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Accelerating progress in early triple-negative breast cancer: A viewpoint on antibody-drug conjugates, back from St Gallen breast cancer conference 2021☆

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ABSTRACT

Metastatic triple-negative breast cancer (mTNBC) is associated with an aggressive disease course, and limited treatment options. The recent accelerated drug development in the space of mTNBC has been driven by a precision-medicine approach, with the potential to deliver more personalized treatments and result in better outcomes. Antibody-drug conjugates (ADCs) have introduced a novel paradigm in the space of mTNBC, leading to the approval of the first targeted agent in this setting. The research and development of ADCs comes in parallel with the identification of tumor-specific targets of pharmacological interest. As a result, ADCs bring the potential for *agnostic* treatment delivery-across multiple histology types, and *theranostically*, by coupling tumor-antigen identification and treatment, as a continuum. In this perspective, recent progress in ADCs development for early and mTNBC are outlined, in the trade-off of patient selection, tumor specificity, precise drug delivery, potent payloads safety and quality of life.

Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast tumors, associated with dismal prognosis [1,2]. Innovative treatments have expanded the therapeutic options for selected patients with advanced disease (mTNBC). *Inter alia*, the new class of molecules of antibody-drug conjugates (ADCs) has rapidly positioned in the setting of mTNBC, providing significant benefits in pretreated patients [3]. With the advent of ADCs, progresses have been marked in targeting TNBC [4]. Tackling this 'untargetable' tumor type has been the real enterprise of the last years, overcoming the original sin of classification of TNBC in a default 'non-positive' category, ultimately grouping together a spectrum of heterogeneous diseases [1]. As such, ADCs have opened an 'identity crisis' for TNBC treatments [3]. These molecules are composed of a backbone of monoclonal antibody (MAb), exploiting the best role they are engineered for: recognize antigens. But ADCs are linked to cytotoxic payloads, resulting in tailored delivery of highly active agents, with the intent to spare non-targeted tissues [3]. At the end, they interpret essentially a new pharmacological delivery model to treat tumors [3,4].

The implementation of ADCs has first modernized the view on MAb clinical utilization: not really only to switch-off hyperactive tumorigenic signaling; ADCs can exert anti-neoplastic activities in disregard of the biologic functions of their pharmacological receptors: antigens are linked, payloads are released, cancer cells are killed via internalized chemotherapies [3]. Such a change in perspective implies that: (i) ADCs can exploit activity across multiple tumor types – delivering *agnostically,* based on antigen expressions; (ii) ADCs offer an attractive perspective for treatment personalization, based on the multiple targetable antigens that can be identified in a single patient - a possible declination of the *theranostic* paradigm. *Agnosticity* and *theranosticity*, however, will be reached only with an optimal trade-off between antibody specificity – to avoid off-target effects and non-specific activity related to the release of the payload in the bloodstream – and patient tolerance of the cumulative toxicities. Pursuing precision in this context will require understanding better how these new ADCs tailor the targets; perhaps, most importantly, there must be better knowledge on what is the minimal amount of membrane antigen to

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List of abbreviations

ADC	antibody-drug conjugate
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
MAb	monoclonal antibody
mTNBC	advanced triple-negative breast cancer
NAT	neoadjuvant therapy
OS	overall survival
pCR	pathological complete response
PFS	progression-free survival
TNBC	triple-negative breast cancer

be expressed, to determine ADCs efficacy, and if traditional techniques like immuno-histochemistry are sensitive enough for this purpose. Table 1.

The experience of ADCs in mTNBC is interesting. The first ADCs approved in the USA for mTNBC is sacituzumab govitecan, a MAb targeting trophoblast cell-surface antigen 2 (Trop-2) and linked to the active metabolite of irinotecan (SN-38) [5]. Sacituzumab govitecan has positioned in a setting of high clinical unmet need, resulting in a benefit for patients with pretreated mTNBC, when compared with standard of care treatments. The phase 3 pivotal trial ASCENT included women after two or more lines of therapy for mTNBC [5]. The first analysis reported an improvement of the progression-free (PFS) and overall-survival (OS), with a median gain of +3.9 months (hazard ratio [HR], 0.41; $P < 0.0001$) and +5.4 months (HR, 0.48; $P < 0.0001$), respectively. Toxicity profile was non-trivial, as some systemic cytotoxic effects were observed, including a half of patients experiencing moderate-severe neutropenia and 6% with febrile events. Trop-2 is largely expressed in tumor cells, including non-TNBC tumors, and clinical activity has been reported across a spectrum of Trop-2 positive diseases [4].

The clinical implementation of ADCs anti-HER2 has reshaped the perspectives in HER2 targetability, and paved new opportunities to treat also mTNBC patients [6]. While HER2 overexpression has been related to an oncogene addiction of a quarter of breast cancers (i.e., HER2-positive), HER2 can also be expressed in the cell membranes in the absence of gene amplifications (i.e., HER2-low): it is estimated that a half of patients presents a HER2-low [6]. Although preliminary, anti-HER2 ADCs have provided some activity for HER2-low mTNBC in early-phase clinical trials, including with the ADCs Trastuzumab deruxtecan and Trastuzumab duocarmazine. With these anti-HER2 ADCs, objective response rates (ORR) in the HER2-low patients ranged between 28 and 40%, with a median PFS of 11.1 moths [5,6]. Similar findings have been reported with other targets, like the anti-HER3 ADC Patritumab deruxtecan, reporting 13–33% ORR, and the *anti*-Liv1 Ladiratuzumab vedotin, with 29% ORR [7].

The identification of cancer-specific antigens has resulted ultimately in an flareup of new ADCs under development, aiming at refining the patient selection, thus offering specific and potentially single-patient tailored treatments [4,7]. As a paradox, the 'untargetable' setting of TNBC is flourishing with a plethora of targeted molecules. Table 2.

Translating new paradigms of care from the lessons learnt in the advanced setting of care is not only important but can boost the benefits for patients [8]. Therefore, when a drug shows activity in resistant diseases and improvement of the survival, there is rationale to understand what impact can be derived in the early setting [8]. This could be the case of some ADCs: as new data will emerge from ongoing trials, the incorporation of these agents in the high-risk early setting is timely expected.

Tumors resistant to neoadjuvant treatments (NAT) do not completely regress, namely do not reach a pathological complete response (pCR). Post-NAT non-pCR status is prognostically unfavorable [9].

The loss of HER2-overexpression, including the switch from HER2-positive to HER2-low, has been described as a mechanism of resistance emerging during NAT, in patients receiving anti-HER2 therapies, without pCR – resulting in resistance to adjuvant trastuzumab [9,10]. However, when non-pCR patients receive an escalated treatment with the ADCs trastuzumab emtansine, including in the cases of switch to HER2-low or HER2-negative in the residual disease, prognosis appears improved [10]. Thus, features of the residual disease can portend therapeutic implications. Then, ADCs can be strategic to tailor high-risk diseases, presenting dynamic heterogeneities matured and/or revealed under NAT

Table 1
Overview of the approved antibody-drug conjugates for cancer treatment.

Name	Target antigen	Payload	DAR	Indication	EMA approval	FDA approval
Brentuximab vedotin[a,c]	CD30	MMAE	~4	CD30-positive HL, Rel/Ref sALCL, CD30-positive TCL	2012	2011
Trastuzumab emtansine[c]	HER2	DM1	3.5	HER2-positive mBC, HER2-positive eBC	2013	2013
Inotuzumab ozogamicin[c]	CD22	Calicheamicin	~4	Relapsed/refractory B-cell precursor ALL	2017	2017
Gemtuzumab ozogamicin[a]	CD33	Calicheamicin	2–3	CD33-positive AML	2018	2017
Moxetumomab pasudotox[c]	CD22	PE38	1	Rel/Ref HCL	ODD (2008)	2018
Polatuzumab vedotin[b]	CD79b	MMAE	3.5	Rel/Ref DLBCL	2020	2019
Loncastuximab tesirine[c]	CD19	Tesirine	2.3	Rel/Ref DLBCL	ODD (2021)	2021
Belantamab mafodotin[c]	BCMA	mcMMAF	~4	Rel/Ref MM	2020	2020
Trastuzumab deruxtecan[c]	HER2	DXd	7–8	HER2-positive mBC	2021	2019
Enfortumab Vedotin[c]	Nectin4	MMAE	3.8	mUC	2021	2019
Sacituzumab govitecan[c]	TROP2	SN-38	7.6	mTNBC	2021	2020

EMA and FDA year of approval are intended for the first approval. MMAE and DM1 are tubulin polymerisation inhibitor. Calicheamicin is a double-strand DNA break inducing agent. DXd and SN-38 are DNA topoisomerase I inhibitor. PE38 is an inhibitor of the protein synthesis. Tesirine is a DNA cross-linking agent.
DAR, drug-to-antibody ratio. EMA, European Medicines Agency. FDA, US Food and Drug Administration. MMAE, Monomethyl auristatin E. DM1, mertansine. PE38, 38 kDa truncated portion of the Pseudomonas exotoxin A. McMMAF, Maleimidocaproyl monomethylauristatin F. DXd, exatecan derivative DXd. SN-38, 7-ethyl-10-hydroxycamptothecin. HER2, human epidermal growth factor receptor 2. BCMA, B-cell maturation antigen. TROP2, trophoblast cell surface protein 2. HL, Hodgkin Lymphoma (multiple setting). sALCL, adult systemic anaplastic large cell lymphoma. TCL, T-cell cutaneous lymphoma. mBC, metastatic breast cancer. eBC, early breast cancer. ALL, acute lymphoblastic leukemia. AML, acute myeloid leukemia. HCL, hairy cell leukemia. DLBCL, diffuse large B cell lymphoma. MM, multiple myeloma. mUC, metastatic urothelial cancer. mTNBC, metastatic triple-negative breast cancer. Rel/Ref, relapsed/refractory. ODD, orphan drug designation.
[a] Used in combination with chemotherapy.
[b] Used with chemotherapy and another monoclonal antibody.
[c] Used as a single agent.

Table 2
Ongoing clinical trials with antibody-drug conjugates for the treatment of patients with triple-negative breast cancer.

Compound	Target Antigen[a]	Payload[a]	Setting	Phase of drug development	ClinicalTrials.gov Identifier
ADC investigated as single agents					
Sacituzumab govitecan	TROP2	SN-38	Post-neoadjuvant	3	NCT04595565 (SASCIA)
Trastuzumab deruxtecan	HER2 ╢	DXd	Metastatic	3	NCT03734029 (DESTINY-Breast04)
MRG002	HER2 ╢	MMAE	Metastatic	2	NCT04742153
NBE-002	ROR1	PNU-159682	Metastatic	1/2	NCT04441099
Patritumab deruxtecan	HER3	DXd	Metastatic	1/2	NCT02980341
Aprutumab ixadotin	FGFR2	BAY1168650	Metastatic	1/2	NCT02368951
MORAb-202	FRα	Eribulin	Metastatic	1/2	NCT04300556
CX-2009	CD166	DM4	Metastatic	1/2	NCT03149549 (PROCLAIM-CX-2009)
Glembatumumab Vedotin	Gp-NMB	MMAE	Neoadjuvant	1	NCT03473691 (Breast50)
Samrotamab vedotin	LRRC15	MMAE	Metastatic	1	NCT02565758
Ladiratuzumab Vedotin	LIV-1	MMAE	Metastatic	1	NCT01969643
ASN 004	TPBG	Dolastatin	Metastatic	1	NCT04410224
Anetumab ravtansine	Mesothelin	DM4	Metastatic	1	NCT02485119 [d]
ADC investigated in combination regimens					
Sacituzumab govitecan; Carboplatin	TROP2	SN-38	Metastatic	2	NCT02161679
Sacituzumab govitecan; Talazoparib	TROP2	SN-38	Metastatic	1/2	NCT04039230
MGC018; Retifanlimab	B7–H3 (CD276)	DUBA	Metastatic	1/2	NCT03729596
Trastuzumab deruxtecan; multiple agents[c]	HER2[b]	DXd	Metastatic	1b	NCT04556773 (DESTINY-Breast08)
Trastuzumab deruxtecan; Pembrolizumab	HER2[b]	DXd	Metastatic	1	NCT04042701
Sacituzumab govitecan; Atezolizumab	TROP2	SN-38	Post-neoadjuvant	2	NCT04434040 (ASPRIA)

ADC, antibody-drug conjugate. Gp-NMB, Transmembrane glycoprotein NMB. ROR1, neurotrophic tyrosine kinase, receptor-related 1. PNU-159682, a metabolite of the anthracycline nemorubicin (DNA topoisomerase I inhibitor). HER2, human epidermal growth factor receptor 2. HER3, human epidermal growth factor receptor 3. FGFR2, fibroblast growth factor receptor 2. Leucine-rich repeat containing 15, Leucine-rich repeat-containing protein 15. Retifanlimab, *anti*-PD1 monoclonal antidbody. B7–H3, B7 Homolog 3. DUBA, seco-DUocarmycin hydroxyBenzamide Azaindole. BAY1168650, microtubule-depolymerizing auristatin W derivative. LIV-1, Zinc transporter ZIP6/solute carrier family 39 member 6. FRα, folate receptor alpha. TPBG (5T4), Trophoblast glycoprotein. DM4, ravtansine. MMAE, Monomethyl auristatin E. DM1, mertansine. DXd, exatecan derivative. HER2, human epidermal growth factor receptor 2. TROP2, trophoblast cell surface protein 2. SN-38, 7-ethyl-10-hydroxycamptothecin.

[a] Referred to the antibody-drug conjugate compound (when multiple agents are tested).
[b] This trial is designed or has a cohort for patients with HER2-low and hormone receptor-negative breast cancer.
[c] Multiple arms in combination with Durvalumab, Paclitaxel, Capivasertib, Anastrozole, Fulvestrant, Capecitabine.
[d] This study is conducted in a Japanese cohort of patients.
Source: clinicaltrial.gov (last access 26 Nov 2021).

[4,7,10]. The bio-selection of patients is critical to understand the need for escalation of treatments, and the opportunity to incorporate new effective agents in the settings of high unmet need.

A pCR-triggered enrollment in clinical trials to escalated treatments can benefit patients with more resistant tumors (i.e., using NAT as a proof of *in-vivo* therapeutic sensitivity), for whom novel strategies can impact on the predictable adverse disease trajectory. A pCR-driven approach has demonstrated to enrich the populations of women deriving benefits from adjunctive therapies, also in the setting of HER2-negative tumors.(10,11) Such a bio-selection has resulted in the clinical uptake of post-neoadjuvant capecitabine and prompted a number of clinical trials ongoing.(11) On the same page, one must carve the results of Olaparib in patients with germinal BRCA mutations and no-pCR after NAT.(11) In summary, ADCs can be instrumental in the early setting, to precisely tailor proved resistant tumors (e.g., no pCR after NAT) expressing membrane antigens deemed adequate and safe pharmacological targets. Currently, the clinical trials SASCIA (NCT04595565, phase 3) and ASPRIA (NCT04434040, phase 2, with atezolizumab) are testing the role of sacituzumab govitecan in the post-NAT non-pCR setting, compared with the standard adjuvant capecitabine, platinum salts, or observation. With invasive-disease free survival as primary endpoint and OS, safety, compliance, and patient reported outcomes as secondary endpoints, SASCIA trial is expected to be completed by 2026–2028.

Advancements in the clinical research will happen with improvement of the understanding of endpoints capable both to track disease trajectory-modifying interventions and include the domains of patient-relevant metrics [8]. The position of ADCs for early TNBC is not around corner, and clinical trials will elucidate how to optimize the treatments. Therefore, the identification of patient-level prognosticators is highly desirable, to refine the selection, and escalate in the precise subset at very high-risk, sparing patients with good prognosis.(8,11) The discussion around new targets, new drugs and benefits can never be dissociated from the dialogue on patient-level prognostic factor - and pCR is far to be a perfect prognosticator, thought presently very useful.

In the complex landscape of patient-level priorities and new drugs development, ADCs will likely help improve the treatment personalization, providing an option in the high-risk setting, based on dynamic tumor characteristics. Presently, understanding the changes in the tumor biology in the early treatment setting is a way to improve the overall outcome, and result in higher curative rates.

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Declaration of competing interest

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