Editorial Commentary

Sacituzumab govitecan: a new opportunity in the treatment of refractory metastatic triple-negative breast cancer

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Bardia and colleagues performed a phase 3 trial to evaluate sacituzumab govitecan (SG) [an antibody-drug conjugate composed of an antibody targeting the human trophoblast cell surface antigen 2 (Trop-2)], compared to single agent chemotherapy of the physician's choice (eribulin, vinorelbine, capecitabine or gemcitabine) in patients with relapsed or refractory metastatic triple negative breast cancer (mTNBC) (1). The primary endopoint was progression free survival (PFS) in 468 patients without known baseline brain metastasis. All were previously treated with taxanes.

The secondary endpoints were overall survival (OS), PFS (investigator assessment), objective response rate (ORR) and safety.

The authors reported that patients with mTNBC pretreated with at least two lines of treatment had a significant superiority of SG over chemotherapy in terms of survival and a tolerable safety profile, with a median progression-free survival of 5.6 *vs.* 1.7 months, and an OS of 12.1 *vs.* 6.7 months, respectively (1). SG had an OR of 35% in the arm of SG and 5% in the arm of chemotherapy.

The median PFS was 4.8 months with SG and 1.7 months with standard chemotherapy. The median OS was 11.8 months with SG and 6.9 months with chemotherapy.

Clinical benefit was obtained in all the subgroups of patients evaluated and was independent from the level of Trop 2 expression as reported in the biomarker analysis of ASCENT study by Bardia *et al.* (2).

In particular, the median relative dose intensity with SG was 99.7%.

The most frequent adverse events related to SG treatment were neutropenia (63% with SG and 43% with chemotherapy), diarrhea (59% with SG and 12% with chemotherapy), nausea (57% with SG and 26% with chemotherapy), alopecia (46% with SG *vs.* 16% with chemotherapy), fatigue (45% with SG *vs.* 30% with chemotherapy), anemia (34% with SG *vs.* 24% with chemotherapy). Despite diarrhea and myelosuppression were the primary adverse events, the discontinuation rates were very low (5% in each group).

The most frequent treatment-related adverse events of grade 3 (severe, according to Common Terminology Criteria for Adverse Events, CTCAE) or higher were neutropenia (51% with SG and 33% with chemotherapy), leukopenia (10% and 5%), diarrhea (10% and <1%), anemia (8% and 5%), and febrile neutropenia (6% and 2%). In particular neutropenia was managed with dose reduction, dose delay, or both and with growth-factor support after day 1 of cycle 1. The incidence of grade 3 and 4 febrile neutropenia was 5% and 1% respectively, with SG and 2% and less than 1%, respectively, with chemotherapy. In addition, at the same time, growth-factor support was given to 49% of the patients treated with SG and 23% of patients treated with chemotherapy.

The results of this study have changed clinical practice of patients with mTNBC from the second line of treatment and beyond.

SG, a first-in-class Trop-2-directed antibody-drug conjugate, demonstrated a significant benefit with respect to progression-free and OS in comparison with standard-

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of-care chemotherapy. It was used at a dose of 10 mg per kilogram intravenously on days 1 and 8 of each 21 day cycle. Myelosuppression and diarrhea, were more the most frequent toxic effects with SG than with chemotherapy.

Despite its toxic effects (up to grade 3 and 4) that can be managed with supportive care measures, the rate of treatment discontinuation due to adverse events was very low (5%).

Given the promising activity of this drug alone from the second line and beyond, we expected even more efficacy of the drug also in previous line of treatment alone or in combination with other drugs such as Pembrolizumab, Atezolizumab, Talazoparib has already done in ongoing trials.

Unfortunately, due to the fact that different countries follow different guidelines given by regulatory agencies such as FDA (Food and Drug Administration), EMA (European Medicine Agency, AIFA (Italian Medicines Agency), disparities emerged among patients in the possibility to be treated with this compound (3). Up to now, in the majority of countries there is a limited availability of the drug. Moreover, due to the lack of AIFA approval, in Italy, the treatment with SG cannot be used in clinical practice (3,4). It is even more important in the mTNBC subgroup given the late stage of this aggressive disease and the patient necessity to be treated in the best appropriate way.

The cost of treatment with SG is very expensive (in US 11.195 dollars a dose for an 80 kg person; this price does not include premedication, infusion chair time, nursing time etc.) (5). Despite the cost of SG is very high, all the selected patients should have the possibility to be treated with this drug.

Other studies are ongoing in other subset of patients such as those treated with neoadjuvant, adjuvant therapy and in the metastatic setting in earlier lines of treatment in combination with immunotherapy-based regimens or with PARP inhibitors in advanced triple negative breast cancer and in hormone-positive and Her2 negative breast cancers.

Then, the effort that has to be done is to demonstrate the efficacy of SG in the early breast cancer, in the neoadjuvant setting and in earlier lines of treatment of metastatic disease alone and in combination with other compounds.

Moreover, other tumor histologies could benefit of this treatment and need to be explored.

In conclusion, SG has good efficacy and tolerable toxicities respect to the standard chemotherapy in a subset of patients with very aggressive disease.

Despite the toxic effects of SG are superior to that of chemotherapy, if well manage, they determine a low incidence of treatment discontinuation. Then, we want to point out that despite differences in SG use can emerged in different countries for the lack of drug availability and delay in the guideline approval, it is important that all patients can have the opportunity to be treated with this drug also in earliest lines of treatment.

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