Phase III postneoadjuvant study evaluating Sacituzumab Govitecan, an Antibody Drug Conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment – SASCIA

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Background

Patients with triple-negative breast cancer (TNBC) without a pathologic complete response[1,2,3] as well as hormone receptor (HR)-positive/HER2-negative patients with a CPS+EG (clinical, pathologic stage + estrogen receptor status and grade) score ≥3 or 2 with ypN+[4] have a high risk of recurrence. In high-risk patients, post-neoadjuvant therapy can significantly improve survival.[5,6,7,8] Sacituzumab govitecan (SG) has shown high activity in heavily pretreated patients with metastatic TNBC[9] and HR-positive/HER2-negative BC,[10,11] even after prior immune-checkpoint inhibitors or CDK4/6 and mTOR inhibitors. Efficacy in TNBC was confirmed in the phase III ASCENT trial,[12] irrespective of Trop-2 expression or g*BRCA1/2* status.[13] A phase III trial in a HR-positive cohort is ongoing.[14]
Based on these studies, SG might be an ideal therapy against the resistant residual disease after standard neoadjuvant chemotherapy (NACT) regardless of HR status.

Study Overview

SASCIA (NCT04595565) is a phase III, prospective, multi-center, randomized, open label, parallel group study in patients with HER2-negative BC with residual disease after NACT at high risk of recurrence with 1:1 allocation to SG or treatment of physician's choice (TPC). In patients with HR-positive BC, endocrine-based therapy will be administered according to local guidelines. SASCIA will randomize 1200 patients with centrally confirmed HER2-negative, HR-positive (≥1% positive stained cells) or HR-negative BC assessed preferably on tumor tissue from post-neoadjuvant residual invasive disease.

Objectives and Endpoints

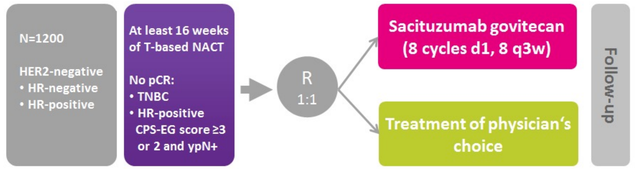
Primary objective:
To compare invasive disease-free survival (iDFS) between patients treated with SG vs. TPC
Secondary objectives (selection):
- To compare overall survival (key secondary objective) and distant DFS between groups.
- To compare safety, compliance, patient reported outcome and quality of life.
- To explore the predictive value of markers (including immune markers) for SG.
- To explore ctDNA dynamics as early predictors of response.

Figure 1: Biomaterial collection

	Screening Phase	Treatment Phase				Follow-up Phase
	Prior to Rando	prior to start of therapy (pre-treatment)	day1 cycle 3 pre-dose	day1 cycle 6 pre-dose	at EOT	Recurrence (at 1st relapse)
FFPE tumor tissue*	x*					x
Plasma ctDNA		x			x	x
Serum		x	x	x	x	x
Whole Blood		x	x	x		

*FFPE from pre-neoadjuvant core biopsy (breast) and FFPE post-neoadjuvant surgically removed tissue from breast for central pathology) or post-neoadjuvant surgically removed tissue from involved lymph node if no residual tumor from breast is available, in case of bilateral BC blocks from both sides are obligatory. Abbreviations: ctDNA, circulating tumor DNA; EOT, End of Treatment; FFPE, Formalin-Fixed Paraffin-Embedded;

Study Design



Stratification factors:

- HR-positive vs HR-negative
- ypN+ vs ypN-

Study Treatment:

Sacituzumab govitecan 10 mg/kg body weight on days 1, 8 q3w

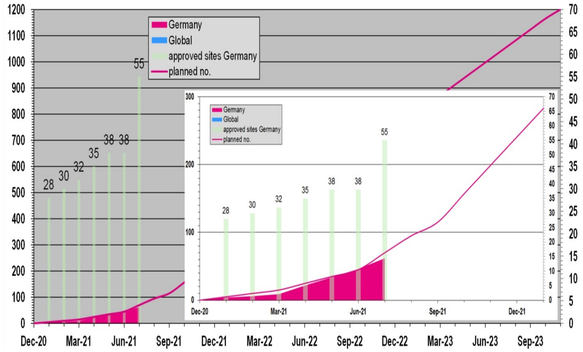
Treatment of physician's choice:
- Capecitabine 2000 mg/m² day 1-14 q21 day cycle for eight cycles
- Carboplatin AUC 5 q3w or AUC 1.5 weekly for eight 3 weekly cycles
- Observation
- Endocrine-based therapy will be administered according to local guidelines.

Sample size determination:

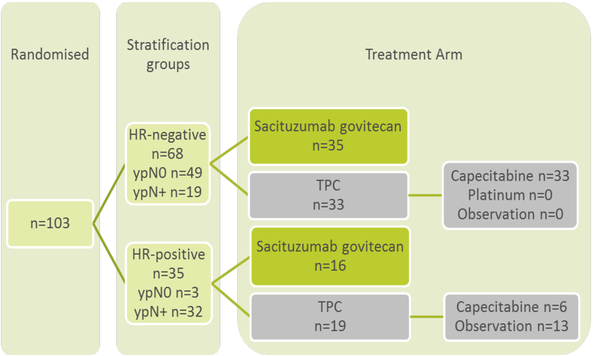
- 5-years iDFS improvement 60.0% to 68.2% with sacituzumab govitecan
- Hazard Ratio=0.75, β=80%,α=0.05
- One interim analysis for overwhelming efficacy at 2/3 of total 385 events.

Abbreviations: CPS+EG, clinical, pathological stage + estrogen receptor status and grade) score; HR, hormone receptor; NACT, neoadjuvant chemotherapy; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

Recrument



Recruitment Overview



*Cut-off 25. August 2021

Abbreviations: TPC, Treatment of physician's choice

Key Inclusion Criteria

- Patients with residual invasive disease after NACT at high risk of recurrence defined by either:
  - HR-negative: any residual invasive disease > ypT1mi
  - HR-positive: CPS+EG score ≥ 3 or CPS+EG score 2 and ypN+ using local ER and grade assessed on core biopsies taken before NACT.
- Patients must have received taxane-based NACT for 16 weeks (anthracyclines are permitted):
  - This period must include 6 weeks of a taxane-containing NACT
  - For patients with progressive disease that occurred after at least 6 weeks of taxane-containing NACT, a total treatment period of less than 16 weeks is also eligible.
- An interval of less than 16 weeks since the date of final surgery or less than 10 weeks from completing radiotherapy (whichever occurs last) and the date of randomization is required.
- Immune checkpoint inhibitor / immunotherapy during NACT is allowed.
- Radiotherapy should be delivered before the start of study treatment.

Key Exclusion Criteria

- Patients with definitive clinical or radiologic evidence of stage IV cancer (metastatic disease) are not eligible.
- Patients with a history of any malignancy are ineligible with the following exceptions:
  - Patient has been disease-free for at least 5 years and is at low risk for recurrence of that malignancy.
  - CIS of the cervix, basal cell and squamous cell carcinomas of the skin.
- Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study, including Gilbert's disease, Crigler-Najjar-Syndrom, known hepatitis B, hepatitis C, known HIV positivity or known autoimmune disease (other than diabetes, vitiligo, or stable thyroid disease).
- Any condition that interferes with the safe administration of the treatment of physician's choice (in TPC arm).
- Receipt of live attenuated vaccines within 30 days prior to study entry or within 30 days of receiving chemotherapy.
- Known or suspected congestive heart failure (>NYHA I) and/or coronary heart disease.
- History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis or active pneumonitis on chest CT scan.
- Known allergic reactions to irinotecan.

Conclusions

SASCIA is a phase III study investigating the efficacy and safety of SG compared to TPC in patients with HER2-negative BC with residual disease after NACT at high risk of recurrence. Recruitment has started in December 2020 and will take an estimated 36 months (42 patients per month). As of 25th August 2021, 103/1200 patients have been randomized in Germany. International study groups will join soon.

References

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