Recent advances in the treatment of childhood cancers

Timothy J.D. Ohlsen, Melissa R. Martos and Douglas S. Hawkins

Purpose of review
Although cancer remains the leading nonaccidental cause of mortality in children, substantial advances in care have led to 5-year overall survival exceeding 85%. However, improvements in outcomes have not been uniform across malignancies or strata of social determinants of health. The current review highlights recent areas of advancement and anticipated directions for future progress.

Recent findings
Incorporation of rational targeted agents into upfront treatment regimens has led to incremental improvements in event-free survival for many children, sometimes with potential reductions in late effects. For rare or challenging-to-treat cancers, the increasing feasibility of molecular profiling has provided specific treatment options to patients with some of the greatest needs. Simultaneously, increased focus is being given to patient-reported outcomes and social determinants of health, the importance of which are becoming readily recognized in providing equitable, quality care. Finally, as survival from malignant diseases improves, breakthroughs in the prevention and management of adverse late effects will promote long-term quality of life.

Summary
Multi-institutional collaboration and risk-adapted approaches have been crucial to recent advancements in the care of children with cancer and inform potential directions for future investigation.

Keywords
cancer outcomes, contemporary treatment, novel therapies, pediatric oncology, survivorship

INTRODUCTION

We are witnessing a truly exciting time in pediatric oncology. Thanks in part to decades of collaborative clinical trials, there has been remarkable advancement in the treatment of cancer in children and adolescents. Five-year overall survival (OS) now exceeds 85%, and there are over 500 000 survivors of cancer in the United States alone, a figure that is growing yearly [1,2]. Unfortunately, progress has not come equally or for all. For example, children with certain malignancies and those who identify with historically marginalized groups still face a less optimistic outlook. Furthermore, many long-term cancer survivors continue to experience burdensome late effects, as well as problematic social and financial impacts. Despite these challenges, the field continues to move toward our ultimate goals of high rates of cure, precise and personalized risk-stratification, and minimal long-term toxicity for all children diagnosed with cancer.

In this review, we will highlight recent developments relevant to the clinical practice of pediatric oncology, with particular focus applied to potential implications for future advances.

Incorporation of targeted agents in upfront therapy

Increasing attention has been given to novel targeted therapies as a means to improve survival and reduce late effects [3]. Until recently, these agents – which include small molecule inhibitors, antibody–drug conjugates, and immune targeted therapies – have typically been limited to relapsed or refractory disease

Division of Hematology/Oncology, Department of Pediatrics, Seattle Children's Hospital, University of Washington, Washington, USA

Correspondence to Timothy J.D. Ohlsen, MD, Seattle Children's Hospital, 4800 Sand Point Way NE, Seattle, WA 98105, USA.
Tel: +1 206 987 2106; fax: +1 206 985 3357;
e-mail: tim.ohlsen@seattlechildrens.org

Curr Opin Pediatr 2024, 36:57–63
DOI:10.1097/MOP.0000000000001310

KEY POINTS

- Targeted agents, previously reserved for relapsed/refractory disease, have demonstrated substantial promise in upfront cancer treatment.
- Identification of targetable mutations in rare and challenging tumors lends hope for patients with otherwise refractory diseases.
- Use of molecular markers in conjunction with traditional clinical factors can provide more accurate risk assessment for treatment selection.
- A growing understanding of disparities in oncology across social determinants of health is paving the way for targeted interventions, and regular use of patient-reported outcomes is incorporating critical patient feedback on clinical trials.
- Increased focus on the prevention and management of late effects can lead to improved long-term patient outcomes.

settings. However, recent clinical trials have established several new standards of care incorporating these agents into upfront treatment regimens.

One impressive example of improvement in overall survival was noted for children with *KMT2A*-rearranged infant acute lymphoblastic leukemia (ALL), a high-risk cancer with historical event-free survival (EFS) below 40%. Investigators from the Interfant collaborative group added blinatumomab, a bispecific T-cell engager targeting CD19, to the Interfant-06 treatment regimen and compared outcomes to historical controls [4▪▪]. Their cohort of 30 patients had exceptional outcomes with a tolerable safety profile. Two-year disease-free survival (DFS) was 82% (versus 49% on Interfant-06). Two-year OS was 93% (versus 66%). Although long-term follow-up is needed to evaluate the durability of blinatumomab's improvement in outcome, these results represent an exciting example of a novel agent, combined with traditional chemotherapy, drastically altering the standard of care and outlook for a challenging disease.

Targeted therapies have also shown success in reducing toxic exposures to chemotherapy. AAML1331, a noninferiority trial conducted by the Children's Oncology Group (COG), evaluated the efficacy of arsenic trioxide and all-trans retinoic acid (ATRA) with substantial chemotherapy reductions for patients with acute promyelocytic leukemia (APL) [5▪]. Patients with standard-risk APL were treated with a chemotherapy-free regimen of arsenic and ATRA, whereas those with high-risk APL received only four doses of idarubicin in addition to these agents. EFS at 2 years was 98 and 95% for the standard-risk and high-risk groups, respectively, with OS exceeding 99% for both. Compared with historical controls treated on AAML0631, for whom 2-year EFS was 97 and 85% for standard-risk and high-risk APL, these results highlight targeted therapies achieving what is perhaps the goal for all treatment regimens: minimal chemotherapy exposures, few late effects, and nearly universal survival.

Recent results from AHOD1331, a phase 3 COG clinical trial, highlight both improved survival and reduced chemotherapy exposures [6▪]. This study of patients 2–21 years with high-risk Hodgkin lymphoma randomized patients to receive a standard North American pediatric six-drug regimen, versus an experimental regimen that substituted the CD30-directed antibody–drug conjugate brentuximab vedotin for bleomycin. The brentuximab arm had a 3-year EFS of 92%, compared with 83% on the control arm. Short-term toxic effects between groups were similar, and the omission of bleomycin from the experimental arm will likely reduce pulmonary late effects. Future investigation will be needed to evaluate whether radiation therapy could be omitted for this cohort, given that involved site radiation therapy was administered to over half of patients on study. Other contemporary work is evaluating the use of nivolumab or brentuximab for pediatric and adult patients with high-risk Hodgkin lymphoma, with promising preliminary results with radiation therapy avoided for nearly all patients [7].

The addition of targeted agents does not consistently lead to improved outcome, as illustrated by the failure of ganitumab, a monoclonal antibody targeting type 1 insulin-like growth factor receptor. When added to standard treatment for metastatic Ewing sarcoma on COG trial AEWS1221, no improvement in outcomes was noted [8▪]. In contrast, the EuroEwing 2012 study illustrates the value in optimizing conventional chemotherapy regimens even without a targeted agent [9▪]. In this randomized clinical trial across 10 countries, 640 patients with Ewing sarcoma were randomly assigned to receive one of two chemotherapy regimens reflecting the European or North American standards of care. The regimen consisting of interval-compressed chemotherapy with vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide was found to be more effective, less toxic, and shorter in duration, establishing a consensus across continents.

Several COG studies are actively testing molecularly targeted agents in the upfront setting (Table 1), and we anticipate additional practice-changing results in coming years.

Table 1. Current and planned Children's Oncology Group clinical trials with molecularly targeted agents in upfront therapy

COG trial number	Cancer type	Targeted agent	Molecular target	National Clinical Trials database identifier
AALL1631	Ph+ ALL	Imatinib	BCR-ABL1	NCT03007147
AALL1731	B-ALL, B-LLy	Blinatumomab	CD-19	NCT03914625
AALL1732	B-ALL	Inotuzumab	CD-22	NCT03959085
AAML1831	AML	Gilteritinib	FLT3	NCT04293562
ANHL1931	PMBCL	Nivolumab	PD-1	NCT04759586
ACNS1723	High-grade glioma	Dabrafenib Trametinib	BRAF MEK	NCT03919071
ACNS1821	High-grade glioma, DIPG	Selinexor	H3K27m	NCT05099003
ACNS1831	Low-grade glioma	Selumetinib	MEK	NCT03871257
ACNS1833	Low-grade glioma	Selumetinib	MEK	NCT04166409
AHOD2131	Hodgkin lymphoma	Brentuximab Nivolumab	CD30 PD-1	NCT05675410
ANBL1531	Neuroblastoma	Lorlatinib	ALK	NCT03126916
ANBL2131	Neuroblastoma	Dinutuximab	GD2	[a]
AOST2032	Osteosarcoma	Cabozantinib	VEFGR2, c-MET	NCT05691478
ARAR2221	Nasopharyngeal carcinoma	Nivolumab	PD-1	NCT06064097

AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; BLLy, B-cell lymphoblastic lymphoma; DIPG, diffuse intrinsic pontine glioma; Ph+ ALL, Philadelphia positive acute lymphoblastic leukemia; PMBCL, primary mediastinal B-cell lymphoma.
[a]No National Clinical Trials identifier at the time of publication.

Application of molecular diagnostics to target rare or challenging tumors

With increasing data on molecular features of malignancy, researchers are developing novel approaches to target rare or challenging tumors. These approaches represent a source of hope for patients whose disease has relapsed or progressed despite multiple lines of conventional therapy.

With the aim of studying and cataloguing the molecular drivers of childhood cancer, the Childhood Cancer Data Initiative was launched in 2019 by the National Cancer Institute (NCI) [10▪]. Part of this project established the Molecular Characterization Initiative (MCI) to offer genomic testing at no cost for children and young adults with selected newly diagnosed cancers receiving treatment at COG-affiliated institutions. With a turnaround time of approximately 2 weeks, clinical reports include molecular alterations that are potentially treatable by an array of targeted agents. Furthermore, aggregated data from the MCI and similar programs may fuel discovery through data mining. Finally, the MCI has massively expanded access to many patients who might once have been excluded from tumor genetic testing, such as those receiving treatment at smaller institutions or with less financial means.

In a landmark national study, the NCI-COG Pediatric MATCH trial investigated the feasibility of widespread testing and targeted agents for refractory cancers [11▪▪]. Among the first 1000 enrolled patients, detailed DNA sequencing was successfully performed in 95%, and actionable mutations were identified in 32%. While provision of targeted therapy to 1 of 13 treatment subprotocols occurred in only 13% of patients (due to conflicting concurrent treatment or clinical status), these results demonstrate the feasibility of detailed screening on a national scale, including at institutions without an early phase clinical trials program.

Several subprotocols from the Pediatric MATCH have recently reported initial results from single targeted agent therapy [12▪,13▪,14–16]. Eckstein *et al.* [12▪] reported results from treating 20 patients with refractory or relapsed disease and detected MAP kinase pathway mutations with the MEK inhibitor selumetinib. A variety of cancer types were represented, including high-grade glioma and rhabdomyosarcoma. Despite promising activity previously seen with MEK inhibitors in plexiform neurofibromas and melanoma, no objective responses were observed, suggesting that monotherapy MAP kinase inhibition is inadequate for these high-risk populations. Similarly, in another Pediatric MATCH subprotocol by Chi *et al.* [13▪], tazematostat was given to 20 patients with mutations in EZH2 or members of the SWI/SNF complex, with only one objective response and four patients with prolonged disease stabilization. Three other Pediatric MATCH subprotocols (erdafitinb, ulixertinib, and palbociclib) also showed limited single-agent

activity despite molecular biomarker selection [14–16]. In contrast, selpercatinib was approved by the FDA for adults and children with refractory solid tumors (including medullary thyroid cancer) carrying the RET mutation based on data from LOXO-RET-17001 [17▪]. In this multicohort trial, the response rate to selpercatinib was 44% for a median duration of 24.5 months, with a well tolerated toxicity profile. Although results from single-agent trials have been mixed, there is hope that novel agents, whether individually or in combination therapy, could improve the outcome for these otherwise refractory tumors. A successor to MATCH, the COMBO-MATCH trial (NCT05564377) aims to assess the potential of targeted drug combinations, with or without chemotherapy, for adult and pediatric patients with rare tumors [18▪]. Seeking to target specific mutations while simultaneously preventing resistance to targeted agents, there is hope of achieving more durable responses for patients with challenging tumors.

Refining risk stratification with molecular data and novel biomarkers

Historically, risk stratification has been based primarily upon clinical features. Over the past decade, we have made substantial progress in refining our understanding of risk by incorporating molecular characteristics and other novel biomarkers, allowing for better prognostication and therapy selection.

Detection of tumor cells in the blood at diagnosis to enhance risk stratification is illustrated in ANHL12P1, a study of anaplastic large cell lymphoma (ALCL) [19▪]. Previously, clinical factors such as age at diagnosis, sites of involvement, stage, and radiographic response to therapy comprised the backbone of risk stratification. In ANHL12P1, patients with the NPM::ALK fusion marker detected by RT-PCR in the peripheral blood at diagnosis were found to have significantly lower 2-year EFS compared with patients without detectable disease (58 versus 86%).

Other studies have demonstrated prognostic utility from sophisticated detection of circulating tumor DNA (ctDNA). In a review of patients with intermediate-risk rhabdomyosarcoma enrolled on COG banking study D9902 [20▪], patients with detectable ctDNA at diagnosis experienced significantly worse EFS and OS compared with those without, a finding that persisted after adjustment for other known prognostic factors. Similar investigation has been undertaken with Wilms tumors [21]. Circulating tumor cells at diagnosis, as well as the dynamic change with therapy, could aid in both prognosis and treatment planning, and ctDNA is being investigated on current frontline studies.

Molecular markers have also changed the face of prognostication for cancers such as neuroblastoma. Irwin *et al.* [22▪] recently developed a revised risk stratification tool by adapting the International Neuroblastoma Risk Group Staging System to include prognostic segmental chromosomal aberrations in addition to classical clinical features to increase accuracy of risk assessment. Application of the latest advances in molecular characterization is anticipated to refine disease prognostication and appropriate allocation to effective treatment regimens across pediatric oncology.

Evolving collection and use of patient-reported outcomes and social determinants of health

As targeted agents alter the landscape of treatment regimens, advances in the collection, application, and management of patient-reported outcomes (PROs) and social determinants of health (SDOH) may revolutionize cancer care delivery. In recent years, marked disparities in outcomes based on factors outside of disease biology – including race, ethnicity, poverty, language of care, and household location – have received greater recognition [23]. For example, disparities related to race and ethnicity were redemonstrated in a recent analysis of eight COG trials for ALL from 2004 to 2019 [24▪]. Leveraging detailed disease and treatment indicators available through trial participation, Gupta and colleagues reported that patients receiving protocolized treatment for B-cell ALL who identified as non-Hispanic Black or Hispanic experienced worse EFS and OS, compared with patients identifying as non-Hispanic White. Furthermore, these disparities were incompletely attenuated after adjusting for important clinical prognosticators and insurance status, highlighting a continued need to examine the impacts of structural racism and devise solutions to provide more equitable care. Disparities in enrollment on pediatric oncology clinical trials must also be addressed to ensure access and representation for all [25,26].

Similarly substantial disparities related to poverty were reported in 2021 by Bona *et al.* [27], who analyzed outcomes of children with high-risk neuroblastoma enrolled on two COG clinical trials evaluating targeted immunotherapy. Retrospective analysis of these trials, which ran from 2005 to 2014, showed that children with proxy measures of household poverty experienced decrements in EFS and OS. These results call for effective, scalable interventions to mitigate these disparities in outcome. PediCARE, an intervention geared toward addressing household material hardship through the provision of resources

for transportation and food [28▪▪], is one potential solution currently under investigation. Preliminary data demonstrate remarkable acceptability, including a 100% study participation and completion rate [29▪]. Participants provided detailed data related to SDOH as part of the study and almost universally reported high perceived benefit from the supports they received. Further work is needed to evaluate the scalability of the intervention, as well as its effectiveness in improving health outcomes.

As more is done to address modifiable social determinants, we must collect reliable and granular data from patients and families to aid in screening and assessment of interventions. We highlight two other examples of PRO collection during treatment. An NCI-funded task force recently sought to develop a core set of PROs for incorporation into clinical trials involving adolescents and young adults (AYAs) [30▪]. Through a modified Delphi approach, these experts prioritized measures of health-related quality of life and treatment toxicity/tolerability to generate a core battery of outcomes that has already been incorporated into several AYA clinical trials. We anticipate these data will provide a standardized and valuable perspective from patients themselves, supplementing other study endpoints. Parent-reported outcomes are also being collected multiinstitutionally, illustrated by the COG study ACCL20N1CD, a prospective examination of the trajectory of financial distress during treatment among families of children with ALL [31▪]. COG institutions are currently surveying parents on elements of financial challenges at multiple timepoints, along with indicators of household socioeconomic status and other SDOHs for correlative analyses. Results from this mixed methods study will improve our understanding of the adverse financial impacts of cancer care and may lead to interventions to improve care quality.

Increased focus on late effects and interventions during survivorship

As long-term survival improves for most cancers, there is strong impetus to reduce secondary late effects and improve quality of life [32]. Advances in the risk assessment, prevention, detection, and treatment of cardiac late effects serve as a paradigm for future progress in all aspects of survivorship care.

In a pooled analysis of five randomized trials of children with ALL or Hodgkin lymphoma who received anthracycline chemotherapy, Chow *et al.* [33▪] evaluated the cardioprotective effects of dexrazoxane nearly 20 years after initial chemotherapy exposure. After adjusting for cumulative anthracycline dose, radiation therapy, and other patient factors, dexrazoxane use was associated with significantly better systolic function and lower risk of cardiomyopathy by echocardiography, as well as lower myocardial stress as measured by b-type natriuretic peptide. Combined with data supporting its safety [34], these results firmly establish dexrazoxane as a standard component of regimens with high cardiotoxic potential. Complementing this, recent advances in prediction models using data from the Childhood Cancer Survivorship Study have enabled more refined assessments of patients' cardiac risks based on treatment exposures [35,36]. Preliminary work from COG research sites has also incorporated longitudinal echocardiogram data into novel regression methods to predict cardiomyopathy risk, years before meeting diagnostic criteria [37]. Such prediction models allow healthcare teams to identify at-risk patients earlier, prompting timely action to slow cardiomyopathy progression.

Exciting strides are also being made in the secondary prevention of cardiomyopathy, evidenced by preliminary results from the COG ALTE1621 study [38▪]. This double-blinded, randomized trial tested low-dose carvedilol for the prevention of cardiomyopathy among a cohort of patients with high-risk cardiac features but preserved systolic function. After 2 years, patients assigned to receive carvedilol demonstrated superior echocardiogram parameters compared with the placebo group, suggesting that treatment may potentially slow or reverse anthracycline-induced cardiac injury. Of the eight cardiac events that occurred, six were among patients on the placebo arm.

While survivors of childhood cancer face risks for a plethora of late effects, recent advances in predicting, preventing, and treating cardiac late effects provide hope for children with cardiotoxic treatment exposures. Similar advances are being made for other late effects, including neurotoxicity, ototoxicity, renal disease, endocrinopathies, secondary malignancies, and psychosocial impacts.

CONCLUSION

As targeted agents establish a growing role within the upfront treatment of many cancers, we anticipate that incorporation of these therapies will improve survival and reduce long-term health impact. In parallel, wider access to molecular diagnostic testing and enhanced cancer care delivery pose tremendous promise to move the needle for our most vulnerable patients. Finally, developments in survivorship will enable clinicians to better prevent, detect, and address late effects. Ongoing collaboration across institutions and countries will be critical to maintaining our momentum toward a better future for children with cancer.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023; 73:17–48.
2. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. Nat Rev Cancer 2014; 14:61–70.
3. Laetsch TW, DuBois SG, Bender JG, *et al.* Opportunities and challenges in drug development for pediatric cancers. Cancer Discov 2021; 11:545–559.
4. ■■ van der Sluis IM, de Lorenzo P, Kotecha RS, *et al.* Blinatumomab added to chemotherapy in infant lymphoblastic leukemia. N Engl J Med 2023; 388:1572–1581.

This clinical trial of patients with infant ALL demonstrated substantial improvements in survival with the addition of blinatumomab to the Interfant-06 chemotherapy backbone, with a 2-year overall survival of 93%. The trial's results represent a remarkable improvement in outcomes, compared with historical controls, from the addition of targeted therapy to an intensive chemotherapy backbone.

5. ■ Kutny MA, Alonzo TA, Abla O, *et al.* Assessment of arsenic trioxide and all-trans retinoic acid for the treatment of pediatric acute promyelocytic leukemia: a report from the Children's Oncology Group AAML1331 Trial. JAMA Oncol 2022; 8:79–87.

This clinical trial of patients with APL tested marked reductions in chemotherapy, having a 2-year overall survival exceeding 99%. A regimen of arsenic trioxide and all-trans retinoic acid achieved excellent outcomes despite the use of little chemotherapy.

6. ■ Castellino SM, Pei Q, Parsons SK, *et al.* Brentuximab vedotin with chemotherapy in pediatric high-risk Hodgkin's lymphoma. N Engl J Med 2022; 387:1649–1660.

This trial showed that the substitution of brentuximab for bleomycin in the treatment of high-risk pediatric Hodgkin lymphoma was effective, with 3-year EFS of 92%. Ongoing follow-up for late effects will test whether the omission of bleomycin reduces pulmonary toxicity.

7. Herrera AF, LeBlanc ML, Castellino SM, *et al.* SWOG S1826, a randomized study of nivolumab(N)-AVD versus brentuximab vedotin (BV)-AVD in advanced stage (AS) classic Hodgkin lymphoma (HL). J Clin Oncol 2023; 41(17 Suppl):LBA4–LBA4.
8. ■ DuBois SG, Krailo MD, Glade-Bender J, *et al.* Randomized phase III trial of ganitumab with interval-compressed chemotherapy for patients with newly diagnosed metastatic Ewing Sarcoma: a report from the Children's Oncology Group. J Clin Oncol 2023; 41:2098–2107.

The addition of ganitumab to chemotherapy did not improve Ewing sarcoma outcomes in this phase 2 trial. Results highlight that targeted agents in upfront therapy do not always improve outcomes and require careful investigation before changing standards of care.

9. ■ Brennan B, Kirton L, Marec-Bérard P, *et al.* Comparison of two chemotherapy regimens in patients with newly diagnosed Ewing sarcoma (EE2012): an open-label, randomised, phase 3 trial. Lancet 2022; 400:1513–1521.

This randomized trial across 10 countries tested the efficacy of two competing chemotherapy regimens in the treatment of Ewing sarcoma. The North American standard, five-drug chemotherapy delivered in an interval-compressed fashion, was shown to be more effective, less toxic, and shorter in duration.

10. ■ Flores-Toro JA, Jagu S, Armstrong GT, *et al.,* Childhood Cancer Data Initiative Working Groups. The childhood cancer data initiative: using the power of data to learn from and improve outcomes for every child and young adult with pediatric cancer. J Clin Oncol 2023; 41:4045–4053.

The Childhood Cancer Data Initiative (CCDI) is a NCI-funded program to aggregate data to drive new discovery and novel treatments in pediatric cancer. The Molecular Characterization Initiative, as part of the CCDI, seeks to provide genomic testing for selected newly diagnosed cancers.

11. ■■ Parsons DW, Janeway KA, Patton DR, *et al.,* NCI-COG Pediatric MATCH Team. Actionable tumor alterations and treatment protocol enrollment of pediatric and young adult patients with refractory cancers in the National Cancer Institute-Children's Oncology Group Pediatric MATCH Trial. J Clin Oncol 2022; 40:2224–2234.

This trial investigated the feasibility of molecular testing and applied use of targeted agents for relapsed and refractory cancers. Detailed DNA sequencing was successfully obtained in almost all patients, and actionable mutations were identified in almost one-third of participants. These results demonstrate ready feasibility of coordinated molecular testing on a national scale. Results from some of the 13 subprotocols have been published, and more results are anticipated.

12. ■ Eckstein OS, Allen CE, Williams PM, *et al.* Phase II study of selumetinib in children and young adults with tumors harboring activating mitogen-activated protein kinase pathway genetic alterations: arm E of the NCI-COG Pediatric MATCH Trial. J Clin Oncol 2022; 40:2235–2245.

Selumetinib monotherapy did not demonstrate any objective responses among patients with relapsed and refractory tumors harboring MAP kinase mutations. Although MEK inhibition has previously shown promising results among plexiform neurofibromas and melanoma, these results show that monotherapy is not effective versus some high-risk subsets of patients.

13. ■ Chi SN, Yi JS, Williams PM, *et al.* Tazemetostat for tumors harboring SMARCB1/SMARCA4 or EZH2 alterations: results from NCI-COG pediatric MATCH APEC1621C. J Natl Cancer Inst 2023; djad085.

Of 20 patients with mutations in EZH2 or members of the SWI/SNF complex who received targeted monotherapy with tazematostat, only one objective response was observed, with four patients seeing prolonged stable disease. These results reiterate that targeted therapy may need to be paired with other treatment modalities for the treatment of some high-risk malignancies.

14. Vo KT, Sabnis AJ, Williams PM, *et al.* Ulixertinib in patients with tumors with MAPK pathway alterations: results from NCI-COG Pediatric MATCH trial Arm J (APEC1621J). J Clin Oncol 2022; 40(16 Suppl):3009–13009.
15. Macy ME, Mody R, Reid JM, *et al.* Palbociclib in solid tumor patients with genomic alterations in the cyclin D-CDK4/6-INK4a-Rb pathway: results from NCI-COG pediatric MATCH trial Arm I (APEC1621I). J Clin Oncol 2023; 41 (16 Suppl):10006–110006.
16. Lee A, Chou AJ, Williams PM, *et al.* Erdafitinb in patients with FGFR-altered tumors: results from the NCI-COG Pediatric MATCH trial arm B (APEC1621B). J Clin Oncol 2023; 41(16_Suppl):10007–110007.
17. ■ Duke ES, Bradford D, Marcovitz M, *et al.* FDA approval summary: selpercatinib for the treatment of advanced RET fusion-positive solid tumors. Clin Cancer Res 2023; 29:3573–3578.

This trial demonstrated a favorable objective response rate to selpercatinib in the treatment of refractory solid tumors with RET mutations. These results suggest that there may be benefit from selected monotherapy regimens for some heavily pretreated tumors.

18. ■ Meric-Bernstam F, Ford JM, O'Dwyer PJ, *et al.* National Cancer Institute Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice (ComboMATCH). Clin Cancer Res 2023; 29:1412–1422.

A successor trial to the Pediatric MATCH trial [11], the COMBO-MATCH trial will test potential targeted agent combinations. This approach may achieve more durable responses to novel targeted agents by reducing mechanisms by which tumors may develop resistance.

19. ■ Lowe EJ, Reilly AF, Lim MS, *et al.* Crizotinib in combination with chemotherapy for pediatric patients with ALK+ anaplastic large-cell lymphoma: the results of Children's Oncology Group Trial ANHL12P1. J Clin Oncol 2023; 41:2043–2053.

In this clinical trial of children with ALCL, RT-PCR detection of the NPM::ALK fusion in the peripheral blood was associated with lower EFS. This study highlights the potential utility of molecular testing results for prognostication and therapy choice.

20. ■ Abbou S, Klega K, Tsuji J, *et al.* Circulating tumor DNA is prognostic in intermediate-risk rhabdomyosarcoma: a report from the Children's Oncology Group. J Clin Oncol 2023; 41:2382–2393.

This study showed that patients with detectable circulating tumor DNA (ctDNA) at diagnosis experienced inferior outcomes. Utilization of ctDNA in the future may aid in prognostication and may potentially aid in therapy choice.

21. Madanat-Harjuoja LM, Renfro LA, Klega K, *et al.* Circulating tumor DNA as a biomarker in patients with stage III and IV Wilms tumor: analysis from a Children's Oncology Group Trial, AREN0533. J Clin Oncol 2022; 40:3047–3056.
22. ■ Irwin MS, Naranjo A, Zhang FF, *et al.* Revised neuroblastoma risk classification system: a report from the Children's Oncology Group. J Clin Oncol 2021; 39:3229–3241.

An expert panel of neuroblastoma experts revised their risk stratification system to incorporate molecular markers at diagnosis. Inclusion of such markers in risk stratification increases the accuracy of risk assessment and will better guide therapy selection.

23. Aristizabal P, Winestone LE, Umaretiya P, Bona K. Disparities in pediatric oncology: the 21st century opportunity to improve outcomes for children and adolescents with cancer. Am Soc Clin Oncol Educ Book 2021; (41): e315–e326.

24. Gupta S, Dai Y, Chen Z, *et al.* Racial and ethnic disparities in childhood and ■ young adult acute lymphocytic leukaemia: secondary analyses of eight Children's Oncology Group cohort trials. Lancet Haematol 2023; 10: e129–e141.

This retrospective study of patients with ALL on several clinical trials analyzed disparities related to race and ethnicity. Leveraging detailed disease and treatment information, this group showed that disparities related to race and ethnicity were incompletely attenuated even when adjusting for clinical prognosticators and insurance status.

25. Aristizabal P, Singer J, Cooper R, *et al.* Participation in pediatric oncology research protocols: racial/ethnic, language and age-based disparities. Pediatr Blood Cancer 2015; 62:1337–1344.

26. Winestone LE, Getz KD, Rao P, *et al.* Disparities in pediatric acute myeloid leukemia (AML) clinical trial enrollment. Leuk Lymphoma 2019; 60:2190–2198.

27. Bona K, Li Y, Winestone LE, *et al.* Poverty and targeted immunotherapy: survival in children's oncology group clinical trials for high-risk neuroblastoma. JNCI J Natl Cancer Inst 2021; 113:282–291.

28. Umaretiya PJ, Revette A, Seo A, *et al.* PediCARE: development of a poverty- ■■ targeted intervention for pediatric cancer. Pediatr Blood Cancer 2021; 68: e29195.

This intervention trial was developed to address disparities in cancer survival related to poverty and material hardship. The trial was designed to test the feasibility of systematically providing resources for transportation and food to reduce material hardship and facilitate cancer care. Interventions to address modifiable SDOH such as this have the potential to revolutionize cancer care delivery and improve outcomes for vulnerable patients.

29. Newman H, Jones E, Umaretiya PJ, *et al.* Feasibility of the Poverty-Targeted ■ Pediatric Cancer Resource Equity (PediCARE) intervention. J Clin Oncol 2023; 41(16 Suppl):10009–110009.

Preliminary data from this intervention of resources to reduce food and transportation insecurity show very high feasibility and acceptability among families at two institutions.

30. Roth ME, Parsons SK, Ganz PA, *et al.* Inclusion of a core patient-reported ■ outcomes battery in adolescent and young adult cancer clinical trials. J Natl Cancer Inst 2023; 115:21–28.

This task force developed a core set of PRO to standardly collect as part of clinical trials involving adolescents and young adults. This core battery is already being incorporated into several upcoming clinical trials that include this population.

31. Beauchemin M, Santacroce SJ, Bona K, *et al.* Rationale and design of ■ Children's Oncology Group (COG) study ACCL20N1CD: financial distress during treatment of acute lymphoblastic leukemia in the United States. BMC Health Serv Res 2022; 22:832.

This longitudinal collection of SDOH data from parents of children with cancer will occur across multiple institutions. Collection of this longitudinal data pertaining to financial challenges may lead to possible interventions for patients and families.

32. Dixon SB, Chow EJ, Hjorth L, *et al.* The future of childhood cancer survivorship: challenges and opportunities for continued progress. Pediatr Clin North Am 2020; 67:1237–1251.

33. Chow EJ, Aggarwal S, Doody DR, *et al.* Dexrazoxane and long-term heart ■ function in survivors of childhood cancer. J Clin Oncol 2023; 41:2248–2257.

This retrospective analysis demonstrates the efficacy of dexrazoxane in preventing anthracycline-related cardiotoxicity, especially for patients with greater risk based on known exposures. These results establish dexrazoxane as a standard component of regimens with high cardiotoxic potential.

34. Chow EJ, Aplenc R, Vrooman LM, *et al.* Late health outcomes after dexrazoxane treatment: a report from the Children's Oncology Group. Cancer 2022; 128:788–796.

35. Chow EJ, Chen Y, Hudson MM, *et al.* Prediction of ischemic heart disease and stroke in survivors of childhood cancer. J Clin Oncol 2018; 36:44–52.

36. Chen Y, Chow EJ, Oeffinger KC, *et al.* Traditional cardiovascular risk factors and individual prediction of cardiovascular events in childhood cancer survivors. J Natl Cancer Inst 2020; 112:256–265.

37. Chow EJ, Stratton K, Armenian S, *et al.* Enhancing prediction of cancer therapy-related cardiomyopathy from surveillance echocardiograms: a Children's Oncology Group (COG) report. J Clin Oncol 2023; 41(16 Suppl):10012–110012.

38. Armenian S, Hudson MM, Lindenfeld L, *et al.* Carvedilol for prevention of heart ■ failure in anthracycline-exposed survivors of childhood cancer: results from COG ALTE1621. J Clin Oncol 2023; 41(16 Suppl):10013–110013.

Preliminary data demonstrate that low-dose carvedilol can prevent or reduce progression to cardiomyopathy among a cohort of patients at high risk for developing cardiomyopathy.