotherapeutic agents, and may help in the identification of the optimal chemotherapy partner for immunotherapy.[8] In particular, results from the KEYNOTE-355 phase III trial (NCT02819518) of pembrolizumab/placebo in combination with chemotherapy (either nab-paclitaxel, paclitaxel, or gemcitabine plus carboplatin) are pending. This trial allowed the enrolment of patients with DFI ≥6 months, and defined PD-L1 status based on a combined positive score (CPS) with the 22C3 PharmDx assay (Agilent). As reported at the recent ASCO 2020 annual meeting, PFS was significantly improved in patients whose tumours had a CPS ≥10 (9.7 *vs.* 5.6 months; HR[95%CI]: 0.65[0.49-0.86], p= 0.0012) and data on OS are still pending.[9] Given the different types of immunotherapy (anti-PD1 *vs.* anti-PDL1) and chemotherapy regimens used, as well as the different assays testing PD-L1 expression and DFI allowed (6 *vs.* 12 months), novel clinical questions may be raised based on these results.

Pembrolizumab has recently shown to increase pathological

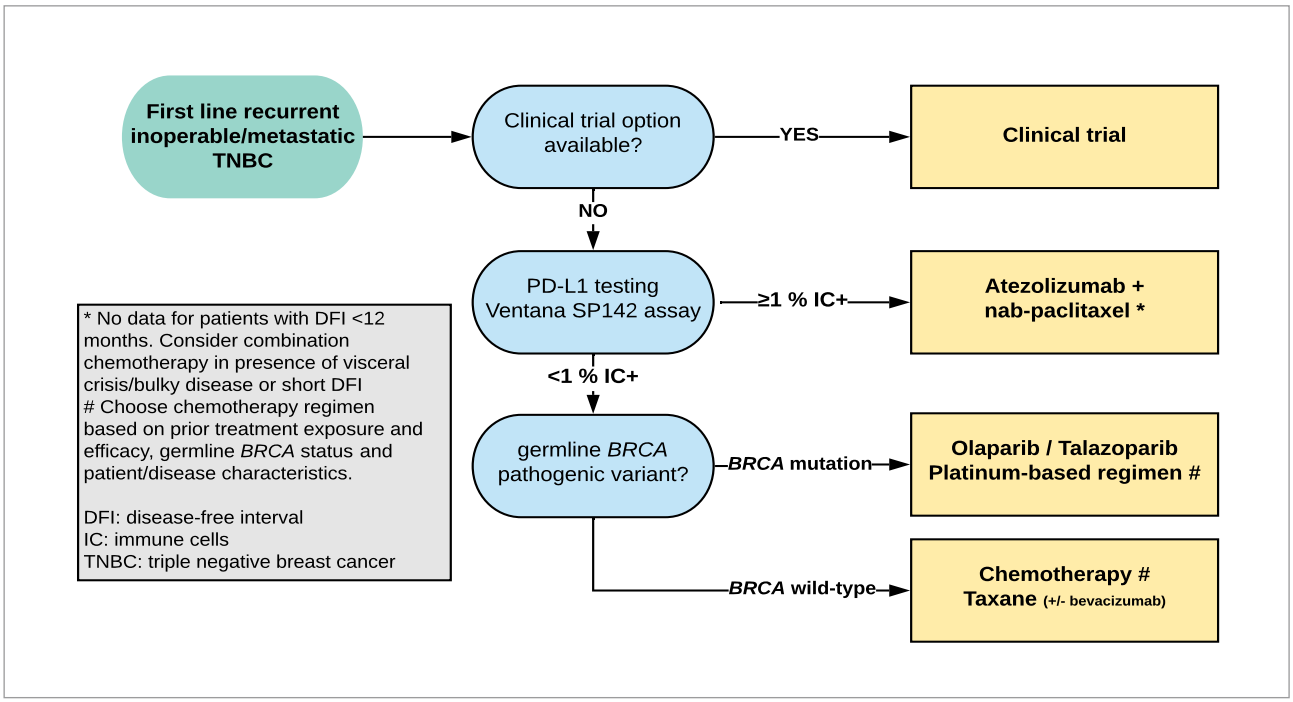

FIGURE 1. Algorithm for the treatment of recurrent inoperable/metastatic TNBC in the first-line setting.

complete response (pCR) rates in patients with early TNBC, when added to standard neoadjuvant based chemotherapy.[10] Thus, the expected incorporation of check-point inhibitors in the treatment of early-stage TNBC will open the discussion on how to treat disease relapse in patients with PD-L1-positive tumours previously treated with (neo-)adjuvant immunotherapy.

PATIENTS CARRYING GERMLINE *BRCA1/2* MUTATIONS

In patients with advanced TNBC, testing for germline *BRCA* (g*BRCA*) mutations may open the opportunity for further treatment options. Germline mutations in *BRCA1* and/or *BRCA2* genes are present in approximately 5% of unselected BC patients and about 10% of all TNBC, with higher rates in younger patients, those with a strong family history of BC and Ashkenazi Jewish ancestry.[11,12]

Genetic counselling and testing should be guided by national/international guidelines and may be considered for all patients with TNBC cases.[4,13] In Belgium, germline testing for hereditary BC syndrome is currently recommended in patients fulfilling the criteria of the Belgian Society of Human Genetics , which include the diagnosis of TNBC in patients with an age <60 years, irrespective of familial history.[14] While several germline aberrations are correlated with an increased risk of BC, to date only mutations in *BRCA1/2* have therapeutic implications with regards to systemic standard of care treatments, limited to metastatic HER2-negative BC.[15]

Pathogenic alterations in *BRCA1/2* lead to a defect in the repair of DNA double-strand breaks through the homologous recombination repair (HRR) machinery.[16] Tumours characterised by *BRCA* mutations show an increased vulnerability to platinum compounds, as well as to anthracyclines and alkylating agents, leading to cell death through a synergistic process called synthetic lethality.[17] The TNT phase III trial tested the activity of carboplatin compared to docetaxel in advanced TNBC and oestrogen receptor-positive BC.[18] While no difference in objective response rate (ORR, primary end-point) was detected in the overall population, carboplatin significantly improved ORR (68% *vs.* 33.3%; interaction p= 0.01) and PFS (6.8 *vs.* 4.4 months; interaction p= 0.002) compared to docetaxel in patients carrying g*BRCA1/2* mutations.

Inhibition of the poly(adenosine diphosphate–ribose) polymerase (PARP) results in synthetic lethality and cell death through multiple mechanisms in *BRCA* mutated tumours.[19,20] Two phase III clinical trials demonstrated the activity of the PARP inhibitors (PARPi) olaparib and talazoparib in advanced HER2-negative BC with g*BRCA* mutations, namely OlympiAD and EMBRACA.[19,20] Both trials had PFS as primary endpoint. Prior treatment with platinum-based therapy was allowed in the (neo)adjuvant setting if DFI was ≥6 months in EMBRACA and ≥12 months in OlympiAD, as well as for advanced BC if no disease progression had been documented during treatment. The subgroup previously treated with platinum-based therapy represented approximately 25-30% and 15-20% of the OlympiAD and

EMBRACA populations, respectively. The OlympiAD trial randomly assigned patients treated with no more than two chemotherapy lines for metastatic disease (with 30% in the first-line setting) to receive either olaparib or single-agent treatment of physician's choice (capecitabine, eribulin, or vinorelbine).[19] Median PFS (7.0 *vs.* 4.2 months; HR[95%-CI]: 0.58[0.43-0.80], p< 0.001), and ORR (59.9% *vs.* 28.8%) were improved in the olaparib arm. The final OS analysis demonstrated no benefit with the use of olaparib (19.3 *vs.* 17.1 months; HR[95%CI]: 0.90[0.66-1.23], p= 0.513); however, an analysis in pre-specified subgroups showed a benefit in the first-line setting (HR[95%CI]: 0.51[0.29-0.90]) compared to further lines (HR[95%CI]: 1.13[0.79-1.64]).[21]

Talazoparib significantly prolonged PFS compared to the treatment of physician's choice (capecitabine, eribulin, gemcitabine or vinorelbine) in the EMBRACA trial (8.6 *vs.* 5.6 months; HR[95%CI]: 0.54[0.41-0.71], p< 0.001).[20] ORR was 62.6% for talazoparib and 27.2% for the control arm, and approximately 39% of the patients were treated in the first-line setting.

Although haematological toxicities were more frequent, quality of life was significantly better in the PARPi arm in both trials, underlining the favourable safety profile of these compounds over the comparator treatments and offering the opportunity of delaying the use of chemotherapy.[4] However, it has to be noted that in both trials the comparator arm was not an optimal regimen in the first-line setting.

Moreover, the BROCADE3 phase III trial evaluated the PARPi veliparib in combination with chemotherapy (carboplatin plus paclitaxel), showing a benefit in PFS compared to chemotherapy plus placebo (14.5 *vs.* 12.6 months per investigator assessment; p= 0.002).[22] Up to two prior lines of chemotherapy were allowed (with 81% treated in the first-line setting), and 48% of the patients had TNBC.

Currently, olaparib and talazoparib are approved in Europe for patients with g*BRCA1/2* mutations previously treated with an anthracycline and/or a taxane in the (neo-)adjuvant or metastatic setting unless not suitable for these treatments, but platinum-based regimens also remain a valid option. To date, data for the predictive effect of somatic *BRCA1/2* mutations and other HRR deficiency-alterations for PARPi and/or platinum-based compounds are lacking, as well as results from trials comparing PARPi with carboplatin as a first-line treatment. Furthermore, results from the OlympiA adjuvant trial (NCT02032823) may raise questions about the efficacy of a rechallenge with PARPi in relapsed g*BRCA* mutated patients. Data in TNBC patients with PD-L1-positive tumours and g*BRCA* mutations are limited to small subgroup analyses and trials comparing immunotherapy with PARPi are lacking. In consideration of the robustness of the data in the first-line setting for immunotherapy and the activity demonstrated in later lines by PARPi, we suggest for these patients the use of immunotherapy as a first-line approach, unless not eligible for chemotherapy.

PATIENTS WITH PD-L1-NEGATIVE TNBC, GERMLINE *BRCA1/2* WILD-TYPE

In situations where there is no access to a clinical trial, chemotherapy represents the only treatment option for patients with PD-L1-negative tumours and no g*BRCA1/2* mutations, with the most active drugs being anthracyclines and taxanes. Both single agent and combination regimens can be used, however combinations provide only an increase in response rate and toxicity, with no survival advantage demonstrated.[23] When choosing the first-line treatment, both disease and patient characteristics need to be considered, including prior chemotherapy regimens received in the (neo-)adjuvant setting, DFI, disease burden (bulky disease *vs.* oligometastatic disease), need for a rapid disease control, performance status, comorbidities, risk of adverse events and patient's preferences.[4] For most patients, a monotherapy with a taxane can be recommended as first-line treatment, with combination regimens (*e.g.*, anthracycline with cyclophosphamide, taxane with platinum compound) reserved for patients with visceral crisis (*i.e.* severe organ dysfunction as assessed by signs and symptoms, laboratory studies and rapid disease progression) or requiring rapid symptom and/or disease control.[4] The antiangiogenic agent bevacizumab has been studied as first-line treatment for metastatic BC in combination with chemotherapy. Despite showing a benefit in terms of PFS, meta-analyses have shown no significant OS improvement.[24–26]

A challenging clinical scenario is represented by the development of central nervous system (CNS) metastases, which can be observed in 25-45% of patients affected by TNBC.[27] Although responses to systemic chemotherapy are reported, to date, prognosis of patients with CNS involvement remains poor, and robust data regarding the efficacy of novel treatments in this patients population are awaited. Locoregional treatments, including surgery and radiotherapy, are recommended in patients with TNBC and single or a small number of potentially resectable brain metastases.[4]

ROLE OF NEXT-GENERATION SEQUENCING (NGS) IN FIRST-LINE TNBC AND FUTURE PERSPECTIVES

NGS is currently not reimbursed in first-line advanced TNBC, but can be considered on an individual basis to select patients for clinical trials or medical-need programs beyond first-line. Highly relevant is the opportunity of NGS testing in the context of prospective molecular programmes. In

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Both clinical and biological features are essential for the optimal clinical management of advanced TNBC, in particular:**
   - **Patient's performance status and preferences;**
   - **(Neo-)Adjuvant treatment received;**
   - **Disease-free interval;**
   - **Presence of bulky disease/visceral crisis;**
   - **PD-L1 expression;**
   - **Presence of germline *BRCA1/2* mutations.**

2. **Inclusion in clinical trials should be considered as first option whenever available.**

3. **Genetic counselling should be considered for all TNBC patients.**

4. **NGS is not reimbursed in Belgium in advanced TNBC. Its use in first-line can only be recommended in molecular screening programmes and in the context of clinical trials.**

this regard, several initiatives are currently ongoing in Belgium, including the AURORA study (NCT02102165), which is focused on patients with metastatic BC starting first- or second-line treatment and uses the OncoDEEP gene panel (OncoDNA, Belgium).[28]

Of interest, in Belgium the IPATUNITY trial (NCT03337724) is assessing the efficacy of the AKT inhibitor ipatasertib in advanced TNBC with alterations in *PIK3CA/AKT1/PTEN*, while the SYNERGY trial (NCT03616886) is evaluating the efficacy and safety of the combination of chemotherapy with immunotherapy (durvalumab +/- the anti-CD73 oleclumab) and includes a translational research programme aiming at understanding resistance mechanisms to immunotherapy.

Guidelines to facilitate the implementation of NGS technologies and to ensure quality control have been developed for Belgium by the Personalised Medicine Commission.[29] Inclusion in the ongoing BSMO Precision1 trial (NCT03873103) ensures insights of the local NGS testing. Matched treatments are shared in a national database to increase knowledge on the value of NGS in current real-world practice, and will give in the near future an opportunity to these patients to be enrolled in an upcoming BSMO trial where the FoundationOne® CDx (Foundation Medicine, US) panel will be offered with the aim to compare its role and the real-world practice in patients with advanced solid tumours.

For clinical trials available in Belgium, we invite the readers to visit *http://www.cancertrials.be/find-clinical-trials/,* a website supported by BSMO.

Of particular interest, antibody-drug conjugates (ADCs) have shown promising results in pre-treated metastatic TNBC patients, with sacituzumab govitecan-hziy, targeting the human trophoblast cell-surface antigen 2 (Trop-2), recently granted accelerated FDA approval after fast track designation based on the results of the phase I/II trial.[30] Full results from the confirmatory phase III ASCENT trial (NCT02574455), recently halted due to compelling efficacy, are awaited. Moreover, clinical trials combining sacituzumab govitecan-hziy with atezolizumab in first-line advanced TNBC (NCT03424005), with talazoparib in advanced TNBC (NCT04039230) and in early TNBC setting (NCT04230109) are planned or ongoing, while a phase III in pre-treated advanced ER+/HER2- breast cancer is currently recruiting (NCT03901339). Several anti-HER2 ADCs are currently under evaluation in HER2-low breast cancer, a disease entity that includes both luminal tumours and TNBC.[31] These compounds have the potential of representing new first-line therapeutic options in the near future.

CONCLUSION

The clinical management of first-line advanced TNBC should take into account clinical trial availability, as well as patient, disease characteristics and patient preferences. Outside clinical trials, PD-L1 testing is routinely recommended to guide first-line treatment in advanced TNBC. Of utmost importance, genetic counselling should be considered for all TNBC patients.

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