# Efficacy of Sacituzumab Govitecan vs Treatment of Physician's Choice in Previously Treated HR+/HER2–Metastatic Breast Cancer: A Meta-Analysis of TROPiCS-02 and EVER-132-002 Trials

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### Conclusions

- This meta-analysis of the global pivotal TROPiCS-02 and EVER-132-002 phase 3 trials showed that SG significantly improved OS and PFS vs TPC in the overall and CDK4/6i-pretreated HR+/HER2- mBC populations
- These results are consistent with trial-level results from TROPiCS-02 and EVER-132-002, reinforcing the efficacy benefits of SG over TPC

## Plain Language Summary

- Sacituzumab govitecan is a drug that is approved in several countries to treat hormone receptor—positive/human epidermal growth factor receptor— 2—negative (HR+/HER2—) metastatic breast cancer (a type of breast cancer that has spread to other parts of the body), the most common subtype of breast cancer
- In the TROPiCS-02 and EVER-132-002 phase 3 clinical trials, participants with HR+/HER2— metastatic breast cancer received either sacituzumab govitecan or a treatment of physician's choice
- This study is a meta-analysis of the above trials. Meta-analyses typically combine and summarize data from 2 or more trials
- Participants in both trials had similar characteristics except that:
- All participants in the TROPiCS-02 trial and only about half of the participants in the EVER-132-002 trial had received prior cyclin-dependent kinase 4/6 inhibitors (CDK4/6i, a class of drugs used to treat breast cancer)
- Most participants in the TROPiCS-02 trial were non-Asian and all participants in the EVER-132-002 trial were Asian
- The results of this meta-analysis showed that participants who took sacituzumab govitecan had more time before their tumor got bigger or spread further or they died from any cause (progression-free survival), and they lived longer (overall survival) compared with participants who took chemotherapy
- Participants benefited from sacituzumab govitecan whether they had previously been given a CDK4/6i or not

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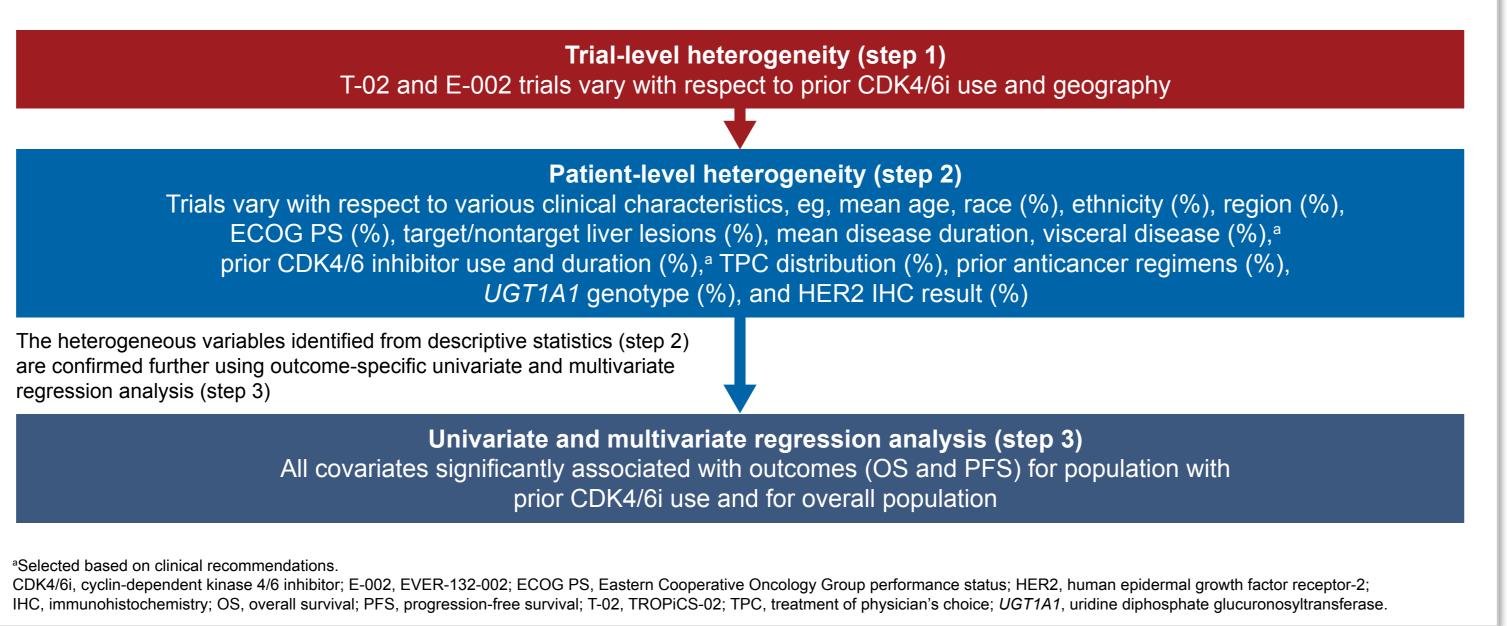
### Introduction

- Sacituzumab govitecan (SG) is a Trop-2—directed antibody-drug conjugate that delivers a topoisomerase inhibitor in solid tumors including HR+/HER2— metastatic breast cancer (mBC)<sup>1,2</sup>
- TROPiCS-02 (T-02) is an open-label, randomized, phase 3 trial that demonstrated the efficacy and manageable safety profile of SG vs treatment of physician's choice (TPC) in patients with HR+/HER2–, locally advanced, inoperable, or mBC, after failure of 2 to 4 prior chemotherapy regimens for metastatic disease<sup>2,3</sup>
- Based on these data, SG is approved in multiple countries worldwide for the treatment of HR+/HER2– mBC following endocrine therapy and at least 2 additional systemic therapies in the metastatic setting<sup>4,5</sup>
- EVER-132-002 (E-002) is another open-label, randomized, phase 3 trial with similar results in this patient population<sup>6</sup>
- T-02 and E-002 had several differences:
- T-02, the pivotal global trial, enrolled predominantly non-Asian patients, whereas the E-002 trial enrolled only Asian patients
- T-02, but not E-002, required prior cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) treatment
- The objective of this meta-analysis is to evaluate the efficacy of SG vs TPC in all patients (overall population) and the subset of patients pretreated with CDK4/6i from T-02 and E-002

### Methods

- A feasibility assessment of the meta-analytic framework was conducted by evaluating the level of availability
  of evidence, trial heterogeneity, and approaches to pool effect sizes of SG vs TPC from trials existing in the
  evidence inventory (Figure 1)
- Meta-analytic models were developed to adjust for cross-trial differences. A one-stage model (results yielded by pooling individual patient level data from T-02 and E-002) and a fixed-effect model (results yielded by pooling trial-level hazard ratios from T-02 and E-002) estimated pooled treatment effects for overall survival (OS) and progression-free survival (PFS) in the overall and CDK4/6i-pretreated populations
- The one-stage model is the model of choice for enhancing statistical power and precision when estimating treatment effects
- The fixed-effect model is the model of choice after taking into consideration cross-trial differences (in this case homogeneity between trials being statistically established) when estimating treatment effect
- The fixed-effect model provides more precise estimates of the treatment effect, especially when the studies are similar in design, population, and variation in treatment outcomes. The fixed-effect model was selected as the base-case model due to nonsignificant Chi² statistic, moderate heterogeneity (< 75% I² statistic), and expert guidance
- The difference in patient geography between the 2 trials cannot be adjusted, but prior studies have suggested that this difference has no significant impact on survival outcomes in breast cancer
- A regression analysis was conducted with respect to the various clinical characteristics, and the significant heterogenous covariates identified during the assessment were adjusted in the meta-analysis (Figure 1)

Figure 1. Heterogeneity Assessment by Comparing Trial- and Patient-Level Characteristics Between T-02 and E-002 Trials



### Results

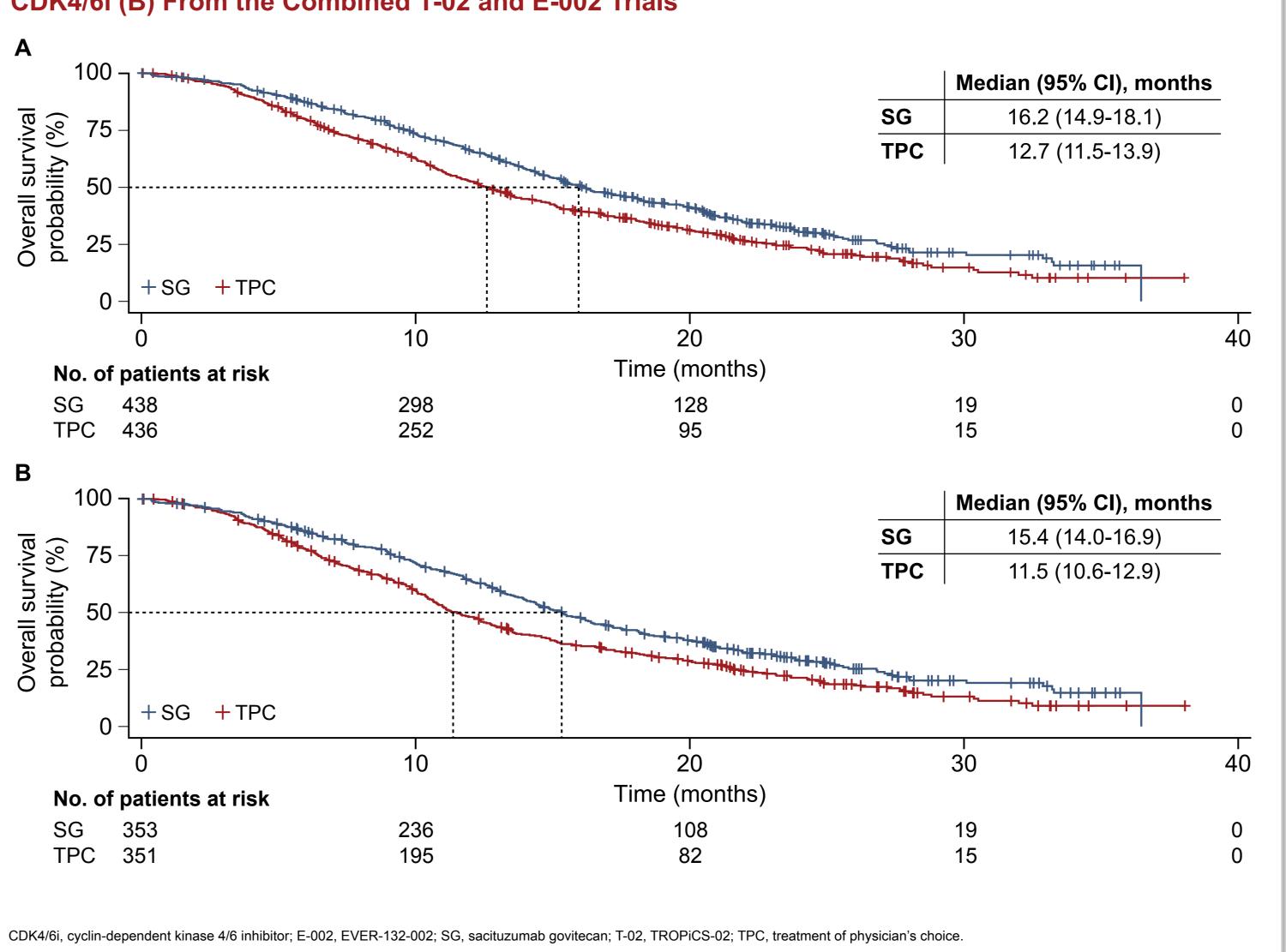
### **Baseline Characteristics**

 In general, T-02 and E-002 had similar distribution of baseline population characteristics (low heterogeneity, l² = 0.0%-9.6%) except for prior CDK4/6i treatment and geography

### **Outcomes**

- Median OS was 16.2 months (95% CI, 14.9-18.1) and 12.7 months (95% CI, 11.5-13.9) for SG and TPC, respectively, in the overall population. Results were similar for patients who received prior CDK4/6i treatment (Figure 2)
- In the fixed-effect model and one-stage approach, SG showed statistically significant improvement vs TPC in OS (Table 1; Figure 3) and PFS (Table 2; Figure 4), both for patients with prior CDK4/6i use and for the overall population

Figure 2. Overall Survival With SG and TPC in the Overall Population (A) and Patients With Prior CDK4/6i (B) From the Combined T-02 and E-002 Trials



# Table 1. Comparison of Overall Survival With SG vs TPC in the Overall Population and Patients With Prior CDK4/6i From the Combined T-02 and E-002 Trials (Fixed-Effect Model and One-Stage Approach)

| Population                      | HR (95% CI) for SG vs TPC         | I <sup>2</sup> Statistic <sup>a</sup> | Q (Chi² Statistic)   |
|---------------------------------|-----------------------------------|---------------------------------------|----------------------|
| Overall population (N = 874     | .)                                |                                       |                      |
| Fixed-effect model <sup>b</sup> | 0.70 (0.58-0.86), <i>P</i> < .001 | 9.6% (no/low)                         | 1.11, <i>P</i> = .29 |
| One-stage approach              | 0.66 (0.55-0.80), <i>P</i> < .001 | _                                     | -                    |
| Prior CDK4/6i use (n = 704)     |                                   |                                       | •                    |
| Fixed-effect model <sup>b</sup> | 0.68 (0.55-0.84), <i>P</i> < .001 | 73.8% (moderate)                      | 3.82, <i>P</i> = .05 |
| One-stage approach              | 0.65 (0.53-0.80), <i>P</i> < .001 | -                                     | -                    |

al<sup>2</sup> and Q (Chi<sup>2</sup>) statistics are measures for evaluating the level of heterogeneity between studies and hence relevant in the fixed-effect model analysis; the higher the l<sup>2</sup> value, the higher the heterogeneity of the studies; a significant Chi<sup>2</sup> value indicates the presence of heterogeneity between the studies.

bThe fixed-effect model assumes that the studies share a single common effect, and therefore, all the variance in the observed effect is attributable to sampling error.

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; E-002, EVER-132-002; HR, hazard ratio; SG, sacituzumab govitecan; T-02, TROPiCS-02; TPC, treatment of physician's choice.

# Figure 3. Comparison of Overall Survival With SG vs TPC in the Overall Population (A) and Patients With Prior CDK4/6i (B) From T-02 and E-002 Trials (Fixed-Effect Model) A B OS HR (95% CI) T-02 0.75 (0.60-0.95) E-002 0.60 (0.42-0.86) E-002 0.70 Overall, IV (I² = 9.6%, P = .293) 0.5 1 Results based on statistical and clinical covariates. CDK4/6i. (ovelin-dependent kinase 4/6 Inhibitor, E-002, EVER-132-002; HR. hazard ratio; IV, Inverse variance; OS, overall survival; SG, sacituzumab govitecan; T-02, TROPICS-02; TPC, treatment of physicians



| Population                      | HR (95% CI) for SG vs TPC         | I <sup>2</sup> Statistic <sup>a</sup> | Q (Chi² Statistic)ª  |  |  |
|---------------------------------|-----------------------------------|---------------------------------------|----------------------|--|--|
| Overall population (N = 874)    |                                   |                                       |                      |  |  |
| Fixed-effect model <sup>b</sup> | 0.67 (0.55-0.83), <i>P</i> < .001 | 0.0% (No)                             | 0.38, <i>P</i> = .54 |  |  |
| One-stage approach              | 0.62 (0.50-0.77), <i>P</i> < .001 | -                                     | -                    |  |  |
| Prior CDK4/6i use (n = 704)     |                                   |                                       | 1                    |  |  |
| Fixed-effect model <sup>b</sup> | 0.66 (0.52-0.84), <i>P</i> = .001 | 0.0% (No)                             | 0.89, <i>P</i> = .35 |  |  |
| One-stage approach              | 0.65 (0.52-0.81), <i>P</i> < .001 | _                                     | _                    |  |  |

Figure 4. Comparison of Progression-Free Survival With SG vs TPC in the Overall Population (A) and Patients With Prior CDK4/6i (B) From T-02 and E-002 Trials (Fixed-Effect Model)

<sup>b</sup>Fixed-effect model assumes the studies share a single common effect, and therefore, all the variance in the observed effect is attributable to sampling error. CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; E-002, EVER-132-002; HR, hazard ratio; SG, sacituzumab govitecan; T-02, TROPiCS-02; TPC, treatment of physician's choice.

