RobotReviewer report

Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer

Risk of bias table

trial	design	n	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment
Bardia A, 2019	RCT	108	?	?	?	?

Characteristics of studies

Bardia A, 2019

Population	1. Discussion Among patients with metastatic triple-negative breast cancer who had received at least two pre- vious therapies for metastatic disease (median, three) and who received treatment with sacitu- zumab govitecan-hziy 2. Copyright Massachusetts Medical Society BACKGROUND Standard chemotherapy is associated with low response rates and short progression-free survival among patients with pretreated metastatic triple-negative breast cancer.
Interventio n	1. All patients with metastatic triple-negative breast cancer in the Sacituzumab Govitecan-hziy for Breast Cancer efficacy data set received treatment at a starting dose of 10 mg per kilogram. 2. A total of 108 patients received sacituzumab govitecan-hziy at a dose of 10 mg per kilogram of body weight after receiving at least two previous antican-cer therapies for metastatic triple-negative breast cancer. 3. METHODS We conducted a phase 1/2 single-group, multicenter trial involving patients with advanced epithelial cancers who received sacituzumab govitecan-hziy intravenously on days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxic effects.
Outcomes	1. Other efficacy end points were the time to response and the duration of re- sponse in patients who had a response, the clinical benefit rate (defined as a complete or partial response or stable disease for at least 6 months), and progression-free and overall survival. 2. The end points included safety; the objective response rate (according to Response Evaluation Criteria in Solid Tumors, version 1.1), which was assessed locally; the duration of response; the clinical benefit rate (defined as a complete or partial response or stable disease for at least 6 months); progression-free survival; and overall survival. 3. Progression-free and overall survival and time- to-event end points were analyzed with the use of Kaplan-Meier methods, with medians and cor- responding 95% confidence intervals determined according to the Brookmeyer and Crowley method with log-log transformation.

Bias	Judgement	Support for judgement
Random sequence generation	high/unclear	1. A 12-lead ECG was to be performed at baseline, after completion of the infusion on day 1 of every even-numbered treatment cycle, at the end of treatment, and at the end of the trial. 2. A confirmatory multicenter, ran- domized, phase 3 trial (ASCENT; ClinicalTrials.gov number, NCT02574455) is currently recruiting patients in North America and Europe to compare sacituzumab govitecan-hziy with the physician's choice of four single-agent types of chemotherapy (capecitabine, gemcitabine, vinorelbine, and eribulin) in patients with metastatic triple-negative breast cancer that is refractory or relapsed after at least two previous forms of chemotherapy (in- cluding a taxane). 3. In 2016, saci- tuz umab govitecan-hziy was assigned a "breakthrough therapy" designation by the Food and Drug Administration (FDA) for the treatment of patients with metastatic triple-negative breast can- cer who have received at least two previous thera- pies for metastatic disease, and, accordingly, the protocol was amended to require further enroll- ment in a more defined population of patients with metastatic triple-negative breast cancer who had received at least two lines of previous therapy, including previous taxane therapy.
Allocation concealment	high/unclear	1. A 12-lead ECG was to be performed at baseline, after completion of the infusion on day 1 of every even-numbered treatment cycle, at the end of treatment, and at the end of the trial. 2. The trial was approved by the institutional review board at each investigational site before initiation of the trial and was performed in ac- cordance with the Declaration of Helsinki, the International Council for Harmonisation guide- lines for Good Clinical Practice, the FDA Code of Federal Regulations, the requirements of national drug and data protection laws, other applicable regulatory requirements, and the standard oper- ating procedures of Immunomedics. 3. Local assessments were used for treatment decisions and for the primary efficacy analysis.
Blinding of participants and personnel	high/unclear	1. This blinded independent review, which was performed by Intrinsic Imaging, included re- views by two independent radiologists and a third adjudicating radiologist, if needed. 2. In animal models, the tumor-to-serum area under the curve ratio for SN-38 was 20 to 40 times as high with sacituz- umab govitecan-hziy as it was with irinotecan, whereas concentrations that were 20 to 136 times as high as those with irinotecan were delivered into the tumor. 3. (grade 4 neu- tropenia, 7%) and the response rate was 12% with eribulin (duration of response, 4.2 months) and 5% with the physician's choice (duration of response, 6.7 months).
Blinding of outcome assessment	high/unclear	1. Three pa- tients (3%) discontinued treatment because of ad- verse events; 2 patients discontinued because of drug-related events, and 1 patient discontinued because of hypertension, which was thought by the investigator not to be drug-related. 2. The response rate (34.3% [95% CI, 25.4 to 44.0]) and median duration of response (9.1 months [95% CI, 4.6 to 11.3]) according to blinded inde- pendent review were similar to those determined by local assessment (Table S5 in the Supplemen- tary Appendix). 3. Sacituzumab-bound tumor cells are killed by intracellular uptake of SN-38, and adja- cent tumor cells are killed by the extracellular release of SN-38. 24 IMMU-132-01 is a phase 1/2, basket design,

open-label, single-group, multicenter trial involv- ing patients with various types of advanced solid cancers who have received at least one previous therapy for metastatic disease.

References

1. Bardia A et al. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer N. Engl. J. Med. 2019. 8(3); 741-751 PMID: 21208101