## 1936P Targeted therapy of desmoplastic small round cell tumor guided by multilayered molecular profiling

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**Background:** Desmoplastic small round cell tumor (DSRCT) is an ultra-rare soft-tissue sarcoma characterized by an *EWSR1::WT1* gene fusion that affects predominantly male adolescents and young adults. Despite intensive multi-modality treatment outcomes remain dismal, with only 25% of patients being alive after five years. Beyond conventional therapies, novel, molecular mechanism-aware therapies are urgently needed.

**Methods:** Patients with advanced DSRCT underwent multilayered molecular profiling as part of NCT/DKFZ/DKTK MASTER (Molecularly Aided Stratification for Tumor Eradication Research), a prospective, multicenter observational study that applies whole-genome/exome, transcriptome, methylome, and — more recently — mass spectrometry-based (phospho-)proteome analysis in young adults with advanced malignancies and patients with rare cancers to inform clinical decision-making and the design of molecularly stratified clinical trials.

**Results:** Between 2013 and 2022, 29 patients with DSRCT were analyzed with a median follow-up of 17 months (range, 0—48). The median age at the time of molecular analysis was 30 years (range, 18—56). The median time between diagnosis and molecular analysis was 12 months (range, 1—216). The median survival and the 4-year survival rate from registration were 2.4 years (95% confidence interval [CI], 1.4—3 years) and 7.4% (95% CI, 1.2—45.2%), respectively. In 8 of 9 samples with available proteomics data, we observed pronounced activation of ERBB (also called HER) signaling and high *ERBB2* mRNA expression levels, providing a rationale for personalized therapy with ERBB2-specific antibody-drug conjugates. In addition, selected somatostatin receptor family members, i.e., SSTR3 and 5, were highly expressed in all patients with available transcriptome data, providing the basis for treatment with pasireotide, a novel multireceptor-targeted somatostatin receptor ligand, within an academic clinical trial, which is currently being prepared.

**Conclusions:** We describe the molecular profiles of patients with DSRCT enrolled in MASTER and demonstrate the utility of broad molecular profiling for the clinical management of this disease, including the application of targeted treatment strategies.

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