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REVIEW

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# Desmoplastic small round cell tumor: from state of the art to future clinical prospects

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**ABSTRACT**

**Introduction:** Desmoplastic small round cell tumor (DSRCT) is an extremely rare and highly aggressive soft tissue sarcoma, presenting mainly in male adolescents and young adults with multiple nodules disseminated within the abdominopelvic cavity. Despite a multimodal approach including aggressive cytoreductive surgery, intensive multi-agent chemotherapy, and postoperative whole abdominopelvic radiotherapy, the prognosis for DSRCT remains dismal. Median progression-free survival ranges between 4 and 21 months, and overall survival between 17 and 60 months, with the 5-year overall survival rate in the range of 10–20%.

**Area covered:** This review discusses the treatment strategies used for DSRCT over the years, the state of the art of current treatments, and future clinical prospects.

**Expert opinion:** The unsatisfactory outcomes for patients with DSRCT warrant investigations into innovative treatment combinations. An international multidisciplinary and multi-stakeholder collaboration, involving both pediatric and adult sarcoma communities, is needed to propel preclinical model generation and drug development, and innovative clinical trial designs to enable the timely testing of treatments involving novel agents guided by biology to boost the chances of survival for patients with this devastating disease.

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Desmoplastic small round cell tumor; chemotherapy; hyperthermic intraperitoneal chemotherapy; novel agents; prognosis; radiotherapy; surgery; biomarker

## 1. Introduction

Desmoplastic small round cell tumor (DSRCT) is an extremely rare and highly aggressive soft tissue sarcoma that generally affects male adolescents and young adults. Its incidence is approximately 0.2 cases per million people [1,2]. When first described by Gerald and Rosai in 1989 [3], DSRCT mainly presents with multiple nodules disseminated within the abdominopelvic cavity and arising from peritoneal surfaces. Its clinical presentation is typically related to an abdominal mass, and patients are usually diagnosed already in advanced stages of the disease: at diagnosis, patients with DSRCT have synchronous peritoneal metastases in more than 90% of cases, and synchronous extraperitoneal metastases in around 50% of cases, mostly to the liver, lung, and bones [4–6]. DSRCT is associated with a chromosomal translocation t(11;22) (p13; q12) that leads to the *EWSR1:WT1* fusion gene [7,8].

To date, there is no consensus on standard treatment approaches. The management of intra-abdominal DSRCT is currently based on a combination of aggressive cytoreductive surgery, intensive multi-agent chemotherapy, and postoperative whole abdominopelvic radiotherapy (WAP-RT). Other strategies that have been explored include high-dose chemotherapy with autologous stem cell transplantation, hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin, targeted therapy and maintenance therapy. Even with an aggressive multimodal approach, the prognosis for DSRCT remains dismal. Median progression-free survival (PFS) ranges between 4 and 21 months, and overall survival (OS) between 17 and 60 months with 3- and 5-year OS rates of 44% and 15%, respectively (Table 1) [4,6,10,11,14,18,22,25,30–32]. Various clinical variables reportedly correlate with the outcome: the presence of hepatic or portal metastases, resistance to neo-adjuvant chemotherapy, and CD99 expression have been described as adverse prognostic factors [8,24,25], while

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**Article highlights**

- Desmoplastic small round cell tumor carries a very poor prognosis
- To date, there is no standard first-line treatment
- A multimodal approach is the common strategy
- Novel agents seem promising, judging from studies in preclinical models.

the absence of extraperitoneal metastases, the feasibility of complete surgical resection, and the use of radiotherapy seem to be favorable prognostic factors [4,8]. Other factors investigated – such as age, gender, postoperative complications, disease extent at diagnosis, and tumor size – revealed no significant impact on the survival of patients with intra-abdominal DSRCT [17,18].

## 2. Pathology and molecular features

DSRCT is histologically characterized by nests of undifferentiated round tumor cells surrounded by dense desmoplastic stroma. The tumor cells co-express several epithelial (cytokeratin, epithelial membrane antigen), mesenchymal (desmin, vimentin), and neural (CD56, neuron-specific enolase) markers that enable its differential diagnosis vis-à-vis other small round cell tumors and in over 90% of cases, DSRCT can show immunoreactivity to antibodies that specifically target the carboxy terminus of the WT1 protein [33,34]. The pathognomonic chimeric protein EWSR1-WT1, encoded by the *EWSR1:WT1* fusion gene, acts as an aberrant transcriptional activator. It is thought to be the key driver behind the oncogenic process in DSRCT, as it influences the expression of several growth factors, receptor genes, and transcriptional regulators [35]. This process leads to collagenous stromal production (a hallmark of DSRCT), inflammatory cell infiltration, neo-angiogenesis, and proliferation. A recently conducted next-generation sequencing analysis of 68 matched DSRCT tumor vs normal samples confirmed that DSRCT is generally a genomically quiet cancer, but several recurrent molecular alterations were identified in *TERT* (3%), *ARID1A* (6%), *HRAS* (4%), *TP53* (3%) and *FGFR4* (7%), which may affect the disease's presentation and course [36]. Other studies (not conducted on matched tumor vs normal samples) identified other genomic alterations associated with DNA damage response (DDR) in various genes, including *ATM, RAD50, BARD1, BRCA1/2, PALB2* and *CHEK2*. Preclinical analyses also demonstrated a transcriptional modulation of several downstream targets of the fusion protein associated with essential biological pathways involved in drug resistance, including the DDR pathway and mesenchymal epithelial reverse transition [35].

For now, the DSRCT cell of origin remains unknown. Studies on the gene expression patterns of DSRCT showed that this tumor clustered separately from adjacent normal tissues and other types of sarcoma [37,38]. DNA methylation analysis confirmed that DSRCT samples have a distinct pattern [39,40]. Since the disease often presents with multiple masses, phylogenetic analyses were performed on mutations and somatic copy-number alterations (SCNAs) in samples from multiple sites to investigate whether they had a shared or independent origin. Identical *EWSR1:WT1* fusion breakpoints and most mutations and SCNAs occurred within the trunks of the phylogenetic trees, confirming that DSRCT develops from a single lesion [36]. Most SCNAs in this tumor involve whole chromosome arms, or whole chromosomes, with very few significant focal events. In around one in two patients, gains have been found in chromosomes 1q, 3, 5, and 21q, and losses in chromosomes 11p, 11q, and 16q [41]. That said, the large number of genes encoded by whole chromosome arms and whole chromosomes makes it hard to establish which SCNA genes contribute to tumor formation.

Reports on single cases or small samples of DSRCT patients only occasionally describe genomic sequencing performed to identify crucial genetic alterations other than *EWSR1:WT1*. These studies found that DSRCT has a low mutation burden with a few recurrently mutated cancer genes [36,37,41,42]. This confirms the role of *EWSR1:WT1* fusion as the main driver of tumor initiation, and is consistent with the idea that fusion-positive sarcomas are driven mainly by the fusion oncoprotein, with few other genomic alterations. The low mutation burden found in DSRCT may be one of the reasons for the low overall immune infiltrate levels primarily associated with this tumor. In fact, PD-L1 expression reportedly varies considerably in DSRCT, and PD-1 is expressed on tumor cells instead of on tumor-infiltrating lymphocytes [43,44]. Interestingly, this tumor is associated with the loss of the whole of chromosome 6, where immunoregulatory genes are located [37].

The lack of specific prognostic biomarkers for DSRCT poses a challenge. Liquid biopsy offers the chance to assess tumor burden by analyzing circulating tumor material (tumor cells, DNA, RNA, exosomes, etc.) in several biofluids, such as blood, ascites, and pleural fluid [45]. Circulating tumor DNA (ctDNA) can be used to perform molecular studies on tumor-derived fragmented DNA in the bloodstream. Two published studies used ctDNA in one and six patients with DSRCT to monitor disease burden based on the detection of *EWSR1:WT1* [46,47]. Such studies may, in the future, enable the early detection of a patient's failure to respond to treatment, and prompt the use of alternative therapies.

MicroRNAs (miRNAs) are short RNA molecules that regulate the post-transcriptional silencing of target genes. They have been investigated as biomarkers in liquid biopsy because miRNA profiles may distinguish between normal and cancerous tissue, reflect tumor expression in the serum of cancer patients, and predict outcomes or responses to therapy [48,49]. EWS reportedly regulates *DROSHA* expression, and modulates miRNA biogenesis, pointing to an alteration of miRNA regulatory mechanisms mediated by this protein [50].

Epithelial–mesenchymal transition (EMT) and mesenchymal–epithelial reverse transition (MErT) are fundamental to DSRCT plasticity and have an important role in tumor progression, metastasis, and chemoresistance. EMT and MErT undergo a dual epigenetic regulation via miRNA-200 or miRNA-34, which govern the switch: high miRNA-200 and/or miRNA-34, and low ZEB1 levels correspond to an epithelial phenotype, whereas high ZEB1 and low miRNA-200 and/or miRNA-34 levels correspond to a mesenchymal phenotype [51].

Circulating miRNAs were also investigated in circulating exosomes, small membrane vesicles 30–100 nm in diameter,

Table 1. Selected studies on desmoplastic small round cell tumor.

| Author | Series | Treatment | Outcome |
|---|---|---|---|
| Kushner et al, 1996, MSKCC, New York, USA [9] | Prospective, single-institution study;<br>Study period: not reported;<br>Number of cases: 12;<br>Median age 14 years (range 7–22) | multiagent intensive chemotherapy (P6 protocol), 11/12 had surgery, 4/12 had local radiotherapy, 4/12 had ASCT | 5 pts alive with NED (10, 13, 14, 34, 39 months after diagnosis) |
| Goodman et al, 2002, MSKCC, New York, USA [10] | Retrospective, single-institution study;<br>Study period: 1992–2001;<br>Number of cases: 21;<br>Median age, years: 16.5 (range 8–34) | multiagent chemotherapy (alkylator-based), surgery, WAP-RT ±ASCT | median PFS 19 mos, 3-year PFS 19%; median OS 32 months, 3-year OS 48% |
| Lal et al, 2005, MSKCC, New York, USA [11] | Retrospective, single-institution study;<br>Study period: 1972–2003;<br>Number of cases: 66;<br>Median age, years: 19 (range 7–58) | 44% had trimodal treatment including chemotherapy (P6 protocol), surgery and WAP-RT | 3-year OS 44%, 5-year OS 15%;<br>3-year OS 55% for pts given trimodal therapy vs 27% for pts with one modality missing;<br>multimodal therapy correlated with survival, while distant metastases did not |
| Hayes-Jordan et al, 2010, MDACC, Houston, USA [12] | Retrospective, single-institution study;<br>Study period: 1995–2008;<br>Number of cases: 24;<br>Median age, years: 12 | 8/24 (33%) had surgery + HIPEC | 3-year OS 71% for pts who were treated with HIPEC vs 26% for patients who were not |
| Bisogno et al, 2010, Italian Pediatric Oncology Association study (AIEOP-RMS4.99) [13] | Prospective, multi-institution study;<br>Study period: 1999–2008;<br>Number of cases: 14;<br>Median age, years: 9 (range 2–18) | all pts had multiagent chemotherapy (10 IVADo, 4 CEVAIE), followed by ASCT in 10/14, 12/14 had surgery, 6/14 had WAP-RT | 3-year EFS 15.5%;<br>3-year OS 38.9% |
| Cook et al, 2012, (CIBMTR) [14] | Retrospective study on registry data;<br>Study period: 1999–2007;<br>Number of cases: 36;<br>Median age, years: 19 (8–46) | 35/36 had ASCT (i.e. thiotepa or etoposide or melphalan or cyclophosphamide) | median OS 31 mos, 1-year OS 83%, 3-year OS 40%;<br>3-year OS was 57% for pts in CR before ASCT (36% of the cases) vs 28% for others |
| Philippe-Chomette P et al. 2012, French national series [7] | Retrospective national multicenter study;<br>Study period: 1995–2006;<br>Number of cases: 38;<br>Median age, year: 13.2 (4–29.7) | all pts had multiagent chemotherapy,<br>9 had limited surgical resection, 22 had extensive resection, 14 had ASCT | 3-year EFS 14.4%;<br>3-year OS 50.5%;<br>no prognostic factors (radiotherapy, ASCT, extend of surgery) |
| Pinnix et al, 2012, MDACC, Houston, USA [15] | Retrospective, single-institution study;<br>Study period: 2006–2010;<br>Number of cases: 8;<br>Median age, years: 11.5 (range 5–20) | multiagent chemotherapy (VAC/IE), surgery, WAP-RT (IMRT) | median PFS 8.7 months;<br>1/8 alive with NED after 20 months |
| Desai et al, 2013, MSKCC, New York, USA [16] | Retrospective, single-institution study;<br>Study period: 1992–2011;<br>Number of cases: 31;<br>Median age, years: 19 (range 7–32) | all pts had multiagent chemotherapy, surgery and WAP-RT (22 2D-RT, 9 IMRT) | 3-year PFS 24%;<br>3-year OS 50%;<br>OS correlated with distant metastases |
| Wong et al, 2013, Royal Marsden Hospital, London, and Addenbrooke's Hospital, Cambridge, UK [17] | Retrospective, multi-institution study;<br>Study period: 1991–2012;<br>Number of cases: 41;<br>Median age, years: 27 (range 16–45) | multiagent chemotherapy (i.e. VIDE, IVADo, VAC/IE), 20% had surgery,<br>15% had WAP-RT | median PFS 4 months;<br>median OS 16 mos, 3-year OS 27%, 5-year OS 16%;<br>VIDE chemotherapy conferred longest TTP;<br>surgery for localized disease and radiotherapy for metastatic disease correlated with improved OS |

(*Continued*)

Table 1. (Continued).

| Author | Series | Treatment | Outcome |
|---|---|---|---|
| Hayes-Jordan et al, 2013, MDACC, Houston, USA [18] | Retrospective, single-institution study;<br>Study period: 2006–2011;<br>Number of cases: 26;<br>Median age, years: 19 (range 6–53) | all pts had multiagent chemotherapy, surgery, HIPEC, ± local radiotherapy | median OS 31 months for pts who had complete surgery, 12.8 months for pts who had partial resection;<br>1-year DFS 42% in cases of abdominal disease vs 0% in cases of extra-abdominal disease;<br>no benefit of HIPEC in pts with extra-abdominal disease;<br>HIPEC morbidity lower in children |
| Zhang et al, 2015, Shandong Cancer Hospital, Jinan, China [19] | Retrospective, single-institution study;<br>Study period: 2004–2014;<br>Number of cases: 11;<br>Median age, years: 31.4 (range 14–64) | multiagent chemotherapy (IAP, CAP),<br>5/11 had local radiotherapy | median PFS 8.8 months, 3-year PFS 27%;<br>median OS 29 months, 3-year OS 36.4%, 5-year OS 10%;<br>median OS 40.8 months for pts given radiotherapy vs 19.2 months for the others |
| Honoré et al, 2015, IGR, Villejuif, France [4] | Retrospective, single-institution study;<br>Study period: 1991–2013;<br>Number of cases: 38;<br>Median age, years: 27 (range 13–57) | multiagent chemotherapy (alkylating/anthracyclines-based, i.e. AI, VAC),<br>61% had surgery, 21% had WAP-RT | median DFS 15.5 months, median OS 37.7 months;<br>2/38 (5%) alive with NED after 32 and 37 months;<br>absence of extra-peritoneal disease, complete surgery, and radiotherapy were prognostic factors;<br>no benefit of surgery for extra-peritoneal metastatic disease |
| Desai et al, 2015, MSKCC, New York, USA [20] | Prospective single-institution study;<br>Study period: 1993–2004;<br>Number of cases: 19;<br>Median age, years: 18.5 (range 10–42) | multiagent chemotherapy followed by myeloablative chemotherapy (carboplatin-thiotepa ± topotecan), with autologous stem cell transplant (in patients with chemoresponsive DSRCT); 17/19 had radiotherapy | 5-year EFS 11%<br>5-year OS 16% |
| Atallah et al, 2016, French sarcoma group [21] | Retrospective, multi-institution study;<br>Study period: 1991–2014;<br>Number of cases: 107;<br>Median age, years: 25 (range 4–58) | 36% of pts had chemotherapy, surgery and WAP-RT, 34% had chemotherapy and surgery | median OS 40.3 months and 3-year OS 63.1% for pts who had surgery and radiotherapy, and 28.3 months and 48.5%, respectively, for pts who had surgery without radiotherapy |
| Osborne et al, 2016, MDACC, Houston, USA [22] | Retrospective, single institution study;<br>Study period: 2006–2014;<br>Number of cases: 32;<br>Median age, years: 18 (range 5–50) | multiagent chemotherapy, surgery HIPEC, WAP-RT (23/32 IMRT) | median DFS 10 months, 3-year DFS 9.9%;<br>median OS 60 months, 3-years OS 64% |
| Honoré et al, 2017, French Network databases [18] | Retrospective, multi-institution, nation-wide study;<br>Study period: 1991–2015;<br>Number of cases: 107 (pts with extra-abdominal metastases were excluded);<br>Median age, years: 22 (range 3–57) | 48% had multimodal therapy with chemotherapy, surgery and WAP-RT, 23% had HIPEC | median DFS 21 months, 2-year DFS 30%, 5-year DFS 12%;<br>median OS 42 months, 2-year OS 72%, 5-year OS 19%;<br>whole-abdomen radiotherapy correlated with DFS |
| Stiles et al, 2018, Tennessee National Cancer Data Base, USA [23] | Retrospective study on registry data;<br>Study period: 2004–2014;<br>Number of cases: 125;<br>Median age, years: 21 | 82% had multiagent chemotherapy,<br>60% had surgery, 17% had radiotherapy, 6% had ASCT | median OS 28 months, 3-year OS 29%, 5-year OS 10%;<br>multimodal treatment correlated with survival;<br>residual postoperative macroscopic disease increased risk of mortality |
| Subbiah et al, 2018, MDACC, Houston, USA [24] | Retrospective, single-institution study;<br>Study period: 1990–2016;<br>Number of cases: 187;<br>Median age, years: 23 (range 0–53) | 98% had multiagent chemotherapy (i.e. VAC/IE, VIDE, P6 protocol),<br>57% had surgery, 44% had HIPEC, 6% had ASCT, 49% had trimodal therapy with chemotherapy, surgery and WAP-RT | median OS 35 months, 3-year OS 48%;<br>whole-abdomen radiotherapy did not improve OS |

(*Continued*)

Table 1. (Continued).

| Author | Series | Treatment | Outcome |
|---|---|---|---|
| Hayes-Jordan et al, 2018, MDACC, Houston, USA [25] | Prospective, single-institution, phase 2 trial;<br>Study period: 2012–2013;<br>Number of cases: 14 (pts with extra-abdominal metastases were excluded);<br>Median age, years: 21 | 14/14 had multiagent chemotherapy + complete surgery + HIPEC + WAP-RT | median RFS 15 months;<br>median OS 58.4 months, 3-year OS 79% |
| Scheer et al, 2019, German Pediatric Group CWS [6] | Retrospective cooperative study;<br>Study period: 1997–2015;<br>Number of cases: 60;<br>Median age, years: 15 (6–38) | all pts had multiagent chemotherapy (i.e. P6 protocol, VAIA, CEVAIE), 35% had surgery, 10% had HIPEC, 33% had radiotherapy, 15% had ASCT | 3-year EFS 11%, 3-year OS 30%;<br>VAIA chemotherapy correlated with longer EFS |
| Honoré et al, 2019, French Sarcoma Group [26] | Retrospective, multi-institution, nation-wide study;<br>Study period: 1991–2018;<br>Number of cases: 100;<br>Median age, years: 25 (range 3–59) | 80% had up-front multiagent chemotherapy (i.e. P6 protocol, VAC/IE, VIDE), 71% had surgery, followed by HIPEC in 28% of them, and by WAP-RT in 50% | median PFS 11 months, 3-year PFS 7%, 5-year PFS 6%;<br>median OS 25 months, 3-year OS 35%, 5-year OS 4%; 5/100 alive with NED;<br>prognostic factors: complete surgery, female sex, whole-abdomen radiotherapy |
| Campos et al, 2020, AC Camargo Cancer Center, São Paulo, Brazil [27] | Retrospective, single-institution study;<br>Study period: 2007–2020;<br>Number of cases: 19;<br>Median age, years: 26 (15–41) | all pts had multiagent chemotherapy (i.e. VAC/IE, VAC, AI), 58% had surgery, 26% had HIPEC, 21% had WAP-RT | median PFS 8.7 months;<br>median OS 27 months, 3-year OS 38%, 5-year 12% |
| Xiang et al, 2020, Chinese databases [8] | Retrospective study on registry data;<br>Study period: 2000–2015;<br>Number of cases: 104;<br>Median age, years: 24 (range 15–54) | 88% had chemotherapy, 66% had surgery, 23% had radiotherapy | median OS 26 months, 3-year OS 33%;<br>prognostic factors: surgical patterns, metastatic status, and adjuvant chemotherapy |
| Liu et al, 2021, Dana-Farber Cancer Institute and Boston Children's Hospital [28] | Retrospective, single-institution study;<br>Study period: 2014–2019;<br>Number of cases: 6;<br>Median age, years: 15 (range 3–16) | multiagent dose-density chemotherapy (VIT/VDC/IE), followed by surgery and WAP-RT | 3/6 pts alive with NED 21, 46 and 60 months after diagnosis; 2-year OS 75% |
| Ferrari et al, 2021, INT, Milano, Italy [29] | Retrospective, single-institution study;<br>Study period: 2017–2018;<br>Number of cases: 3;<br>Median age, years: 16 (range 10–20) | multiagent dose-density chemotherapy (IrIVA/IVAd/IVE), surgery, WAP-RT, maintenance chemotherapy (vinorelbine and low-dose oral cyclophosphamide) | dose-density treatment with irinotecan was feasible;<br>1/3 alive with NED 37 months after diagnosis, 2 alive with disease after abdominal relapse |
| Giani, et al. 2023, INT, Milan [30] | Retrospective, single-institution study;<br>Study period: 2000–2021;<br>Number of cases: 38;<br>Median age, years: 25 (range 7–64) | multiagent chemotherapy ± surgery (71%) ± HIPEC (26%) ± WAP-RT (24%) ± high-dose chemotherapy (13%)<br>± maintenance chemotherapy (32%) | median-EFS 15 months;<br>median-OS 37 months;<br>long-term survivors had no liver/extra-abdominal disease, and were treated with complete surgery, and possibly WAP-RT and maintenance therapy |

Note: Legend: pts = patients; OS = overall survival; PFS = progression-free survival; PPFS = peritoneal progression-free survival; DFS = disease-free survival; RFS = relapse-free survival; EFS = event-free survival; TTP = time to progression; NED = no evidence of disease; mos = months; WAP-RT = whole abdominopelvic radiotherapy; HIPEC = hyperthermic intraperitoneal chemotherapy; 2D = two-dimensional; IMRT = intensity-modulated radiation therapy; ASCT = autologous stem cell transplantation; P6 Protocol = HD-CAV (cyclophosphamide, doxorubicin, vincristine) alternating with ifosfamide, etoposide; VIDE = vincristine, ifosfamide, doxorubicin, etoposide; IVADo = ifosfamide, vincristine, actinomycin D, doxorubicin; VAC/IE = vincristine, adriamycin, cyclophosphamide/ifosfamide, etoposide; IAP = ifosfamide, doxorubicin, cisplatin; CAP = cyclophosphamide, doxorubicin, cisplatin; AI = doxorubicin, ifosfamide; VIT/VDC/IE = vincristine, irinotecan, temozolomide/vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide; IrIVA = irinotecan, ifosfamide, vincristine, actinomycin-D; IVAd = ifosfamide, vincristine, adriamycin; IVE = ifosfamide, vincristine, etoposide; CEVAIE = ifosfamide, vincristine, actinomycin D, carboplatin, epirubicin, etoposide; EAM = extra-abdominal metastases, CR = complete response; MSKCC = Memorial Sloan Kettering Cancer Center; MDACC = Anderson Cancer Center; IGR = Institut Gustave Roussy; CWS = Cooperative Weichteilsarkom Studiengruppe (German Cooperative Group); INT = Istituto Nazionale dei Tumori.

isolated in the plasma of three patients with different stages of DSRCT [52]. Among the five miRNAs modulated in all three patients, three (miR-34a-5p, miR-22-3p, and miR-324-5p) were upregulated compared with four healthy pediatric controls, while two (miR-150-5p and miR-342-3p) were downregulated. These miRNAs were found dysregulated in several cancers, and involved in cell growth, proliferation, migration, and invasion. Among them, miR-34 was strongly upregulated. All these studies shed light on the potential role of miRNAs in DSRCT pathogenesis.

## 3. Loco-regional treatment: surgery

Aggressive cytoreductive surgery is generally part of the standard approach to intra-abdominal DSRCT, which usually involves resecting all peritoneal metastases, but preserving macroscopically unaffected peritoneum [4]. As reported in various studies, complete macroscopic cytoreductive surgery has been associated with a longer survival [4,8,11,19,23,32,53,54]. In a series described by the French cooperative group, for example, the median OS was 38 months for patients who underwent complete surgery versus 21 months for those with incomplete or no surgery [4]. Similarly, in the series from the Mayo Clinic, the median OS was 34 months for patients treated with complete cytoreductive surgery and chemotherapy, and 14 months for those who had biopsy alone [53]. In another series from the MD Anderson Cancer Center, the median OS was 31 months for patients who had undergone complete surgery, and 13 months for those whose surgery was incomplete [32]. These findings reflect a selection bias, however, as patients who were candidates for surgery had generally responded better to chemotherapy. Macroscopically complete resection is also generally achievable in only a limited proportion (25% to 44%) of cases [11,55].

Despite surgery, the most common site of recurrence for intra-abdominal DSRCT is the peritoneum, reflecting the difficulty of eradicating all microscopic residual tumors even with an aggressive frontline approach. The extent of disease can be measured preoperatively in terms of the peritoneal cancer index (PCI), but in two MD Anderson series there was no correlation with survival [25,32]. The French group suggested using a PCI of 12 as the cutoff for selecting potential candidates for extensive surgery. Patients with no liver metastases are candidates for surgery whenever it is feasible, and complete cytoreduction can be achieved. Patients with synchronous liver metastases are generally not considered for surgery because their survival afterward is comparable with the results achieved with systemic chemotherapy alone [26].

The indication for aggressive surgery should be balanced against the postoperative morbidity and decline in quality of life due, for instance, to multiple visceral resections. It is extremely important for the surgeon to remove all macroscopic disease because incomplete resections do not bring any survival benefit compared with chemotherapy alone. Accurate patient selection remains the key to identifying patients who can benefit from aggressive surgery [35,56].

## 4. Loco-regional treatment: hyperthermic intraperitoneal chemotherapy

HIPEC is a procedure involving the application of a concentrated chemotherapeutic solution at a high temperature inside the peritoneal cavity. It is performed after cytoreductive surgery in cases of gastric cancer, for instance, peritoneal mesothelioma, or ovarian cancer with disseminated peritoneal carcinomatosis [57–59]. After the surgical removal of all cancerous lesions, the heated chemotherapeutic agents are applied directly inside the abdomen to eliminate any remaining cancer cells.

HIPEC has been used in patients with intra-abdominal DSRCT as well, adopting various chemotherapy regimens [12,18,25,32,60–63]. It is worth mentioning the phase 1 study that identified the maximum tolerated dose of intraperitoneal cisplatin as 100 mg/m$^2$ (90 min, 41°C). Chemotherapeutic agents administered at high temperatures can cause significant morbidity, which reportedly ranges from 12% to 52% in adults, but the treatment is better tolerated in children [12,57–59].

HIPEC was shown to increase patient survival in selected series (generally from single centers) [12,18,25,32,60–62]. In the sizable MD Anderson experience, there were survival benefits for patients with no liver or portal metastases [25,62]. A 3-year OS of 79% was reported in a selected series of patients given HIPEC in addition to the multimodal treatment regimens described by the group at the Memorial Sloan-Kettering Cancer Center [11]. On the other hand, a French randomized study on patients with all types of peritoneal sarcomatosis failed to demonstrate any improvement in OS for patients who received intraperitoneal chemotherapy (IPEC) after the surgical resection of their tumors [60]. A retrospective nationwide French survey involving 107 patients treated for DSRCT with no extraperitoneal metastases (EPM) between 1991 and 2015 also found no benefit deriving from HIPEC after complete cytoreductive surgery [18].

The lack of any standardization of the chemotherapeutic agents used and the procedures for their administration, and – more importantly – the absence of any standard patient selection criteria make it very difficult to assess the value of HIPEC in patients with DSRCT.

## 5. Loco-regional treatment: radioimmunotherapy

Intra-compartmental delivery of radioimmunotherapy (RIT) could be a promising approach for intraperitoneal DSRCT. A recent phase I study investigated the murine monoclonal antibody $^{131}$I-omburtamab targeting antigen B7H3, which is expressed on cancer cells. The study included 48 patients with DSRCT and showed that the intraperitoneal administration of RIT was well tolerated, with minimal toxicities and low radiation exposure to normal organs, suggesting that this locoregional approach could be combined with other therapies [64].

## 6. Loco-regional treatment: radiotherapy

Radiotherapy generally has two main indications in DSRCT: i) postoperative WAP-RT for consolidation or adjuvant purposes; or ii) local irradiation in the palliative setting.

Consolidation WAP-RT as part of a multimodal approach, after cytoreductive surgery and intensive multidrug chemotherapy, was first described in a series from the Memorial Sloan-Kettering Cancer Center, the aim being to improve loco-regional disease control [9]. A multimodal treatment that included systemic chemotherapy, complete cytoreductive surgery, and postoperative whole abdominal irradiation prolonged survival in a series of DSRCT patients with no extraperitoneal metastases treated at the MD Anderson Cancer Center [4]. These results were confirmed in a retrospective analysis by the French GSF-GETO team: postoperative WAP-RT was the only variable associated with a longer peritoneal recurrence-free survival and disease-free survival after complete cytoreductive surgery [18]. Another study from the Memorial Sloan-Kettering Cancer Center remarked on the role of trimodal treatment, reporting a 3-year OS of 55% in patients receiving chemotherapy, surgery, and radiotherapy, as opposed to 27% in patients when one of these three treatment modalities was missing [11]. A retrospective French study on 103 patients identified a survival benefit deriving from the use of WAP-RT [21]. Two subsequent reports (from the French cooperative group and the Dana-Faber Cancer Institute) reiterated the call to include WAP-RT as part of the first-line multi-modal treatment strategy for DSRCT [26,28].

Concerning the technique involved, WAP-RT is administered postoperatively for a maximum allowable total dose of 30 Gy, with or without a focal boost on residual disease. Gastrointestinal and hematological toxicities are quite common, especially after neoadjuvant chemotherapy, but might be contained by using an intensity-modulated radiation therapy (IMRT) technique [15,16].

## 7. Systemic treatments: conventional multi-agent chemotherapy

DSRCT responds to chemotherapy, which can induce significant, though only transient disease regressions [65]. Neoadjuvant chemotherapy is always indicated in patients with unresectable, advanced intra-abdominal DSRCT due to evidence of a clinical benefit in chemo-sensitive tumors correlating with a longer OS, compared with unresponsive tumors [24].

Generally speaking, the chemotherapy regimens conventionally administered to DSRCT patients resemble the protocols used for Ewing sarcoma. They include a combination of anthracyclines, alkylating agents, and vinca alkaloids, in both neoadjuvant and adjuvant settings [65]. The so-called P6 protocol originally developed by the Memorial Sloan-Kettering Cancer Center is used at many centers: it combines cyclophosphamide, doxorubicin and vincristine, alternating with ifosfamide and etoposide [9]. Other regimens that have been described involve vincristine, ifosfamide, doxorubicin and etoposide (VIDE) [17]; vincristine, actinomycin-D ifosfamide and adriamycin (VAIA) [6]; and cyclophosphamide, pirarubicin, etoposide and cisplatin (the modified PAVEP regimen) [66]. No remarkable differences in response rates and in outcome according to the different chemotherapy regimens adopted have been clearly reported. In addition, no prospective studies have been conducted on DSRCT, because of the disease's rarity. Therefore, it remains extremely difficult to consider any chemotherapy regimen as the best choice or as the standard of care.

In various studies, high-dose chemotherapy was followed by autologous stem cell transplantation, with unclear results [13,14,67–71]. A study by the Italian pediatric cooperative group showed limited improvements in terms of prognosis [13]. A retrospective analysis conducted by the University of Wisconsin on 36 cases included in an international registry showed a benefit for the subset of patients with no residual disease before myeloablative chemotherapy: the median OS was 36 months, as opposed to 21 months for patients with a residual tumor before consolidation [14]. A prospective study conducted at Memorial Sloan-Kettering Cancer Center enrolled 19 patients who received myeloablative chemotherapy with autologous stem cell transplantation and reported 5-year EFS and OS of 11% and 16%, respectively [20]. High-dose chemotherapy is consequently no longer used to manage DSRCT, as confirmed by the French experience in which only one patient received this treatment [26].

Maintenance therapy with low-dose oral cyclophosphamide and weekly intravenous vinorelbine may be used, as it has proved effective in rhabdomyosarcoma, but its use in DSRCT has yet to be validated. Other strategies have been tested in cases of disease recurrence, with disappointing results. In patients with progressive disease resistant to first-line treatment according to the P6 protocol or similar chemotherapy schedules, a transient efficacy has been reported with second- or third-line treatments involving temozolomide/irinotecan, cyclophosphamide/topotecan, gemcitabine/docetaxel or high-dose ifosfamide (as used in Ewing-like strategies) [17,24,72]. Irinotecan (in combination with vincristine) and vinorelbine (in combination with low-dose cyclophosphamide) have been proposed as potentially effective options (Table 2) [66,80]. Irinotecan seems a promising drug for DSRCT. It is a camptothecin derivative with a multifaceted mechanism of action that stops replication and induces double-strand breaks in the DNA by inhibiting the topoisomerase I. In various solid tumors, irinotecan also prevents the effect of several transcription factors, such as the epidermal growth factor receptor (EGFR) [92]. It may be useful in DSRCT, considering the transcriptional activation induced by the *EWS:WT1* fusion protein. Recent studies in the sphere of pediatric oncology examined the feasibility of a dose-dense approach that integrated irinotecan in standard chemotherapy for high-risk pediatric sarcomas [29]. A recent study by the Istituto Nazionale Tumori in Milan envisaged adding irinotecan to standard ifosfamide-based regimens (including doxorubicin and etoposide) in cases of DSRCT, followed by maintenance chemotherapy with vinorelbine and low-dose oral cyclophosphamide [29]. A study at the Dana-Faber Cancer Institute considered adding vincristine and temozolomide, as well as irinotecan, to interval-compressed chemotherapy for pediatric DSRCT, suggesting another tolerable and potentially active strategy worth further investigating [28].

Table 2. Potential therapeutic agents for desmoplastic small round cell tumor.

| Agent | Author | Findings |
|---|---|---|
| Trabectidin | Lopez-Gonzalez et al, 2011 [73] | 1 patient with PR, 8 months of PFS |
| | Brunetti et al, 2014 [74] | 1 patient with SD, 4 months of PFS |
| | Frezza et al, 2014 [75] | 2 patients with SD, 4 months of PFS |
| | Verret et al, 2017 [76] | 6 patients, 2 with SD and 4 with PD, 1–4 months of PFS |
| Irinotecan | Ambar et al. [66] | irinotecan + vincristine (plus radiotherapy)<br>1 patient with PR, 26 months of PFS |
| Irinotecan and trabectidin | Ferrari et al, 2022 [77] | trabectidin + irinotecan: 2 patients, 1 with CR, 1 with SD |
| Temsirolimus | Thijs et al, 2010 [78] | 1 patient with SD, 9 months of PFS |
| | Naing et al, 2012 [79] | temsirolimus + cixutumumab:<br>3 patients, 2 with PR, 5 months of PFS |
| | Tarek et al, 2018 [80] | temsirolimus + vinorelbine + cyclophosphamide:<br>5 patients with PR, 8.6 months of PFS |
| Vinorelbine | Ferrari et al, 2007 [81] | vinorelbine + cyclophosphamide:<br>2 patients with PR, 4 months of PFS |
| | Tarek et al, 2018 [71] | vinorelbine + cyclophosphamide + temsirolimus:<br>5 patients with PR, 8.6 months of PFS |
| Antiangiogenic agents | Bétrian et al, 2017 [82] | sunitinib, bevacizumab, sorafenib:<br>9 patients, 2 with PD, 7 with SD, 3 months of PFS |
| Pazopanib | Frezza et al, 2014 [75] | 9 patients, 5 with SD, 2 with PD, 2 with PR, <16 months of PFS |
| | Menegaz et al, 2018 [83] | 29 patients, 16 with SD, 1 with PD, 11 with PR, 5 months of PFS |
| Imatinib | De Sanctis et al, 2017 [84] | 8 patients, 1 with SD, 7 with PD, 3 months of PFS |
| Ganitumab | Tap et al, 2012 [85] | 16 patients, 6 with PR, 10 with SD, 19 months of PFS |
| Sunitinib | Italiano et al. 2013 [86] | 8 patients, 3 with SD, 3 with PD, 2 with PR, 1–20 months of PFS |
| Eribulin | Emambux et al. 2017 [87] | 3 patients, 2 with SD, 1 with PD, 2–9 months of PFS |
| Anlotinib | Chen et al, 2019 [88] | 1 patient with PR |
| | Cheng et al, 2022 [89] | 1 patient with PR |
| Apatinib | Tian et al, 2020 [82] | 1 patient with PR |
| Androgen receptor pathway | Fine, 2007 [90] | bicalutamide + leuprorelin: 6 patients, 3 with SD, 3–4 months of PFS<br>bicalutamide: 1 patient with PD, 2.5 months of PFS |
| Prexasertib | Slotkin, et al 2022 [91] | Prexasertib+irinotecan<br>19 patients, 9 with SD, 6 with PR, 3 with SD, 1 with PD |

Note: Legend: PFS = progression-free survival; PD = progressive disease; SD = stable disease; PR = partial response; CR = complete remission.

Table 3. Trials recruiting patients with desmoplastic small round cell tumor as of October 2022.

| Phase | Title/design/age criteria | Primary outcome | ClinicalTrials.gov Identifier |
|---|---|---|---|
| Phase I/II | Ramucirumab IV + Cyclophosphamide p.o. + Vinorelbine IV (experimental arm), versus Cyclophosphamide p.o. + Vinorelbine IV.<br>Age inclusion criteria: 12 months −29 years | PFS | NCT04145349 |
| Phase II | 131 I-Omburtamab in Combination with External Beam Radiotherapy.<br>Age inclusion criteria: >1 year | PFS | NCT04022213 |
| Phase I/II | PBI-200 in Subjects with NTRK-Fusion-Positive Advanced or Metastatic Solid Tumors.<br>Age inclusion criteria: >18 years | Safety and tolerability<br>ORR | NCT04901806 |
| Phase II | Trabectedin and Low-dose Radiation Therapy in Advanced/Metastatic Sarcomas.<br>Age inclusion criteria: 16–75 years | ORR in irradiated nodules | NCT05131386 |
| Phase I | LSD1 Inhibitor Seclidemstat (SP 2577) With and Without Topotecan and Cyclophosphamide in Patients with Relapsed or Refractory Ewing Sarcoma and Selected Sarcomas.<br>Age inclusion criteria: 12 years | Safety and tolerability | NCT03600649 |
| Phase I | B7-H3-Specific Chimeric Antigen Receptor Autologous T-Cell Therapy for Pediatric Patients with Solid Tumors (3CAR),<br>Age inclusion criteria: < 21 years | Safety of B7-H3-CAR T cells | NCT04897321 |
| Phase I | EGFR806 CAR T Cell Immunotherapy for Recurrent/Refractory Solid Tumors in Children and Young Adults,<br>Age inclusion criteria: 1–30 years | Safety and tolerability | NCT03618381 |
| Phase I | B7H3 CAR T Cell Immunotherapy for Recurrent/Refractory Solid Tumors in Children and Young Adults<br>Age inclusion criteria: 0–26 years | Safety and tolerability | NCT04483778 |
| Phase II | Multimodal Immune Characterization of RAre Soft Tissue Sarcoma – MIRAS Project from SARRA (SARcome RAre) Project of the French Sarcoma Group.Age inclusion criteria: >18 years | MFS for localized disease, PFS for metastatic disease | NCT03967834 |
| Phase I | A Prospective Study of Heated Intra-Peritoneal Chemotherapy (HIPEC) with Doxorubicin and Cisplatin in Pediatric Patients with Pelvic and Abdominal Tumors.<br>Age inclusion criteria: 1–25 years | Adverse events of surgery with HIPEC | NCT04213794 |
| Phase II | A Study of the Drug I131-Omburtamab in People With Desmoplastic Small Round Cell Tumors and Other Solid Tumors in the Peritoneum | PFS | NCT04022213 |
| Phase I/II | A Study of Repotrectinib in Combination With Chemotherapy in Children and Young Adults With Solid Tumor Cancer | Safety and tolerability | NCT05004116 |

Note: Legend:.
IV, intravenous; p.o., per os; PFS, progression-free survival; ORR, overall response rate; MFS, metastasis-free survival; HIPEC, Hyperthermic intraperitoneal chemotherapy; CAR T cell, chimeric antigen receptor T-cell.

## 8. Systemic treatments: new therapeutic options

Given the unsatisfactory outcomes for patients with DSRCT, further investigations are needed on new agents and innovative treatment combinations. Clinical trials recruiting patients with DSRCT (as in October 2022) are reported in Table 3.

The identification of new therapeutic targets, and the rational design of clinical trials for DSRCT have been hindered over time, however, by the lack of preclinical models and the rarity of the disease. For over twenty years, most of the preclinical research exploited the single published cell-line JN-DSRCT-1, first described in 2002 [93,94]. Four fully characterized cell lines, and two patient-derived xenograft (PDX) models recently provided an opportunity for more representative preclinical research into new therapeutic targets, which were identified in studies that extensively profiled DSRCT [95].

On the clinical side, various conventional anticancer agents, such as eribulin [87] or trabectedin, have been used in clinical trials or as an off-label option for patients with relapsing and advanced DSRCT. Trabectedin's mechanism of action in DSRCT is thought to involve a reduced expression of EWS-WT1 mRNA and impaired binding of the fusion protein to the promoter of its target genes, such as insulin-like growth factor 2 (IGF2), platelet-derived growth factor A (PDGFA), and EGFR [87]. Trabectedin would consequently affect the expression of genes involved in cell proliferation and apoptosis in cases of DSRCT. Interestingly, androgen receptor (AR) and vascular endothelial growth factor receptor (VEGFR) are also included in these genes [96]. There has recently been a report on the potential efficacy of a combination of trabectedin and irinotecan [77].

A further promising clinical candidate for DSRCT may be lurbinectedin, a synthetic alkaloid derived from the natural product trabectedin. With a similar mechanism of action, lurbinectedin inhibits EWS-WT1 transcription factor and blocks the expression of downstream targets. Preclinical data showed very interesting results with tumor regressions in multiple mice in PDX model of DSRCT [77,97] and led to upcoming trials with this drug.

The specific chromosomal rearrangement t(11; 22)(p13; q12) and the fusion protein EWS-WT1 form the primary driver of tumorigenesis, upregulating several growth factor genes, such as PDGFRα. Several pathways have been targeted in the treatment of DSRCT, including androgen receptor pathway inhibition, angiogenesis, tyrosine kinase receptor inhibition, PI3K/AKT/mTOR pathway inhibition, DNA damage repair protein inhibition, c-MET and insulin growth factor pathway inhibition [65]. The use of tyrosine kinase inhibitors directed against proteins involved in the tumor's vascular proliferation is supported by the capacity of *EWSR1:WT1* to induce PDGFA expression, and activation of the *IGF1R* gene [50,82,84,85,88,89,98–100]. Retrospective studies on anti-angiogenic agents in DSRCT suggest that pazopanib, sunitinib, sorafenib, and apatinib may have some effect [100,101]. The French group described a series of eight patients with advanced DSRCT treated with sunitinib, with a median PFS of 2.6 months [86]. The activity of the mTOR inhibitor temsirolimus has also been reported [78,79].

Androgen receptor (AR) emerged as a therapeutic target for DSRCT after it was suggested that the disease's relatively high incidence in young males might be partly related to an AR dependence. In a preliminary report from Fine et al in 2007, about two in three DSRCTs exhibited some level of AR positivity on immunohistochemistry (IHC), and half of these tumors stained strongly [90,102]. Remarkably, treatment *in vitro* with dihydrotestosterone (DHT) of DSRCT cells derived from one patient's peritoneal fluid confirmed AR functionality, based on tumor growth induction. A small cohort of patients with DSRCT who tested positive for AR ($N = 6$) was treated with combined androgen blockade (CAB) therapy, consisting of the AR blocker biculatamide (50 mg p.o. QD for 1 week), then Lupron (7.5 mg im. monthly). Three patients showed some clinical benefit, including a partial response, that persisted for 3–4 months. Following this report, AR blockade has been considered by some clinicians for relapsing DSRCT [78]. A very recent, comprehensive preclinical analysis on the molecular impact and therapeutic potential of AR expression and signaling in DSRCT examined 60 DSRCT tumor tissues, the JN-DSRCT cell-line model, and several patient-derived xenograft (PDX) models of DSRCT, comparing them with prostate cancer tissues and cells. This study confirmed nuclear overexpression of AR in 65% of DSRCT on immunohistochemistry. Intriguingly, the study went on to compare AR expression and the preclinical effects of its inhibition with older- and newer-generation AR inhibitors to prostate cancer tumor tissue and cell lines [103,104]. In preclinical, in vitro and in vivo models of DSRCT (including JN-DSRCT and PDX lines), enzalutamide and AR-directed antisense oligonucleotides (AR-ASO) were effective in counteracting tumor proliferation induced by 5α-dihydrotestosterone (DHT). Unsupervised double-hierarchical clustering analysis, conducted in this study using the 1500 most variable genes across all samples, placed DSRCT ($n = 22$) next to prostate cancer ($n = 12$), and away from 71 other sarcoma samples. This may suggest that DSRCT is a type of cancer in which AR may have a key part in the tumor's biology, as in prostate cancer, and AR inhibition therapy could have a disease-transforming impact.

In the pediatric oncology setting, a drug development statement in 2017 that focused on the mechanism of action of AR inhibitors (relying on information available at the time) judged that they were 'not relevant' for pediatric cancer [105]. This view now has to be revisited, and clinical studies should be undertaken with AR inhibitors, ideally already in combination with chemotherapy, as developed for prostate cancer. When the mechanism of action of these AR inhibitory agents in DSRCT was investigated in depth, using gene expression analysis and chromatin immunoprecipitation sequencing (ChIP-seq), it emerged that AR signaling regulated cellular epigenetic programs through novel DSRCT-specific AR DNA binding sites adjacent to key oncogenic regulators – including WT1, which is the C-terminal partner of the fusion protein. AR also occupied enhancer sites that regulate other pathways, such as the Wnt pathway, and those involved in neural differentiation and embryonic organ development.

DSRCT harbors features of a multiphenotypic differentiation, expressing proteins on IHC that are associated with neural/neuroendocrine differentiation [106]. When staining for neuron-specific enolase (NSE) was examined in a small morphological study on nine tumors, eight of them showed at least a focal expression of NSE [105]. This preliminary evidence was confirmed when a

thorough characterization of the tumor's molecular profile showed that DSRCT lacking AR expression has a transcriptomic profile resembling that of neuroendocrine prostate cancer [107,108]. At tumor presentation, the presence of a neuroendocrine genotype and phenotype in prostate cancer is extremely rare; it is an event that can occur during the course of the disease, and the treatment options are very limited. In DSRCT, nobody knows whether neuroendocrine features present with different expression levels at the disease's onset might also be acquired during the course of the disease, or following the onset of resistance to anti-cancer therapies.

Similarities between prostate cancer and DSRCT suggest that therapeutic strategies involving the AR receptor in prostate cancer might be effective for DSRCT as well. For instance, DSRCT strongly expresses polymerase 1 (PARP-1) [109]. PARP inhibitors are effective in the treatment of patients with metastatic castration-resistant prostate cancer, particularly in cases of homologous recombination deficiency (HRD), although such an event is not necessary when PARP inhibition is combined with new-generation hormone therapies [110].

A phase II study was designed to consider the neuroendocrine phenotype and genotype of DSRCT. ONC201 is an antagonist of the tumor dopamine-like DRD2, and an agonist of the antagonist/caseinolytic protease P (ClpP) that causes an increased integrated stress response, a decreased Ras signaling (lower ERK/AKT), and TRAIL induction. These mechanisms result in more cell death signals and fewer cell survival signals in cancer cells. In a preclinical study on DSRCT cell lines and orthotropic peritoneal xenotransplants, ONC201 induced the protein expression of TRAIL and DR5, a receptor that – together with DR4 – triggers TRAIL-induced apoptosis. This orally administered drug was subsequently tested in a phase II clinical trial on patients with neuroendocrine tumors or DSRCT [111]. Two of 10 patients with DSRCT enrolled in this study were treated, one for more than a year, the other for more than 4 years. A further patient, who had limited disease progression at 3 months, came off the study and was given radiotherapy for progressive lung metastases: he has remained off any therapy and without any relapse for more than 3 years.

Another neural marker, the neurotrophic tyrosine kinase receptor 3 (NTRK3) is considered a druggable receptor tyrosine kinase in DSRCT. NTRK3 mRNA is more strongly expressed in DSRCT than in other sarcomas (particularly those driven by a specific transcription factor), or cancers harboring fusion proteins involving NTRK3 [94]. In fact, most DSRCTs are strongly immunoreactive for the NTRK3 protein. The fusion protein EWSR1-WT1 activates the NTRK promoter, and increases the expression of NTRK3, resulting in the promotion of tumor growth [95]. Preclinical evidence in DSRCT cell lines and patient-derived xenografts showed that the NTRK inhibitor entrectinib counteracts this oncogenic mechanism. These recent results point to the need for investigations on NTRK inhibitors in the clinical setting, and a clinical trial is currently testing a combination of irinotecan, repotrectinib and temozolomide [95] (Clinicaltrial.gov NCT05004116).

Other hypotheses paving the way to clinical trials were formulated following the development of new cell lines and PDX models. One example concerns the Salt-Inducible Kinase 1 (SIK1), a member of the AMPK-related kinase family involved in a broad spectrum of biological processes, which is a direct target of the *EWSR1:WT1* fusion protein[112]. Interestingly, a reduction in SIK1 causes a tumor cell growth inhibition comparable with what happens when *EWSR1:WT1* expression is abolished, and SIK1 silencing leads to the cessation of DNA replication and tumor growth inhibition. Targeting SIK1 with the YKL-05-099 small-molecule inhibitors resulted in significant cytotoxicity. Another relevant example concerns the activation of the ERBB pathway in DSRCT, which occurred through the fusion protein *EWSR1:WT1* and resulted in the upregulation of EGFR, ERBB2, ERK1/2, and AKT, and the stimulation of cell growth. DSRCT cell line proliferation could be blocked by antagonizing EGFR function with shRNAs, the small-molecule inhibitors afatinib and neratinib, or the anti-EGFR antibody cetuximab [113]. Remarkably, a combination of cetuximab and afatinib inhibited tumor growth in PDX of DSRCT, giving rise to a preclinical hypothesis promoting the clinical testing of agents that target EGFR in DSRCT.

Further agents of interest may be DNA damage response agents. Prexasertib is an inhibitor of CHK1: it prevents DNA repair leading to mitotic catastrophe and can enhance the activity of DNA-damaging chemotherapy. Translocation driven sarcomas (including DSRCT) have demonstrated susceptibility to CHK1 inhibition in preclinical models. A very recent phase I/II study on prexasertib in combination with irinotecan (on 19 patients with DSRCT) showed preliminary interesting findings [91].

Finally, studies are analyzing the different sequences and the lengths of peptides that are found in the fusion gene of DSCRT [114]. This data may lead to the generation of mRNA-based anti-cancer vaccine that select the best neoantigens accounting for HLA type and neoantigen binding.

## 9. Conclusions

Despite the multimodal approach to their treatment, including aggressive cytoreductive surgery, intensive multi-agent chemotherapy, and postoperative WAP-RT, the prognosis for patients with DSRCT remains dismal, with a 5-year overall survival rate in the range of 10–20%.

Such unsatisfactory outcomes make it essential to conduct further collaborative research and clinical trials in an effort to improve these patients' chances. Preclinical models are needed, and multidisciplinary collaborative programs should be established, involving both the pediatric and the adult sarcoma communities [27,115]. Extensive international cooperation can improve our knowledge of the pathogenesis of DSRCT, explore new molecular targets, and find potentially effective biological agents for this aggressive disease.

## 10. Expert opinion

The treatment of patients with DSRCT remains a huge challenge for sarcoma specialists. Attempts to improve patient outcomes over the past two decades have produced very limited results, and a standard treatment approach is still lacking. Generally speaking, patients are still treated with alky-

lating and anthracycline-based conventional multi-agent chemotherapy regimens, which often prompt an initial tumor response but fail to improve overall survival. Surgery should still be considered the mainstay of treatment and should be performed by an expert team at a highly qualified sarcoma reference center. The aim should be to achieve a microscopically complete resection, which correlates with better outcomes. The role of postoperative whole-abdomen radiotherapy, high-dose chemotherapy with autologous stem cell rescue or hyperthermic intraperitoneal chemotherapy remains unclear.

We believe that there are two aspects to consider in our efforts to improve our understanding of DSRCT and our patients' outcomes.

- First, we need to rise to the challenge to establish highly predictive preclinical models of DSRCT because the lack of such models has hindered efforts to identify new therapeutic strategies for these patients. It is only recently that some PDX models and patient-derived cell lines have been generated, and used to test new targets. These targets were identified in retrospective series managed at sarcoma reference centers, where cases of DSRCT were profiled to assess the disease's genomic vulnerabilities and over-expressed druggable genes. These new models have led to the identification of novel potentially effective therapies and are informing the design of new clinical trials. Some of these trials are already opening, while others are expected to be designed soon. The generation of further, histologically and molecularly well-characterized patient-derived models should be strongly encouraged with a view to setting the preclinical stage for next-generation clinical trials.

- Second, it is crucially important to develop international collaborative schemes involving multiple stakeholders – including clinicians (both pediatric and adult oncologists), pharma, parent/patient advocacy groups, regulatory bodies, and clinical statisticians/trialists – to tackle a rare and complex disease like DSRCT. Only such large-scale and far-reaching efforts can generate up-to-date and timely clinical investigations on innovative agents and promising drug combinations for this cancer, relying on an effective, modern trial design.

Since nothing has come to light so far to indicate that the tumor biology and/or clinical presentation of DSRCT differ between pediatric and adult patients, the ultimate goal should be to develop shared clinical trials for children, adolescents and adults with the same disease. On the other hand, the latest preclinical studies do suggest that there may be at least two different biological subtypes of DSRCT (as seen in prostate cancer), one AR-positive and the other neuroendocrine. Although such a hypothesis will require prospective validation, this biological/molecular distinction might enable patients to be pre-selected for targeted therapies. Since there are no clear prognostic markers at diagnosis (apart from likely localized disease), DSRCT is known to quickly become chemo-resistant, and patient survival rates are extremely low, it would be tempting to propose an international frontline clinical study with several biology-driven treatment arms – including novel agents, not only alone, but also in combinations with known multimodal therapies.

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## References

1. de Pinieux G, Karanian M, le Loarer F, et al. Nationwide incidence of sarcomas and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network. PLoS ONE. 2021 Feb 25;16(2):e0246958.
2. Stacchiotti S, Frezza AM, Blay J, et al. Ultra-rare sarcomas: a consensus paper from the connective tissue oncology society community of experts on the incidence threshold and the list of entities. Cancer. 2021 Aug 15;127(16):2934–2942.
3. Gerald WL, Rosai J. Case 2 desmoplastic small cell tumor with divergent differentiation. Pediatr Pathol. 1989 Jan 9;9(2):177–183.
4. Honoré C, Amroun K, Vilcot L, et al. Abdominal desmoplastic small round cell tumor: multimodal treatment combining chemotherapy, surgery, and radiotherapy is the best option. Ann Surg Oncol. 2015 Apr 10;22(4):1073–1079.
5. Hendricks A, Boerner K, Germer C, et al. Desmoplastic small round cell tumors: a review with focus on clinical management and therapeutic options. Cancer Treat Rev. 2021 Feb;93:102140.
6. Scheer M, Vokuhl C, Blank B, et al. Desmoplastic small round cell tumors: multimodality treatment and new risk factors. Cancer Med. 2019 Feb;8(2):527–542.
7. Philippe-Chomette P, Kabbara N, Andre N, et al. Desmoplastic small round cell tumors with EWS-WT1 fusion transcript in children and young adults. Pediatr Blood Cancer. 2012 Jun;58(6):891–897.
8. Xiang T, Zhang SY, Wang SS, et al. A nationwide analysis of desmoplastic small round cell tumor. Medicine. 2020 Jul 24;99(30):e21337.
9. Kushner BH, LaQuaglia MP, Wollner N, et al. Desmoplastic small round-cell tumor: prolonged progression-free survival with aggressive multimodality therapy. J Clin Oncol. 1996 May;14(5):1526–1531.
10. Goodman KA, Wolden SL, la Quaglia MP, et al. Whole abdominopelvic radiotherapy for desmoplastic small round-cell tumor. Int J Radiat Oncol Biol Phys. 2002 Sep;54(1):170–176.
11. Lal DR, Su WT, Wolden SL, et al. Results of multimodal treatment for desmoplastic small round cell tumors. J Pediatr Surg. 2005 Jan;40(1):251–255.
12. Hayes-Jordan A, Green H, Fitzgerald N, et al. Novel treatment for desmoplastic small round cell tumor: hyperthermic intraperitoneal perfusion. J Pediatr Surg. 2010 May;45(5):1000–1006.
13. Bisogno G, Ferrari A, Rosolen A, et al. Sequential intensified chemotherapy with stem cell rescue for children and adolescents with desmoplastic small round-cell tumor. Bone Marrow Transplant. 2010 May;45(5):907–911.
14. Cook RJ, Wang Z, Arora M, et al. Clinical outcomes of patients with desmoplastic small round cell tumor of the peritoneum undergoing autologous HCT: a CIBMTR retrospective analysis. Bone Marrow Transplant. 2012 Nov 2;47(11):1455–1458.
15. Pinnix CC, Fontanilla HP, Hayes-Jordan A, et al. Whole abdominopelvic intensity-modulated radiation therapy for desmoplastic small round cell tumor after surgery. Int J Radiat Oncol Biol Phys. 2012 May 1;83(1):317–326.

16. Desai NB, Stein NF, LaQuaglia MP, et al. Reduced toxicity with intensity modulated radiation therapy (IMRT) for desmoplastic small round cell tumor (DSRCT): an update on the whole abdominopelvic radiation therapy (WAP-RT) experience. Int J Radiat Oncol Biol Phys. 2013 Jan 1;85(1):e67–72.
17. Wong HH, Hatcher HM, Benson C, et al. Desmoplastic small round cell tumour: characteristics and prognostic factors of 41 patients and review of the literature. Clin Sarcoma Res. 2013 Dec 26;3(1):14.
18. Honoré C, Atallah V, Mir O, et al. Abdominal desmoplastic small round cell tumor without extraperitoneal metastases: is there a benefit for HIPEC after macroscopically complete cytoreductive surgery? PLoS ONE. 2017 Feb 24;12(2):e0171639.
19. Zhang S, Zhang Y, Yu YH, et al. Results of multimodal treatment for desmoplastic small round cell tumor of the abdomen and pelvis. Int J Clin Exp Med. 2015;8(6):9658–9666.
20. Forlenza CJ, Kushner BH, Kernan N, et al. Myeloablative chemotherapy with autologous stem cell transplant for desmoplastic small round cell tumor. Sarcoma 2015;2015:269197 [Epub 2015 Apr 7].
21. Atallah V, Honore C, Orbach D, et al. Role of adjuvant radiation therapy after surgery for abdominal desmoplastic small round cell tumors. Int J Radiat Oncol Biol Phys. 2016 Jul;95(4):1244–1253.
22. Osborne EM, Briere TM, Hayes-Jordan A, et al. Survival and toxicity following sequential multimodality treatment including whole abdominopelvic radiotherapy for patients with desmoplastic small round cell tumor. Radiother Oncol. 2016 Apr;119(1):40–44.
23. Stiles ZE, Dickson PV, Glazer ES, et al. Desmoplastic small round cell tumor: a nationwide study of a rare sarcoma. J Surg Oncol. 2018 Jun;117(8):1759–1767.
24. Subbiah V, Lamhamedi-Cherradi SE, Cuglievan B, et al. Multimodality treatment of desmoplastic small round cell tumor: chemotherapy and complete cytoreductive surgery improve patient survival. Clin Cancer Res. 2018 Oct 1;24(19):4865–4873.
25. Hayes-Jordan AA, Coakley BA, Green HL, et al. Desmoplastic small round cell tumor treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: results of a phase 2 trial. Ann Surg Oncol. 2018 Apr 30;25(4):872–877.
26. Honoré C, Delhorme JB, Nassif E, et al. Can we cure patients with abdominal desmoplastic small round cell tumor? Results of a retrospective multicentric study on 100 patients. Surg Oncol. 2019 Jun;29:107–112.
27. Campos F, Coutinho DL, Silva MLG, et al. Clinical characteristics, management, and outcomes of 19 nonpediatric patients with desmoplastic small round cell tumor: a cohort of Brazilian patients. Sarcoma. 2020 Oct 28;2020:1–7.
28. Liu KX, Collins NB, Greenzang KA, et al. The use of interval-compressed chemotherapy with the addition of vincristine, irinotecan, and temozolomide for pediatric patients with newly diagnosed desmoplastic small round cell tumor. Pediatr Blood Cancer. 2020 Oct 19;67(10). DOI:10.1002/pbc.28559
29. Bisogno G, Ferrari A, Tagarelli A, et al. Integrating irinotecan in standard chemotherapy: a novel dose-density combination for high-risk pediatric sarcomas. Pediatr Blood Cancer. 2021 Jul 10;68(7). DOI:10.1002/pbc.28951
30. Giani C, Radaelli S, Miceli R, et al. Long-term survivors with desmoplastic small round cell tumor (DSRCT): results from a retrospective single-institution case series analysis. Cancer Med. 2023 Mar 23. DOI:10.1002/cam4.5829
31. Bent MA, Padilla BE, Goldsby RE, et al. Clinical characteristics and outcomes of pediatric patients with desmoplastic small round cell tumor. Rare Tumors. 2016 Mar 31;8(1):24–26.
32. Hayes-Jordan A, Green HL, Lin H, et al. Complete cytoreduction and HIPEC Improves survival in desmoplastic small round cell tumor. Ann Surg Oncol. 2014 Jan 18;21(1):220–224.
33. Ordóñez NG. Desmoplastic small round cell tumor. Am J Surg Pathol. 1998 Nov;22(11):1303–1313.
34. Thway K, Noujaim J, Zaidi S, et al. Desmoplastic small round cell tumor: pathology, genetics, and potential therapeutic strategies. Int J Surg Pathol. 2016 Dec;24(8):672–684.
35. Mello CA, Campos FAB, Santos TG, et al. Desmoplastic small round cell tumor: a review of main molecular abnormalities and emerging therapy. Cancers (Basel). 2021 Jan 28;13(3):498.
36. Slotkin EK, Bowman AS, Levine MF, et al. Comprehensive molecular profiling of desmoplastic small round cell tumor. Mol Cancer Res. 2021 Jul 1;19(7):1146–1155.
37. Wu CC, Beird HC, Lamhamedi-Cherradi SE, et al. Multi-site desmoplastic small round cell tumors are genetically related and immune-cold. NPJ Precis Oncol. 2022 Apr 4;6(1):21.
38. Hingorani P, Dinu V, Zhang X, et al. Transcriptome analysis of desmoplastic small round cell tumors identifies actionable therapeutic targets: a report from the children's oncology group. Sci Rep. 2020 Jul 23;10(1):12318.
39. Koelsche C, Hartmann W, Schrimpf D, et al. Array-based DNA-methylation profiling in sarcomas with small blue round cell histology provides valuable diagnostic information. Mod Pathol. 2018 Aug 23;31(8):1246–1256.
40. Koelsche C, Schrimpf D, Stichel D, et al. Sarcoma classification by DNA methylation profiling. Nat Commun. 2021 Jan 21;12(1):498.
41. Devecchi A, de Cecco L, Dugo M, et al. The genomics of desmoplastic small round cell tumor reveals the deregulation of genes related to DNA damage response, epithelial-mesenchymal transition, and immune response. Cancer Commun. 2018 Dec;38(1):70.
42. Bulbul A, Shen JP, Xiu J, et al. Genomic and proteomic alterations in desmoplastic small round blue-cell tumors. JCO Precis Oncol. 2018 Nov;(2):1–9. DOI:10.1200/PO.17.00170
43. Wedekind MF, Haworth KB, Arnold M, et al. Immune profiles of desmoplastic small round cell tumor and synovial sarcoma suggest different immunotherapeutic susceptibility upfront compared to relapse specimens. Pediatr Blood Cancer. 2018 Nov;65(11):e27313.
44. Va Erp AEM, Versleijen-Jonkers YMH, Hillebrandt-Roeffen MHS, et al. Expression and clinical association of programmed cell death-1, programmed death-ligand-1 and CD8+ lymphocytes in primary sarcomas is subtype dependent. Oncotarget. 2017 Sep 19;8(41):71371–71384.
45. Lone SN, Nisar S, Masoodi T, et al. Liquid biopsy: a step closer to transform diagnosis, prognosis and future of cancer treatments. Mol Cancer. 2022 Mar 18;21(1):79.
46. Ferreira EN, Barros BDF, de Souza JE, et al. A genomic case study of desmoplastic small round cell tumor: comprehensive analysis reveals insights into potential therapeutic targets and development of a monitoring tool for a rare and aggressive disease. Hum Genomics. 2016 Dec 18;10(1):36.
47. Shukla NN, Patel JA, Magnan H, et al. Plasma DNA-Based molecular diagnosis, prognostication, and monitoring of patients with ewsr1 fusion-positive sarcomas. JCO Precis Oncol. 2017 Nov;1:1–11. DOI:10.1200/PO.16.00028
48. Iorio MV, Croce CM. MicroRNA dysregulation in cancer: diagnostics, monitoring and therapeutics. A comprehensive review. EMBO Mol Med. 2012 Mar 20;4(3):143–159.
49. Smolarz B, Durczyński A, Romanowicz H, et al. miRnas in cancer (review of literature). Int J Mol Sci. 2022 Mar 3;23(5):2805.
50. Kim KY, Hwang YJ, Jung MK, et al. A multifunctional protein EWS regulates the expression of Drosha and microRnas. Cell Death Differ. 2014 Jan 1;21(1):136–145.
51. Negri T, Brich S, Bozzi F, et al. New transcriptional-based insights into the pathogenesis of desmoplastic small round cell tumors (DSRCTs). Oncotarget. 2017 May 16;8(20):32492–32504.
52. Colletti M, Paolini A, Galardi A, et al. Expression profiles of exosomal miRnas isolated from plasma of patients with desmoplastic small round cell tumor. Epigenomics. 2019 Apr;11(5):489–500.
53. Hassan I, Shyyan R, Donohue JH, et al. Intraabdominal desmoplastic small round cell tumors. Cancer. 2005 Sep 15;104(6):1264–1270.
54. Wei G, Shu X, Zhou Y, et al. Intra-abdominal desmoplastic small round cell tumor: current treatment options and perspectives. Front Oncol. 2021 Sep 15; 11. DOI:10.3389/fonc.2021.705760
55. Saab R, Khoury JD, Krasin M, et al. Desmoplastic small round cell tumor in childhood: the St. Jude Children's Res Hosp Exper Pediatr Blood Cancer. 2007 Sep;49(3):274–279.

56. Quaglia MPL, Brennan MF. The clinical approach to desmoplastic small round cell tumor. Surg Oncol. 2000 Aug;9(2):77–81.
57. Yan TD, Black D, Sugarbaker PH, et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann Surg Oncol. 2007 Sep 19;14(10):2702–2713.
58. Yan TD, Welch L, Black D, et al. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. Ann Oncol. 2007 May;18(5):827–834.
59. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006 Jan 5;354(1):34–43.
60. Bonvalot S, Cavalcanti A, le Péchoux C, et al. Randomized trial of cytoreduction followed by intraperitoneal chemotherapy versus cytoreduction alone in patients with peritoneal sarcomatosis. Eur J Surg Oncol. 2005 Oct;31(8):917–923.
61. Berthet B, Sugarbaker TA, Chang D, et al. Quantitative methodologies for selection of patients with recurrent abdominopelvic sarcoma for treatment. Eur J Cancer. 1999 Mar;35(3):413–419.
62. Hayes-Jordan A. Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy in DSRCT: progress and pitfalls. Curr Oncol Rep. 2015 Aug 21;17(8):38.
63. Gil A, Gomez Portilla A, Brun EA, et al. Clinical perspective on desmoplastic small round-cell tumor. Oncology. 2004;67(3–4):231–242.
64. Modak S, Zanzonico P, Grkovski M, et al. B7H3-directed intraperitoneal radioimmunotherapy with radioiodinated omburtamab for desmoplastic small round cell tumor and other peritoneal tumors: results of a phase i study. J Clin Oncol. 2020 Dec 20;38(36):4283–4291.
65. Farhat F, Culine S, Lhommé C, et al. Desmoplastic small round cell tumors: results of a four-drug chemotherapy regimen in five adult patients. Cancer. 1996 Apr 1;77(7):1363–1366.
66. Ambar NBD, de Seixas Alves MT, Lederman HM, et al. Irinotecan and vincristine for the treatment of refractory desmoplastic small round cell tumor in a developing country: a case report. J Med Case Rep. 2019 Dec 10;13(1):77.
67. Siddiqui A, Pinto N, Applebaum MA, et al. The addition of autologous stem cell transplantation to neoadjuvant chemotherapy, radiation, and HIPEC for patients with unresectable desmoplastic small round cell tumor: a single center case series. Int J Surg Oncol (N Y). 2021 Jan 20;5(6):95.
68. Bailey K, Roth M, Weiser D, et al. High-dose chemotherapy with stem cell rescue in desmoplastic small round cell tumor: a single-institution experience and review of the literature. Sarcoma. 2018;2018:1–10.
69. Fraser CJ, Weigel BJ, Perentesis JP, et al. Autologous stem cell transplantation for high-risk Ewing's sarcoma and other pediatric solid tumors. Bone Marrow Transplant. 2006 Jan 1;37(2):175–181.
70. Bertuzzi A, Castagna L, Quagliuolo V, et al. Prospective study of high-dose chemotherapy and autologous peripheral stem cell transplantation in adult patients with advanced desmoplastic small round-cell tumour. Br J Cancer. 2003 Oct 30;89(7):1159–1161.
71. Bertuzzi A, Castagna L, Nozza A, et al. High-dose chemotherapy in poor-prognosis adult small round-cell tumors: clinical and molecular results from a prospective study. J Clin Oncol. 2002 Apr 15;20(8):2181–2188.
72. Jayakrishnan T, Moll R, Sandhu A, et al. Desmoplastic small round-cell tumor: retrospective review of institutional data and literature review. Anticancer Res. 2021 Aug;41(8):3859–3866.
73. López-González A, Cantos B, Tejerina E, et al. Activity of trabectidin in desmoplastic small round cell tumor. Med Oncol. 2011 Dec 7;28 (S1):644–646.
74. Brunetti AE, Delcuratolo S, Lorusso V, et al. Third-line trabectedin for a metastatic desmoplastic small round cell tumour treated with multimodal therapy. Anticancer Res. 2014;34(7):3683–3688.
75. Frezza AM, Whelan JS, Dileo P. Trabectedin for desmoplastic small round cell tumours: a possible treatment option? Clin Sarcoma Res. 2014 Dec 25;4(1):3.
76. Verret B, Honore C, Dumont S, et al. Trabectedin in advanced desmoplastic round cell tumors. Anticancer Drugs. 2017 Jan;28(1):116–119.
77. Ferrari A, Chiaravalli S, Bergamaschi L, et al. Trabectedin-irinotecan, a potentially promising combination in relapsed desmoplastic small round cell tumor: report of two cases. J Chemother. 2023 Apr;35(2):163–167.
78. Thijs AMJ, van der Graaf WTA, van Herpen CML. Temsirolimus for metastatic desmoplastic small round cell tumor. Pediatr Blood Cancer. 2010 Dec 15;55(7):1431–1432.
79. Naing A, LoRusso P, Fu S, et al. Insulin growth factor-receptor (IGF-1R) antibody cixutumumab combined with the mTOR inhibitor temsirolimus in patients with refractory ewing's sarcoma family tumors. Clin Cancer Res. 2012 May 1;18(9):2625–2631.
80. Tarek N, Hayes-Jordan A, Salvador L, et al. Recurrent desmoplastic small round cell tumor responding to an mTOR inhibitor containing regimen. Pediatr Blood Cancer. 2018 Jan;65(1):e26768. DOI:10.1002/pbc.26768
81. Ferrari A, Grosso F, Stacchiotti S, et al. Response to vinorelbine and low-dose cyclophosphamide chemotherapy in two patients with desmoplastic small round cell tumor. Pediatr Blood Cancer. 2007 Nov;49(6):864–866.
82. Tian Y, Cheng X, Li Y. Chemotherapy combined with apatinib for the treatment of desmoplastic small round cell tumors: a case report. J Cancer Res Ther. 2020;16(5):1177.
83. Menegaz BA, Cuglievan B, Benson J, et al. Clinical activity of pazopanib in patients with advanced desmoplastic small round cell tumor. Oncology. 2018 Mar;23(3):360–366.
84. de Sanctis R, Bertuzzi A, Bisogno G, et al. Imatinib mesylate in desmoplastic small round cell tumors. Future Oncol. 2017 Jun;13 (14):1233–1237.
85. Tap WD, Demetri G, Barnette P, et al. Phase II study of ganitumab, a fully human anti–type-1 insulin-like growth factor receptor antibody, in patients with metastatic Ewing family tumors or desmoplastic small round cell tumors. J Clin Oncol. 2012 May 20;30(15):1849–1856.
86. Italiano A, Kind M, Cioffi A, et al. Clinical activity of sunitinib in patients with advanced desmoplastic round cell tumor: a case series. Target Oncol. 2013 Sep 6;8(3):211–213.
87. Emambux S, Kind M, le Loarer F, et al. Clinical activity of eribulin in advanced desmoplastic small round-cell tumor. Anticancer Drugs. 2017 Oct;28(9):1053–1055.
88. Chen HM, Feng G. Use of anlotinib in intra-abdominal desmoplastic small round cell tumors: a case report and literature review. Onco Targets Ther. 2018;12:57–61.
89. Cheng K, Liu X, Chen Y, et al. Response to chemotherapy combined with anlotinib plus anlotinib maintenance in intra-abdominal desmoplastic small round cell tumors (IADSRCT): a case report and literature review. BMC Gastroenterol. 2022 Aug 17;22(1):388.
90. Fine RL, Shah SS, Moulton TA, et al. Androgen and c-Kit receptors in desmoplastic small round cell tumors resistant to chemotherapy: novel targets for therapy. Cancer Chemother Pharmacol. 2007 Jan 15;59(4):429–437.
91. Slotkin EK, Mauguen A, Ortiz MV, et al. A phase I/II study of prexasertib in combination with irinotecan in patients with relapsed/refractory desmoplastic small round cell tumor and rhabdomyosarcoma. J Clin Oncol. 2022 Jun 01;40(16_suppl):11503.
92. De Cesare M, Lauricella C, Veronese SM, et al. Synergistic antitumor activity of cetuximab and namitecan in human squamous cell carcinoma models relies on cooperative inhibition of EGFR expression and depends on high EGFR gene copy number. Clin Cancer Res. 2014;20(4):995–1006.
93. Ferrari A, Bergamaschi L, Chiaravalli S, et al. Multiagent chemotherapy including IrIVA regimen and maintenance therapy in the treatment of desmoplastic small round cell tumor. Tumori J. 2022 Feb 17;108(1):93–97.
94. Nishio J, Iwasaki H, Ishiguro M, et al. Establishment and characterization of a novel human desmoplastic small round cell tumor cell line, JN-DSRCT-1. Lab Invest. 2002 Sep;82(9):1175–1182.
95. Ogura K, Somwar R, Hmeljak J, et al. Therapeutic potential of NTRK3 inhibition in desmoplastic small round cell tumor. Clin Cancer Res. 2021 Feb 15;27(4):1184–1194.
96. Uboldi S, Craparotta I, Colella G, et al. Mechanism of action of trabectedin in desmoplastic small round cell tumor cells. BMC Cancer. 2017 Dec 6;17(1):107. DOI:10.1186/s12885-017-3091-1

97. Gedminas JM, Kaufman R, Boguslawski EA, et al. Lurbinectedin inhibits the EWS-WT1 transcription factor in desmoplastic small round cell tumor. Mol Cancer Ther. 2022 Aug 2;21(8):1296–1305.
98. Lee SB, Kolquist KA, Nichols K, et al. The EWS-WT1 translocation product induces PDGFA in desmoplastic small round-cell tumour. Nat Genet. 1997 Nov;17(3):309–313.
99. Chao J, Budd GT, Chu P, et al. Phase II clinical trial of imatinib mesylate in therapy of KIT and/or PDGFRalpha-expressing Ewing sarcoma family of tumors and desmoplastic small round cell tumors. Anticancer Res. 2010 Feb;30(2):547–552.
100. Shi C, Feng Y, Zhang LC, et al. Effective treatment of apatinib in desmoplastic small round cell tumor: a case report and literature review. BMC Cancer. 2018 Dec 27;18(1):338.
101. Bétrian S, Bergeron C, Blay JY, et al. Antiangiogenic effects in patients with progressive desmoplastic small round cell tumor: data from the French national registry dedicated to the use of off-labeled targeted therapy in sarcoma (Outc's). Clin Sarcoma Res. 2017 Dec 10;7(1):10.
102. Bexelius TS, Wasti A, Chisholm JC. Mini-review on targeted treatment of desmoplastic small round cell tumor. Front Oncol. 2020 Apr 21; 10; 10. DOI:10.3389/fonc.2020.00518
103. Yamamoto Y, Loriot Y, Beraldi E, et al. Generation 2.5 antisense oligonucleotides targeting the androgen receptor and its splice variants suppress enzalutamide-resistant prostate cancer cell growth. Clin Cancer Res. 2015;21(7):1675–1687. DOI:10.1158/1078-0432.CCR-14-1108
104. De Velasco MA, Kura Y, Sakai K, et al. Targeting castration-resistant prostate cancer with androgen receptor antisense oligonucleotide therapy. JCI Insight. 2019;4(17):e122688. Published 2019 Sep 5. DOI:10.1172/jci.insight.122688
105. Pearson ADJ, Pfister SM, Baruchel A, et al. From class waivers to precision medicine in paediatric oncology. Lancet Oncol. 2017;18 (7):e394–404.
106. Mohamed M, Gonzalez D, Fritchie KJ, et al. Desmoplastic small round cell tumor: evaluation of reverse transcription-polymerase chain reaction and fluorescence in situ hybridization as ancillary molecular diagnostic techniques. Virchows Arch. 2017 Nov 26;471(5):631–640.
107. Lamhamedi-Cherradi SE, Maitituoheti M, Menegaz BA, et al. The androgen receptor is a therapeutic target in desmoplastic small round cell sarcoma. Nat Commun. 2022;13(1):3057. Published 2022 Jun 1. DOI:10.1038/s41467-022-30710-z
108. Truong DD, Lamhamedi-Cherradi S, Maitituoheti M, et al. EPIGENETIC IMPACT and THERAPEUTIC OPPORTUNITY of AR-DIRECTED THERAPY for DSRCT – 2022 annual meeting of the connective tissue oncology society (CTOS).
109. van Erp AEM, van Houdt L, Hillebrandt-Roeffen MHS, et al. Olaparib and temozolomide in desmoplastic small round cell tumors: a promising combination in vitro and in vivo. J Cancer Res Clin Oncol. 2020;146(7):1659–1670. DOI:10.1007/s00432-020-03211-z
110. Antonarakis ES, Gomella LG, Petrylak DP. When and how to use parp inhibitors in prostate cancer: a systematic review of the literature with an update on on-going trials. Eur Urol Oncol. 2020;3(5):594–611.
111. Anderson PM, Trucco MM, Tarapore RS, et al. Phase II study of ONC201 in neuroendocrine tumors including pheochromocytoma-paraganglioma and desmoplastic small round cell tumor. Clin Cancer Res. 2022 May 2;28(9):1773–1782.
112. Hartono AB, Kang HJ, Shi L, et al. Salt-inducible kinase 1 is a potential therapeutic target in desmoplastic small round cell tumor. Oncogenesis. 2022 Apr 20;11(1):18.
113. Smith RS, Odintsov I, Liu Z, et al. Novel patient-derived models of desmoplastic small round cell tumor confirm a targetable dependency on ERBB signaling. Dis Model Mech. 2022 Jan 1;15(1): dmm047621.
114. Anderson PM, Tu ZJ, Kilpatrick SE, et al. Routine EWS fusion analysis in the oncology clinic to identify cancer-specific peptide sequence patterns that span breakpoints in Ewing sarcoma and DSRCT. Cancers (Basel). 2023;15(5):1623. [2023 Mar 6]. DOI:10.3390/cancers15051623
115. Olivier-Gougenheim L, Orbach D, Atallah V, et al. Desmoplastic small round cell tumors with EWS-WT1 transcript expression: should we consider children and adult patients differently? J Pediatr Hematol Oncol. 2022 Apr;44(3):e637–642.