Sacituzumab Govitecan in HR-positive HER2-negative metastatic breast cancer

Simone Nardin[1,2]^, Lucia Del Mastro[1,2]^

[1]U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy; [2]Department of Internal Medicine and Medical Sciences (DiMI), School of Medicine, University of Genova, Genova, Italy

Correspondence to: Lucia Del Mastro. Department of Internal Medicine and Medical Sciences (DiMI), School of Medicine, University of Genova, Genova, Italy. Email: lucia.delmastro@hsanmartino.it.

Comment on: Rugo HS, Bardia A, Marmé F, *et al.* Sacituzumab Govitecan in Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer. J Clin Oncol 2022;40:3365-76.

Keywords: Breast cancer; Sacituzumab Govitecan (SG); Trastuzumab Deruxtecan; antibody-drug conjugate (ADC); hormone-receptor positive

Submitted Dec 09, 2022. Accepted for publication Dec 26, 2022. Published online Jan 09, 2023.
doi: 10.21037/atm-22-6266
View this article at: https://dx.doi.org/10.21037/atm-22-6266

Background

Breast cancer is the most frequently tumor diagnosed among women worldwide: according to Global Cancer Observatory, the incidence of breast cancer in 2020 was 2.26 million, with a mortality of 685 thousand nearly (1). The most frequent subtype of breast cancer (nearly 60%) is the luminal one, characterized by the presence of hormone receptors and the lack of overexpression of the human epidermal growth factor receptor 2 (HR+/HER2–) (2). Therefore, therapeutic advances in this subgroup of breast cancer do benefit a very high number of patients.

Therapeutic status of endocrine resistant breast cancer and new choices

The treatment of luminal metastatic breast cancer (MBC) patients is mainly based on the endocrine sensitivity or resistance status. European Society for Medical Oncology (ESMO) guidelines defines the endocrine resistance as primary or secondary according to relapse or progression time: endocrine resistance is considered primary if the relapse occurs on the first 2 years of adjuvant endocrine therapy (ET), or progression disease (PD) within first 6 months of first line ET for MBC; secondary endocrine resistance is defined as a relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or PD 6 months after initiating ET for MBC; otherwise, the endocrine status is considered sensitive (3). ASCO and ESMO guidelines agree upon the choice of first line therapy, as ET plus cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i) is considered the standard of care (4,5). Second line too is almost standardized: it is recommended to test for target therapy such as *PIK3CA* and germline *BRCA1/2* for treatment with Alpelisib or PARP inhibitor respectively; if no mutations are found, the therapy is related to a sequence of ET, even if there is not a standard order, since it depends on many factors (previous ET in adjuvant or metastatic setting, new ET with selective estrogen receptor modulators and downregulators, time before relapse/progression, cancer burden and toxicities, etc.). Management of HR+/HER2– MBC, when no longer amenable for endocrine treatment because of the endocrine resistance or because no additional endocrine drugs are available, is a major challenge for oncologist, because a wide pot of chemotherapy is available, without a clear layout due to the absence of comparative trials: the only entrustment is to prefer single-agent chemotherapy over combination treatment. Guidelines recommend the use of anthracyclines and taxanes, based

^ ORCID: Simone Nardin, 0000-0001-6150-5895; Lucia Del Mastro, 0000-0002-9546-5841.

on the previous use of these drugs in early setting, but also capecitabine is considered a valid chemotherapy option.

During last years, we observed a great development of antibody-drug conjugates (ADCs), compounds of an antibody and a toxic substance: the main goals of these drugs are tailoring the treatment and avoiding the systemic toxicities related to classic chemotherapy. The clinically relevant efficacy showed in phase III studies led to a quick modification of the therapeutic pathways of both HER2 positive MBC, with the introduction of Trastuzumab-DXd (T-DXd), and triple negative MBC with the introduction of Sacituzumab Govitecan (SG). The mechanism of action of these two ADC are tied not only to a direct impact over cells that express the ligand, but also to an indirect effect of the drug payloads that could penetrate the membrane of adjacent cells in order to kill them, even if those do not express the same ligand: this mechanism is known as bystander effect (6,7). This mechanism action prompts the design of studies aiming to evaluate their efficacy also in HR+/HER2– MBC patients.

The most important phase III studies are related to SG (NCT03901339, whose results have been published by Rugo *et al.* (8), and NCT04639986), Trastuzumab Deruxtecan for patients HER2-low (NCT03734029, NCT04494425). An additional phase III study is evaluating the role of Datopotamab Deruxtecan (Dato-DXd) (NCT05104866) There are many other ADCs agents, such as Ladiratuzumab Vedotin or Patritumab Deruxtecan, but their trials are still on phase I or II (9) (*Table 1*).

SG trials require, as eligibility criteria, that patients had received 2 to 4 lines of prior treatment in the inoperable/metastatic setting, including at least 1 ET and 1 CKD4/6i. Similarly, Dato-DXd trial requires that patients had received 1 or 2 lines of prior chemotherapy in the inoperable/metastatic setting, after ET too. On the contrary, T-DXd trial NCT04494425 (DESTINY-Breast06) requires that patients had not received chemotherapy in the inoperable/metastatic setting. These different criteria of inclusion could be useful for choosing the treatment sequence, but make the comparison between ADCs challenging.

The efficacy and safety of Antibody drug conjugates in HR+/HER2– MBC

Efficacy data in triple negative MBC [phase III ASCENT (10) trial] and in other type of cancer (phase II TROPHY-U-01 (11) study in metastatic urothelial carcinoma) as well as the results of a phase I/II study in previously treated HR+/HER2– MBC (12), prompted the design of TROPiCS-02 trial. TROPiCS-02 trial evaluated the role of the ADC SG in HR+/HER2– MBC. This phase III study enrolled 571 patients pretreated with a median of three lines of chemotherapy for advanced disease and randomized them 1:1 to SG or to chemotherapy of physician's choice. Physician could choice among eribulin, capecitabine, gemcitabine or vinorelbine before randomization. The objective response rate (ORR) of SG was 21% in patients treated with SG, compared to 14% in those treated with standard chemotherapy; the median progression free survival (PFS) was 5.5 months [95% confidence interval (CI), 4.2–7.0 months] for SG and 4.0 months (95% CI, 3.1–4.4 months) for chemotherapy [hazard ratio (HR) 0.66; 95% CI, 0.53–0.83], and overall survival (OS) data, presented at ESMO 2022, reported 14.4 *vs.* 11.2 months respectively (HR 0.79; 95% CI, 0.65–0.96); safety profile, with only a 6% of discontinuation due to adverse events (AEs) , reported a grade ≥3 of AEs higher in SG group compared to chemotherapy group, especially for neutropenia and diarrhea, respectively 51% *vs.* 38% and 9% *vs.* 1% (8,13). It is important to underline that almost all patients received a prior treatment with CDK4/6i (99%) and a median of 3 prior lines of chemotherapy in the metastatic setting (57% at least three lines); Palbociclib, as CDK4/6i (86% of patients), and Capecitabine, as chemotherapy (85% of patients), were the most used previous drugs. Most patients (93%) had at least 10% of estrogen receptor positive. A further evaluation comes from subgroup analysis, with better PFS in patients affected by early relapse, defined as recurrence within 12 months after the end of (neo)adjuvant treatment, and ≤12 months of CDK4/6i therapy, suggesting a major impact of SG among more aggressive diseases. Regarding the Trop-2 expression, target of that ADC, the data showed that Trop-2 expression is not predictive, since all patients had benefit regardless the level of the signal transducer, but a higher expression was related to better outcome. Further studies are needed to better define the role of Trop-2 expression.

The other important phase III trials about ADCs in HR+/HER2– MBC is the DestinyBreast-04. In this trial, T-DXd was compared to chemotherapy of physician's choice (capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel) in HER2-low (defined as a score of 1+ on immunohistochemical analysis or score of 2+ and negative results on *in situ* hybridization) MCB patients previously treated for advanced setting. Nearly 90% of the patients were patients with hormone-receptor positive tumors. The

Table 1 Principal active and recruiting study for advanced HR+/HER2– breast cancer

Drug	Target	Study phase	No of pt.	No of prior CT	Prior ET	Note	ID
Datopotamab Deruxtecan (DS-1062a)	Anti-Trop2	III	700	1 to 2	No more	–	NCT05104866
Sacituzumab Govitecan (IMMU-132)	Anti-Trop2	III	330	2 to 4	≥1	–	NCT04639986
Sacituzumab Govitecan (IMMU-132) ± Pembrolizumab	Anti-Trop2; anti-PD-1	II	110	≤1	≥1	–	NCT04448886
Sacituzumab Govitecan (IMMU-132)	Anti-Trop2	II	44	NS	NS	Presence of brain metastasis	NCT04647916
Patritumab Deruxtecan (U3-1402)	Anti-HER3	II	100	≤1	CDK4/6i	HER3+	NCT04965766
Enfortumab Vedotin (ASG-22CE)	Anti-Nectin-4	II	280	1 to 2	≥1	Not only BC; not only HR+/HER–	NCT04225117
Patritumab Deruxtecan (U3-1402)	Anti-HER3	II	120	≤1	CDK4/6i	HER+ not only HR+/HER2–	NCT04699630
PRO1184	Anti-FRα	I/II	134	NS	NS	No more treatments that can confer any clinically meaningful benefit; not only BC; not only HR+/HER2–	NCT05579366
Datopotamab Deruxtecan (DS-1062a)	Anti-Trop2	I	770	1 to 3	NS	No more treatments that can confer any clinically meaningful benefit; not only BC; not only HR+/HER–	NCT03401385
Ladiratuzumab Vedotin (SGN-LIV1A)	Anti-LIV1	I	448	≤1	No more	Not only HR/HER2–	NCT01969643
XB002	Anti-TF	I	451	NS	NS	Not only BC; not only HR+/HER2–	NCT04925284
OBT076	Anti-CD205	I	150	NS	NS	No more treatments that can confer any clinically meaningful benefit; not only BC; not specified subtypes	NCT04064359
ASN004	Anti-5T4 oncofetal antigen	I	43	NS	NS	Not only BC; not only HR+/HER2–	NCT04410224
Sacituzumab Govitecan (IMMU-132); Alpelisib	Anti-Trop2; anti-PI3K	I	18	No limit	No limit	Not only HR+	NCT05143229

HR, hormone receptor; HER2, human epidermal growth factor receptor 2; pt., patients; CT, chemotherapy; ET, endocrine therapy; NS, not specified; BC, breast cancer.

median number of previous chemotherapies for metastatic disease in this cohort of HR+ patients was 1. The 557 patients were randomized 2:1 to T-DXd *vs.* chemotherapy. Among them, 88.7% were HR+, previously treated with one or two lines of chemotherapy; in particular, in HR+ patients, median PFS was 10.1 *vs.* 5.4 months (HR 0.51; 95% CI, 0.40–0.64) and OS was 23.9. *vs.* 17.5 months (HR 0.64; 95% CI, 0.48–0.86). The safety profile was similar to other study with T-DXd: hematological disorder, fatigue and nausea were the most frequent AEs of grade ≥3 (13.7% neutropenia, 7.5% and 4.6% respectively); interstitial lung disease or pneumonitis occurred in 12.1% of patients, with

0.8% of grade 5 (14).

New therapeutic options for advanced HR+/HER2– MBC

The results of TROPiCS-02 and DestinyBreast-04 trials are changing the therapeutic pathways of HR+/HER2– MBC.

The overlapping population in these two studies comprises the HR+/HER2-low cohort. A post hoc analysis of TROPiCS-02 presented at ESMO 2022 by Schmid *et al.* (15) showed that SG improved efficacy outcomes vs treatment of physician's choice in HER2-low and HER2 IHC0 HR+/HER2– MBC, consistent with that of the intention-to-treat population: median PFS was 6.4 *vs.* 4.2 months (HR 0.58; 95% CI, 0.42–0.79) in the HER2-low group, and 5.0 *vs.* 3.4 months (HR 0.72; 95% CI, 0.51–1.00) in the HER2 IHC0 group. ORR was 26% *vs.* 12% in the HER2-low group, and 16% *vs.* 15% in the HER2 IHC0 group. The safety profile of SG in the HER2-low and HER2 IHC0 groups was manageable and consistent with that of the overall TROPiCS-02 safety population and with previous studies.

The burning question could be: what is the ADC to be preferred as first choice in HR+/HER2-low patients?

According to the inclusion criteria of the two studies, patients pretreated with only 1 line of chemotherapy should be preferentially treated with T-DXd whilst patients pretreated with more than one line of chemotherapy should receive SG. Further data will come from DestinyBreast-06 (NCT04494425), a phase III trial for HR+/HER2-low MBC patients who never received chemotherapy in advanced setting: in this study patients with HER2 IHC score 0 could be enrolled

For HR+/HER2– 0 patients in whom there are still no data on the efficacy of T-DXd, the preferred treatment at the time of progression from previous chemotherapy is SG.

The results from TROPiCS-02 trial are an important step toward the improvement of therapeutic pathways of HR+/HER2– patients who can now benefit of very effective treatment after the failure of standard endocrine therapies. Future studies should identify HR+ patients with primary resistance to available endocrine therapies in order to anticipate the use of these very effective ADC treatments.

Acknowledgments

Funding: This study was partly supported by Ministero della Salute, Ricerca corrente and 5×1,000.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6266/coif). LDM received grants or contracts from Eli Lilly, Novartis, Roche, Daiichi Sankyo, and Seagen; fees or honoraria from Roche, Novartis, Pfizer, Eli Lilly, AstraZeneca, MSD, Seagen, Gilead, Pierre Fabre, Eisai, Exact Science, and Ipsen; and participation on a data safety monitoring or advisory board from Novartis, Roche, Eli Lilly, Pfizer, Daiichi Sankyo, Exact Science, Gilead, Pierre Fabre, Eisai, and AstraZeneca, outside the submitted work. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Arnold M, Morgan E, Rumgay H, et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. Breast 2022;66:15-23.
2. Pandit P, Patil R, Palwe V, et al. Prevalence of Molecular Subtypes of Breast Cancer: A Single Institutional Experience of 2062 Patients. Eur J Breast Health 2020;16:39-43.
3. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast 2014;23:489-502.
4. Burstein HJ, Somerfield MR, Barton DL, et al. Endocrine Treatment and Targeted Therapy for Hormone Receptor-

Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer: ASCO Guideline Update. J Clin Oncol 2021;39:3959-77.
5. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32:1475-95.
6. Corti C, Giugliano F, Nicolò E, et al. Antibody-Drug Conjugates for the Treatment of Breast Cancer. Cancers (Basel) 2021;13:2898.
7. Li L, Zhang D, Liu B, et al. Antibody-drug conjugates in HER2-positive breast cancer. Chin Med J (Engl) 2021;135:261-7.
8. Rugo HS, Bardia A, Marmé F, et al. Sacituzumab Govitecan in Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer. J Clin Oncol 2022;40:3365-76.
9. Marmé F. Antibody-Drug Conjugates for Breast Cancer. Oncol Res Treat 2022;45:26-36.
10. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med 2021;384:1529-41.
11. Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. J Clin Oncol 2021;39:2474-85.
12. Kalinsky K, Diamond JR, Vahdat LT, et al. Sacituzumab govitecan in previously treated hormone receptor-positive/HER2-negative metastatic breast cancer: final results from a phase I/II, single-arm, basket trial. Ann Oncol 2020;31:1709-18.
13. Rugo HS, Bardia F, Marné F, et al. LBA76 Overall survival (OS) results from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HR+/HER2- metastatic breast cancer (mBC). Ann Oncol 2022;33:S1386.
14. Modi S, Jacot W, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med 2022;387:9-20.
15. Schmid P, Cortés J, Marmé F, et al. 214MO Sacituzumab govitecan (SG) efficacy in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) metastatic breast cancer (MBC) by HER2 immunohistochemistry (IHC) status in the phase III TROPiCS-02 study. Ann Oncol 2022;33:S635-6.

Cite this article as: Nardin S, Del Mastro L. Sacituzumab Govitecan in HR-positive HER2-negative metastatic breast cancer. Ann Transl Med 2023;11(5):228. doi: 10.21037/atm-22-6266

