Cancer Treatment Reviews 111 (2022) 102468

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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

Multiple Bayesian network meta-analyses to establish therapeutic algorithms for metastatic triple negative breast cancer

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https://doi.org/10.1016/j.ctrv.2022.102468
Received 3 July 2022; Received in revised form 20 September 2022; Accepted 22 September 2022
Available online 28 September 2022

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ARTICLE INFO

Keywords:
Triple negative breast cancer
Bayesian network meta-analysis
Therapeutic algorithm
PD-L1
BRCA
PARP inhibitors
Immunotherapy
Sacituzumab govitecan
Trastuzumab deruxtecan
HER2-low
Pembrolizumab

ABSTRACT

Metastatic triple-negative breast cancer (mTNBC) is a poor prognostic disease with limited treatments and uncertain therapeutic algorithms. We performed a systematic review and multiple Bayesian network meta-analyses according to treatment line to establish an optimal therapeutic sequencing strategy for this lethal disease. We included 125 first-line trials (37,812 patients) and 33 s/further-lines trials (11,321 patients). The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall response rates (ORR), overall survival (OS) and safety, for first and further lines, separately. We also estimated separate treatment rankings for the first and subsequent lines according to each endpoint, based on (surface under the cumulative ranking curve) SUCRA values. No first-line treatment was associated with superior PFS and OS than paclitaxel ± bevacizumab. Platinum-based polychemotherapies were generally superior in terms of ORR, at the cost of higher toxicity.. PARP-inhibitors in germline-*BRCA*1/2-mutant patients, and immunotherapy + chemotherapy in PD-L1-positive mTNBC, performed similar to paclitaxel ± bevacizumab. In PD-L1-positive mTNBC, pembrolizumab + chemotherapy was better than atezolizumab + nab-paclitaxel in terms of OS according to SUCRA values. In second/further-lines, sacituzumab govitecan outperformed all other treatments on all endpoints, followed by PARP-inhibitors in germline-*BRCA*1/2-mutant tumors. Trastuzumab deruxtecan in HER2-low mTNBC performed similarly and was the best advanced-line treatment in terms of PFS and OS after sacituzumab govitecan, according to SUCRA values. Moreover, comparisons with sacituzumab govitecan, talazoparib and olaparib were not statistically significant. The most effective alternatives or candidates for subsequent lines were represented by nab-paclitaxel (in ORR), capecitabine (in PFS) and eribulin (in PFS and OS).

Introduction

Triple negative breast cancer (TNBC) represents approximately 10–15 % of all breast tumors and is defined by the absence of endocrine receptors (ER) and HER2 gene overexpression/amplification [1]. Metastatic TNBC (mTNBC) remains an incurable disease with unfavorable prognosis [2]. However, the scenario is quickly changing. 10.6–41.9 % TNBC harbor a germline mutation in the homologous recombination repair (HRR) genes *BRCA*1/2 [3]. In these cases, following positive results from respective pivotal trials, it is now possible to administer the PARP-inhibitors (PARPi) olaparib or talazoparib in first or further lines [4,5]. Additionally, the TNT phase III first-line trial recently demonstrated that carboplatin was more effective than the standard of care docetaxel in germline *BRCA*1/2-mutant (g*BRCA*-mut) mTNBC [1]. Intriguingly, in the same trial, in a broader condition of HRR deficiency (HRD), none of the 2 drugs was superior to the other [1]. Recently, two randomized phase III studies showed that PD-L1 positive (+) mTNBC (though selected with different methodologies) derive benefit from the addition of an anti-PD-L1/PD-1 immune-checkpoint inhibitor (ICI) to upfront chemotherapy (CT) [6,7]. However, the majority of mTNBC are PD-L1-negative (40–80 %) and germline *BRCA*1/2-wild type (g*BRCA*-wt) (60–90 %) [3,8,9], thus being only manageable with mono- or poly-CT, with the possibility (only in Europe) to use a first-line combination of bevacizumab with either paclitaxel or capecitabine [10,11].

Importantly, the novel anti-TROP2 antibody-drug conjugate (ADC) sacituzumab govitecan provided unprecedented overall response rates (ORR), progression-free survival (PFS) and overall survival (OS) benefit in heavily pretreated mTNBC [12,13], quickly leading to a US Food and Drug Administration (FDA) approval in this subset. Although preliminary, similar findings have been recently observed with the novel ADC trastuzumab deruxtecan (T-DXd) in the subset of TNBC with low expression levels of HER2 [14,15].

In this complex and changing scenario, uncertainties exist on whether and when to prefer single-agent over multi-agent treatments and most regimens have not undergone head-to-head comparisons. Also, the role of platinum-based regimens is unclear and therapeutic sequencies uncertain [11,16,17]. To date, only network meta-analyses (NMA) provides a methodologically reliable statistical framework to indirectly compare treatments that have never been confronted in head-to-head studies, given that such therapies have been compared to at least one common comparator [18,19]. NMA also allows to determine the amount of agreement between the results obtained when different linking treatments are used; it can incorporate results from direct comparisons, to account for both direct and indirect evidences at the same time, and it can provide a rank ordering of the interventions [18,19].

Therefore, we conducted a systematic literature search to identify all phase II/III randomized controlled trials (RCT) published in the last 20 years comparing all CT and target therapies (TT) in metastatic HER2-negative breast cancer (BC) and carried out multiple Bayesian NMA to define the best therapeutic options for mTNBC according to treatment line.

Methods

Search strategy and selection criteria

We performed a systematic literature search on Pubmed® and CENTRAL to identify all phase II/III RCT published between 01/01/2000 and 30/06/2020 comparing all CT and TT in metastatic HER2-negative BC. The time span was selected to both retrieve studies more uniformly conceived and presented, and include all currently available and most promising therapeutic options. The full search query is reported in the Supplementary Methods. Articles relevant to the topic published between July 2020 and June 2022 were manually included in the networks before conducting final analyses. Online archives of the San Antonio Breast Cancer Symposium, European Society for Medical Oncology (ESMO)'s Congress, ESMO Breast Congress and American Society of Clinical Oncology (ASCO)'s Annual Meeting were also consulted. No language restrictions were adopted. Records had to be preferably full papers, however, for each trial where only an abstract was available and results were adequately provided, the study was included in our analyses. In case of more publications for the same study, the most

[1] co-first authors for equal contribution.

updated one was considered. Two independent reviewers (FS and MG) carried out the systematic revision of the literature and a third one (DG) was consulted in case of controversy. Some cross-references from main international guidelines were also included.

Endpoints

We aimed at identifying the best therapeutic option for the first-line and second/further (advanced) lines, separately, according to efficacy/activity and safety. PFS was the primary endpoint whereas ORR, OS and safety were secondary endpoints.

Data extraction

To be included, a publication had to provide at least the data for one of the three endpoints of this study (detailed response rates and/or hazard ratios [HR] of PFS and/or OS). In case HR for Time-to-Progression (TTP) instead of PFS were provided, TTP was considered for the analysis. TTP and PFS are very similar endpoints, which have been frequently mixed-up in other previously published NMA [20–22]. The HR and associated 95 % confidence intervals (CI) for OS and PFS/TTP were extracted from each paper. The number of patients achieving a partial or complete response as their best response according to treatment arm were extracted to calculate the ORR.

Data concerning the following variables were also extracted from all the studies: full publication reference, publication year, line of treatment, phase of the trial, investigated treatments, single center vs multicenter studies, follow-up period (months), total number of patients, proportion of patients with ER + BC, median age, age range, proportion of patients with PD-L1+, g*BRCA*-mut and altered PI3K/PTEN pathway, as well as proportion of visceral, lung, liver and bone metastases, and main grade (G)3–5 adverse events (AEs).

Several adjustments regarding data extraction need to be disclosed. Firstly, when a study set in first and further lines presented with a result for the entire population enrolled and separate results for the first line and for the following, results according to treatment lines were extracted. Secondly, three trials specifically enrolled patients with g*BRCA*-mut tumors [4,5,23]. Therefore, our results concerning the therapeutic agents administered within these studies have to be intended only for the specific subgroup of g*BRCA*-mut TNBC. Third, the same three studies presented separate aggregate data for TNBC and ER + tumors, although such results were not provided according to treatment line. To better estimate the therapeutic efficacy in the first and subsequent lines, we preferred to include results according to treatment line, although a proportion of ER + BC was comprised in these estimates. Fourth, the studies of pembrolizumab and atezolizumab included both patients with and without PD-L1+ tumors [7,24–26]. Considering that such drugs have been FDA and/or European Medicine Agency (EMA)-approved only in mTNBC with a PD-L1 combined positive score (CPS) $\geq$ 10 % or PD-L1 levels $\geq$ 1 % according to the Ventana SP142 assay, respectively, only results for these subpopulations have been included. As a consequence, our results concerning the therapeutic agents administered within these studies have to be intended only for the specific subgroup of PD-L1+ mTNBC, with PD-L1 positivity defined according to the relative trials' assays. Finally, AKT-inhibitors ipatasertib in Kim et al. 2017 and capivasertib in Schmid et al. 2019 were tested in TNBC with and without alterations in PIK3CA, AKT1 or PTEN, whilst the former was tested in Dent et al. 2021 only in *PIK3CA/PTEN/AKT*-altered mTNBC [27–29]. For ipatasertib, which failed to prove a significant benefit transferrable to the clinical practice, the results for the intention-to-treat (ITT) trials' population were included. Conversely, capivasertib was included for the obtained results in the *PIK3CA/PTEN/AKT*-altered population, a subset with a potential approval; although results from the phase III trial are required to draw definitive conclusions. Finally, in order to include some trials in the networks, some links had to be forced. More specifically, the capecitabine-containing treatment of physician's choice (TPC) arms from Litton et al. and Robson et al. were linked to the capecitabine arm of Harbeck et al. to include olaparib and talazoparib in the first-line networks [4,5,30]. The CT arm of Cortes et al., which included also paclitaxel, and the taxane-containing arm of Takashima et al. were linked to weekly paclitaxel and the CT arm of Von Minckwitz et al. was considered as a TPC arm, allowing its inclusion in the second/further-lines networks [25,31,32]. Additionally, TPC arms did not differ too much among different trials, therefore they were always linked together, whenever possible.

Data analysis

A Bayesian NMA framework was used for each endpoint and for each treatment line for a total of 6 networks, i.e. first-line and advanced lines networks of PFS/TTP, ORR and OS, respectively [18,19,33].

We also provided a ranking of treatments based on the surface under the cumulative ranking curve (SUCRA). The SUCRA values range from 0 to 100 %. The higher the SUCRA value, and the closer to 100 %, the higher the likelihood that a therapy is in the top rank; the closer to 0 the SUCRA value, the more likely that a therapy is in the bottom rank [34].

The parameters of the different models (HR of PFS/TTP and OS with 95 % credible intervals [CrI] and OR for ORR with 95 %CrI) were estimated using a Markov Chain Monte Carlo method as implemented in the WinBUGS software package [33]. For all the analyses, the WinBUGS sampler, using three chains, was run for 1,000,000 iterations that were discarded as 'burn-in', and the model was run for a further 2,000,000 iterations on which inferences were based. A thinning rate of 100 iterations was used to reduce autocorrelation of the sampled values, thus leaving 20,000 iterations per chain to use for estimation and inference. Convergence of the chains was confirmed by the Gelman-Rubin statistic and by inspection of the trace plots [35,36]. For each NMA, the model providing the best fit to the data between random- and fixed-effect was chosen based on the Deviance Information Criterion (DIC). The DIC provides a measure of model fit that penalizes model complexity. The model with the lowest DIC was considered the model providing the best fit to the data, otherwise, wherever DIC values were similar (difference of < 5) a fixed-effect model was preferred [33]. For the NMA of the HR, we assumed that the logHR were normally distributed with the logHR mean equaling the true logHR observed in each study and the variance equaling the observed variability in each study.

We used a vague flat (i.e., uniform) prior distribution for between-study standard deviation τ. Moreover, as for the correlations between the random effects for each trial, we adopted the standard approach to set this correlation equal to 0.5 [37]. We used a common between-study variance parameter τ^2 for all studies.

The PRISMA guidelines for NMA were followed [38]. Inconsistency of the results was explored, as recommended [38–40]. For all treatment line networks according to each endpoint, an inconsistency model was obtained by omitting the consistency equations. Then, for each endpoint, the consistency and inconsistency models were compared in terms of goodness of fit by using their relative DIC [39,40]. A difference of less than 5 points was considered to be not significant.

All the analyses were performed with WinBUGS version 1.4.3 and the results were processed using R version 4.2.0 [33,41]. All the equations adopted had been published elsewhere and adapted for our analyses [37]. Internal validity of eligible studies was assessed with Review Manager version 5.4 according to the Cochrane guidelines [42].

The study protocol was registered on PROSPERO (ID: CRD42020211971).

Results

Overall, 139 studies were included in our networks for a total of 118 different therapeutic regimens for the first-line and 33 for the following lines (all references in Supplementary Methods). The study selection process is summarized in Supplementary Fig. 1. First-line networks

included 125 RCT whilst advanced-line networks included 33 RCT (Supplementary Tables 1–2 and Supplementary Figs. 2–7). The first-line PFS, OS and ORR networks were based on trial-level data deriving from 31,203, 22,848 and 36,015 patients, respectively. Advanced-line PFS, OS and ORR networks were based on trial-level data deriving from 7,185, 6,467 and 11,321 patients, respectively. Eighteen (56.2 %) advanced-line studies included a proportion of first-line patients and were also incorporated in first-line networks. Ninety-two (73.6 %) first-line studies also included ER + metastatic BC (MBC) (minimum–maximum [min–max] range of ER + MBC patients in the included studies: 14 % – 91 %). Twenty-one (63.6 %) advanced-line studies involved ER + MBC (min–max range: 26.1 % – 83.3 %), as well. Considering all included studies, the median proportion of patients with ER + MBC *per* treatment arm was 59.5 % (interquartile range [IQR] of 35.3 % – 74.0 %) and endocrine therapy (ET) for the metastatic disease had been administered before study treatments in 37 % of the cases in at least a proportion of patients *per* treatment arm. Four (2.9 %) trials explicitly included a proportion of PD-L1+ tumors [6,7,26,43], 5 (3.6 %) trials included, exclusively or in part, g*BRCA*-mut MBC [1,4,5,13,23], and 3 (2.2 %) trials included patients with *PIK3CA/PTEN/AKT*-altered tumors [27–29]. Overall, 49 (35.3 %) studies evaluated TT, with or without CT while the remaining 91 (64.7 %) only compared different CT regimens or schedules. Study characteristics are extensively reported in Supplementary Tables 1–2.

To graphically visualize the results, paclitaxel + bevacizumab was chosen as the reference treatment for the first-line, being a potentially good compromise between mono-CT and poly-CT, while capecitabine was the reference for the advanced lines, as in numerous RCT.

Inconsistency and consistency models' DIC for each network are reported in the Supplementary Methods. A marginally significant inconsistency was observed only for the first-line ORR network (a difference between the DIC of consistency and inconsistency models of 6.49).

First-line networks

A total of 92 different regimens were compared for PFS/TTP. None was deemed to be significantly superior to paclitaxel + bevacizumab, including poly-CT regimens such as anthracycline/taxane combinations or other anthracycline-based regimens and taxanes + platinum agents (Fig. 1). At the same time, paclitaxel + bevacizumab was not likely to be superior to any first-line mono-CT, such as weekly paclitaxel, pegylated

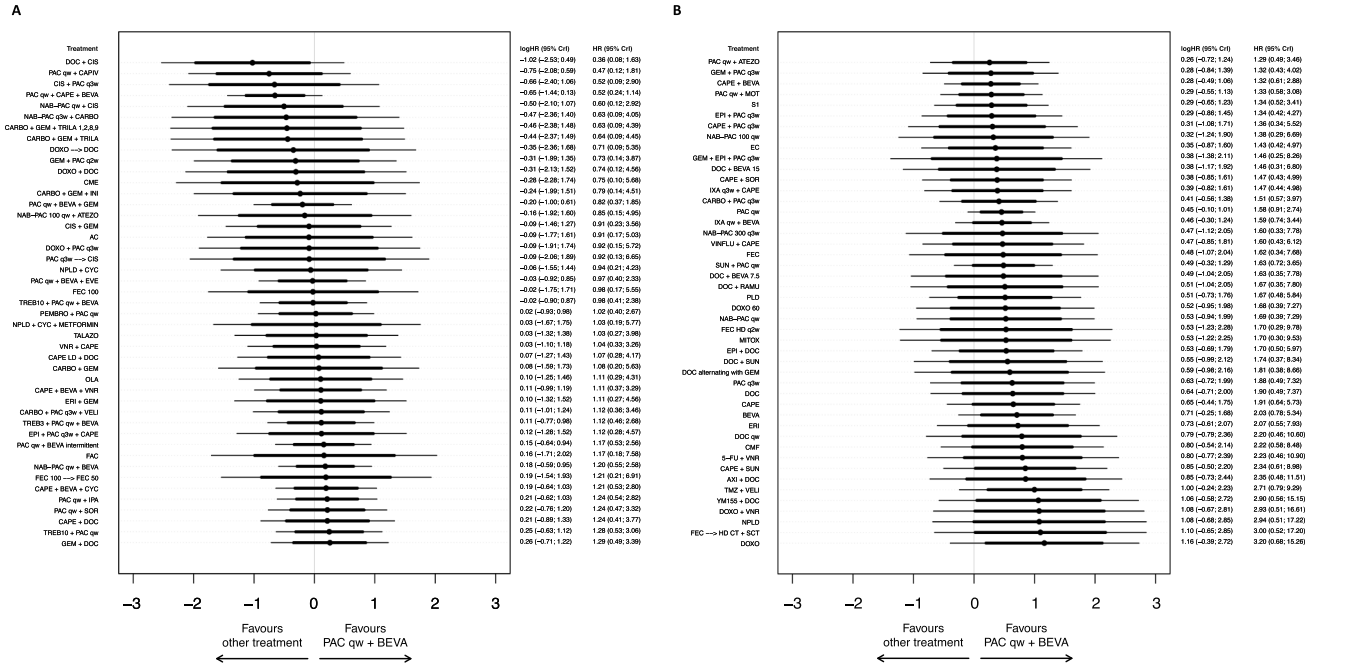

Fig. 1. Forest plot of all first-line regimens compared to paclitaxel + bevacizumab in terms of PFS/TTP. The figure has been split in two panels (A and B) to improve its readability. The forest plot includes the log hazard ratios (HR) of each treatment *versus* paclitaxel + bevacizumab. Central dots represent posterior medians; thin lines represent 95 % credible intervals (CrI), while thicker ones represent 80 % CrI. Log scale was adopted to graphically represent the 95 % CrI. The first column of values on the right reports the log HR with 95 % CrI, the second column reports HR with 95 % CrI. Statistically significant results according to Bayesian posterior medians and 95 % credible intervals are highlighted by asterisks. 5-FU: 5-fluorouracil; AC: doxorubicin + cyclophosphamide; ATEZO: atezolizumab; AXI: axitinib; BEVA: bevacizumab 10 mg/kg IV q2w; BEVA 7.5: bevacizumab 7.5 mg/kg IV q3w; BEVA 15: bevacizumab 15 mg/kg IV q3w; BMF: bendamustine + methotrexate + 5-FU; CAPE: capecitabine; CAPE LD: capecitabine low dose/metronomic; CAPI: capivasertib; CYC: cyclophosphamide; CARBO: carboplatin; CIS: cisplatin; CME: cyclophosphamide + mitoxantrone + etoposide; CMF: cyclophosphamide + methotrexate + 5-FU; CT: chemotherapy; DOC: docetaxel; DOXO: doxorubicin 75 mg/m^2 q3w; DOXO 60: doxorubicin 60 mg/m^2 q3w; EC: epirubicin + cyclophosphamide; EPI: epirubicin; ERI: eribulin; EVE: everolimus; FAC: 5-FU + doxorubicin + cyclophosphamide; FEC: 5-FU + epirubicin 75 mg/m^2 + cyclophosphamide q3w; FEC 100: 5-FU + epirubicin 100 mg/m^2 + cyclophosphamide q3w; FEC 50: 5-FU + epirubicin 50 mg/m^2 + cyclophosphamide q3w; *GEM*: gemcitabine; INI: iniparib; IPA: ipatasertib; IXA: ixabepilone; LONI: lonidamine; MITO C: mitomycin C; MITOX: mitoxantrone; MMM: mitoxantrone + mitomycin C + methotrexate; MOT: motesanib; NAB-PAC: nab-paclitaxel 260/300 mg/m2 q3w; NAB-PAC 100 qw: nab-paclitaxel 100 mg/m2 q3/4w; NAB-PAC qw: nab-paclitaxel 125/130/150 mg/m^2 q3/4w; NPLD: non-pegylated liposomal doxorubicin; OLA: olaparib; PAC within schedules and PAC q3w: paclitaxel 175 mg/m^2 q3w; PAC 210: paclitaxel 210 mg/m^2 q3w; PAC 250: paclitaxel 250 mg/m^2 q3w; PAC qw: paclitaxel 80/90 mg/m^2 q3/4w; PEMBRO: pembrolizumab; PEMBRO + CT: pembrolizumab + nab-paclitaxel/paclitaxel/carboplatin + gemcitabine; PLD: pegylated liposomal doxorubicin 50 mg/m^2 IV q4w; PLD 40 mg: peghylated liposomal doxorubicin 40 mg/m^2 IV q4w; PLD 60 mg: pegylated liposomal doxorubicin 60 mg/m^2 IV q4w; RAMU: ramucirumab; SCT: stem cell transplant; SOR: sorafenib; SUN: sunitinib; TALAZO: talazoparib; TMZ: temozolomide; TREB3: trebananib 3 mg/kg qw; TREB10: trebananib 10 mg/kg qw; TRILA: trilaciclib 240 mg/m^2 d1,8 IV q3w; TRILA 1,2,8,9: Trilaciclib 240 mg/m^2 d1,2,8,9 IV q3w; VELI: veliparib; VINFLU: vinflunine; VNR: vinorelbine; IV: intravenous; d: day; qw: weekly schedule; q2w: biweekly schedule; q3w: threeweekly schedule; q3/4w: 3 weeks out of 4 schedule; q4w: every-4-weeks schedule; →: followed by; DD: dose dense; HD: high dose; TI: time intensive; *: statistically significant results.

liposomal doxorubicin (PLD) or nab-paclitaxel (Fig. 1). Sixty-four regimens included in the PFS/TTP analysis were also comparable in terms of OS with consistent results (Fig. 2). In contrast, when compared to other 117 regimens, paclitaxel + bevacizumab was likely to be significantly associated with superior ORR than several poly-CT regimens like cyclophosphamide + methotrexate + 5-fluorouracil (CMF) (odds ratio [OR]: 6.57, 95 % credible intervals [CrI]: 2.05–21.63), FEC (OR: 4.44, 95 %CrI: 1.33–15.23), ixabepilone + capecitabine (OR: 3.45, 95 %CrI: 1.02–12.03) or capecitabine + bevacizumab (OR: 2.47, 95 %CrI: 1.08–5.73) (Supplementary Fig. 8). The reference regimen was associated with lower ORR only when compared to docetaxel + cisplatin (OR: 0.13, 95 %CrI: 0.02–0.82). Additionally, paclitaxel + bevacizumab was likely to be significantly superior to several mono-CT, like PLD (OR: 6.89, 95 %CrI: 1.30–36.67) or capecitabine (OR: 5.47, 95 %CrI: 1.89–16.17) (Supplementary Fig. 8).

Notably, similar results were observed with weekly paclitaxel, as well as with atezolizumab + nab-paclitaxel or pembrolizumab + CT in PD-L1+ TNBC, and with olaparib or talazoparib in g*BRCA*-mut TNBC (data not shown). Direct comparisons based on indirect evidence of atezolizumab + nab-paclitaxel vs pembrolizumab + CT or talazoparib vs olaparib did not show significant differences, respectively (Supplementary Table 3).

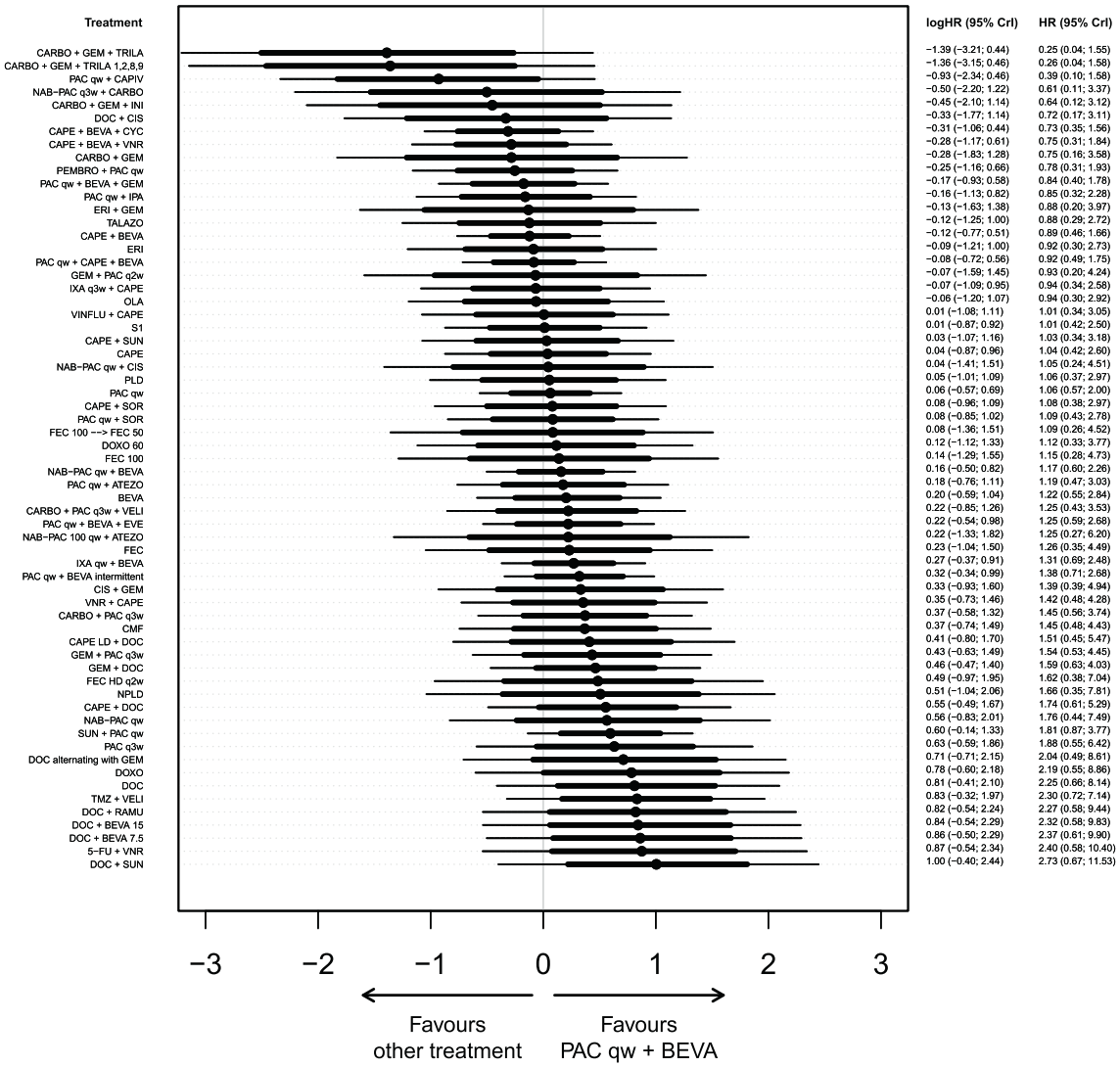

Fig. 2. Forest plot of all first-line regimens compared to paclitaxel + bevacizumab in terms of OS. The forest plot includes the log hazard ratios (HR) of each treatment *versus* paclitaxel + bevacizumab. Central dots represent posterior medians; thin lines represent 95 % credible intervals (CrI), while thicker ones represent 80 % CrI. Log scale was adopted to graphically represent the 95 % credible intervals. The first column of values on the right reports the log HR with 95 % credible intervals, the second column reports HR with 95 % credible intervals. Statistically significant results according to Bayesian posterior medians and 95 % credible intervals are highlighted by asterisks. 5-FU: 5-fluorouracil; ATEZO: atezolizumab; BEVA: bevacizumab 10 mg/kg IV q2w; BEVA 7.5: bevacizumab 7.5 mg/kg IV q3w; BEVA 15: bevacizumab 15 mg/kg IV q3w; CAPE: capecitabine; CAPE LD: capecitabine low dose/metronomic; CAPI: capivasertib; CYC: cyclophosphamide; CARBO: carboplatin; CIS: cisplatin; CMF: cyclophosphamide + methotrexate + 5-FU; DOC: docetaxel; DOXO: doxorubicin 75 mg/m^2 q3w; DOXO 60: doxorubicin 60 mg/m^2 q3w; ERI: eribulin; EVE: everolimus; FEC: 5-FU + epirubicin 75 mg/m^2 + cyclophosphamide q3w; FEC 100: 5-FU + epirubicin 100 mg/m^2 + cyclophosphamide q3w; FEC 50: 5-FU + epirubicin 50 mg/m^2 + cyclophosphamide q3w; GEM: gemcitabine; INI: iniparib; IPA: ipatasertib; IXA: ixabepilone; NAB-PAC: nab-paclitaxel 260/300 mg/m2 q3w; NAB-PAC 100 qw: nab-paclitaxel 100 mg/m2 q3/4w; NAB-PAC qw: nab-paclitaxel 125/130/150 mg/m^2 q3/4w; NPLD: non-peghylated liposomal doxorubicin; OLA: olaparib; PAC within schedules and PAC q3w: paclitaxel 175 mg/m^2 q3w; PAC qw: paclitaxel 80/90 mg/m^2 q3/4w; PLD: peghylated liposomal doxorubicin 50 mg/m^2 q4w; SOR: sorafenib; SUN: sunitinib; TALAZO: talazoparib; TMZ: temozolomide; TRILA: Trilaciclib 240 mg/m^2 d1,8 IV q3w; TRILA 1,2,8,9: Trilaciclib 240 mg/m^2 d1,2,8,9 IV q3w; VELI: veliparib; VINFLU: vinflunine; VNR: vinorelbine; qw: weekly schedule; q2w: biweekly schedule; q3w: threeweekly schedule; q3/4w: 3 weeks out of 4 schedule; q4w: every-4-weeks schedule; →: followed by; DD: dose dense; HD: high dose.

Advanced lines networks

Seventeen regimens entered the advanced-line network of PFS/TTP. Compared to capecitabine, sacituzumab govitecan (HR: 0.51, 95 %CrI: 0.36–0.72), ixabepilone + capecitabine (HR: 0.75, 95 %CrI: 0.64–0.88), and talazoparib (HR: 0.67, 95 %CrI: 0.46–0.97) were likely to be superior. Conversely, commonly used alternatives like eribulin and vinorelbine, or olaparib in g*BRCA*-mut tumors, showed comparable results (Fig. 3). T-DXd in HER2-low TNBC showed a numerically similar result to sacituzumab govitecan, although not significant (Fig. 3).

Fifteen of the 16 previous regimens entered the network of OS. Only sacituzumab govitecan was significantly superior to capecitabine (HR: 0.52, 95 %CrI: 0.38–0.72) (Fig. 4).

When considering ORR, 33 treatments were comparable. Among clinically relevant regimens, only sacituzumab govitecan (OR: 3.34, 95 %CrI: 1.16–9.45) and ixabepilone + capecitabine (OR: 3.19, 95 %CrI: 2.24–4.61) were associated with better ORR than capecitabine (Supplementary Fig. 9). Importantly, sacituzumab govitecan showed the best survival results, being significantly superior to many common therapies, including eribulin and ixabepilone + capecitabine (in PFS and OS), vinorelbine (in PFS), pembrolizumab in PD-L1+ mTNBC (in PFS and OS), olaparib and talazoparib in g*BRCA*-mut tumors (in OS) (not shown). No significant difference was observed in PFS/TTP and OS between sacituzumab govitecan and T-DXd in HER2-low tumors, as well as between olaparib and talazoparib in gBRCA-mut patients (Supplementary Table 3).

Treatment rankings based on SUCRA and safety

We estimated separate rankings for the first and subsequent lines based on SUCRA values (Supplementary Figs. 10–11). For practical purposes, we refined the rankings by including only the currently US National Comprehensive Cancer Network (NCCN)-recommended [10] and/or FDA/EMA-approved treatments, as of June 2022 (Table 1). Nevertheless, the ranking includes also T-DXd, which is likely to be approved in the near future for HER2-low TNBC.

A formal comparison of toxicities could not be carried out due to the heterogeneity of reporting side effects across trials. However, we

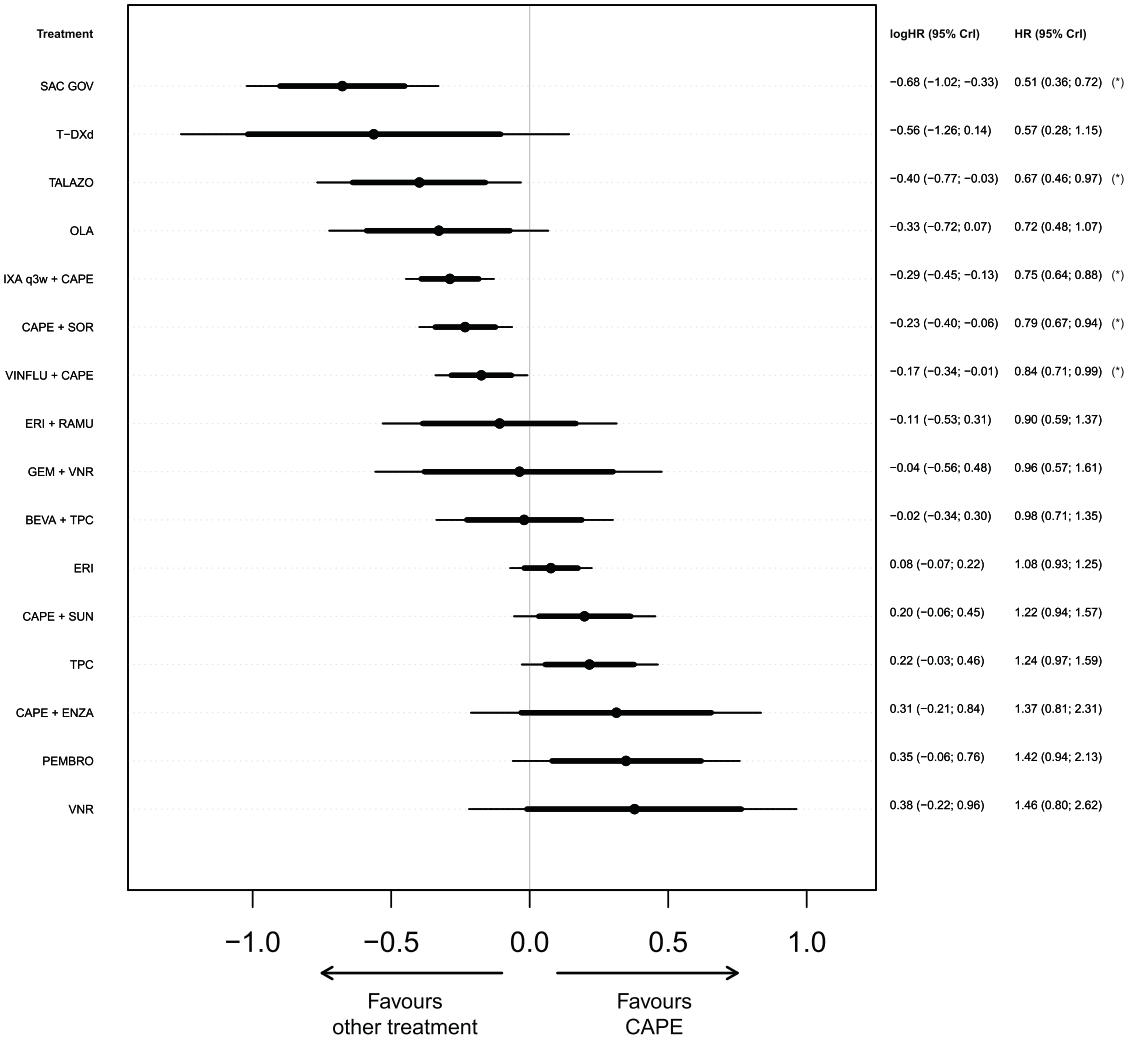

Fig. 3. Forest plot of all advanced lines regimens compared to capecitabine in terms of PFS/TTP. The forest plot includes the log hazard ratios (HR) of each treatment *versus* capecitabine. Central dots represent posterior medians; thin lines represent 95 % credible intervals (CrI), while thicker ones represent 80 % CrI. Log scale was adopted to graphically represent the 95 % CrI. The first column of values on the right reports the log HR with 95 % CrI, the second column reports HR with 95 % CrI. Statistically significant results according to Bayesian posterior medians and 95 % credible intervals are highlighted by asterisks. BEVA: bevacizumab 10 mg/kg q2w; CAPE: capecitabine; ENZA: enzastaurin; ERI: eribulin; *GEM*: gemcitabine; IXA: ixabepilone; OLA: olaparib; PEMBRO: pembrolizumab; RAMU: ramucirumab; T-DXd: trastuzumab deruxtecan; SAC GOV: sacituzumab govitecan; SOR: sorafenib; SUN: sunitinib; TALAZO: talazoparib; TPC: treatment of physician's choice (mostly CAPE, ERI, or VNR); VINFLU: vinflunine; VNR: vinorelbine; qw: weekly schedule; q2w: biweekly schedule; q3w: three weekly schedule; *: statistically significant results.

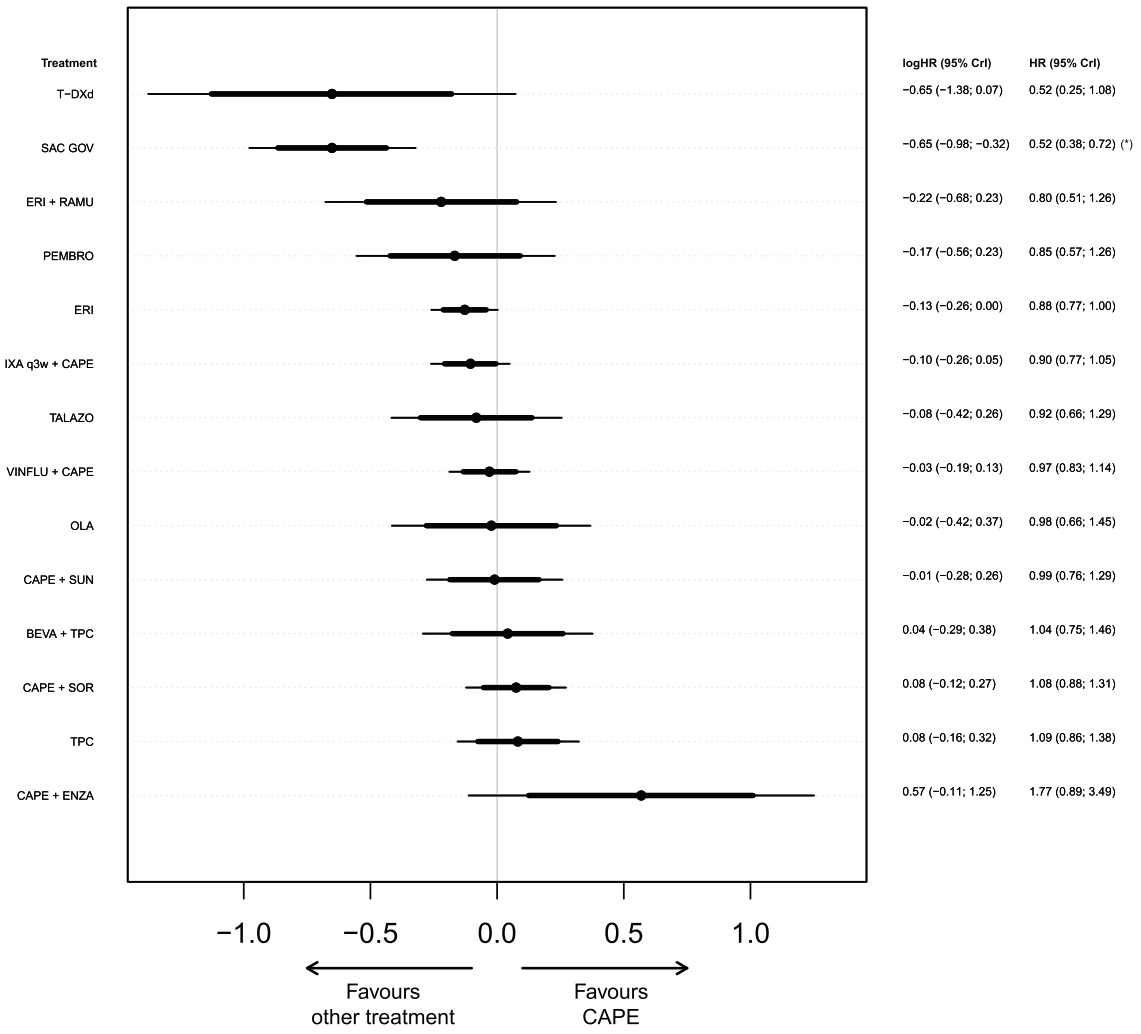

Fig. 4. Forest plot of all second/further-lines regimens compared to capecitabine in terms of OS. The forest plot includes the log hazard ratios (HR) of each treatment *versus* capecitabine. Central dots represent posterior medians; thin lines represent 95 % credible intervals (CrI), while thicker ones represent 80 % CrI. Log scale was adopted to graphically represent the 95 % credible intervals. The first column of values on the right reports the log HR with 95 % credible intervals, the second column reports HR with 95 % credible intervals. Statistically significant results according to Bayesian posterior medians and 95 % credible intervals are highlighted by asterisks. BEVA: bevacizumab 10 mg/kg q2w; CAPE: capecitabine; ENZA: enzastaurin; ERI: eribulin; IXA: ixabepilone; OLA: olaparib; PEMBRO: pembrolizumab; RAMU: ramucirumab; SAC GOV: sacituzumab govitecan; SOR: sorafenib; SUN: sunitinib; TALAZO: talazoparib; TPC: treatment of physician's choice (mostly CAPE, ERI, or VNR); VINFLU: vinflunine; VNR: vinorelbine; qw: weekly schedule; q2w: biweekly schedule; q3w: threeweekly schedule; *: statistically significant result.

extensively described the proportion of G3-5 AEs observed for each regimen in $\geq$ 2 % of study patients (Supplementary Tables 4–5). As expected, combination CT presented with the highest proportion of moderate/severe AEs. Neverthless, G3-5 neutropenia and leucopenia were relatively frequent also with mono-CT. Doxorubicin, docetaxel, vinorelbine, paclitaxel and gemcitabine were associated with the highest rates of severe alopecia, as like capecitabine with hand-foot syndrome and doxorubicin with stomatitis and febrile neutropenia. Anthracycline-based regimens, excluding pegylated and non-pegylated liposomal doxorubicin, were typically associated with cardiotoxicity. Bevacizumab-containing regimens typically showed proteinuria and hypertension. Although ICI-based combinations (pembrolizumab + CT and atezolizumab + nab-paclitaxel) are usually associated with immune-related AEs, including thyroiditis, pneumonitis, skin alterations and colitis, G3-5 rates of such toxicities were not observed, except for pneumonitis, hypo/hyperthyroidism and skin reactions (all $<$ 2 %). PARPi were characterized by an overall better toxicity profile than mono-CT, except for partially comparable hematologic toxicities. Finally, sacituzumab govitecan and *T*-DXd presented with a chemo-like toxicity profile, with diarrhea, nausea/vomiting, hematotoxicity and fatigue as most frequent moderate/severe AEs. Both drugs can frequently induce alopecia (46.0 % and 37.7 %) and *T*-DXd was associated with interstitial lung disease/pneumonitis ($<$20 % cases), although the vast majority of cases was mild or moderate [13,15].

Risk of bias analysis

Internal validity of eligible studies was assessed with a risk of bias (RoB) analysis as recommended by the Cochrane Handbook for Systematic Reviews of Interventions [42]. There were no specific concerns regarding 5/9 RoB domains (Supplementary Fig. 12). However, the RoB was high in approximately half trials included with respect to blinding of participants and personnel and outcome assessments, as well as regarding the selective reporting bias (Supplementary Figs. 12–13).

Discussion

We performed multiple Bayesian NMA to identify the best treatment for the first and subsequent lines of mTNBC, in terms of PFS/TTP, OS and ORR. We found that among the most commonly adopted first-line regimens, there were no substantial differences in terms of PFS/TTP and OS whereas paclitaxel + bevacizumab was associated with better ORR than

Table 1
Ranking of available regimens according to treatment line.

FIRST-LINE								
Treatment	SUCRA	PFS/TTP Ranking	Treatment	SUCRA	OS Ranking	Treatment	SUCRA	ORR Ranking
DOC + CIS	0.9135	1	NAB-PAC q3w + CARBO	0.7660	1	DOC + CIS	0.9800	1
CIS + PAC q3w	0.8174	2	PEMBRO + CT	0.7355	2	CIS + PAC q3w	0.8896	2
NAB-PAC q3w + CARBO	0.7537	3	DOC + CIS	0.7268	3	NAB-PAC qw + ATEZO	0.7326	3
DOXO + DOC	0.7147	4	CARBO + *GEM*	0.6948	4	PAC qw + BEVA	0.6980	4
NAB-PAC qw + ATEZO	0.6696	5	CAPE + BEVA	0.6797	5	GEM + DOC	0.6893	5
CIS + GEM	0.6535	6	TALAZO	0.6638	6	NAB-PAC q3w + CARBO	0.6833	6
PAC qw + BEVA	0.6430	7	ERI	0.6455	7	PAC qw	0.6802	7
NPLD + CYC	0.6369	8	IXA q3w + CAPE	0.6369	8	CAPE + PAC q3w	0.6779	8
AC	0.6365	9	OLA	0.6259	9	DOXO + DOC	0.6198	9
DOXO + PAC q3w	0.6291	10	PAC qw + BEVA	0.6060	10	*EPI* + PAC q3w	0.6126	10
FEC 100	0.6184	11	S1	0.5940	11	CAPE + DOC	0.5936	11
VNR + CAPE	0.6158	12	PAC qw	0.5683	12	OLA	0.5766	12
PEMBRO + CT	0.6132	13	CAPE	0.5649	13	NAB-PAC q3w	0.5722	13
TALAZO	0.6080	14	PLD	0.5567	14	DOXO + PAC q3w	0.5632	14
CAPE + DOC	0.5907	15	DOXO 60	0.5165	15	NAB-PAC qw	0.5455	15
OLA	0.5764	16	FEC 100	0.5089	16	CARBO + PAC q3w	0.5453	16
CARBO + *GEM*	0.5613	17	NAB-PAC 100 qw + ATEZO	0.4895	17	GEM + PAC q3w	0.5258	17
FAC	0.5250	18	FEC	0.4522	18	TALAZO	0.5214	18
GEM + DOC	0.4998	19	CIS + GEM	0.4145	19	NPLD + CYC	0.5189	19
CAPE + BEVA	0.4942	20	VNR + CAPE	0.4068	20	VNR + CAPE	0.5110	20
GEM + PAC q3w	0.4853	21	CARBO + PAC q3w	0.3852	21	EPI + DOC	0.5087	21
EPI + PAC q3w	0.4785	22	CAPE LD + DOC	0.3815	22	AC	0.4845	22
NAB-PAC qw	0.4760	23	CMF	0.3641	23	EC	0.4255	23
CAPE + PAC q3w	0.4755	24	GEM + PAC q3w	0.3563	24	DOXO	0.4250	24
IXA q3w + CAPE	0.4472	25	NPLD	0.3419	25	DOC	0.4065	25
EC	0.4437	26	GEM + DOC	0.3327	26	NAB-PAC q3w	0.4048	26
CARBO + PAC q3w	0.4124	27	NAB-PAC qw	0.3120	27	VNR + GEM	0.3835	27
FEC	0.4094	28	CAPE + DOC	0.2896	28	CARBO	0.3770	28
NAB-PAC q3w	0.4074	29	PAC q3w	0.2578	29	CAPE + BEVA	0.3593	29
DOXO	0.3914	30	DOC	0.1806	30	FAC	0.3499	30
PLD	0.3855	31	–	–	–	CARBO + GEM	0.3327	31
PAC qw	0.3837	32	–	–	–	CIS + GEM	0.3052	32
EPI + DOC	0.3569	33	–	–	–	FEC 100	0.2981	33
PAC q3w	0.3247	34	–	–	–	PAC q3w	0.2787	34
DOC	0.3134	35	–	–	–	IXA + CAPE	0.2696	35
CAPE	0.3124	36	–	–	–	VNR	0.2479	36
CMF	0.2661	37	–	–	–	PLD	0.1979	37
–	–	–	–	–	–	FEC	0.1880	38
–	–	–	–	–	–	CAPE	0.1420	39
–	–	–	–	–	–	CMF	0.1070	40

SECOND/FURTHER LINES								
Treatment	SUCRA	PFS/TTP Ranking	Treatment	SUCRA	OS Ranking	Treatment	SUCRA	ORR Ranking
SAC GOV	0.965	1	SAC GOV	0.9595	1	CAPE + DOC	0.8082	1
T-DXd*	0.8581	2	T-DXd*	0.9110	2	NAB-PAC q3w	0.7993	2
TALAZO	0.8158	3	ERI	0.6487	3	IXA q3w + CAPE	0.7518	3
OLA	0.7555	4	PEMBRO	0.6443	4	SAC GOV	0.7504	4
IXA q3w + CAPE	0.7481	5	IXA q3w + CAPE	0.5962	5	PAC qw	0.7151	5
GEM + VNR	0.4781	6	TALAZO	0.5361	6	CAPE LD + DOC	0.7088	6
CAPE	0.4263	7	OLA	0.4366	7	DOC	0.6328	7
ERI	0.3281	8	CAPE	0.3711	8	T-DXd*	0.5516	8
VNR	0.1346	9	–	–	–	GEM + DOC	0.5359	9
PEMBRO	0.1152	10	–	–	–	GEM + VNR	0.5038	10
–	–	–	–	–	–	PAC q3w	0.4709	11
–	–	–	–	–	–	OLA	0.4519	12
–	–	–	–	–	–	DOC	0.4167	13
–	–	–	–	–	–	CAPE + SUN	0.4060	14
–	–	–	–	–	–	TALAZO	0.3862	15
–	–	–	–	–	–	CAPE	0.3704	16
–	–	–	–	–	–	ERI	0.3532	17
–	–	–	–	–	–	VNR	0.3251	18
–	–	–	–	–	–	PEMBRO	0.2539	19

CMF: cyclophosphamide + methotrexate + 5-FU; 5-FU: 5-fluorouracil; BEVA: bevacizumab; ATEZO: atezolizumab; EPI: epirubicin; FEC: 5-FU + epirubicin + cyclophosphamide; FAC: 5-FU + doxorubicin + cyclophosphamide; DOXO: doxorubicin; DOC: docetaxel; PAC: paclitaxel; PLD: pegylated liposomal doxorubicin; NPLD: non-pegylated liposomal doxorubicin; CYC: cyclophosphamide; TALAZO: talazoparib; OLA: olaparib; IXA: ixabepilone; CAPE: capecitabine; GEM: gemcitabine; VNR: vinorelbine; ERI: eribulin; PEMBRO: pembrolizumab; NAB-PAC: nab-paclitaxel; CT: chemotherapy; CIS: cisplatin; CARBO: carboplatin; AC: doxorubicin + cyclophosphamide; EC: epirubicin + cyclophosphamide; SAC GOV: sacituzumab govitecan; ERI: eribulin; T-DXd: trastuzumab deruxtecan; LD: low dose; q3w: three weekly schedule; qw: weekly schedule; *: although still not approved, T-DXd is the new standard of care for HER2-low breast cancer and might enter quickly the therapeutic armamentarium also for this subset of triple negative tumors.

numerous mono-CT and several poly-CT, with less G3-5 AEs compared to CT combinations. Docetaxel + cisplatin was the only regimen significantly favored in terms of ORR, at the cost of higher toxicities (Figs. 1-2, Supplementary Fig. 8, Table 1, Supplementary Tables 4–5). These results, taken together with the available evidence, despite conflicting results on its potential OS benefit [20,44–48], support paclitaxel + bevacizumab as a suitable first-line option. At the same time, the lack of a clear superiority in survival endpoints, especially in comparison to mono-CT options, makes the combination of paclitaxel with bevacizumab a valuable regimen mostly when a rapid and/or potent tumor shrinkage is the required therapeutic goal (e.g. high tumor burden, visceral crisis). In this case, the better safety profile of this regimen compared to those of poly-CT plays in favor of paclitaxel + bevacizumab. To note, this regimen is no longer available in the USA and, where available (e.g. Europe), its higher costs compared to mono-CTs and numerous poly-CT regimens should be properly taken into account at the moment of therapeutic decision-making.

Interestingly, platinum-based regimens, especially in combination with taxanes, resulted in very high SUCRA values for all endpoints, but their potential benefits should be weighed against their higher toxicities (e.g. nausea/vomiting, peripheral neuropathy, hemato-toxicity) and patients' inclination to receive the appropriate supportive care, when required [49–51].

A viable alternative in patients unfit for/unwilling to receive poly-CT, or with low tumor burden, is the use of mono-CT. The best-ranked single-agents in terms of both PFS and OS appeared to be weekly paclitaxel and PLD (Table 1). Single-agent carboplatin is another option, with many mono-CTs being not significantly superior to it in terms of ORR (data not shown), including taxanes (coherently with the TNT trial) [1]. Yet, it could not be included in the PFS and OS networks, limiting the evidence to support it as a clear standard. The choice among one of those drugs should be properly discussed and adapted to patients' preferences, especially with regard to their different toxicity profile and different administration schedule.

Notably, talazoparib and olaparib in gBRCA-mut patients were among the highest ranked available treatments, without superior mono-CTs (Table 1). Conversely, many multiagent regimens, although not selectively tested in g*BRCA*-mut patients, were associated to better outcomes (Table 1). Therefore, PARPi might reasonably represent an optimal first-line option in g*BRCA*-mut cases when no combinations are strictly required. Notably, signals of activity beyond *BRCA*1/2 mutant TNBC might lead to an expansion of their therapeutic indication, if further confirmed [52–55]. Importantly, recently published positive results on adjuvant olaparib in g*BRCA*-mut early-stage TNBC already lead to FDA approval in this subset [56]. Whether this might affect the efficacy of first-line PARPi in case of relapse will be a matter of debate in the next years.

Regarding PD-L1+ mTNBC, no treatment was significantly superior to atezolizumab + nab-paclitaxel for all the 3 endpoints investigated and to pembrolizumab + CT in terms of PFS/TTP and OS (data not shown). These combinations also showed a relatively favorable and manageable toxicity profile compared to numerous poly-CT regimens (Supplementary Tables 4–5). Overall, based on these results and considering that ICI + CT regimens are limited to the first-line setting, atezolizumab + nab-paclitaxel or pembrolizumab + CT might be the preferred upfront treatment for PD-L1+ mTNBC. Importantly, the comparison between the two regimens in our study was not statistically significant but pembrolizumab + CT was favored over more first-line regimens and obtained the best position in the OS SUCRA-based ranking. In addition, atezolizumab + nab-paclitaxel pivotal trial's result was formally negative due to its hierarchical testing plan [7]. Furthermore, following the manufacturer's request, the FDA (but not EMA) also recently withdrew its indication for atezolizumab in this setting [24,57,58].

In case of concomitant PD-L1+/g*BRCA*-mut tumors, the evidence is still too scarce to draw any meaningful conclusion. Yet, PARPi can be administered also in advanced lines, while, at present, ICI-based therapy cannot. Interestingly, an ongoing phase II/III RCT of pembrolizumab + olaparib vs pembrolizumab + CT after induction with pembrolizumab + CT in mTNBC will provide additional important insights [59].

Another open question is whether to prefer first-line platinum agents or PARPi in PD-L1-negative/g*BRCA*-mut TNBC, considering that *BRCA*1/2 dysfunction has been associated with increased response to platinum agents [60]. Our results suggest that platinum-based regimens in unselected TNBC (potentially including also g*BRCA*-mut tumors) are likely better than PARPi in g*BRCA*-mut tumors on all 3 endpoints (Table 1). Importantly, roughly 20 % and 30 % of patients receiving talazoparib and olaparib in their pivotal trials, respectively, had been pretreated with platinum agents [4,5]. Hence, the sequencing might not impair PARPi's efficacy, although those subpopulations had not progressed on platinums [4,5]. Nevertheless, the evidence to unequivocally support either strategy is still insufficient. The different toxicity profile among these agents may help guiding treatment choice according to individual patient characteristics and preferences.

Finally, as observable in the full treatment rankings (Supplementary Fig. 10), paclitaxel + capivasertib, in *PIK3CA/PTEN/AKT*-altered TNBC, and carboplatin + gemcitabine + CDK4/6-inhibitor trilaciclib, in unselected mTNBC, proved to be particularly effective. In both cases, confirmatory phase III trials are ongoing and results eagerly awaited [61,62], especially after the unexpected negative results of the IPATunity130 phase III trial of first-line paclitaxel + ipatasertib [28].

Concerning advanced lines, sacituzumab govitecan was associated to the best PFS, OS and ORR results (Figs. 3-4, Supplementary Fig. 9, Table 1). These data strongly support sacituzumab govitecan being the preferred second-line in mTNBC. At the same time, olaparib and talazoparib in g*BRCA*-mut tumors were favored among all other treatments in terms of PFS/TTP, with no difference between the two PARPi on all endpoints (Fig. 3, Table 1, Supplementary Table 3). Hence, in the absence of sacituzumab govitecan, a PARPi might represent the preferable second-line in g*BRCA*-mut mTNBC, if not previously used. In the subset of HER2-low tumors, representing ~ 37 % of all TNBC [14], *T*-DXd provided also extremely promising results, being one of the best options in terms of all 3 endpoints. The overall comparisons led to a better positioning of sacituzumab govitecan in SUCRA-based rankings. Still, a direct comparison between the two ADCs did not show significant differences. No significant difference was also observed with PARPi, but overall results, especially in OS, were in favor of T-DXd. However, considering the low number of patients treated with T-DXd, these results have to be taken carefully. T-DXd might be well positioned either after sacituzumab govitecan or before/right after PARPi in gBRCA-mut HER2-low TNBC. Direct comparisons in RCT, especially between the two ADCs should be pursued to draw more definitive conclusions.

Subsequent most effective mono-CT were represented by nab-paclitaxel (ORR), capecitabine (PFS/TTP) and eribulin (PFS/TTP, OS) (Table 1). The former could not enter survival networks but solid efficacy data concur in supporting its use also in taxane-pretreated patients [63,64]. Whether to administer one or the others is a decision that should be individualized based on toxicity profile, drug delivery method (oral for capecitabine vs intravenous for eribulin and nab-paclitaxel), previous therapies, patients' clinical conditions and preferences. Conversely, not many poly-CT could enter our networks and the ones that could, did not show any significant advantage on all endpoints to justify their use in advanced lines compared to mono-CT, providing also their worse toxicity profile.

Finally, single-agent pembrolizumab appeared to be another valuable option in advanced lines. However, the results hereby reported are based on PD-L1+ mTNBC, whereas it is currently FDA-approved in patients with high microsatellite instability/mismatch repair deficiency or high tumor mutational burden [65,66].

This study has several limitations to consider. First, several assumptions and simplifications fully disclosed in the Methods section (including forcing some links), were required to include the majority of the most relevant therapeutic options and should be carefully taken into

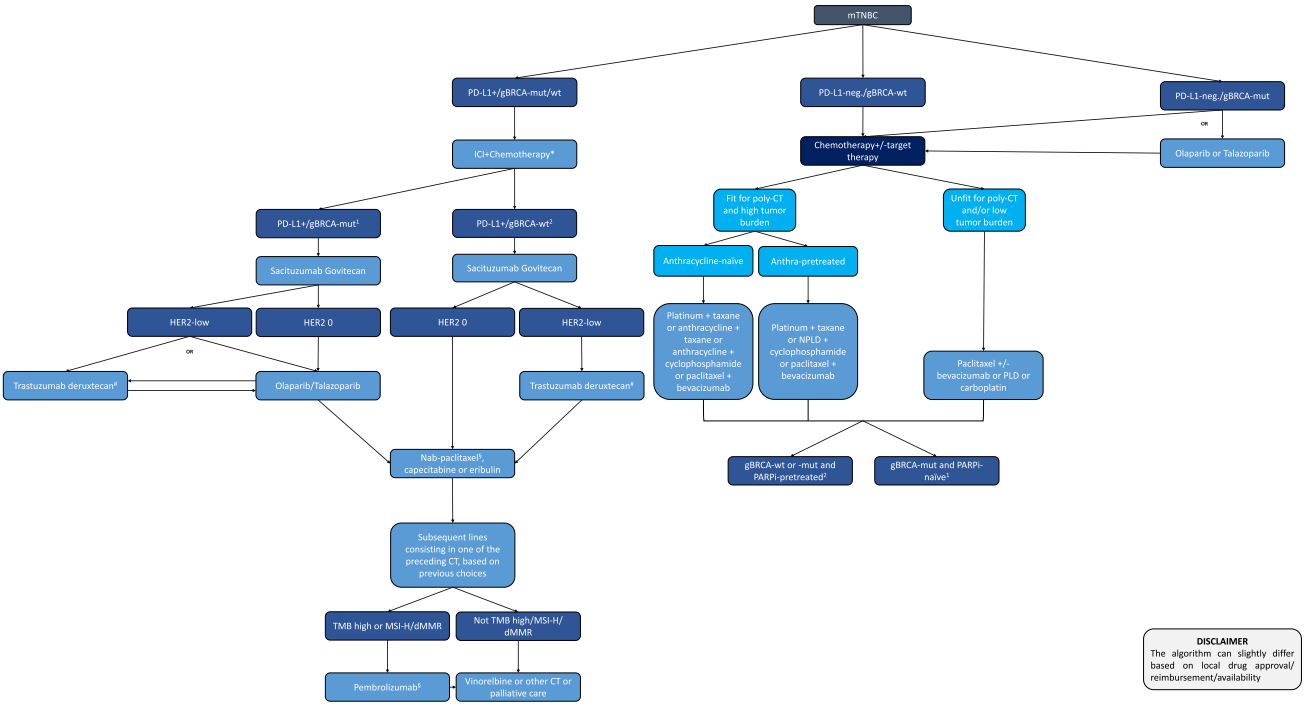

Fig. 5. Proposed therapeutic algorithms for the first and following lines. mTNBC: metastatic triple negative breast cancer; wt: wild-type; mut: mutant; gBRCA: germline *BRCA*1 and/or 2; CT: chemotherapy; ICI: immune-checkpoint inhibitors (atezolizumab or pembrolizumab); PLD: pegylated liposomal doxorubicin; NPLD: non– pegylated liposomal doxorubicin; neg.: negative; +: positive; PARPi: PARP inhibitor; TMB high: tumor mutational burden ≥ 10 mutations/megabase; MSI-H: high microsatellite instability (≥30 % mutations); dMMR: dysfunctional mismatch repair; 1: indicate the same advanced lines algorithm of PD-L1+/gBRCA-mut, independently from PD-L1 status; 2: indicate the same advanced lines algorithm of PD-L1+/gBRCA-wt, independently from PD-L1 status; *: pembrolizumab should be preferred over atezolizumab, where available, considering the more methodologically solid results in its pivotal trial and the better position in the SUCRA-based overall survival ranking. Moreover, atezolizumab is no longer approved in the USA for this setting; #: still not approved in Europe, but recently FDA-approved for HER2-low metastatic breast cancer, irrespective of hormone receptor status; §: if not previously administered in first-line with chemotherapy. The algorithm is based on the results published in Table 1, Figs. 1-4, Supplementary Figs. 8–9, Supplementary Tables 3–5 and results not shown for space reasons. All data were then interpreted according to the available literature reviewed plus the most updated American and European Society for Clinical/Medical Oncology (ASCO and ESMO) and US National Comprehensive Cancer Network (NCCN) guidelines.

account when evaluating this study results. Second, we did not report publication bias since the approaches developed to assess this type of bias in NMA are challenging and still present limitations that make their effectiveness often debated [67]. However, our analysis includes most of the available literature on the topic, somewhat mitigating the impact of publication bias. Third, some results are based on specific biomarker-defined subpopulations (i.e. PD-L1+, *gBRCA*-mut, HER2-low or *PIK3CA/PTEN/AKT*-altered), hence they cannot be generalized to the totality of mTNBC. However, considering that these subgroups represent a limited proportion of TNBC and their concomitant presence is uncommon, it is likely that no RCT will ever be conducted comparing the most appropriate biomarker-based treatments within such nested subgroups. Moreover, no evidences are available to conduct specific biomarker-restricted networks. In this scenario, this study provides unique results that might be valuable for clinicians. Furthermore, while sufficient evidence suggest novel biomarker-based treatments are not effective in all TNBC patients, there is no biologic rationale or published evidence supporting lack of efficacy of previous standard treatments in biomarker-based subgroups. Fourth, ~72 % of studies included also ER+/HER2-negative MBC. Given that mTNBC are usually considered to be more CT-sensitive than ER+/HER2-negative tumors [11,20], it is possible that the efficacy of several regimens might have been diluted in favor of some treatments tested in TNBC-restricted trials. At the same time, in 40 % of study treatment arms, the ER positivity proportion was < 50 %, meaning that the TN population was overall highly represented. Furthermore, in such studies, ET for the metastatic disease had been administered before CT in more than 1/3 cases, further reducing the proportion of fully endocrine-sensitive ER + MBC, which are potentially less sensitive to CT than endocrine pre-treated tumors [11,17,68]. To note, a certain heterogeneity in the proportion of patients with visceral/non-visceral/brain metastases among included studies was also present and should be taken into account when considering results. Fifth, the highest risks of bias were observed in the domains of the performance bias, blinding of outcome assessment and selective reporting bias. Concerning the latter, since our study was focused on 3 endpoints (i.e. PFS, OS and ORR) we decided to adopt a comprehensive approach in the RoB analysis by taking into account all endpoints concomitantly. However, the limit of this approach is that at least one of the 3 endpoints was not published in many cases (usually OS), for reasons attributable to the same study design (roughly a third were phase II RCT). However, the primary endpoint (i.e. PFS) was only partially affected by this issue (~74 % first-line and ~ 82 % advanced-line studies reported PFS data) and results for the three different endpoints were substantially coherent among them. Regarding blinding of outcome and performance bias, the risk was high because approximately half studies were not blinded. At a closer look, this was often justified by different ways of drug administration that made it impossible, unethical or useless to apply any blinding procedure. Those issues could not be overcome and sub-analysis on the restricted casuistry of studies with no blinding bias was unfeasible because of the impossibility of closing meaningful networks. Nevertheless, most of these studies led to the approval of regimens and schedules commonly used in clinical practice. Importantly, no substantial inconsistency was observed (Supplementary Methods). Finally, we point out that NMA share the same limitations of standard pairwise meta-analyses [69,70], with the addition of a set of specific assumptions, including transitivity and consistency, on which a lot of

research is still ongoing [37,71,72].

In conclusion, despite limitations, this is the first study comparing all available systemic treatments for the management of mTNBC, providing timely and methodologically reliable results. In this perspective, we propose a consensus therapeutic algorithm resumed in Fig. 5, based on our original data, literature review and main international guidelines to support daily-practice therapeutic decision-making [10,11,17,73].

CRediT authorship contribution statement

Drs F. Schettini, D. Generali, M. Giuliano and prof. S. Venturini had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr F. Schettini and prof S. Venturini contributed equally to this work and served as co–first authors.

Concept and design: Drs F. Schettini, D. Generali.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Drs F. Schettini, D. Generali, A. Prat, G. Curigliano, M. Giuliano, G. Jerusalem, R. Bartsch and prof S. Venturini.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Prof S. Venturini.

Obtained funding: N/A.

Administrative, technical, or material support: N/A.

Supervision: Dr D. Generali.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Giuliano, Arpino and De Placido S have declared honoraria from Roche, Pfizer, Astra-Zeneca, Novartis, Celgene, Eli Lilly, Amgen, and Eisai, outside of the submitted work.

Dr Lambertini has declared personal fees (advisory role and/or speaker honoraria) from Roche, Takeda, Sandoz, Eli Lilly, Pfizer, AstraZeneca, Novartis Exact Sciences and Ipsen, outside of the submitted work.

Dr Bartsch has declared honoraria from AstraZeneca, Daiichy Sankyo, Eli Lilly, Novartis, Pfizer, Pierre Fabre, Roche, consulting or advisory role for AstraZeneca, Daiichi, Eisai, Eli Lilly, MSD Oncology, Novartis, Pfizer, Pierre Fabre, Puma Biotechnology, Roche, research funding from Daiichi-Sankyo, travel, accommodations, expenses from Roche, Pfizer, outside of the submitted work.

Dr Pinato has received lecture fees from ViiV Healthcare and Bayer Healthcare and travel expenses from BMS and Bayer Healthcare; consulting fees for Mina Therapeutics, EISAI, Roche, and Astra Zeneca; research funding (to institution) from MSD and BMS, outside of the submitted work.

Dr Harbeck has declared stocks and other ownership interests in the West German Study Group, honoraria from Roche, Novartis, Daiichi-Sankyo, Amgen, Pfizer, Exact Sciences, AstraZeneca, Pierre Fabre, SeaGen; consulting or advisory role for Roche/Genentech, Novartis, Pfizer, Eli Lilly, Sandoz, Daiichi Sankyo, AstraZeneca, Merck Sharp & Dohme, Sandoz, SeaGen, Pierre Fabre and research funding to institution from Roche/Genentech, Eli Lilly, Merck Sharp & Dohme, outside of the submitted work.

Dr Lüftner has received honoraria from Amgen, AstraZeneca, Celgene, Eisai, Genomic Health, Eli Lilly, Loreal, MSD, Novartis, Pierre Fabre, Pfizer, Tesaro, Teva, outside of the submitted work.

Dr Denys has reported consulting fees (advisory role) paid to her institution by Pfizer, Roche, PharmaMar, AstraZeneca, Eli Lilly, Novartis, Amgen, Tesaro; grants from Research Funding institutional Roche; and other fees (travel, accommodations, expenses) by Pfizer, Roche, PharmaMar, Teva, AstraZeneca, outside of the submitted work.

Dr Zaman has reported travel, accommodation and expenses from Roche, Pierre Fabri and MSD Oncology, research funding from Roche/Genentech consulting/advisory role for Roche, Eli Lilly, MSD Oncology, Mylan, Novartis, Daiichy and Pierre Fabre, and other relationships with Pierre Fabre, all outside the submitted work.

Dr Gligorov has declared speakers' bureau honoraria from Roche-Genentech, Novartis, Eisai, Genomic Health, Ipsen, Pfizer, Mylan, Eli Lilly, Sandoz, and Pierre-Fabre; consultant/advisory board member for Roche-Genentech, Novartis, Onxeo, Daichii Sanyo, MSD, Eisai, Genomic Health, Ipsen, Macrogenics, Pfizer, Mylan, Eli Lilly, Immunomedics, Pierre-Fabre; grant support from Roche-Genetech, Eisai, Genomic Health, Pfizer, Mylan; travel, accommodation paid by Roche-Genentech, Novartis, Eisai, Genomic Health, Pfizer, Eli Lilly, Pierre-Fabre; personal fees and non-financial support from Daichii Sanyo, MSD, outside of the submitted work.

Dr Awada reports advisory roles, travel grants, and speaker fees from Roche, Eli Lilly, Amgen, ESAI, BMS, Pfizer, Novartis, MSD, Ipsen, and Leopharma. Dr Campone has declared honoraria from Novartis, Eli Lilly, GT1, Consulting or Advisory Role from Novartis, Servier, Menarini, Sanofi, Eli Lilly, Pfizer, AstraZeneca/MedImmune, Abbvie, Pierre Fabre, Accord Healthcare, Sandoz-Novartis, Seattle Genetics, Daiichi Sankyo Europe GmbH, Speakers' Bureau from Novartis, Amgen, Research Funding from Novartis, Travel, Accommodations, Expenses from Novartis, AstraZeneca, Pfizer, Other Relationship from Roche, outside of the submitted work.

Dr Wildiers has declared Consulting or Advisory Role from Roche, Eli Lilly, Pfizer, Sirtex Medical, Orion Corporation, Puma Biotechnology, AstraZeneca, Biocartis, Novartis, Daiichi Sankyo, Research Funding from Roche, Novartis, Travel, Accommodations, Expenses from Pfizer, Roche, outside of the submitted work.

Dr Gennari has declared consulting/advisory role for Roche, MSD, Eli Lilly, Pierre Fabre, EISAI, and Daichii Sankyo; speakers bureau for Eisai, Novartis, Eli Lilly, Roche, Teva, Gentili, Pfizer, Astra Zeneca, Celgene, and Daichii Sankyo; research funds from EISAI, Eli Lilly, and Roche, outside of the submitted work.

Dr Tjan-Heijnen has declared Honoraria and Travel expenses from Novartis, Roche, Eli Lilly, Pfizer and Honoraria from Daichii Sankyo, as well as Research Funding from Roche, Eisai, Pfizer, Novartis, Eli Lilly, AstraZeneca and Daichii Sankyo, outside of the submitted work.

Dr Cortes has declared **Stock and Other Ownership Interests from** MedSIR, **Honoraria from** Novartis, Eisai, Celgene, Pfizer, Roche, Samsung, Eli Lilly, Merck Sharp & Dohme, Daiichi Sankyo, **Consulting or Advisory Role from** Celgene, Cellestia Biotech, AstraZeneca, Biothera, Merus, Roche, Seattle Genetics, Daiichi Sankyo, ERYTECH Pharma, Polyphor, Athenex, Eli Lilly, Servier, Merck Sharp & Dohme, GlaxoSmithKline, Leuko, Clovis Oncology, Bioasis, Boehringer Ingelheim, **Research Funding from** ARIAD, Astrazeneca, Baxalta, Bayer, Eisai, Guardant Health, Merck Sharp & Dohme, Pfizer, Puma Biotechnology, Queen Mary University of London, Roche, Piqur, **Travel, Accommodations, Expenses from** Roche, Pfizer, Eisai, Novartis, Daiichi Sankyo, outside of the submitted work.

Dr Del Mastro acted as a consultant for Roche, Novartis, MSD, Pfizer, Ipsen, AstraZeneca, Genomic Health, Eli Lilly, Seattle Genetics, Eisai, Pierre Fabre, and Daiichi Sankyo, received speaker honoraria from Roche, Novartis, Eli Lilly and MSD, and travel grants from Roche, Pfizer and Celgene, outside the submitted work.

Dr Martin has declared Honoraria from Roche/Genentech, Eli Lilly, Pfizer, Novartis, Pierre Fabre, Consulting or Advisory Role from Roche/Genentech, Novartis, Pfizer, Eli Lilly, AstraZeneca, Taiho Pharmaceutical, PharmaMar, Speakers' Bureau from Eli Lilly/ImClone, Roche/Genentech, Pierre Fabre, Research Funding from Novartis, Roche, Puma Biotechnology, outside of the submitted work.

Dr Curigliano has reported personal fees from Roche, Pfizer, Novartis, Eli Lilly, Foundation Medicine, BMS, Samsung, Astra Zeneca, Daichii Sankyo Boeringer, GSK, Seagen, non-financial support from Roche, Pfizer, grants from Merck, other from Ellipsis, outside the submitted work.

Dr Jerusalem has reported grants, personal fees and non-financial

support from Novartis, Roche and Pfizer, personal fees and non-financial support from Eli Lilly, Amgen, BMS and Astra-Zeneca, personal fees from Daiichi Sankyo and Abbvie, non-financial support from Medimmune and MerckKGaA, outside the submitted work.

Dr Prat reports grants and personal fees from Pfizer, grants and personal fees from Eli Lilly, personal fees from Nanostring tecnologies, grants and personal fees from Amgen, grants from Roche, personal fees from Oncolytics Biotech, Daiichi Sankyo, PUMA, BMS, consulting/advisory role for NanoString Technologies, Amgen, Roche, Novartis, Pfizer and Bristol-Myers Squibb and patent PCT/EP2016/080056, outside of the submitted work. Dr Prat is also an equity stockholder, founder and consultant of Reveal Genomics and has a patent HER2DX and WO 2018/103834 licensed to Reveal Genomics, all outside of the submitted work.

Dr Generali has declared Honoraria from Novartis and Eli Lilly, Research Funding from Novartis and Astra-Zeneca, outside of the submitted work.

All other authors declared nothing to disclose.

Data availability.

All data have been retrieved from already published papers.

Code availability.

No proprietary codes were used for the analyses reported in this study.

Acknowledgements

Dr F. Schettini is the recipient of an ESMO Fellowship – Translational and a BBVA Foundation – Hospital Clinic of Barcelona Joan Rodes – Josep Baselga Advanced Research Contract in Oncology. However, any views, opinions, findings, conclusions or recommendations expressed in this material are those solely of the authors and do not necessarily reflect those of Funders. This study was supported by MEDNotE, spin-off - University of Trieste, within the Mozart Program.

Funding

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2022.102468.

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