

# Expert Answers to Clinician Questions on Caring for Patients With Triple-Negative Breast Cancer

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*The text below is adapted from expert answers to healthcare professionals' questions submitted as part of the program, "Cases and Challenges in the Optimal Treatment of Triple-Negative BC." To view downloadable slides associated with this program, please visit [here](#).*

## Molecular Testing

### Do you recheck biomarkers with each progression of disease and how often do you see a change?

We routinely rebiopsy and retest biomarkers in triple-negative breast cancer (TNBC) because the results can guide therapy. Biomarkers change about 10% to 30% of the time, so it is important to rebiopsy if a patient progresses from early to metastatic disease.<sup>[de Dueñas 2014; Amir 2012]</sup> Even within their metastatic disease course, it is important to rebiopsy to double check estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), at a minimum.

It is also important to check PD-L1 status at the time of progression from early-stage to metastatic disease. One of the first-line therapy options for metastatic TNBC is chemotherapy plus pembrolizumab.<sup>[NCCN Breast; Pembrolizumab PI]</sup> Eligibility for this regimen requires a PD-L1 combined positive score (CPS)  $\geq 10$  using the 22C3 antibody. By contrast, you do not need to check PD-L1 status for early-stage disease because there is no PD-L1 requirement for the KEYNOTE-522 perioperative regimen of chemotherapy plus pembrolizumab.

## Treatment Considerations

### Is sacituzumab govitecan active against brain metastases?

This is a very important question because approximately 30% of women with metastatic TNBC will develop brain metastases.<sup>[Kadamkulam Syriac 2022]</sup> The answer is yes, the chemotherapy payload, SN-38, that is linked to sacituzumab govitecan can cross the blood-brain barrier, and is active against brain metastases.<sup>[Diéras 2021]</sup> We see this in the phase III ASCENT trial, which compared sacituzumab govitecan vs single-agent chemotherapy in patients with advanced TNBC previously treated by 2 or more chemotherapy regimens.<sup>[Bardia 2021]</sup> Patients with stable brain metastases were eligible but excluded from the primary endpoint analysis.



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Sacituzumab govitecan significantly prolonged overall survival (OS) in the population without brain metastases and in the full population, which included patients with stable brain metastases. The median OS for the full population was 11.8 vs 6.9 months with chemotherapy (HR: 0.51; 95% CI: 0.41-0.62). That being said, an exploratory subanalysis of 61 patients with stable brain metastases reported that sacituzumab govitecan numerically improved response and progression-free survival, but not OS.<sup>[Diéras 2021]</sup>

### **Do you sequence trastuzumab deruxtecan before or after sacituzumab govitecan for HER2-low metastatic breast cancer?**

This is a controversial area and we do not yet have definitive data on how to sequence these therapies. When I have sequenced these agents, I have unfortunately found that the responses are not quite as robust as what was reported in the clinical trials. For example, if I begin with sacituzumab govitecan and then go to trastuzumab deruxtecan at the time of progression, I do not see that median OS of 18.2 months reported in the hormone receptor–negative cohort of the registrational DESTINY-Breast04 trial with trastuzumab deruxtecan.<sup>[Modi 2022]</sup> This may be because both agents have payloads that are topoisomerase I inhibitors and there is too much overlap of the mechanisms of action.<sup>[Sacituzumab Govitecan PI; Trastuzumab Deruxtecan PI]</sup>

### **Adverse Event (AE) Management**

#### **Are there differences in immune-related adverse events (irAEs) when pembrolizumab is given for early vs metastatic TNBC?**

With the usual caveats about comparing across trials, irAEs occurred at slightly higher rates with the KEYNOTE-522 regimen in early-stage disease (33.5%) vs the KEYNOTE-355 regimen in the metastatic setting (26.5%).<sup>[Cortes 2022; Schmid 2022]</sup> This is consistent with what I have noticed in my clinical practice.

#### **Would you be concerned about giving prednisone to a patient because of potential adrenal involvement of the tumor?**

Adrenal involvement is uncommon in TNBC; this type of tumor involvement is more common in, for example, non-small-cell lung cancer.<sup>[Tang 2020; Bazhenova 2014]</sup> You probably would not want to give prednisone to a patient with adrenal involvement and would instead use fludrocortisone or hydrocortisone. Those agents have greater mineralocorticoid activity.<sup>[Samuel 2017]</sup>

I have not encountered this issue specifically, but if we consider an extreme example where the patient had both of their adrenal glands completely overtaken by tumor and they were in adrenal insufficiency, I would favor providing them fludrocortisone that would help provide mineralocorticoid support. In any case where there is adrenal involvement, I would definitely partner with an endocrinologist.

#### **How do you manage diarrhea caused by sacituzumab govitecan?**

Diarrhea is an important side effect of sacituzumab govitecan and can occur either early through cholinergic hyperactivation or because of the payload, SN-38.<sup>[Spring 2021]</sup> The acute form requires treatment with diphenoxylate/atropine or IV atropine. I have never encountered the acute form in my practice, but later diarrhea is certainly an issue. You may need to provide intensified regimens of loperamide to manage this diarrhea. I try to avoid dose reductions unless the patient is having significant diarrhea that is not manageable.

It is very important to counsel patients on the gastrointestinal issues that can come with sacituzumab govitecan and to make sure that they know to reach out to us promptly. I once had a patient hospitalized for hypovolemic shock, yet who did not alert us when they were having 15 bowel movements at night. Fortunately, they recovered and are tolerating sacituzumab govitecan really well after we were able to help them manage the diarrhea. The patient also had a dose reduction of sacituzumab govitecan.

### How do you manage anemia caused by poly (ADP-ribose) polymerase (PARP) inhibitors?

Anemia is one of the most common class effects of PARP inhibitors.<sup>[Hurvitz 2020; LaFargue 2019]</sup>

Myelosuppression occurs frequently with olaparib and talazoparib, and patients need to be closely monitored within the first 180 days. It can have a very sudden onset: The patient will have normal hemoglobin, and then suddenly drop to a level so low they must be hospitalized, receive substantial amounts of blood products, and have their PARP inhibitor dose reduced. You need to be diligent about monitoring for myelosuppression with PARP inhibitors.

For anemia related to PARP inhibitors, mild to moderate events can be managed with transfusions and supportive care. More severe anemia requires treatment being withheld and consideration of dose reductions as outlined in the package inserts for olaparib and talazoparib.

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