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Novel Therapies for Relapsed and Refractory Neuroblastoma

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Abstract: While recent increases in our understanding of the biology of neuroblastoma have allowed for more precise risk stratification and improved outcomes for many patients, children with high-risk neuroblastoma continue to suffer from frequent disease relapse, and despite recent advances in our understanding of neuroblastoma pathogenesis, the outcomes for children with relapsed neuroblastoma remain poor. These children with relapsed neuroblastoma, therefore, continue to need novel treatment strategies based on a better understanding of neuroblastoma biology to improve outcomes. The discovery of new tumor targets and the development of novel antibody- and cell-mediated immunotherapy agents have led to a large number of clinical trials for children with relapsed neuroblastoma, and additional clinical trials using molecular and genetic tumor profiling to target tumor-specific aberrations are ongoing. Combinations of these new therapeutic modalities with current treatment regimens will likely be needed to improve the outcomes of children with relapsed and refractory neuroblastoma.

Keywords: neuroblastoma; relapsed neuroblastoma; recurrent neuroblastoma; refractory neuroblastoma; personalized treatment; ALK; RET; MIBG; retinoic acid

1. Introduction

With new treatment strategies, including immunotherapy and therapies directed against tumor-specific molecular aberrations, the outcomes of children with high-risk neuroblastoma have significantly improved over the past two decades. Despite these recent successes, however, many of these children continue to suffer from refractory or relapsed disease, and to date, there are no established curative treatment options for many of these patients. Relapsed neuroblastoma has been considered invariably fatal in the past [1], with a median overall survival time for patients with refractory neuroblastoma of only 27.9 months and with an overall survival of only 11.0 months for patients with relapsed disease [2]. However, the reported 5-year overall survival rate for children after the initial relapse of neuroblastoma is 20% [3,4]. These outcomes were dependent on both the time of relapse and the initial patient tumor stage [3–5], suggesting that a subset of patients with recurrent neuroblastoma can be cured with appropriate treatment and also emphasizing the need for additional treatment options for these patients.

Recent data presented by Modak and colleagues and Manole and colleagues indicate that patients with isolated local recurrence can be treated successfully with surgical tumor resection and/or radiation therapy at sites of active disease [6,7]. These authors further recommend using chemotherapy regimens with demonstrated activity in children with recurrent neuroblastoma, rather than experimental therapy for localized relapses. However, children with neuroblastoma who suffer disease relapse often develop metastatic tumors resistant to standard therapies, and the underlying molecular profiles and signaling pathway activity in these relapsed tumors are likely significantly different from those in untreated...
tumors due to novel molecular and genetic aberrations induced or selected by prior therapy [8,9]. The goals of treatment in these patients historically have not been curative, but rather to prolong survival and minimize the toxicities of additional therapy. However, recent data have suggested that more aggressive treatment of these patients to achieve a complete or nearly complete response, followed by additional consolidation or maintenance therapy, can lead to durable disease remission and even cure [10], suggesting that the goals of treatment for many children with relapsed and refractory neuroblastoma may need to be modified.

2. Systemic Chemotherapy and Radiotherapy

2.1. Systemic Chemotherapy

Initial treatment regimens for patients with relapsed or refractory neuroblastoma typically include chemotherapy combinations distinct from those previously used. Topotecan and irinotecan have both demonstrated activity as single agents in preclinical and clinical studies of neuroblastoma via inhibition of the topoisomerase I enzyme [11–16] and are both commonly used for the treatment of children with relapsed neuroblastoma. An early phase II study using a combination of topotecan and cyclophosphamide in children with relapsed neuroblastoma demonstrated objective responses in 6 of 13 patients [17]. A follow-up study demonstrated that children with recurrent neuroblastoma who were treated with the combination of cyclophosphamide and topotecan had increased response rates compared to those who received topotecan as a single agent, although no difference in overall survival rates was observed in treated patients [18,19]. Using a combination of higher doses of cyclophosphamide and topotecan with vincristine, children with primary refractory neuroblastoma had an overall response rate of 19%, while the response rate was 52% for those with their initial neuroblastoma relapse [20]. A phase II study of topotecan combined with doxorubicin and vincristine (TVD) demonstrated a 64% overall response rate in 25 patients with relapsed neuroblastoma, with 4 patients having complete responses to the TVD combination [21]. The TVD regimen was subsequently incorporated into the SIOPEN HR-NBL-1 treatment protocol for high-risk neuroblastoma as salvage therapy for refractory patients with insufficient responses to induction therapy. Following two courses of TVD, 4 of 63 patients (6.4%) enrolled on this protocol had an overall complete response (CR), while 28 of 63 (44.4%) had a partial response (PR). Of note, 23 patients achieved sufficient response to be eligible to receive myeloablative therapy with stem cell rescue [22]. However, the long-term benefits of TVD in these patients will likely need to be established in further clinical trials.

Combinations of irinotecan with the alkylating agent temozolomide have also demonstrated efficacy in children with relapsed neuroblastoma. A single-institution study reported 2 complete responses to the combination of irinotecan and temozolomide among 19 patients with refractory disease, with 7 patients with mixed responses and 10 with stable disease (SD) [23]. Children with relapsed neuroblastoma treated on a separate multi-institutional study using lower doses of irinotecan and temozolomide had an overall response rate of 15%, while an additional 53% had SD [24]. Subsequent clinical trials have attempted to improve on these results with the addition of bevacizumab [25] and temsirolimus [26] to the irinotecan/temozolomide combination. Although these combinations were well tolerated by patients, the additional agents unfortunately did not significantly improve patient outcomes. A subsequent phase I study utilized irinotecan alone combined with the proteasome inhibitor bortezomib, and 2 of 17 evaluable children with refractory or relapsed neuroblastoma demonstrated responses (including one CR), and another 4 children had prolonged stable disease [27], suggesting that this combination might prove more effective in children with relapsed neuroblastoma and should be tested in further studies.

Combinations of ifosfamide, carboplatin, and etoposide (ICE) have also been routinely employed for children with relapsed neuroblastoma. In a single institution study, ICE was well tolerated and led to disease regression in 14 of 17 patients (82%) who were treated after their first neuroblastoma relapse. Disease regression was also seen in 13 of 26 patients (50%) with refractory neuroblastoma...
and in 12 of 34 patients (35%) who developed progressive disease during frontline treatment [28]. In a separate study, 37% of patients with relapsed or refractory neuroblastoma responded to the ICE regimen, while an additional 17% had SD [29]. Additionally, 15 of 16 children with high-risk neuroblastoma receiving ICE for upfront treatment had either partial or complete responses [30], further demonstrating the efficacy of ifosfamide-based chemotherapy regimens for both frontline treatment of high-risk neuroblastoma and for initial treatment of patients with relapsed neuroblastoma.

Prior studies have also suggested that some patients with relapsed or refractory neuroblastoma might benefit from more aggressive treatment consisting of myeloablative chemotherapy followed by autologous stem cell rescue (ASCR). One recent study demonstrated that children with relapsed neuroblastoma who received myeloablative therapy followed by ASCR had improved survival rates compared to those who received chemotherapy alone (43.5% vs. 9.6%), with 7 of 23 patients achieving either CR or PR after ASCR. However, 2 of the 23 patients experienced transplant-related mortality, suggesting that further studies to identify which patients would receive the most benefit from this approach are needed [31]. Additional studies have suggested that haploidentical stem cell transplantation may also be beneficial for children with relapsed and refractory neuroblastoma, with 5-year event-free survival (EFS) and overall survival (OS) rates of 19% and 23%, respectively, and no treatment-related mortality [32]. However, patients with residual disease who underwent these transplants had significantly worse outcomes than those in complete remission, and a large number of patients experienced acute or chronic graft-versus-host disease (GVHD), suggesting that further study is required.

2.2. Radiotherapy

Additional forms of therapy for children with relapsed and refractory neuroblastoma have directly targeted markers expressed on the surfaces of neuroblastoma tumor cells. The vast majority of neuroblastoma tumors demonstrate tumor cell surface expression of the norepinephrine transporter (NET), suggesting that the use of benzylguanidine analogues, such as meta-iodobenzylguanidine (MIBG), that bind to this transporter would selectively target these neuroblastoma tumor cells [33]. Approximately 90% of children with neuroblastoma have tumors that are detectable by radiolabeled MIBG imaging, and infusion of radiolabeled MIBG, therefore, allows for targeted delivery of radiation therapy directly to sites of active disease. Initial studies of $^{131}$I-MIBG used therapeutically in children with recurrent neuroblastoma showed overall response rates of 21–47% [34–36]. Although useful disease palliation and responses were seen in approximately one-third of patients, clinical benefit was often only temporary [37]. Subsequent studies used MIBG treatment followed by ASCR, as dose escalation was often associated with significant hematopoietic toxicity, particularly in heavily pretreated patients [38]. In a large multi-institutional phase II study, 36% of children with either relapsed or refractory neuroblastoma who were treated with increasing doses of $^{131}$I-MIBG had either complete or partial responses, while another 34% of patients demonstrated stable disease with a median time to progression of 6 months [39]. A subsequent retrospective analysis of 218 patients treated with $^{131}$I-MIBG therapy at a single institution demonstrated a 27% overall response rate. However, 24% of relapsed patients had progressive disease compared to only 9% of refractory patients, and 39% of relapsed patients had stable disease compared to 59% of refractory patients [40], suggesting patients with refractory neuroblastoma are most likely to benefit from $^{131}$I-MIBG therapy. The efficacy of $^{131}$I-MIBG therapy against neuroblastoma has led to subsequent clinical trials incorporating $^{131}$I-MIBG therapy as a component of frontline treatment for children with high-risk neuroblastoma, and ongoing clinical trials through the New Approaches to Neuroblastoma Therapy (NANT) consortium are evaluating the efficacy of additional anticancer agents combined with $^{131}$I-MIBG therapy (NCT02035137) in children with relapsed and refractory neuroblastoma. Despite the established efficacy of $^{131}$I-MIBG therapy in children with relapsed neuroblastoma, however, only a limited number of institutions have the resources to support the administration of radioactive iodine to pediatric patients, and the limited availability and accompanying need for available stem cells for ASCR remain major challenges to the more widespread use of $^{131}$I-MIBG therapy.
Prior studies have also shown that 77–89% of neuroblastoma cells express the somatostatin receptor (SSTR) [41–43], suggesting that agents targeting the SSTR may also be effective for neuroblastoma therapy. In adults with neuroendocrine tumors (NETs), peptide receptor radionuclide therapy (PRRT) with high-activity $^{111}$In-, $^{177}$Lu-, and $^{90}$Y-labeled somatostatin analogues has been successfully used [44,45]. In a single-institution study of PRRT, four children with relapsed neuroblastoma received 17 cycles of palliative PRRT using either $^{111}$In-DOTATATE, $^{177}$Lu-DOTATATE, or $^{90}$Y-DOTATATE. All four had objective responses, with two long-term survivors [46], supporting ongoing clinical trials.

3. Molecularly Targeted Therapy

While regimens incorporating chemotherapy and radiotherapy with $^{131}$I-MIBG have demonstrated efficacy in the treatment of children with relapsed and refractory neuroblastoma, treatment options for children who suffer from subsequent disease relapses and progression remain limited. However, ongoing investigations exploring the molecular mechanisms underlying the etiology and pathogenesis of neuroblastoma have identified a number of novel therapeutic targets, and several novel targeted agents have been shown to be highly active in preclinical models of neuroblastoma. Many of these agents have been tested or are currently being evaluated in early phase clinical trials for children with relapsed and refractory neuroblastoma (Table 1). Although untreated neuroblastoma tumors have a relative paucity of mutations in therapeutically relevant gene targets [47,48], relapsed neuroblastoma tumors have been found to have a number of actionable mutations [8,9], and initial clinical trials employing therapies selected based on genomic alterations identified in individual patient tumors have demonstrated both feasibility and efficacy, suggesting that molecularly targeted therapy and individualized treatment may lead to increased rates of response and improved outcomes for children with relapsed and refractory neuroblastoma.

3.1. Anaplastic Lymphoma Kinase (ALK)

Early efforts to identify gene mutations and other genetic aberrations in neuroblastoma tumors that could serve as therapeutic targets focused on familial neuroblastoma, which accounts for approximately 2% of all patients with neuroblastoma. Initial efforts determined that the majority of these cases are associated with activating germline mutations in the anaplastic lymphoma kinase (ALK) gene [49–52], and subsequent studies identified ALK gene mutations or gene amplifications in up to 15% of sporadic high-risk neuroblastoma tumors [49,53]. High-risk neuroblastoma tumors were also found to have increased ALK gene expression when compared to low-risk tumors [54], further suggesting a potential role for ALK inhibitors in neuroblastoma therapy. In a subsequent phase I trial, 79 children were enrolled and treated with the ALK inhibitor crizotinib, including 34 with neuroblastoma, 11 of which had known ALK mutations [55]. Despite an objective tumor response rate of 67% in children with other tumors with ALK mutations, only 1 of 11 children with neuroblastoma with ALK mutations (9%) demonstrated an objective response, suggesting that ALK inhibitors will likely need to be combined with other therapies for maximal benefit. Initial studies have identified synergistic combinations of ALK inhibitors with mTOR inhibitors [56] and with CDK4/6 inhibitors [57], and these combinations may serve to overcome some of the limitations of single-agent ALK inhibitor treatment for neuroblastoma. Additionally, novel second-generation ALK inhibitors, such as lorlatinib (PF06463922), ceritinib (LDK378), and ensartinib, that are effective against the crizotinib-resistant ALK$^{F1174L}$ mutant [58,59] are currently being evaluated in clinical trials for children with neuroblastoma (NCT01742286, NCT03107988, NCT03213652), with early results showing responses to ceritinib in six of nine patients with anaplastic large cell lymphoma (ALCL) and myofibroblastic tumors with ALK gene aberrations. To date, one patient with relapsed neuroblastoma with an ALK$^{F1174L}$ mutation had shrinkage of a retroperitoneal mass but concurrently experienced central nervous system (CNS) disease progression [60], suggesting that higher doses may be required to achieve adequate levels in neuroblastoma sanctuary sites such as the CNS.
| NCT Number | Title | Drug | Molecular Target | Therapeutic Class | Study Enrollment Target | Eligibility Age Range | Primary Site/Group or Sponsor | Status |
|------------|-------|------|------------------|-------------------|------------------------|----------------------|-----------------------------|--------|
| NCT0089245 | Radiolabeled Monoclonal Antibody Therapy in Treating Patients with Refractory, Recurrent, or Advanced CNS or Leptomeningeal Cancer | Intrathecal $^{131}$I-8H9 | B7-H3 | Systemic Radiotherapy | 120 | any | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, recruiting |
| NCT00107289 | Iodine $^{131}$I Metaodobenzylguanidine in Treating Patients with Recurrent, Progressive, or Refractory Neuroblastoma or Malignant Pheochromocytoma or Paraganglioma | $^{131}$I-MIBG | NET | Systemic Radiotherapy | 80 | over 1 year | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, recruiting |
| NCT00601003 | Study of Nifurtimox to Treat Refractory or Relapsed Neuroblastoma or Medulloblastoma | Nifurtimox, cyclophosphamide, topotecan | Reactive Oxygen Species | Systemic Chemotherapy | 100 | up to 21 years | Beat Childhood Cancer (BCC) | Active, recruiting |
| NCT00638898 | Busulfan, Melphalan, Topotecan Hydrochloride, and a Stem Cell Transplant in Treating Patients with Newly Diagnosed or Relapsed Solid Tumor | Busulfan, melphalan, topotecan | N/A | Systemic Chemotherapy | 25 | 6 months to 40 years | Duarte, CA (City of Hope Cancer Center) | Active, not recruiting |
| NCT00788125 | Dasatinib, Ifosfamide, Carboplatin, and Etoposide in Treating Young Patients with Metastatic or Recurrent Malignant Solid Tumors | Carboplatin, dasatinib, etoposide, ifosfamide | Multiple Kinases (Abl, Src, c-Kit, PDGFRβ) | Molecularly Targeted Therapy | 143 | 1–25 years | Duarte, CA (City of Hope Cancer Center) | Active, not recruiting |
| NCT00877110 | Anti-GD2 3F8 Antibody and Allogeneic Natural Killer Cells for High-Risk Neuroblastoma | Cyclophosphamide, vincristine, topotecan, NK cells, 3F8 | GD2 | Systemic Chemotherapy plus Immunotherapy | 71 | any | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, not recruiting |
| NCT0091560 | Bivalent Vaccine with Escalating Doses of the Immunological Adjuvant OPT-821, in Combination with Oral β-glucan for High-Risk Neuroblastoma | Adjuvant OPT-821 in a vaccine containing two antigens (GD2L and GD3L) covalently linked to KLH | GD2L, GD3L | Immunotherapy | 215 | up to 21 years | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, recruiting |
| NCT01183884 | 3F8/GM-CSF Immunotherapy Plus 13-Cis-Retinoic Acid for Consolidation of Second or Greater Remission of High-Risk Neuroblastoma | 3F8, GM-CSF, isotretinoin | GD2 | Immunotherapy | 63 | over 18 months | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, not recruiting |
| NCT01183897 | 3F8/GM-CSF Immunotherapy Plus 13-Cis-Retinoic Acid for Primary Refractory Neuroblastoma in Bone Marrow | 3F8, GM-CSF, isotretinoin | GD2 | Immunotherapy | 31 | over 18 months | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, not recruiting |
| NCT Number     | Title                                                                 | Drug                                                                 | Molecular Target                      | Therapeutic Class                  | Study Enrollment Target | Eligibility Age Range | Primary Site/Group or Sponsor | Status              |
|---------------|----------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------|-------------------------------------|------------------------|------------------------|-------------------------------|---------------------|
| NCT01331135   | Aflac ST0901 CHOANOME—Sirolimus in Solid Tumors (Aflac ST0901)       | Sirolimus                                                            | mTOR                                  | Molecularly Targeted Therapy        | 24                     | up to 30 years            | Atlanta, GA (Children’s Healthcare of Atlanta) | Active, not recruiting |
| NCT01419834   | Humanized 3F8 Monoclonal Antibody (Hu3F8) in Patients with High-Risk Neuroblastoma and GD2-Positive Tumors | Hu3F8                                                               | GD2                                   | Immunotherapy                       | 74                     | over 2 years             | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, recruiting    |
| NCT01467986   | Multimodal Molecular Targeted Therapy to Treat Relapsed or Refractory High-Risk Neuroblastoma | Dasatinib, sirolimus, irinotecan, temozolomide                       | Multiple Kinases (Abl, Src, c-Kit, PDGFRβ), mTOR | Molecularly Targeted Therapy        | 114                    | up to 25 years           | Regensburg, Germany (University Hospital Regensburg) | Active, recruiting    |
| NCT01492673   | Cyclophosphamide, Topotecan, and Bevacizumab (CTB) in Patients with Relapsed/Refractory Ewing’s Sarcoma and Neuroblastoma | Cyclophosphamide, topotecan, bevacizumab                            | Angiogenesis                          | Molecularly Targeted Therapy        | 9                      | up to 21 years            | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, not recruiting |
| NCT01576692   | Combination Chemotherapy, Monoclonal Antibody, and Natural Killer Cells in Treating Young Patients with Recurrent or Refractory Neuroblastoma | Cyclophosphamide, topotecan, Hu14.18K322A, cisplatin, etoposide, doxorubicin, Vincristine, busulfan, melphalan, natural killer cells, GM-CSF, interleukin-2 | GD2                                   | Systemic Chemotherapy plus Immunotherapy | 34                     | up to 21 years            | Memphis, TN (St. Jude Children’s Research Hospital) | Active, not recruiting |
| NCT01601535   | Study of MLN8237 in Combination with Irinotecan and Temozolomide       | Alisertib (MLN8237), irinotecan, temozolomide                       | Aurora A Kinase                       | Molecularly Targeted Therapy        | 4                      | 1–30 years               | New Approaches to Neuroblastoma Therapy (NANT) | Active, not recruiting |
| NCT01606878   | Crizotinib and Combination Chemotherapy in Treating Younger Patients with Relapsed or Refractory Solid Tumors or Anaplastic Large Cell Lymphoma | Crizotinib, cyclophosphamide, topotecan, vincristine, doxorubicin | ALK, c-Met                            | Systemic Chemotherapy plus Molecularly Guided Therapy | 65                     | 1–21 years               | Children’s Oncology Group | Active, not recruiting    |
| NCT01625351   | A Study of CD38RA+ Depleted Haploidentical Stem Cell Transplantation in Children with Relapsed or Refractory Solid Tumors and Lymphomas | Alemtuzumab, fludarabine, sirolimus, busulfan, melphalan             | mTOR                                  | Systemic Chemotherapy plus Immunotherapy | 23                     | 2–21 years               | Memphis, TN (St. Jude Children’s Research Hospital) | Active, not recruiting    |
| NCT01662804   | Humanized 3F8 Monoclonal Antibody (Hu3F8) When Combined with Interleukin-2 in Patients with High-Risk Neuroblastoma and GD2-positive Solid Tumors | Hu3F8, IL-2                                                          | GD2                                   | Immunotherapy                       | 14                     | over 13 months           | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, not recruiting    |
| NCT Number   | Title                                                                 | Drug                                                | Molecular Target          | Therapeutic Class         | Study Enrollment Target | Eligibility Age Range | Primary Site/Group or Sponsor                        | Status               |
|--------------|-----------------------------------------------------------------------|-----------------------------------------------------|---------------------------|---------------------------|-------------------------|-----------------------|---------------------------------------------------|----------------------|
| NCT01711554 | Lenalidomide and Dinutuximab With or Without Isotretinoin in Treating Younger Patients with Refractory or Recurrent Neuroblastoma | Lenalidomide, dinutuximab, isotretinoin             | GD2                       | Immunotherapy             | 62                      | up to 21 years          | New Approaches to Neuroblastoma Therapy (NANT)      | Active, recruiting    |
| NCT01742286 | Phase I Study of LDK378 in Pediatric, Malignancies with a Genetic Alteration in Anaplastic Lymphoma Kinase (ALK) | Ceritinib (LDK378)                                  | ALK                       | Molecularly Guided Therapy | 83                      | 1–17 years             | Novartis Pharmaceuticals                            | Active, not recruiting |
| NCT01757626 | Combination Therapy of Antibody Hu3F8 With Granulocyte- Macrophage Colony Stimulating Factor (GM-CSF) in Patients with Relapsed/Refractory High-Risk Neuroblastoma | Hu3F8 with GM-CSF                                   | GD2                       | Immunotherapy             | 224                     | any                   | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, recruiting    |
| NCT01804634 | A Phase II Trial of Reduced Intensity Conditioning and Haploidentical BMT for High-risk Solid Tumors | Cyclophosphamide, fludarabine, XRT                 | N/A                       | Systemic Chemotherapy plus Immunotherapy | 20                      | up to 40 years          | Baltimore, MD (Sidney Kimmel Cancer Center at Johns Hopkins) | Active, recruiting    |
| NCT01956669 | A Phase II Study of Pazopanib GW786034, NSC# 737754 in Children, Adolescents, and Young Adults with Refractory Solid Tumors | Pazopanib                                           | Multiple Kinases (VEGFR-1, VEGFR-2, VEGFR-3, PDGFRβ, c-kit) | Molecularly Targeted Therapy | 154                     | 1–18 years             | Children's Oncology Group                           | Active, recruiting    |
| NCT02013336 | Phase 1 Study of MM-398 Plus Cyclophosphamide in Pediatric Solid Tumors | MM-398 (Irinotecan sucrosate liposomes), cyclophosphamide | N/A                       | Systemic chemotherapy      | 30                      | 1–20 years             | South Plains Oncology Consortium                    | Active, recruiting    |
| NCT02030964 | N2012-01: Phase 1 Study of Diffuromethylnitroiline (DFMO) and Celecoxib with Cyclophosphamide/Topotecan (DFMO) | DFMO, celecoxib, cyclophosphamide, topotecan       | ODC                       | Molecularly Targeted Therapy | 30                      | 2–30 years             | New Approaches to Neuroblastoma Therapy (NANT)      | Active, not recruiting |
| NCT02034981 | Phase 2 Study Assessing Efficacy and Safety of Crizotinib in Patients Harboring an Alteration on ALK, MET or ROS1 | Crizotinib                                          | ALK, c-Met                | Molecularly Guided Therapy | 246                     | over 1 year            | Villejuif, France (Institut Gustave Roussy)         | Active, not recruiting |
| NCT02035137 | 131I-MIBG Alone VS. 131I-MIBG With Vincristine and Irinotecan VS. 131I-MIBG With Vortinostat (N2011-01) | 131I-MIBG, vorinostat, vincristine/irinotecan      | NET                       | Systemic radiotherapy plus Chemotherapy | 105                     | 2–30 years             | New Approaches to Neuroblastoma Therapy (NANT)      | Active, recruiting    |
| NCT Number | Title                                                                 | Drug                                                                 | Molecular Target | Therapeutic Class | Study Enrollment Target | Eligibility Age Range | Primary Site/Group or Sponsor | Status                      |
|------------|-----------------------------------------------------------------------|----------------------------------------------------------------------|------------------|--------------------|-------------------------|------------------------|-------------------------------|-----------------------------|
| NCT02076906 | MR-guided High Intensity Focused Ultrasound (HIFU) on Pediatric Solid Tumors | MR-HIFU                                                              | N/A              | N/A                | 14                      | up to 30 years          | Washington, DC (Children’s National Medical Center) | Active, recruiting          |
| NCT02095132 | WEE1 Inhibitor MK-1775 and Irinotecan Hydrochloride in Treating Younger Patients with Relapsed or Refractory Solid Tumors | Irinotecan, AZD1775 (adavosertib)                                     | Wee1             | Molecularly Targeted Therapy | 154                     | 2–21 years              | Children’s Oncology Group     | Active, recruiting          |
| NCT02100891 | Phase 2 STIR Trial: Haploidentical Transplant and Donor Natural Killer Cells for Solid Tumors (STIR) | NK cells                                                              | N/A              | Immunotherapy      | 20                      | any                    | Milwaukee, WI (Medical College of Wisconsin) | Active, recruiting          |
| NCT02124772 | Study to Investigate Safety, Pharmacokinetic (PK), Pharmacodynamic (PD) and Clinical Activity of Trametinib in Subjects with Cancer or Plexiform Neurofibromas and Trametinib in Combination with Dabrafenib in Subjects with Cancers Harboring V600 Mutations | Trametinib, dabrafenib                                              | MEK              | Molecularly Guided Therapy | 142                     | 1–17 years              | Novartis Pharmaceuticals      | Active, recruiting          |
| NCT02139397 | Study of DFMO in Combination with Bortezomib for Relapsed or Refractory Neuroblastoma | DFMO, bortezomib                                                     | ODC, Proteasome   | Molecularly Targeted Therapy | 38                      | up to 21 years          | Beat Childhood Cancer (BCC)   | Active, recruiting          |
| NCT02162732 | Molecular-Guided Therapy for Childhood Cancer                           |                                                                       | Precision Medicine | Molecularly Guided Therapy | 200                     | 13 months to 21 years   | Beat Childhood Cancer (BCC)   | Active, recruiting          |
| NCT02163356 | Ferretinide Lym-X-Serb + Ketoconazole + Vincristine for Recurrent or Resistant Neuroblastoma (SPOC2013-001) | Ferretinide, ketoconazole, vincristine                               | N/A              | Systemic Chemotherapy | 42                      | up to 30 years          | South Plains Oncology Consortium | Active, recruiting          |
| NCT02169609 | Safety Study of Dinutuximab Combined with Immunotherapy to Treat Neuroblastoma | Dinutuximab, GM-CSF, isotretinoin, IL-2                              | GD2              | Immunotherapy      | 25                      | any                    | Barcelona, Spain (Hospital Sant Joan de Deu) | Active, not recruiting       |
| NCT02173993 | Activated T Cells Armed with GD2 Bispecific Antibody in Children and Young Adults with Neuroblastoma and Osteosarcoma | IL-2, GD2Bi-aATC, GM-CSF                                             | GD2              | Immunotherapy      | 40                      | 13 months to 29 years   | Detroit, MI (Children’s Hospital of Michigan) | Active, recruiting          |
| NCT02298348 | Sorafenib and Cyclophosphamide/Topotecan in Patients with Relapsed and Refractory Neuroblastoma (N2013-02) | Sorafenib, cyclophosphamide, topotecan                               | Multiple Kinases  (Raf, VEGFR-2, VEGFR-3, c-Kit) | Molecularly Targeted Therapy | 18                      | up to 30 years          | New Approaches to Neuroblastoma Therapy (NANT) | Active, not recruiting       |
| NCT02304458 | Nivolumab With or Without Ipilimumab in Treating Younger Patients with Recurrent or Refractory Solid Tumors or Sarcomas | Ipilimumab, nivolumab                                               | PD-1, CTLA-4     | Immunotherapy      | 484                     | 1–30 years             | Children’s Oncology Group     | Active, recruiting          |
| NCT Number   | Title                                                                 | Drug                                      | Molecular Target                | Therapeutic Class                  | Study Enrollment Target | Eligibility Age Range | Primary Site/Group or Sponsor | Status                  |
|--------------|------------------------------------------------------------------------|-------------------------------------------|----------------------------------|-------------------------------------|-------------------------|------------------------|-------------------------------|--------------------------|
| NCT02308527 | Activity Study of Bevacizumab with Temozolomide ± Irinotecan for Neuroblastoma in Children | Bevacizumab, temozolomide, irinotecan, topotecan | Angiogenesis                     | Molecularly Targeted Therapy        | 160                     | 1–21 years              | Cancer Research UK            | Active, recruiting         |
| NCT02311621 | Engineered Neuroblastoma Cellular Immunotherapy (ENCIT)-01              | Anti-CD171 CAR-T cells                    | CD171                            | Immunotherapy                       | 40                      | 18 months to 26 years  | Seattle, WA (Seattle Children’s Hospital) | Active, recruiting         |
| NCT0232668 | A Study of Pembrolizumab (MK-3475) in Pediatric Participants with an Advanced Solid Tumor or Lymphoma (MK-3475-051/KEYNOTE-051) | Pembrolizumab                             | PD-1                             | Immunotherapy                       | 310                     | 6 months to 17 years   | Merck Sharp & Dohme Corp.     | Active, recruiting         |
| NCT02343718 | Vinblastine and Temsirolimus in Pediatric Patients with Recurrent or Refractory Lymphoma or Solid Tumours Including CNS Tumours | Temsirolimus, vinblastine                | mTOR                             | Molecularly Targeted Therapy        | 7                       | 1–18 years              | Toronto, ON (Hospital for Sick Children) | Active, not recruiting     |
| NCT02378428 | MIBG Therapy for Patients with MIBG Avid Tumors (MIBG)                 | $^{131}$I-MIBG                             | NET                              | Systemic Radiotherapy               | 65                      | 1–40 years              | Columbus, OH (Nationwide Children’s Hospital) | Active, recruiting         |
| NCT02390843 | Simvastatin with Topotecan and Cyclophosphamide in Relapsed and/or Refractory Pediatric Solid and CNS Tumors (AflacST1402) | Simvastatin, cyclophosphamide, topotecan | HMG-coA Reductase                | Systemic Chemotherapy               | 36                      | 1–29 years              | Atlanta, GA (Children’s Healthcare of Atlanta) | Active, recruiting         |
| NCT0241088  | Theranostics: $^{68}$GaDOTATOC and $^{90}$YDOTATOC (PRRT)             | $^{90}$Y-DOTA-tyr3-Octreotide ($^{90}$Y-DOTATOC) | SSTR                             | Systemic Radiotherapy               | 25                      | over 6 months           | Iowa City, IA (University of Iowa) | Active, not recruiting     |
| NCT02452554 | Lorvotuzumab Mertansine in Treating Younger Patients with Relapsed or Refractory Wilms Tumor, Rhabdomyosarcoma, Neuroblastoma, Pleuropulmonary Blastoma, Malignant Peripheral Nerve Sheath Tumor, or Synovial Sarcoma | Lorvotuzumab mertansine (IMGN-901) | CD56                             | Immunotherapy                       | 114                     | 1–30 years              | Children’s Oncology Group     | Active, not recruiting     |
| NCT02508038 | TCRαβ+/CD19+ Depleted Haploidentical HSCT + Zoledronate               | Zoledronate, TCRαβ+/CD19+ depleted Haploidentical HSCT | N/A                              | Immunotherapy                       | 21                      | 7 months to 21 years   | Madison, WI (University of Wisconsin) | Active, recruiting         |
| NCT02520713 | The iCat2, GAIN (Genomic Assessment Informs Novel Therapy) Consortium Study | Precision Medicine                       | Molecularly Guided Therapy       | 825                                  | up to 30 years           |                         | Boston, MA (Dana-Farber Cancer Institute) | Active, recruiting         |
| NCT Number       | Title                                                                                                                                  | Drug                                                                                     | Molecular Target | Therapeutic Class          | Study Enrollment Target | Eligibility Age Range | Primary Site/Group or Sponsor       | Status                        |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|------------------|----------------------------|-------------------------|------------------------|-----------------------------------|---------------------------------|
| NCT02536183      | A Phase I Study of Lyso-thermosensitive Liposomal Doxorubicin and MR-HIFU for Pediatric Refractory Solid Tumors                    | MR-HIFU hyperthermia + lyso-thermosensitive liposomal doxorubicin                        | N/A              | Systemic Chemotherapy      | 34                      | up to 30 years          | Washington, DC (Children’s National Medical Center) | Active, recruiting             |
| NCT02541604      | A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, Immunogenicity, and Preliminary Efficacy of Atezolizumab (Anti-Programmed Death-Ligand 1 [PD-L1] Antibody) in Pediatric and Young Adult Participants with Solid Tumors | Atezolizumab                                                                            | PD-L1            | Immunotherapy              | 90                      | up to 30 years          | Hoffmann-La Roche                 | Active, not recruiting         |
| NCT02557854      | HIFU Hyperthermia with Liposomal Doxorubicin (DOXIL) for Relapsed or Refractory Pediatric and Young Adult Solid Tumors            | Doxil + MR-HIFU Hyperthermia                                                           | N/A              | Systemic Chemotherapy      | 14                      | 1–40 years              | Dallas, TX (University of Texas Southwestern Medical Center) | Active, recruiting             |
| NCT02573896      | Immunotherapy of Relapsed Refractory Neuroblastoma with Expanded NK Cells                                                            | NK cells, dinutuximab, imnaldimide                                                      | CD2              | Immunotherapy              | 24                      | 1 month to 30 years    | New Approaches to Neuroblastoma Therapy (NANT) | Active, not yet recruiting       |
| NCT02574728      | Sirolimus in Combination with Metronomic Chemotherapy in Children with Recurrent and/or Refractory Solid and CNS Tumors        | Sirolimus, celecoxib, etoposide, cyclophosphamide                                        | mTOR             | Molecularly Targeted Therapy | 60                      | 1–30 years              | Atlanta, GA (Children’s Healthcare of Atlanta) | Active, recruiting             |
| NCT02624388      | Study of Genistein in Pediatric Oncology Patients (UVA-Gen001) (UVA-Gen001)                                                        | Genistein                                                                                | N/A              | Systemic Chemotherapy      | 50                      | 1–21 years              | Charlottesville, VA (University of Virginia) | Active, recruiting             |
| NCT02630043      | Trial of Tolcapone With Oxaliplatin for Neuroblastoma                                                                                | Tolcapone, oxaliplatin                                                                  | N/A              | Systemic Chemotherapy      | 21                      | up to 21 years          | Beat Childhood Cancer (BCC)       | Active, recruiting             |
| NCT02638428      | Genomics-Based Target Therapy for Children with Relapsed or Refractory Malignancy                                                      | Ifosfamide, carboplatin, etoposide, axitinib, crizotinib, dasatinib, erlotinib, everolimus, imatinib, pazopanib, ruxolitinib, sorafenib, vandetanib, vemurafenib, trastuzumab, pazopanib, sorafenib | Precision Medicine | Molecularly Guided Therapy | 90                      | up to 18 years          | Seoul, Korea (Samsung Medical Center) | Active, recruiting             |
| NCT02639546      | Safety and Pharmacokinetics of Cobimetinib in Pediatric and Young Adult Participants with Previously Treated Solid Tumors       | Cobimetinib                                                                              | MEK              | Molecularly Targeted Therapy | 50                      | 6 months to 30 years  | Hoffmann-La Roche                | Active, recruiting             |
Table 1. Cont.

| NCT Number      | Title                                                                 | Drug                                                                 | Molecular Target                      | Therapeutic Class                | Study Enrollment Target | Eligibility Age Range | Primary Site/Group or Sponsor                                      | Status               |
|-----------------|-----------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------------|----------------------------------|------------------------|-----------------------|-------------------------------------------------------------------|----------------------|
| NCT02641314     | Metronomic Treatment in Children and Adolescents with Recurrent or Progressive High Risk Neuroblastoma | Propranolol, celecoxib, cyclophosphamide, vinblastine, etoposide     | N/A                                   | Systemic Chemotherapy            | 26                     | 2–20 years            | Cologne, Germany (University of Cologne)                          | Active, recruiting   |
| NCT02644460     | Abemaciclib in Children with DIPG or Recurrent/Refractory Solid Tumors (AflacST1501) | Abemaciclib (LY2835219)                                             | CDK4/6                                 | Molecularly Targeted Therapy      | 50                     | 2–25 years            | Atlanta, GA (Children’s Healthcare of Atlanta)                     | Active, recruiting   |
| NCT02650401     | Study of RXDX-101 in Children with Recurrent or Refractory Solid Tumors and Primary CNS Tumors, With or Without TRK, ROS1, or ALK Fusions | RXDX-101 (Entrectinib)                                              | TRK, ROS1, ALK                        | Molecularly Guided Therapy       | 190                    | 2–22 years            | Hoffmann-La Roche                                                 | Active, recruiting   |
| NCT02650648     | Humanized Anti-GD2 Antibody Hu3F8 and Allogeneic Natural Killer Cells for High-Risk Neuroblastoma | Hu3F8, cyclophosphamide, NK cells, IL-2                              | GD2                                   | Immunotherapy                    | 36                     | any                  | New York, NY (Memorial Sloan Kettering Cancer Center)             | Active, recruiting   |
| NCT02743429     | Phase II Study of Monoclonal Antibody ch14.18/CHO Continuous Infusion in Patients with Primary Refractory or Relapsed Neuroblastoma | ch14.18/CHO                                                        | GD2                                   | Immunotherapy                    | 40                     | 1–21 years           | Greifswald, Germany (University Medicine Greifswald)              | Active, recruiting   |
| NCT02748135     | A Two-Part Study of TB-403 in Pediatric Subjects with Relapsed or Refractory Medulloblastoma | TB-403                                                              | N/A                                   | Systemic Chemotherapy            | 36                     | 6 months to 18 years   | Beat Childhood Cancer (BCC)                                       | Active, recruiting   |
| NCT02761915     | A Cancer Research UK Trial of Anti-GD2 T-cells (IRG-CART)              | Anti-GD2 CAR-T cells, cyclophosphamide, fludarabine                  | GD2                                   | Immunotherapy                    | 27                     | over 1 year           | London, UK (University College London)                             | Active, recruiting   |
| NCT02765243     | Anti-GD2 4th Generation CART Cells Targeting Refractory and/or Recurrent Neuroblastoma | Anti-GD2 CAR-T cells                                               | GD2                                   | Immunotherapy                    | 30                     | 1–14 years           | China (Zhujiang Hospital)                                         | Active, recruiting   |
| NCT02780128     | Next Generation Personalized Neuroblastoma Therapy (NEPENTHE)          | Ceritinib, trametinib, HDM201, ribociclib                           | ALK, RAS-MAPK, p53                    | Molecularly Guided Therapy       | 105                    | 1–21 years           | Philadelphia, PA (Children’s Hospital of Philadelphia)            | Active, recruiting   |
| NCT02813135     | European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (ESMART) | Ribociclib, topotecan, temozolomide, everolimus, AZD1775, carboplatin, olaparib, irinotecan, AZD2014, nivolumab, Vistusertib, selumetinib, enasidenib, lirilumab | Precision Medicine                   | Molecularly Guided Therapy       | 397                    | up to 18 years        | Villejuif, France (Institut Gustave Roussy)                        | Active, recruiting   |
| NCT Number | Title                                                                 | Drug                                                                 | Molecular Target | Therapeutic Class          | Study Enrollment Target | Eligibility Age Range | Primary Site/Group or Sponsor | Status         |
|------------|----------------------------------------------------------------------|----------------------------------------------------------------------|------------------|-----------------------------|-------------------------|------------------------|------------------------------|----------------|-----------------|
| NCT02909777 | Trial of CUDC-907 in Children and Young Adults with Relapsed or Refractory Solid Tumors, CNS Tumors, or Lymphoma | CUDC-907 (fimepinostat)                                               | PI3K, HDAC       | Molecularly Targeted Therapy | 44                      | 1–21 years             | Boston, MA (Dana-Farber Cancer Institute) | Active, recruiting |
| NCT02919046 | Study Evaluating the Efficacy and Safety With CAR-T for Relapsed or Refractory Neuroblastoma in Children | Anti-GD2 CAR-T cells                                                 | GD2              | Immunotherapy               | 22                      | 1–14 years             | China (Nanjing Children’s Hospital) | Active, recruiting |
| NCT02982941 | Enoblituzumab (MGA271) in Children with B7-H3-expressing Solid Tumors | Enoblituzumab (MGA271)                                               | B7-H3            | Immunotherapy               | 112                     | 1–35 years             | Buenos Aires, Argentina (Hospital Universitario Austral) | Active, recruiting |
| NCT02998983 | Racotumomab in Patients with High risk Neuroblastoma                  | Racotumomab                                                          | N-glycolyl (NGs) GM3 (NGcGM3) | Immunotherapy               | 39                      | 1–12 years             | Children’s Oncology Group | Active, recruiting |
| NCT03107988 | Study of Lorlatinib (PF-06463922)                                       | Lorlatinib, cyclophosphamide, topotecan                              | ALK, ROSI        | Molecularly Targeted Therapy | 40                      | 1–90 years             | New Approaches to Neuroblastoma Therapy (NANT) | Active, recruiting |
| NCT03155620 | Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients with Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders (Pediatric MATCH) | Palbociclib, selumetinib, ensartinib, vemurafenib, olaparib, larotrectinib, LY3023414, erdafitinib | Precision Medicine | Molecularly Guided Therapy | 49                      | 1–21 years             | Children’s Oncology Group | Active, recruiting |
| NCT03189706 | Pilot Study of Chemoimmunotherapy for High-Risk Neuroblastoma         | Hu3F8, irinotecan/temozolomide, GM-CSF                              | GD2              | Immunotherapy               | 20                      | any                    | New York, NY (Memorial Sloan Kettering Cancer Center) | Active, recruiting |
| NCT03209869 | Treatment of Relapsed or Refractory Neuroblastoma with Expanded Haploidentical NK Cells and Hu14.18-IL2 | Hu14.18-IL2, NK cells                                               | GD2              | Immunotherapy               | 6                       | 7 months to 21 years | Madison, WI (University of Wisconsin) | Active, recruiting |
| NCT03226857 | A Study of the Safety and Pharmacokinetics of Venetoclax in Pediatric and Young Adult Patients with Relapsed or Refractory Malignancies | Venetoclax                                                        | BCL-2            | Molecularly Targeted Therapy | 135                     | up to 25 years       | AbbVie | Active, recruiting |
| NCT03242603 | Immunotherapy of Neuroblastoma Patients Using a Combination of Anti-GD2 and NK Cells (NKEXPGD2) | Haploidentical NK cells, ch14.18/CHO                                 | GD2              | Immunotherapy               | 5                       | 6 months to 25 years | Singapore (National University Hospital) | Active, recruiting |
| NCT03273712 | Dosimetry-Guided, Peptide Receptor Radiotherapy (PRRT) With 90Y-DOTA-tyr3-Octreotide (90YDOTATOC) | 90Y-DOTA-tyr3-Octreotide (90YDOTATOC)                               | SSTR             | Systemic Radiotherapy      | 20                      | 6 months to 90 years | Iowa City, IA (University of Iowa) | Active, recruiting |
Table 1. Cont.

| NCT Number       | Title                                                                 | Drug                                    | Molecular Target                                                                 | Therapeutic Class                 | Study Enrollment Target | Eligibility Age Range | Primary Site/Group or Sponsor                      | Status                      |
|------------------|------------------------------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------|----------------------------------|------------------------|------------------------|---------------------------------------------------|-----------------------------|
| NCT03275402      | 131I-burtomab Radioimmunotherapy for Neuroblastoma Central Nervous System/Leptomeningeal Metastases | 131I-burtomab (8H9)                     | B7-H3                                                                            | Systemic Radiotherapy            | 32                     | up to 18 years           | Y-mAbs Therapeutics                             | Active, not yet recruiting |
| NCT03294954      | GD2 Specific CAR and Interleukin-15 Expressing Autologous NKT Cells to Treat Children with Neuroblastoma (GINAKIT2) | NKT cells, cyclophosphamide, fludarabine | GD2                                                                              | Immunotherapy                    | 24                     | 1–21 years              | Houston, TX (Baylor College of Medicine)          | Active, recruiting          |
| NCT03332667      | MIBG With Dinutuximab                                                  | 131I-MIBG dinutuximab                  | NET, GD2                                                                         | Systemic Radiotherapy plus Immunotherapy | 24                     | 1–30 years              | New Approaches to Neuroblastoma Therapy (NANT)    | Active, not yet recruiting |
| NCT03373097      | Anti-GD2 CAR T Cells in Pediatric Patients Affected by High Risk and/or Relapsed/Refractory Neuroblastoma | Anti-GD2 CAR-T cells                   | GD2                                                                              | Immunotherapy                    | 42                     | 1–18 years              | Italy (Bambino Gesù Hospital and Research Institute) | Active, recruiting          |
| NCT03434262      | SJDAWN: St. Jude Children’s Research Hospital Phase I Study Evaluating Mole lurally-Driven Doublet Therapies for Children and Young Adults with Recurrent Brain Tumors | Ribociclib, gemcitabine, trametinib, sonidegib | Precision Medicine                                                              | Molecularly Guided Therapy       | 108                    | 1–30 years              | Memphis, TN (St. Jude Children’s Research Hospital) | Active, recruiting          |
| NCT03458728      | Safety, Tolerability, Efficacy and Pharmacokinetics of Copanlisib in Pediatric Patients | Copanlisib (BAY806946)                 | PI3K                                                                             | Molecularly Targeted Therapy     | 130                    | 6 months to 21 years   | Bayer Pharma                                     | Active, recruiting          |
| NCT03478462      | Dose Escalation Study of CLR 131 in Children and Adolescents with Relapsed or Refractory Malignant Brain Cancer, Neuroblastoma, Rhabdomyosarcoma, Ewings Sarcoma, and Osteosarcoma | CLR 131                                | N/A                                                                              | Systemic Radiotherapy            | 30                     | 2–21 years              | Madison, WI (University of Wisconsin)             | Active, not yet recruiting |
| NCT03507491      | Nab-paclitaxel in Combination with Gemcitabine for Pediatric Relapsed and Refractory Solid Tumors | Nab-paclitaxel, gemcitabine            | N/A                                                                              | Systemic Chemotherapy            | 24                     | 6 months to 30 years   | Atlanta, GA (Children’s Healthcare of Atlanta)    | Active, not yet recruiting |
| NCT03561259      | A Study of Therapeutic Iobenguane (131I) for High-Risk Neuroblastoma at the Time of First Relapse (OPTIMUM) | 131I-MIBG                              | NET                                                                              | Systemic Radiotherapy            | 65                     | over 1 year             | Jubilant DraxImage Inc.                           | Active, recruiting          |

Molecularly Targeted Therapy—Targeted agent used in non-targeted fashion; Molecularly Guided Therapy—Targeted agent used in targeted patient population based on molecular aberration or phenotype; NET—norepinephrine transporter; SSTR—somatostatin receptor; XRT—radiation therapy; ODC—ornithine decarboxylase; HIFU—high-intensity focused ultrasound; HDAC—histone deacetylase; MIBG—meta-iodobenzylguanidine; CAR-T cells—chimeric antigen receptor T cells; ALK—anaplastic lymphoma kinase; NK cells—natural killer cells.
3.2. Aurora A Kinase

Additional efforts to identify novel targets in neuroblastoma tumors have identified a critical role for mitotic spindle regulation in neuroblastoma pathogenesis, suggesting that regulators of the mitotic spindle represent potential therapeutic targets. Aurora A kinase represents one such potential target and is essential for appropriate completion of mitosis through regulation of the mitotic checkpoint complex [61]. Aberrant overexpression of aurora A kinase leads to tumor cell resistance to apoptosis and genomic instability [62], and, in neuroblastoma tumors, aurora A kinase expression correlates with high-risk disease and advanced tumor stage [63,64]. Inhibitors of aurora A kinase were shown to block neuroblastoma cell growth and to increase neuroblastoma cell responses to chemotherapy [63], and, in initial phase I trials, children with relapsed neuroblastoma treated with the aurora A kinase inhibitor MLN8237 (alisertib), both alone and in combination with irinotecan and temozolomide, demonstrated clinical responses [65,66]. More recent studies have identified polo-like kinase 4 (PLK4) as a potential target in neuroblastoma tumor cells [67], further implicating the process of mitotic spindle regulation in neuroblastoma pathogenesis and suggesting that children with relapsed neuroblastoma will benefit from the use of inhibitors of aurora A kinase and PLK4 for treatment.

3.3. Ornithine Decarboxylase (ODC1)

Ornithine decarboxylase (ODC1), the rate-limiting enzyme in polyamine synthesis, is frequently deregulated in neuroblastoma tumors [68,69] and represents another potential therapeutic target. ODC inhibitors, such as difluoromethylornithine (DFMO), have been shown to be effective in neuroblastoma preclinical models [70–72] and, although single-agent DFMO did not demonstrate efficacy in children with relapsed neuroblastoma in a recent phase I clinical trial [73], more recent studies have demonstrated that extended maintenance therapy with DFMO for children with neuroblastoma in second remission results in 2-year overall and event-free survival rates of 54% and 84% [74], respectively, suggesting that ODC1 inhibition is an effective strategy for prolonging survival in these patients. The efficacy of DFMO in combination with other anticancer agents, including cyclophosphamide, topotecan, and celecoxib (NCT02030964) and the proteasome inhibitor bortezomib (NCT02139397), is also currently being evaluated in clinical trials for children with relapsed neuroblastoma, in the hopes of observing synergistic efficacy.

3.4. PI3K/AKT/mTOR

Further studies in neuroblastoma preclinical models have confirmed a role for the PI-3 kinase/AKT/mTOR pathway in neuroblastoma pathogenesis. SF1126 is a pan-PI-3 kinase inhibitor that has been demonstrated to be effective against neuroblastoma in preclinical models [75], suggesting this pathway represents a therapeutic target in neuroblastoma, and clinical trials have been opened to test the safety and tolerability of SF1126 in children with relapsed neuroblastoma (NCT02337309). The AKT inhibitor perifosine has been tested in multiple phase I clinical trials, with 1 complete response and 8 of 27 children with relapsed neuroblastoma demonstrating prolonged stable disease in one phase I study [76], and response rates and disease control rates of 9% and 55% in 11 children with measurable disease [77]. Early studies also determined that mTOR inhibitors were effective in neuroblastoma models [78,79], and one of two patients with relapsed neuroblastoma had a CR in initial phase I studies with the mTOR inhibitor temsirolimus [80]. A follow-up phase II study did not meet predetermined efficacy criteria, but 7 of 19 patients with neuroblastoma demonstrated clinical benefit (1 PR, 6 SD) [81], and 2 patients with relapsed neuroblastoma had prolonged stable disease in response to the combination of vinblastine and sirolimus [82], suggesting that a subset of patients may benefit from the inhibition of this pathway.
3.5. Epigenetic Modifications

Epigenetic modifications to DNA involve heritable genomic modifications that are not due to changes in the DNA sequence, including DNA and histone methylation and histone acetylation. These modifications influence chromatin structure and play a key role in regulating gene expression [83]. Epigenetic regulation of gene expression is critical for both normal development and maintenance of tissue-specific gene expression, but aberrant epigenetic mechanisms can contribute to the malignant process, and epigenetic changes contribute to the genomic instability that is a hallmark of cancer [84]. The epigenomic landscape has been shown to contribute to neuroblastoma pathogenesis, leading to early phase clinical trials investigating the safety and efficacy of epigenetic agents [85–87], including drugs that target epigenetic writers, such as DNA methyltransferases, as well as epigenetic erasers, such as histone deacetylases [88]. An early phase I study using the demethylating agent decitabine combined with chemotherapy resulted in prolonged stable disease in 5 of 14 patients with relapsed neuroblastoma, although the doses of decitabine were limited due to toxicity [89]. A subsequent study of the combination of the HDAC inhibitor vorinostat combined with bortezomib did not show any responses in the three patients with relapsed neuroblastoma enrolled [90], and further combination studies using vorinostat in children with neuroblastoma are ongoing (NCT02035137, NCT02559778) to identify patient populations that may have improved responses.

Modulation of the epigenetic readers—proteins that recognize and bind to epigenetic chromatin modifications to modulate gene transcription—has recently emerged as a therapeutic strategy for anticancer treatment. Bromodomain and extraterminal domain (BET) proteins are epigenetic readers that regulate gene transcription, and BET inhibitors preferentially bind to super-enhancers—regions of DNA comprising multiple enhancers occupied by transcription factors and regulators of gene transcription that control the expression of genes critical for cell identity, growth, and survival [91]. Further studies have identified critical roles for chromatin structure and super-enhancers in neuroblastoma [92], and BET inhibitors have been shown to be effective against neuroblastoma via targeting of MYCN gene expression [93,94]. A number of BET inhibitors are in clinical development and early phase clinical trials, including a novel dual PI3K–BRD4 inhibitor that was effective in neuroblastoma preclinical models [95]. BET inhibitors therefore represent an exciting new class of therapeutic agents for children with relapsed neuroblastoma.

3.6. Reactive Oxygen Species (ROS)

Reactive oxygen species (ROS) have been shown to impact a variety of critical intracellular signaling pathways, and prior studies have identified a role for ROS in cancer pathogenesis [96]. However, the role of ROS in neuroblastoma tumors is less clear. Nifurtimox is a nitrofuran derivative that has been used for decades as a primary treatment for Chagas’ disease, a parasitic infection caused by the protozoan Trypanosoma cruzi [97,98]. Nifurtimox was shown to inhibit neuroblastoma cell growth both in vitro and in vivo in preclinical studies, most likely via inhibition of ROS production [99,100], and in early phase clinical trials, patients treated with nifurtimox both as a single agent and in combination with chemotherapy demonstrated responses [101], leading to an ongoing national phase II trial (NCT00601003). A separate study investigating the combination of melphalan with buthionine sulfoximine (BSO) resulted in 6 of 31 patients with relapsed neuroblastoma demonstrating objective responses (5PR, 1MR) [102], and the recent demonstration of synergy between nifurtimox and BSO in other solid tumor models [100] suggests that further testing of the combination of nifurtimox and BSO in neuroblastoma preclinical models is warranted.

3.7. Retinoids

Retinoid therapy has been shown to increase EFS rates when used as a component of maintenance therapy for high-risk neuroblastoma [103], and studies have demonstrated potential synergy of retinoids with epigenetic modifying agents [104,105]. An initial phase I study of the combination of
the HDAC inhibitor vorinostat with 13-cis-retinoic acid had one patient with neuroblastoma who had a CR following treatment [106], and a more recent phase I study of vorinostat in combination with 13-cis-retinoic acid for children with relapsed neuroblastoma found no objective responses, but 11 of 29 evaluable patients had SD, with 7 of the 11 receiving at least 11 cycles of therapy [107]. Additionally, the RET tyrosine kinase, which is primarily expressed in cells and tissues derived from the neural crest, has been shown to be required for maturation of the peripheral nervous system, and RET was further shown to be required for neuroblastoma differentiation induced by retinoic acid [108]. RET inhibition has been found to be effective in in vitro and in vivo preclinical models of neuroblastoma [109–111], and a recently opened clinical trial (NCT03611595) will evaluate the efficacy of the combination of RET inhibition and retinoid therapy in children with neuroblastoma and other solid tumors.

3.8. Molecularly Guided Therapy

With the rapid advances in our understanding of the biology of cancer, the use of molecular tumor profiling to develop individualized treatment plans is increasingly employed for many adults with a variety of cancers [112]. Although the efficacy of this strategy in children with cancer remains mostly unknown, recently completed clinical trials have evaluated the potential feasibility and efficacy of utilizing molecular and genetic tumor profiling to develop personalized therapy for children with recurrent neuroblastoma. An initial pilot study demonstrated the feasibility of obtaining tumor biopsies from children with relapsed neuroblastoma and then performing DNA sequencing and RNA expression profiling on the relapsed tumor sample, which allowed investigators to generate individualized patient treatment plans in less than 12 days [113]. A follow-up multi-institutional phase I trial employing the same strategy showed that 64% of patients achieved either partial or complete response or disease stabilization for at least one cycle of therapy, with a 7% overall response rate and a progression-free survival time of 59 days [114]. A subsequent single-institution study also demonstrated that the utilization of DNA sequencing data from relapsed tumors to generate prospective treatment plans for children with neuroblastoma was feasible, with nearly half of patients enrolled in the study having potentially actionable genetic findings. Tumor DNA sequencing also led to changes in patient treatment and to genetic counseling for relatives and families of patients found to be at risk of other hereditary disorders [115]. Additional concurrent studies have also demonstrated the feasibility of using genomic data [116] and more comprehensive molecular profiling [117] to identify potential therapeutic targets in children with high-risk, relapsed, or refractory cancers. These results all clearly demonstrate the feasibility of employing molecular profiling to guide individualized treatment strategies for children with neuroblastoma. However, the lack of control groups in these and other studies has limited the ability to assess whether this individualized molecularly targeted treatment resulted in better clinical outcomes for patients when compared with outcomes using standard non-targeted treatment or molecularly targeted agents in an untargeted fashion. Clinical trials to further evaluate the efficacy of molecularly guided, individualized therapy in children with relapsed neuroblastoma and other pediatric solid tumors are currently being developed or are ongoing (NCT02162732, NCT02520713, NCT02638428, NCT03155620, NCT03434262).

4. Immunotherapy

Although a number of recent studies have demonstrated the efficacy of various forms of immunotherapy against neuroblastoma and other pediatric solid tumors, the role of immunotherapy in the treatment of patients with relapsed or refractory neuroblastoma is the focus of numerous prior and ongoing studies. Early studies demonstrated promising results for anti-GD2 antibody therapy in children with relapsed neuroblastoma [118–120], leading to the evaluation of the efficacy of the chimeric anti-GD2 antibody ch14.18 (dinutuximab) as a component of maintenance therapy for children with high-risk neuroblastoma [121]. Additional studies demonstrated significant efficacy of the mouse anti-GD2 antibody 3F8 in children with relapsed neuroblastoma, with 33% 5-year progression-free survival (PFS) in patients who were treated for relapsed neuroblastoma and achieved either a CR or
very good partial response (VGPR) and were then treated with 3F8 plus GM-CSF and 13-cis-retinoic acid [10].

4.1. Antibody Immunotherapy

Further studies have attempted to expand the use of anti-GD2 antibody therapy in children with relapsed neuroblastoma by employing combinations with other therapies, in addition to the development and evaluation of modified forms of the antibodies themselves. A recent trial combining irinotecan and temozolomide with the anti-GD2 antibody dinutuximab demonstrated promising results, with 9 objective responses (including 5 with CR) among 17 patients receiving the combination [122]. Preliminary data from a follow-up study through the Children’s Oncology Group included data from 53 total eligible patients, with 21 patients (40%) experiencing objective responses, including 11 with CR [123], confirming this combination as a treatment regimen to be considered for children with neuroblastoma at the time of initial relapse. A phase I trial using a humanized version of the ch14.18 antibody with a mutation engineered to reduce side effects (hu14.18K322A) found 6 of 39 enrolled patients had either PR or CR, with 9 additional patients having prolonged SD [124]. A humanized version of the anti-GD2 antibody 3F8 also recently underwent phase I testing, with increased PFS among patients with a higher anti-GD2 antibody titer and reduced overall immunogenicity [125]. In a separate study, 39 patients with recurrent neuroblastoma were treated with the Hu14.18-IL-2 immunocytokine—a fusion protein combining the humanized 14.18 anti-GD2 antibody with IL-2. Of 13 patients with measurable soft tissue neuroblastoma tumors treated with Hu14.18-IL-2, no objective responses were seen, but in those with only MIBG-avid disease or with disease limited to the bone marrow, there were 5 complete responses out of 23 patients [126], suggesting that patients with minimal residual disease are most likely to benefit from this therapy. Further analyses have also shown that mismatches among natural killer (NK) cell KIR/KIR-ligand genotypes and polymorphisms in the Fcγ receptor are also associated with improved responses to anti-GD2 immunotherapy [127,128], suggesting that further strategies for improvement in antibody design and patient selection may result in improved outcomes.

One of the drawbacks to antibody therapy for neuroblastoma is that neuroblastoma tumors use a variety of strategies to evade the host immune response, including downregulation or weak immunogenicity of target antigens and creation of an immune-suppressive tumor environment. With the significant side effects experienced by patients receiving anti-GD2 antibody immunotherapy and with the challenges of antibody administration to patients, a number of alternative immunotherapy strategies are currently under investigation. Immunomodulatory checkpoint inhibitors, such as ipilimumab and nivolumab, have been employed in adult cancers to overcome the immune-suppressive tumor microenvironment. Although ipilimumab was well tolerated in a phase I study for children with relapsed solid tumors, only one patient enrolled in the study had neuroblastoma, and no objective tumor regressions were observed [129]. Ongoing studies evaluating the efficacy of nivolumab with and without added ipilimumab (NCT02304458), with the PD-1 inhibitor pembrolizumab (NCT02332668), and with the anti-PD-L1 antibody atezolizumab (NCT02541604) will hopefully provide more insight to their potential efficacy in children with relapsed neuroblastoma.

Anticancer vaccines have been tested in clinical trials for a number of different tumor types, and an early clinical trial of anti-neuroblastoma vaccine therapy showed the ability to induce an antitumor immune response, although the immune response was insufficient to induce tumor responses or prevent disease progression [130]. A subsequent trial using decitabine combined with a dendritic cell vaccine targeting MAGE-A1, MAGE-A3, and NY-ESO-1 resulted in 1 complete response out of 10 evaluable patients [131], and ongoing cancer vaccine trials include one trial exploring the efficacy of a vaccine using the GD2L and GD3L antigens linked to KLH and administered with the adjuvant OPT-821 and beta-glucan (NCT00911560).
4.2. Cell-Based Immunotherapy

CD8+ T lymphocytes play a key role in cell-mediated immunity and, when infused as a form of immunotherapy, offer the advantage of direct tumor targeting that can avoid or overcome the tumor cell strategies to evade the host’s own immune system. Cell therapy with CD8+ T cells has been employed in early phase clinical trials for children with relapsed neuroblastoma, with some notable successes. EBV-specific T lymphocytes engineered to express a chimeric antigen receptor (CAR) directed against GD2 resulted in 3 patients with complete responses out of 11 total treated patients with active disease [132,133]. CAR-T cell persistence was associated with improved responses and longer times to progression in these patients. Next-generation CAR-T cells, using constructs with modified costimulatory domains to regulate T cell activation, are currently being developed [134], and a number of national and international clinical trials are currently ongoing to further explore the efficacy of novel CAR-T cell products targeted against GD2 in children with relapsed neuroblastoma (NCT02239861, NCT02761915, NCT02765243, NCT02919046, NCT03373097). Other trials using CAR-T cells targeted against other cell surface markers, such as CD171, are also currently undergoing testing in clinical trials for children with neuroblastoma (NCT02311621).

Natural killer (NK) cells are another type of cytotoxic lymphocyte that can act in an MHC-unrestricted fashion to target cancer cells. Cell-based immunotherapy using NK cells for children with relapsed neuroblastoma has also been explored, particularly after the report of a child with relapsed neuroblastoma who received haploidentical donor NK cells combined with temozolomide, topotecan, and IL-2 and had a complete response [135]. Ongoing clinical trials are evaluating the efficacy of ex vivo expanded haploidentical NK cells infused after haploidentical allogeneic stem cell transplants for children with solid tumors, including neuroblastoma (NCT02100891), and a recently opened clinical trial will explore the efficacy of expanded autologous natural killer T (NKT) cells engineered to express the GD2-specific CAR and IL-15 (NCT03294954). A trial using the hu14.18K322A anti-GD2 antibody combined with chemotherapy, cytokines, and haploidentical NK cells demonstrated a 61% response rate in 13 heavily pretreated patients, with 4 complete responses, 1 very good partial response, and 3 partial responses, in addition to 5 patients with stable disease and 10 of the 13 patients (77%) surviving for at least 1 year [136], demonstrating the efficacy of treatment regimens that combine multiple immunotherapeutic strategies. A number of other trials are investigating the combination of haploidentical NK cells combined with anti-GD2 antibody therapy, including NK cells combined with dinutuximab and lenalidomide (NCT02573896), humanized 3F8, cyclophosphamide, and IL-2 (NCT02650648), the immunocytokine Hu14.18-IL-2 (NCT03209869); and ch14.18/CHO (NCT03242603). Further studies of this approach are clearly warranted in patients with relapsed neuroblastoma.

5. Summary

The treatment of children with relapsed and refractory neuroblastoma remains a challenge, and the outcomes for these children remain poor despite decades of effort by clinicians and scientists. Recent advances in our understanding of the biology of neuroblastoma and of novel strategies to target tumor-specific pathways and antigens have led to a dramatic increase in the number of available treatment options for these patients and give hope that, in the future, novel treatment regimens will increase the responses of tumors to upfront therapy, limit the overall chances of relapse, and, in those hopefully rare cases of relapse, provide safe and effective therapies to eradicate neuroblastoma tumors. Continued development of novel therapies and therapeutic regimens directed against biologically relevant pathways and of novel approaches to harness the therapeutic potential of the innate immune system will provide new treatment strategies to improve the outcomes for these children.

The relative paucity of therapeutically actionable gene mutations has limited the development of individualized treatment regimens for children with neuroblastoma, but as we obtain increased knowledge of other mechanisms of altered gene and protein expression and aberrant function in neuroblastoma tumors, we are likely to identify additional relevant therapeutic targets. Studies to further delineate the critical genetic and proteomic aberrations that either contribute to neuroblastoma
pathogenesis or influence neuroblastoma tumor responses to treatment are ongoing, and these aberrations will hopefully lead to the development of individualized patient treatment regimens and also hopefully serve as targets for future drug development. A number of novel therapies directed against recently identified molecular targets are currently being evaluated both in preclinical models and in early phase clinical trials, and established national and international collaborations and cooperative groups will provide opportunities to evaluate these new treatments in carefully controlled clinical trials, leading to more precise and effective therapeutic regimens.

The future holds promise for making considerable advances in our treatment of relapsed neuroblastoma, although continued difficulties in the management of metastatic, widespread relapse and in specific cases of isolated relapses, such as relapse in the CNS, represent ongoing challenges for the future. Although recent results need to be validated in future trials, these results do suggest that we should reconsider our treatment goals for many patients, particularly with the successes of treatments using extended maintenance therapy and immunotherapy for those patients who can achieve disease remission after relapse. Future treatment decisions need to be made based on not only the underlying diagnosis and clinical features of the patient, but also on the molecular features of the tumor itself and the feasibility and availability of tumor-specific treatment. The goals of future clinical and translational research should include identification and validation of the most effective treatment combinations, determination of the most appropriate patients and situations for use of effective therapies, and further delineation of the molecular subgroups of recurrent and refractory neuroblastoma to tailor treatment regimens to the patient populations most likely to benefit. Continued attempts to both develop novel therapeutic agents with efficacy against neuroblastoma tumors and to identify critical intracellular signaling pathways relevant for neuroblastoma pathogenesis and treatment resistance are underway, potentially leading to both individualized and improved treatment and to improved outcomes for children with relapsed and refractory neuroblastoma.

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