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Association of *CTNNB1* mutation subtypes with responses to systemic therapy in patients with desmoid tumors.

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Desmoid tumors (DT) exhibit unpredictable behavior; while many DT are indolent or spontaneously resolve, some are prone to multiple recurrences leading to patient morbidity and mortality. Cytotoxic chemotherapies including doxorubicin-based regimens, methotrexate/vinblastine, and sorafenib are among the most effective treatments for progressive DT but are associated with toxicity. Prior studies suggest that patients with *CTNNB1* S45F mutations were more likely to recur compared to *CTNNB1* T41A mutations. We established a multi-institutional retrospective database of DT patients to evaluate whether *CTNNB1* mutation subtype correlated with responses to systemic therapies. Mutation testing was available for 177 patients. Overall survival was significantly worse in patients with *APC* mutations relative to T41A, S45F, or other mutations (p=0.028), and for mesenteric/intraabdominal and other location relative to extremity/trunk (p=0.004). No mutation group was associated with worse clinical PFS across all 1st or 2nd line therapies. In multivariate analysis, *APC* mutation status was associated with progression (HR 4.93, p=0.026), whereas doxorubicin/dacarbazine (HR 0.32, p=0.023) and liposomal doxorubicin (HR 0.39, p=0.047) treatment were associated with improved 1st line clinical PFS. Across all treatment lines, no significant differences in clinical progression-free survival were observed with different systemic therapies by mutation, though a trend towards was observed with sorafenib therapy in S45F mutated DT relative to T41A mutations. In summary, cytotoxic chemotherapies retain significant clinical activity against DT regardless of mutation subtype. An observed trend towards improved outcomes with sorafenib in S45F mutant DT warrants further prospective investigation. *APC* mutations and mesenteric/intraabdominal DT location remain useful prognostic factors to identify higher risk patients who may warrant more intensive surveillance or earlier initiation of chemotherapy.