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Sacituzumab govitecan efficacy in HR+/HER2– metastatic breast cancer by HER2 immunohistochemistry status in the phase 3 TROPiCS-02 study

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Presenter: Dr. Frederik Marmé

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DECLARATION OF INTERESTS

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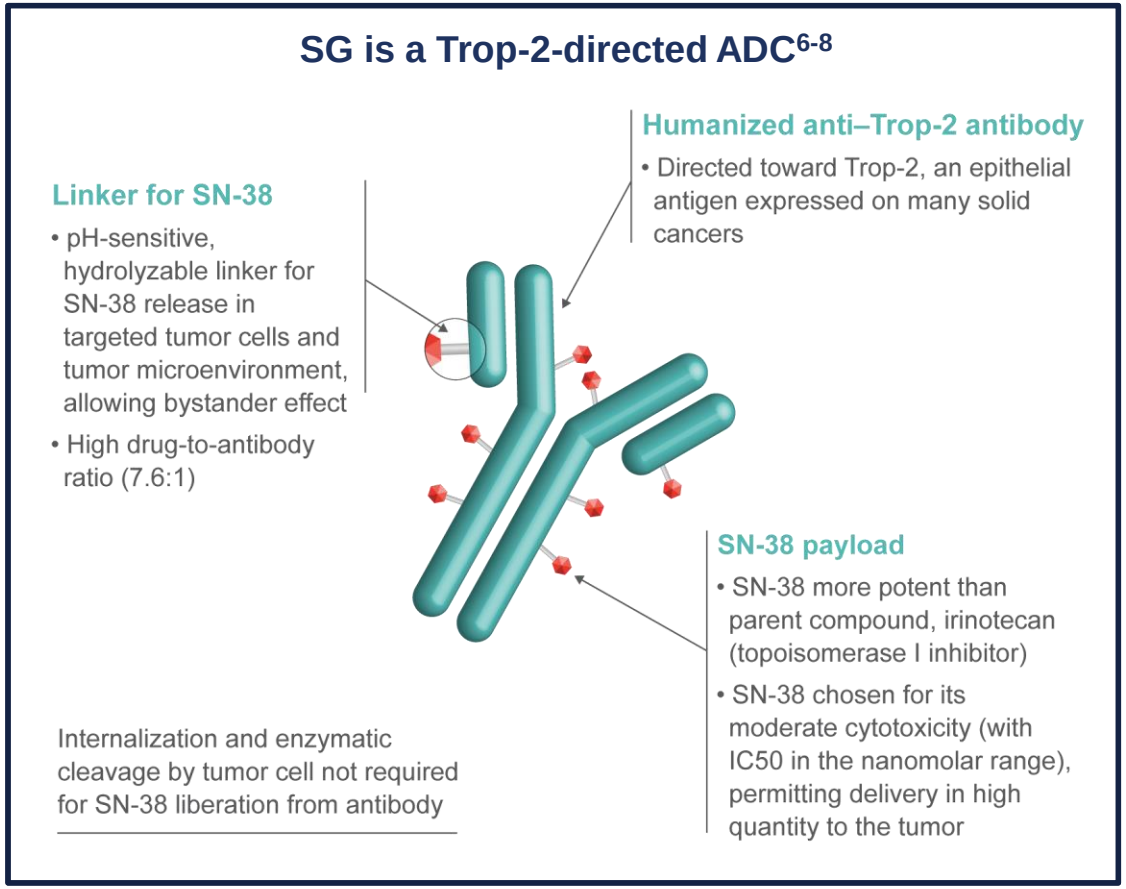
HR+/HER2– and HER2-Low Breast Cancer

- Sacituzumab govitecan is approved for patients with mTNBC who received ≥2 prior systemic therapies (≥1 in the metastatic setting)[1,2]
- In the phase 3 TROPiCS-02 study, SG demonstrated a significant reduction in risk of progression or death (HR, 0.66; *P*<0.001) and significantly improved OS (median 14.4 vs 11.2 mo; HR, 0.79; *P*=0.020) vs TPC in pretreated, endocrine-resistant HR+/HER2– mBC, with a manageable safety profile[3,4]
- "HER2-Low" tumors (IHC1+, or IHC2+ and ISH-negative), a newly defined subcategory of HER2-negative breast cancer, accounts for ~65% of patients with HR+/HER2– breast cancer[5]

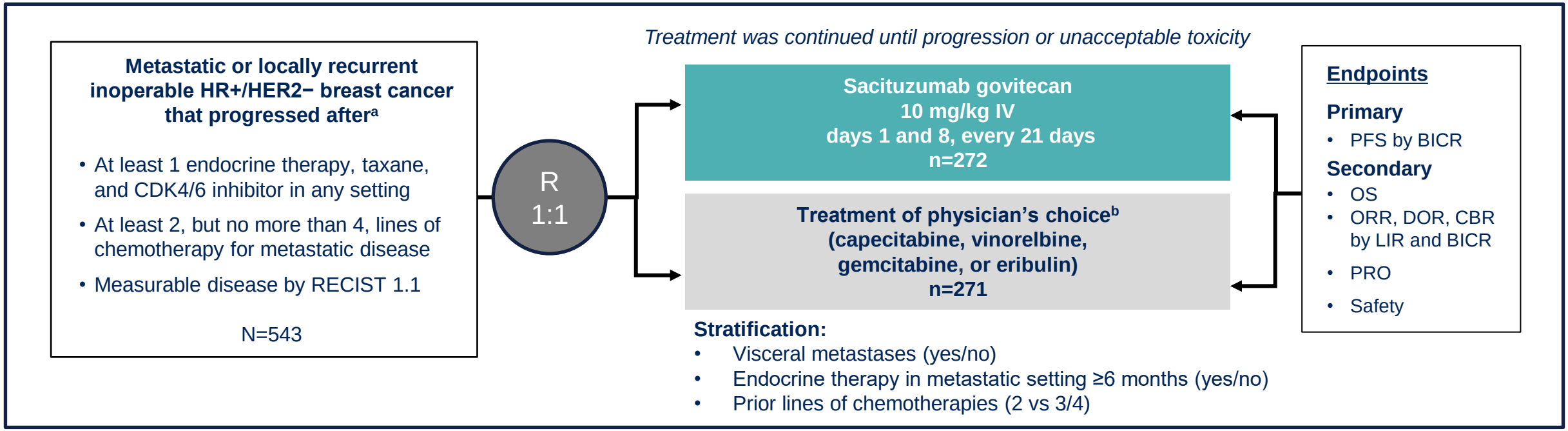
This post hoc subgroup analysis of the TROPiCS-02 study evaluates the efficacy of SG in HER2-Low and HER2 IHC0 HR+/HER2– mBC



ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

1. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Gilead Sciences, Inc.; October 2021. 2. European Medicines Agency:Trodelvy, INN-sacituzumab govitecan, https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf, June 2022. 3. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print). 4. Rugo HS, et al. ESMO 2022. LBA76. 5. Schettini F, et al. *NPJ Breast Cancer.* 2021;7:1. 6. Goldenberg DM, et al. *Expert Opin Biol Ther.* 2020;20:871-885. 7. Nagayama A, et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 8. Goldenberg DM, et al. *Oncotarget.* 2015;6:22496-22512.

Methods



- For this post hoc subgroup analysis, local IHC and ISH results for the ITT population of TROPiCS-02 were analyzed retrospectively to determine SG efficacy by HER2 IHC status:
  - 52% were HER2-Low (IHC1+, IHC2+ [ISH-negative/unverified[c]]): N=283 (SG, n=149; TPC, n=134)
  - 40% were HER2 IHC0: N=217 (SG, n=101; TPC, n=116)
  - 8% were excluded from the analysis due to missing HER2 IHC status: N=43 (SG, n=22; TPC, n=21)

[a]Disease histology based on the ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator. [c]39 patients with HER2 IHC2+ did not have ISH data documentation available for verification and were presumed to be HER2-Low, consistent with the trial eligibility criteria to enroll HER2-negative patients. A separate sensitivity analysis excluding the 39 ISH-unverified patients was also performed, with consistent results.
HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; SG, sacituzumab govitecan; Trop-2, trophoblast cell surface antigen 2.
1. Rugo HS,et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print).

Demographics and Baseline Characteristics

	HER2-Low[a]		HER2 IHC0		ITT[1]	
	SG (n=149)	TPC (n=134)	SG (n=101)	TPC (n=116)	SG (n=272)	TPC (n=271)
Female, n (%)	148 (99)	133 (99)	100 (99)	114 (98)	270 (99)	268 (99)
Median age at study entry, y (min, max)	58 (29, 86)	57 (27, 77)	58 (29, 84)	55 (32, 78)	57 (29, 86)	55 (27, 78)
Race, n (%)						
White	98 (66)	80 (60)	68 (67)	78 (67)	184 (68)	178 (66)
Non-white	14 (9)	11 (8)	3 (3)	12 (10)	19 (7)	23 (8)
Not reported	37 (25)	43 (32)	30 (30)	26 (22)	69 (25)	70 (26)
ECOG PS, n (%)						
0	61 (41)	52 (39)	43 (43)	62 (53)	116 (43)	126 (46)
1	88 (59)	82 (61)	58 (57)	54 (47)	156 (57)	145 (54)
Number of prior chemotherapies, n (%)						
2	65 (44)	53 (40)	42 (42)	49 (42)	113 (42)	113 (42)
3-4	84 (56)	81 (60)	59 (58)	67 (58)	159 (58)	158 (58)
Prior CDK4/6 inhibitor use, n (%)[b]						
≤12 mo	84 (58)	81 (62)	65 (65)	74 (64)	161 (60)	166 (62)
>12 mo	61 (42)	50 (38)	35 (35)	42 (36)	106 (40)	102 (38)
Missing	4 (3)	3 (2)	1 (1)	0	5 (2)	3 (1)

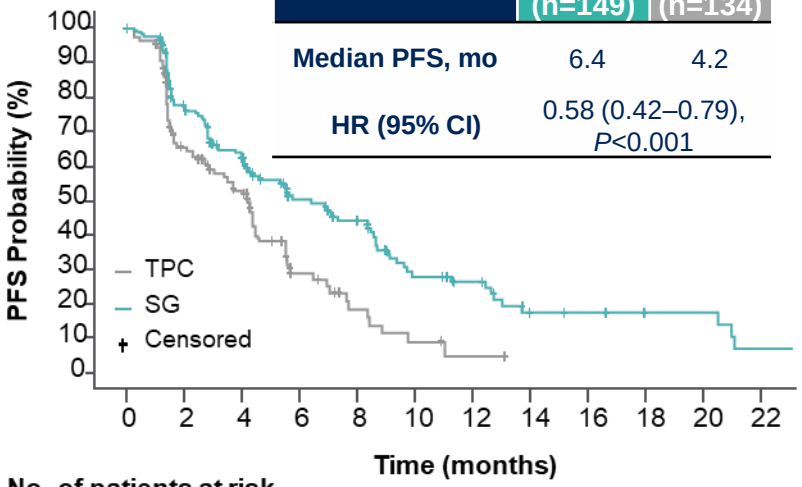
- Of the 543 patients from the TROPiCS-02 ITT population, 92% were HER2-evaluable by IHC
- Demographics and baseline characteristics between the HER2-Low, HER2 IHC0, and ITT populations were comparable

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified. [b]Percentage calculations for prior CDK4/6 inhibitor use ≤12 or >12 mo are based on the total number of patients with available data; percentage calculations for patient missing CDK4/6 inhibitor use data are pared on total number of patients in each group.
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print).

SG Improved PFS vs TPC in HER2-Low and HER2 IHC0 Groups, Consistent with Outcomes in the ITT Population

HER2-Low[a]

	SG (n=149)	TPC (n=134)
Median PFS, mo	6.4	4.2
HR (95% CI)	0.58 (0.42–0.79), *P*<0.001	

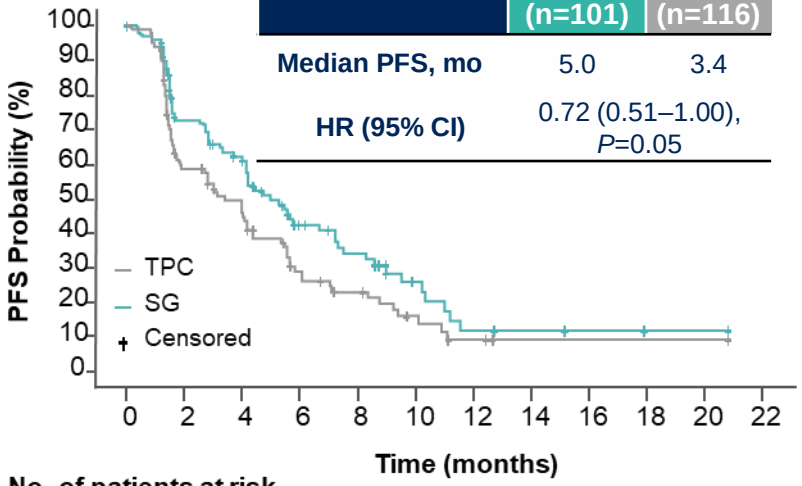


No. of patients at risk

TPC	134	65	43	16	8	4	1	0	0	0	0	0
SG	149	99	77	50	38	22	16	8	7	5	5	2

HER2 IHC0

	SG (n=101)	TPC (n=116)
Median PFS, mo	5.0	3.4
HR (95% CI)	0.72 (0.51–1.00), *P*=0.05	

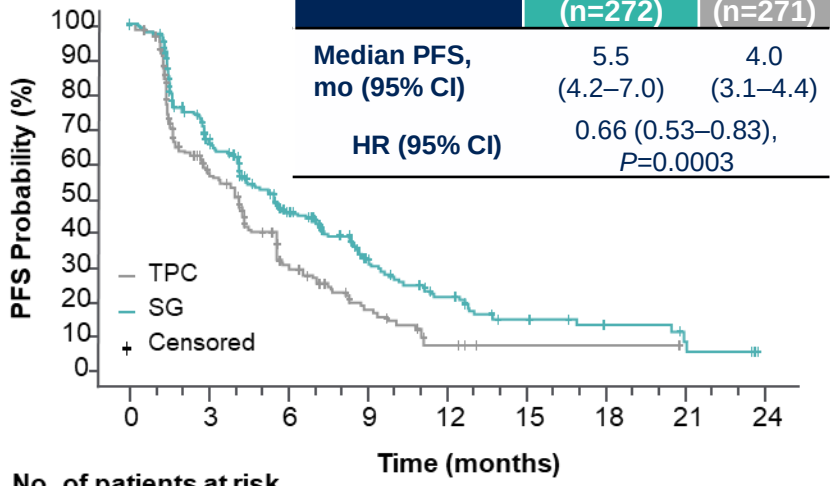


No. of patients at risk

TPC	116	53	39	20	14	7	3	1	1	1	1	0
SG	101	64	50	27	20	9	4	3	2	1	1	0

ITT[1]

	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
HR (95% CI)	0.66 (0.53–0.83), *P*=0.0003	



No. of patients at risk

TPC	271	105	41	17	4	1	1	0		
SG	272	148	82	44	22	12	6	3	0	

- Within the HER2-Low population, median PFS with SG vs TPC for the IHC1+ and IHC2+ subgroups was 7.0 vs 4.3 (HR, 0.57) and 5.6 vs 4.0 (HR, 0.58) months, respectively
- The hazard ratio for median PFS in a sensitivity analysis of the HER2-Low subgroup (excluding ISH-unverified[b]) was similar (HR, 0.53)

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified.
[b]39 patients with HER2 IHC2+ did not have ISH data documentation available for verification and were presumed to be HER2-low, consistent with the trial eligibility criteria to enroll HER2-negative patients.
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print). Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology.

Overall Response by HER2 Status

	HER2-Low[a]		HER2 IHC0		ITT[1]	
	SG (n=149)	TPC (n=134)	SG (n=101)	TPC (n=116)	SG (n=272)	TPC (n=271)
ORR, n (%)	38 (26)	16 (12)	16 (16)	17 (15)	57 (21)	38 (14)
Odds ratio (95% CI)	2.52 (1.33-4.78)		1.10 (0.52-2.30)		1.63 (1.04-2.55)	
Best overall response, n (%)						
CR	2 (1)	0	0	0	2 (1)	0
PR	36 (24)	16 (12)	16 (16)	17 (15)	55 (20)	38 (14)
SD	73 (49)	61 (46)	56 (55)	39 (34)	142 (52)	106 (39)
SD ≥6 mo	18 (12)	10 (7)	15 (15)	8 (7)	35 (13)	21 (8)
PD	29 (19)	36 (27)	23 (23)	38 (33)	58 (21)	76 (28)
NE	9 (6)	21 (16)	6 (6)	22 (19)	15 (6)	51 (19)
CBR, n (%)	56 (38)	26 (19)	31 (31)	25 (22)	92 (34)	59 (22)
Odds ratio (95% CI)	2.50 (1.46-4.30)		1.61 (0.87-2.97)		1.84 (1.25-2.69)	
Median DOR, mo (95% CI)	7.4 (5.8-8.9)	4.1 (2.8-6.1)	8.1 (4.1-NE)	6.1 (2.8-8.3)	7.4 (6.5-8.6)	5.6 (3.8-7.9)

[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified.

CBR, clinical benefit rate; CR, complete response; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; NE, not evaluable; ORR, objective response rate; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print).

Safety Summary

	HER2-Low[a]		HER2 IHC0		Overall Safety Population[1]	
	SG (n=147)	TPC (n=124)	SG (n=99)	TPC (n=107)	SG (n=268)	TPC (n=249)
Grade ≥3 TEAE	109 (74)	73 (59)	70 (71)	66 (62)	198 (74)	149 (60)
TEAEs leading to treatment discontinuation	9 (6)	2 (2)	7 (7)	8 (7)	17 (6)	11 (4)
TEAEs leading to dose delay	98 (67)	44 (35)	61 (62)	56 (52)	178 (66)	109 (44)
TEAEs leading to dose reductions	54 (37)	37 (30)	26 (26)	37 (35)	89 (33)	82 (33)
TE SAEs	38 (26)	25 (20)	33 (33)	15 (14)	74 (28)	47 (19)
TEAEs leading to death[b]	3 (2)	0	3 (3)	0	6 (2)	0
Treatment-related	1 (1)	0	0	0	1 (<1)	0

- The safety profile of SG in the HER2-Low and HER2 IHC0 groups were generally consistent with that of the overall TROPiCS-02 safety population

Treatment-emergent adverse events are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date. Assessed in the safety population of patients who received ≥1 dose of study treatment. Patients may report more than one event per preferred term.
[a]HER2-Low defined as IHC1+, or IHC2+ and ISH-negative/unverified. [b]Of 6 TEAEs leading to death, only 1 was considered by the investigator as treatment-related (septic shock due to neutropenic colitis). The other 5 were: COVID-19 pneumonia, pulmonary embolism, pulmonary sepsis, nervous system disorder, and arrhythmia. Upon detailed review of the TEAEs leading to death, no patterns were identified.
AE, adverse event; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; TE, treatment-emergent; TEAE, treatment-emergent adverse event; SAE, serious adverse event; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print).

Conclusions

- SG improved efficacy outcomes vs TPC in HER2-Low and HER2 IHC0 HR+/HER2– mBC, consistent with that of the TROPiCS-02 ITT population:
  - Median PFS was 6.4 vs 4.2 mo (HR, 0.58) in the HER2-Low group, and 5.0 vs 3.4 mo (HR, 0.72) 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[1-3]
- SG should be considered an effective treatment option for patients with HR+/HER2– mBC, regardless of HER2 IHC status

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intention-to-treat; mBC, metastatic breast cancer; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print). 2. Kalinsky K, et al. *Ann Oncol.* 2020;31(12):1709-1718. 3. Bardia A, et al. *N Engl J Med*. 2021;384:1529-1541.

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