

Pathway for the Development of ATR Inhibitors in Pediatric Malignancies: An ACCELERATE Multistakeholder Analysis

Susanne A. Gatz, MD, PhD, FRCPC^{1,2} ; Julia Glade-Bender, MD³ ; Andrew D.J. Pearson, MBBS, MD, DCH⁴ ; Michael V. Ortiz, MD⁵ ; Ronald Bernardi, PhD⁵; Lou Chesler, MD, PhD⁶ ; Steve Clifford, PhD⁷ ; Sarah Cohen-Gogo, MD, PhD⁸ ; Esther De La Cuesta, MD, MBA⁹ ; Teresa de Rojas, MD, PhD⁴ ; Kaat Durinck, PhD^{10,11} ; Sara Federico, MD¹² ; Elizabeth Fox, MD¹² ; Sally George, MBBS, PhD^{6,13} ; Ioannis Gounaris, MD, PhD¹⁴ ; Anton George Henssen, MD¹⁵ ; Meredith Irwin, MD⁸ ; Marcel Kool, PhD^{16,17,18,19}; Alan Lau, PhD²⁰ ; Karsten Nysom, MD, PhD²¹ ; Alberto Pappo, MD¹² ; Gregory K. Pennock, MD²²; Stefan M. Pfister, MD²³; Nicole Scobie⁴ ; Emily K. Slotkin, MD³ ; Malcolm Smith, MD, PhD²⁴ ; Frank Speleman, PhD^{10,11}; Elizabeth A. Stewart, MD¹²; Brenda J. Weigel, MD, MSc¹² ; and Gilles Vassal, MD, PhD^{4,25} 

DOI <https://doi.org/10.1200/PO-25-00642>

ABSTRACT

Accepted December 11, 2025

Published January 15, 2026

JCO Precis Oncol 10:e2500642

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Clinical Oncology

PURPOSE High levels of DNA replication stress and defects in the DNA damage response (DDR) pathways are vulnerabilities of many poor prognosis childhood malignancies. Ataxia telangiectasia and Rad3-related protein (ATR) is a key regulator of these pathways and constitutes an attractive target, especially in combination. However, the malignancies where ATR inhibitors have maximum benefit and synergistic combinations differ between adults and children.

DESIGN ACCELERATE convened a multistakeholder meeting and conducted review and analysis to propose the optimal pathway for the development of ATR inhibitors in pediatric malignancies.

RESULTS Considering the lack of identified biomarkers, the initial evaluation of ATR inhibitors should focus on Ewing sarcoma, rhabdomyosarcoma, and neuroblastoma in view of their high levels of DNA replication stress and defects in DDR pathways. Early phase trials of ATR inhibitors should be iterative, based on a clear hypothesis with responders and nonresponders undergoing detailed molecular analysis and a revised new hypothesis generated. Trial designs should restrict monotherapy evaluation to a brief exposure in a small number of patients and progress rapidly to combinations. Highlighted combination partners are poly(ADP-ribose) polymerase inhibitors and antibody drug conjugates with topoisomerase I inhibitor payloads. Combinations with ALK inhibitors (in *ALK/MYCN*-aberrant neuroblastoma) and aurora A kinase (in *MYCN*-amplified) are supported by robust mechanisms of action and preclinical data. Early interactions with regulators are crucial, and early phase clinical trials should be conducted in regulatory-approved, academic-sponsored, industry-supported, platform trials.

CONCLUSION ATR inhibitors are a prototype for the development of medicinal products in a limited pediatric population. For the substantial potential of ATR inhibitors in children with malignancy to be realized, strategic planning between academia, industry, regulators, and patient advocates is vital.

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INTRODUCTION

High levels of DNA replication stress and defects in the DNA damage response (DDR) pathways, which are critical for maintaining genomic integrity,^{1,2} are vulnerabilities of many poor prognosis childhood malignancies.³⁻⁹ Ataxia telangiectasia and Rad3-related protein (ATR) is a key regulator of the DDR machinery and functions in the replication stress response.¹ ATR is an attractive therapeutic target holding

significant promise, and several ATR inhibitors (ATRi) are undergoing clinical studies in adults,¹ but no drugs are approved. Although the class of drugs has potential benefit for children with cancer, especially in combination, there are many aspects regarding their development which are unclear. Moreover, there are challenges in evaluating multiple new products in rare populations, making it of value to identify for ATRi: (1) the optimal diseases and/or biomarker-defined populations; (2) the value of monotherapy trials and

best clinical trial design; (3) the most beneficial combinations; and (4) the best approach to a coordinated and integrated drug development strategy of available assets, in the context of the population size.

To address these issues, ACCELERATE, an international multistakeholder organization, whose objective is to advance the timely investigation of new anticancer drugs,^{10,11} convened multistakeholder meetings following the Paediatric Strategy Forum on DDR pathway inhibitors.¹² This is a review and analysis of the issues identified and proposed potential solutions focused on ATRi.

THE ROLE OF ATR IN DDR

ATR is a mediator of the cellular replication stress response, which regulates the activation of cell cycle checkpoints and DNA replication to control cell division and safeguard genomic integrity, and is a member of the phosphatidylinositol 3-kinase-related kinase (PI3-K) family, which includes DNAPK and ATM.¹³⁻¹⁶ The ATR-CHK1-CDC25C-CDK1 pathway preferentially responds to replication-associated damage in S and G2/M to inhibit cell cycle progression into mitosis. ATR principally senses, and is activated by, the presence of extensive single-stranded DNA (ssDNA) at sites of stalled replication forks or single-strand breaks incurred from other sources of DNA damage.¹⁷⁻²¹ On activation, ATR initiates a cascade of coordinated downstream reactions that lead to arrest of cell cycle progression and stabilization of stalled replication forks, thus enabling DNA repair.^{6,21} The ATR-CHK1 signaling pathway acts as an important rheostat in normal cells, but cancer cells can become addicted to this pathway because of oncogene-induced enhanced replicative stress.²²⁻²⁴ These replication events lead to increased levels of fork stalling and collapse, resulting in increased ssDNA and toxic double-strand DNA breaks. Cancer cells may also acquire increased dependency on co-occurrent loss or inactivation of other key components of the DDR machinery⁴ and are potentially susceptible to synthetically lethal combinations. For example, poly(ADP-ribose) polymerase (PARP) plays a key role in the repair of ssDNA. PARP inhibitors (PARPi) have demonstrated clinically relevant synthetic lethality in patients with breast cancer harboring DDR pathway alterations, most commonly *BRCA1* or *BRCA2* mutations.^{25,26} However, PARPi can also trap PARP1/2 at sites of DNA damage, leading to stalled replication forks and augmenting replication stress requiring ATR for resolution; coincidentally, ATR inhibition can suppress homologous recombination repair (HRR) potentially sensitizing cells to PARPi.^{27,28} ATM preferentially responds to and repairs DNA double-strand breaks, inhibits cell cycle progression into S-phase, and represents a complementary mechanism to ATR-mediated DDR; thus, loss of ATM may also result in synthetic lethality during ATR inhibition. ATR plays an important role in development, and ATR deficiency during embryogenesis results in high levels of replicative stress and accelerated aging.²⁹ Furthermore, the ATR to ATM signaling axis plays a role in the maintenance of telomere homeostasis

and the surveillance of telomere dysfunction during neurogenesis.^{30,31}

ATR INHIBITORS IN ADULT ONCOLOGY

Clinical trials of six ATR kinase inhibitors (berzosertib,^{32,33} ceralasertib,³⁴⁻³⁶ elimusertib,^{37,38} camonsertib,^{39,40} tuvusertib,⁴¹ and ART0380⁴²) have been conducted, with berzosertib and elimusertib being discontinued because of the lack of activity. ATRi are generally tolerable with myelosuppression, particularly anemia, and nausea being the most clinically relevant toxicities in adults.

Generally, data from phase I dose-escalation cohorts of unselected adult patients with advanced-stage cancer indicate limited efficacy of ATRi as monotherapies.⁴¹⁻⁴⁴ No single integral biomarker of sensitivity to ATRi has been established; potential biomarkers studied include individual genomic alterations that predispose to HRR deficiency and measurements of replication stress accumulation, including gene signatures and functional assays.^{1,28,40} Phase I single-agent trials, which specifically recruited patients with advanced-stage solid tumors harboring DDR defects, reported higher overall response rates.^{39-41,45} An early phase trial of camonsertib used a chemogenomic screen for DDR alterations across approximately 100 genes to identify patients for enrollment and demonstrated both response and meaningful clinical benefit across multiple histologies.⁴⁰ In addition, preclinical investigation demonstrated that in vitro models of ATM loss malignancies (either *ATM* mutation or protein loss) are very sensitive to ATR inhibition.^{46,47} Accordingly, the phase I trial of elimusertib in adults focused on patients with *ATM* aberrations and showed partial responses in patients whose tumors lacked detectable ATM protein expression. Unfortunately, this signal could not be confirmed in the expansion cohorts.⁴⁵ ATRi delaying or overcoming resistance to PARP⁴⁸ and in combination with immune checkpoint inhibitors^{49,50} are being explored.

ATR INHIBITORS IN CHILDREN

Biomarkers for ATR inhibitor activity in children are likely to be different compared with that in adults. Generally, in pediatric cancer, there are a relative lack of mutations and a prominence of copy number aberrations, for example, 11q deletion.⁵¹ For example, loss of HRR genes, especially biallelic loss, is exceedingly rare in pediatric tumors, as are mutations of *BRCA1* and *BRCA2* and *ATM* (<1%).⁵¹⁻⁵⁵ Loss of function of ATM and the role of ATM mutations or ATM protein expression have been problematic to determine^{37,45} because of (1) the difficulty in predicting whether a specific mutation is deleterious or a variant of uncertain significance,⁵⁶ (2) the zygosity of the alteration which may affect the loss of protein function,⁵⁷ and (3) nonharmonized immunohistochemistry protocols.

Although the most discriminatory predictive biomarkers for ATRi in pediatric malignancies are unknown, there are

biological changes in pediatric malignancy which have been related to the activity of ATRi: *ATM* deletion because of 11q loss⁵⁸; *MYCN/MYC* amplification⁵⁹⁻⁶¹; aberrant transcription factor gene fusion (*PAX3-FOXO1*,^{7,62} *EWSR1-FLI3*,⁶³); epigenetic modifier gene fusions (*SS18-SSX1/2*); *ATRX* mutation/loss; *STAG2* mutation; *SETD2* mutation/loss; *CHEK1/gH2AF*, *MRE11A* loss; histone mutations (H3K27, H3K36); *TP53* mutations; and alternative lengthening of telomeres (ALT). ALT is an independent mechanism of telomere maintenance, in the absence of direct telomerase activation because of high telomerase reverse transcriptase (TERT) expression.⁶⁴ Pre-clinical reports of the relevance of ALT as a biomarker of ATR inhibitor activity are conflicting,⁶⁵⁻⁶⁸ and ALT-positive neuroblastoma displays skewed sensitivity for ATM versus ATR inhibition.⁶⁹

Ongoing trials in pediatrics are evaluating ceralasertib⁶⁹⁻⁷⁴ and elimusertib^{75,76} (Table 1):

1. A phase I/II study Bay 18953444 (elimusertib) in pediatric patients with relapsed or refractory solid tumors (PEPN2112).^{75,76} This study is based on preclinical data demonstrating that Ewing sarcoma and fusion-positive rhabdomyosarcoma are susceptible to in vitro and in vivo ATR inhibition.^{3,4,7}
2. Arm N of ESMART⁶⁹⁻⁷⁶ uses the PARPi, olaparib, with ceralasertib. Tumors have advanced molecular profiling (whole-exome sequencing or whole-genome sequencing [WGS] with or without RNA sequencing) allowing for both enrichment of patients with certain molecular features and detailed retrospective molecular analyses of responders and nonresponders. Eligibility for cohort 1 is HRR deficiency with a focus on *ATM* alterations, and that for cohort 2 is increased replication/transcription stress including transcription factor fusions and amplifications.
3. Olaparib with ceralasertib in recurrent osteosarcoma⁷²⁻⁷⁴ was recently completed. Only one of 37 patients had an objective response. Data analysis is ongoing.

A PLAN FOR THE INCLUSION OF BIOMARKERS IN CLINICAL TRIALS

At the Paediatric Strategy Forum on DDR pathway inhibitors, the disparity of assessments to identify biomarkers for ATRi hindered a comparison between the results generated between clinical trials.¹² It was concluded that “an integrated strategy and a consensus to assess biomarkers, both in academic and industry trials, of the investigations and biomarkers to be explored would greatly enhance efficiency. Tumor biopsies, prior to therapy, with a common portfolio of investigations for DNA sequencing are crucial, in order that the responders and non-responders have similar molecular analyses, helping to validate responder hypotheses.” Thus, to be informative, it is mandatory that clinical trials of ATRi have embedded, biocorrelative studies.

Tumor material: The goal should be to collect fresh-frozen tumor tissue (high quality DNA), before entry to trial, in

addition to formalin-fixed paraffin-embedded material. Data from paired diagnosis and relapse samples have demonstrated that mutations in certain genes, including proposed biomarkers of ATRi (eg, Death Domain-Associated protein [*DAXX*]), change at the time of relapse,^{77,78} as do protein fusions and associated transcription/replication stress, and thus, rebiopsy is required.⁷⁹ With interventional radiology, the risks of such biopsies are minimal and should be considered safe and feasible. In several pediatric precision oncology programs such as Stratified Medicine Paediatrics,^{54,77,80-82} biopsy at the time of relapse is considered standard of care. The results from biopsies at the time of relapse can identify genomic abnormalities which will guide enrollment on precision medicine trials. Patients and parents are increasingly requesting to be offered the possibility of biopsy at relapse. Patient advocates believed that the probability of obtaining a biopsy before enrollment and at relapse would be increased by ensuring that results are made available to academia, patients, and parents. From an industry perspective, Clinical Laboratory Improvement Amendments and College of American Pathologists validated that confirmation of eligibility is desirable and having material available for a retrospective in-depth study is also supported.

Details of potential biomarkers and their relevance to pediatrics are given in Table 2. The current prioritized investigations are WGS sequencing and transcriptome sequencing, protein expression (*ATM*, *ATRX*, *RB1*, *SLFN11*, *PGBD5*, and *TP53*) detected by immunohistochemistry, and ALT (C-circle and associated promyelocytic leukaemia nuclear bodies-fluorescence in situ hybridization) for high TERT RNA sequencing or reverse transcription-polymerase chain reaction for TERT RNA levels and/or TERT rearrangements) and phosphoproteomic analyses. The objective is to conduct all these investigations; however, in exceptionally small samples, WGS sequencing, transcriptome sequencing, and obtaining circulating tumor DNA should be prioritized.

POTENTIAL COMBINATIONS

There are some data for synthetic lethality of ATR alone, but this can be substantially potentiated by combinations which should be based on, and test, robust biological hypotheses, underpinned by preclinical in vivo data of synergy generated by panels of representative models and/or adult clinical studies and nonoverlapping toxicity. It is crucial that in vivo studies use clinically relevant doses and schedules to inform clinical investigations. There is a strong biological rationale for combinatorial approaches to target DDR and replication including (1) pharmacologically induced replication stress, such as by irinotecan and PARPi; (2) overcoming single-agent resistance¹⁰⁷; and (3) inducing synthetic lethality in DDR mechanisms.¹⁰⁸ However, there are concerns that synergistic toxicity may require that doses be reduced to levels which are not active, and therefore, toxicity and dose require careful monitoring.

TABLE 1. ATR Inhibitors Evaluated in Patients Younger Than 18 Years

Drug	Combination	Trial/Status	Eligibility (tumor type)	Eligibility (biomarker)	Trial Design	Preliminary Results
Ceralasertib (AstraZeneca)	Olaparib	NCT02813135 ESMART Arm N ^{69,71}	Relapsed/refractory solid tumors	HR-deficient OR replication/transcription stress	Phase I—Escalation follows a Bayesian optimal interval design starting at 100% of the adult-optimized dose to determine the RP2D based on the MTD and toxicity and early signals of activity 28-day cycles. Continuous oral dosing: days 1-28 olaparib and days 1-14 ceralasertib followed by expansion cohorts (1) HRR-deficient with a focus on ATM alterations (including 11q loss) (2) Replication stress (<i>MYC/MYCN</i> amplification, <i>CCNE1</i> amplification, and gene fusions, <i>EWSR1: FLI1</i> , <i>SSE18: SSX</i> , <i>PAX3/7: FOXO1</i>)	N = 18 patients—8 sarcomas, 5 CNS, 4 neuroblastomas, 1 carcinoma 2 PR (neuroblastoma and pineoblastoma), 8 SD 1 neuroblastoma (11q LOH, ATRX VUS) with SD converted to PR, cycle 10 RP2D—olaparib 150 mg twice daily on days 1 to 28 and ceralasertib 80 mg twice daily on days 1-14 for children 12 years and older Main toxicities—hematologic and gastrointestinal (nausea) ⁶⁷
Ceralasertib (AstraZeneca)	Olaparib	NCT04417062 ⁷²⁻⁷⁴	Recurrent osteosarcoma		2 cohorts age 12-40 years with recurrent osteosarcoma 1—Unresectable disease and 2—resectable disease limited to the lung receive olaparib 300 mg orally twice a day on days 1-28 and ceralasertib 160 mg orally once a day on days 1-7 of a 28-day cycle	N = 37, 1 ORR
Elimusertib (Bayer)	Monotherapy	NCT05071209 PEPN2112 ^{75,76}	Relapsed/refractory solid tumors	No molecular eligibility for EWS or RMS Other tumors DDR alterations: <i>ATM</i> , <i>ATR</i> , <i>BRCA1</i> , <i>BRCA2</i> , <i>CDK12</i> , <i>CHEK1</i> , <i>CHECK2</i> , <i>FANCA</i> , <i>MSH2</i> , <i>MRE11</i> , <i>PALB2</i> , <i>PARP1</i> , <i>POLD1</i> , <i>RAD51</i> , <i>XRCC2</i>	Initial phase I cohort followed by expansion cohorts: (1) EWS or related <i>EWSR1</i> fusion-positive tumors (2) Alveolar RMS, <i>PAX3-FOXO1</i> fusion-positive (3) Non-CNS primary tumors exhibiting specific DDR pathway defects anticipated to sensitize to ATR inhibition	N = 8 patients, 6 evaluable, received adult RP2D of 24 mg/m ² per maximum dose (40 mg, with 3 days of drug administration and 4-day rest) No dose-limiting toxicities, pharmacokinetics were similar to adults Trial not designed for dose escalation, to determine the optimal biological dose or MTD (June 2023) ³²

Abbreviations: ANR, active not recruiting; DDR, DNA damage response; EWS, Ewing sarcoma; HRR, homologous recombination repair; MTD, the maximal tolerated dose; OR, objective response; ORR, overall response rate; PR, partial response; RMS, rhabdomyosarcoma; RP2D, recommended phase 2 dose; SD, stable disease; Trial status R, recruiting.

TABLE 2. Details of Potential Biomarkers and Their Relevance to Pediatrics

Investigation	Description	Relevance to Pediatrics
Genomic investigation	Gene panels have very good depth and accuracy; however, they lack breadth, and several genes are not represented on commonly used panels. WES and WGS have good breadth but may not detect specific variants at very low allele frequencies. Rearrangements are included on many fusion panels, but novel fusion partners may be more likely to be detected by RNA or WGS. Notably, some actionable targets may derive from the germline. ^{54,83-85}	Preferred approach would be to have a NGS panel including specific genes of interest to rapidly determine eligibility, followed by retrospective, comprehensive analyses by WGS and RNAseq to identify candidate biomarkers of response and confirm eligibility
Protein investigations	Protein expression can be detected by several assays including immunohistochemistry. ATM, ATRX, RB1, SLFN11, PGBD5, and TP53 are the priority proteins to be measured. Phosphoproteomic analysis will provide greater insight; however, technical issues complicate widespread use and often fresh-frozen tumor material is required. ⁸⁶ As new platforms for spatial transcriptome and proteome analysis become more available and well-established, these will likely yield valuable information	Immunohistochemistry at present; in the future, spatial transcriptome and proteome analysis
Biomarkers of TMMs	With RNA sequencing, ALT can be identified by a combination of low hTERT and high telomeric repeat containing RNA (TERRA) expression. ⁸⁷⁻⁸⁹ If present, DNA mutations in <i>ATRX</i> and <i>DAXX</i> are almost always associated with ALT activity. However, there are ALT-positive tumors that do not have these mutations. Two investigational ALT-specific assays are ALT-associated PML bodies and c-circles. ⁸⁷⁻⁸⁹ Determination of ALT-associated PML bodies can use FFPE material, but interpretation is subjective and limited by expertise. C-circle assays present various challenges to clinical implementation: (1) ssDNA is unstable at room temperature, (2) fresh-frozen material is required, (3) the tumor material must remain frozen, and (4) the intensity of signal depends on tumor content. ⁹⁰⁻⁹² Real-time PCR assays are being developed to more reliably and reproducibly quantify c-circles	There is no international consensus for ALT determination, and a combination of techniques demonstrating low hTERT expression and an ALT-specific assay should be used
ctDNA	Collection of ctDNA is crucial and should be mandatory as a complementary assay to tissue sequencing; results should also be considered in cases where biopsy is unavailable. The amount of detectable ctDNA may vary across tumor types, with neuroblastoma being the greatest, ⁹³ potentially limiting its applicability. Detection of allelic imbalance can be challenging with low tumor fraction in cell-free DNA ⁹⁴⁻⁹⁸ ; however, if there are sufficient ctDNA and a high allele frequency of a relevant mutation, ctDNA is feasible and reliable. By contrast, if a very low allelic fraction of a point mutation is detected, the interpretation can be complicated when the actual tumor fraction is not known	Collection of ctDNA is high priority in view of (1) relative ease of collection, (2) ability to collect serial samples, and (3) reflecting the totality of the disease
DNA mutational signature	DNA mutation signatures of HRR deficiency (eg, HRD BRCAness) have been developed through WES or WGS. Data have recently reported the low prevalence of Signature 3 (COSMIC v3) ^{90,99} in pediatric tumors	These signatures have not been confirmed in the pediatric clinical setting
Genomic instability signatures	There are several assays to interrogate genomic instability. ¹⁰⁰⁻¹⁰³ The MyChoice CDx HRD from Myriad Genetics determines a genomic instability score. The Foundation Medicine T5 NGS LOH test only examines loss of heterozygosity and FMI HRD-Sig. In addition, WGS or WES data can be processed by open-source tools, such as scarHRD, to generate a genomic instability score	The utility of these assays for ATRi has not been fully explored nor validated in pediatric populations
Multigene expression signatures	At the RNA level, multigene expression signatures have potential promise as dynamic biomarkers of HRR function and PARPi sensitivity. ¹⁰⁴⁻¹⁰⁶	Highly variable, experience is based on PARP, not ATRi, and no signature has been validated in pediatrics

Abbreviations: ALT, alternative lengthening of telomeres; ctDNA, circulating tumor DNA; FMI, Foundation Medicine Inc; HRD, homologous recombination repair deficiency; HRR, homologous recombination repair; hTERT, human telomerase reverse transcriptase; LOH, loss of heterozygosity; PARP, poly(ADP-ribose) polymerase; PARPi, PARP inhibitors; PCR, polymerase chain reaction; PML, promyelocytic leukemia; ssDNA, single-stranded DNA; TMMs, telomere maintenance mechanisms; WES, whole-exome sequencing; WGS, whole-genome sequencing.

The acute toxicity profile of combinations is very likely to be the same in older children as in adults, but long-term toxicity is difficult to assess.

There are many potential combination partners, which are supported by preclinical investigations (Table 3):

- Novel agents

- *PARPi*. There is a strong biological rationale for combinations of PARP and ATRi: (1) PARPi create PARP-DNA adducts which stall replication forks; (2) ATR catalytic inhibition interferes with the repair of single-strand breaks, leading to replication fork damage that requires HR repair^{112,113}; and (3) ATRi may delay or overcome resistance to PARPi.^{48,114-117} Preclinical data,

including in neuroblastoma, suggest that the combined inhibition of ATR and PARP is synergistic at sublethal doses.^{6,114,115} Concomitant administration of an ATR and PARPi in vitro had a better sustained efficacy than sequential administration.^{104,118} In neuroblastoma cells, there is enhanced sensitivity to a PARPi, which may correlate with DDR and replication stress alterations, and this effect is further increased by inhibition of ATR.⁶

- *PARP 1 selective inhibitors* are attractive as they hold promise for reducing myelosuppression and increasing the therapeutic window when used in combination, but this class of agents is early in development.^{119,120}
- *ALK inhibitors specific to ALK-aberrant neuroblastoma*. In *ALK*-mutated, *MYCN*-amplified models, *ALK* signaling

TABLE 3. Potential Indications for ATR Inhibitors in Children

Indication	Combination
Molecularly defined indications	
ALK-mutated neuroblastoma	ALK + ATR ^{109,110}
MYCN-amplified neuroblastoma	Aurora kinase A + ATR ^{35,111}
Histology-defined populations	
<i>Replication stress</i>	PARP + ATR
EWS fusions, desmoplastic round cell tumor clear cell sarcoma ²	ADC + ATR
PAX3-FOXO1 fusion ⁷	Topoisomerase I inhibitors + ATR
Neuroblastoma ⁶	
<i>Alternative lengthening of telomeres</i> ⁶⁵⁻⁶⁷	PARP + ATR
Osteosarcoma ⁸⁸	ADC + ATR
Neuroblastoma	Topoisomerase I inhibitors + ATR
ATR mutations (eg, osteosarcoma, neuroblastoma, medulloblastoma, high-grade glioma)	PARP + ATR ADC + ATR Topoisomerase I inhibitors + ATR

NOTE. *ATM* mutation or protein loss/11q loss^{45,46} could be an indication, but data are not available, and there are methodological issues with measurement of *ATM* mutation or protein loss.

Abbreviations: ADC, antibody drug conjugate; ALK, anaplastic lymphoma kinase; PARP, poly(ADP-ribose) polymerase.

leads to phosphorylation of ATR and CHK1 to support an effective DDR, suggesting that combined ALK/ATR inhibition would be superior to monotherapy. In *in vivo* models, ATR inhibitor monotherapy resulted in a robust initial response, but eventual relapse; however, combinations of ALK inhibitors and ATR inhibitors resulted in a durable response.^{109,121}

- **Aurora A kinase (AURKA) inhibitor (in MYCN-amplified neuroblastoma).** During the S phase, MYCN protein is stabilized through its physical interaction with AURKA. Pharmacologic inhibition of AURKA is known to inflict transcription-replication stress. Combined inhibition of AURKA and ATR induces extensive tumor-specific apoptosis and tumor regression in MYCN-amplified transgenic mouse models.^{110,111}
- **Cytotoxic chemotherapy—Topoisomerase I inhibitors,** low-dose cisplatin, and gemcitabine are known to synergize with ATRi.^{35,122,123}
- **Antibody drug conjugate (ADC) linked to a topoisomerase I inhibitor payload.** Here, the delivery as an ADC should reduce the toxicity of topoisomerase I inhibition. Trials in adults with HER2 ADCs may be very informative, and new dose-limiting toxicities, for example, lung damage, may be important.^{124,125}
- **Combination with WEE1 inhibition and ribonuclease reductase inhibitors** are still early in development and may be limited by a potential feedback loop with DNA-PK for CHK1 activation.²⁵

In conclusion, early phase trials in pediatrics of ATRi and ALK inhibitors (in ALK-aberrant neuroblastoma), PARP 1 selective inhibitors (in Ewing sarcoma, rhabdomyosarcoma, and other malignancies), and AURKA inhibitors (in

MYCN-amplified neuroblastoma) are required to determine the safety profile and the recommended phase II dose and determine whether there are early signals of activity. Development of these combinations would address current unmet needs.

ATR inhibition influences the immune system and the tumor microenvironment,^{109,126,127} potentially leading to further combinations. Specifically, ATR inhibition stimulates the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway, recruits T cells (including antigen-specific CD8⁺ T cells), and augments the antitumor immune response of PD-L1 blockade. Scheduling of ATRi might have important effects on activity, for example, a short (3 day) course of ATR inhibition, when given with radiotherapy, generates an antigen-specific CD8⁺ T-cell response, but this effect is not observed with a more prolonged course of ATR inhibition.¹²⁶ This observation should be considered when designing clinical trials.

EARLY PHASE TRIAL DESIGN:

The need for limited monotherapy trials: Strong biological rationale and clinical experience suggest that multiple agents will be more efficacious than monotherapy for most diseases.¹²⁸ Preclinically, in Ewing sarcoma¹²⁹ and rhabdomyosarcoma,⁷ single-agent ATR inhibition only resulted in slowing of growth, and in adult patients, complete loss of *ATM* was required to achieve clinically relevant synthetic lethality. Molecular profiling from nonresponders to olaparib and irinotecan in arm D of ESMART suggested possible primary resistance to this combination and the potential need for additional ATR inhibition.¹³⁰

It is proposed that early phase trials incorporate limited monotherapy evaluation in a small number of patients to fulfill any regulatory requirements during the initial cycle, to be followed swiftly by a combination in the second cycle.¹²⁸ The brief monotherapy evaluation can characterize dose, pharmacokinetics, and toxicity, whereas the intention of the combinatorial approach is to accelerate drug development and maximize the potential for patient benefit. Limited data on monotherapy in children can be complemented with data extrapolated from adults. The results of the phase I/II study of single-agent elimusertib should help inform subsequent studies of ATR.⁷⁶ Although scientifically and statistically robust, a randomized trial of an ATRi versus an ATRi and another product is likely not feasible.¹³¹ In most instances, however, the dose of the ATRi in combination will likely be lower than the monotherapy dose because of potential overlapping toxicity. For example, in arm N of ESMART, the cerasertib and olaparib doses are lower than the maximal tolerated dose of each agent alone but optimized for more continuous exposures and based on adult dosing.⁷¹ Notably, there have been late responses to ATRi seen in pediatric trials and this agrees with studies in adults.

GENERAL STRATEGY

Going forward, there is strong support for the approach taken in ESMART, which includes combination therapy and enrichment for patients with biomarker-positive tumors, but broader eligibility criteria.^{70-72,128} There are some histologies (neuroblastoma and translocation-driven sarcomas) that appear to be enriched for susceptibilities to DDR inhibitors. There is strong preliminary evidence that there will not be a single biomarker but rather a constellation of molecular findings, and there are disadvantages to being too stringent in restricting investigations of biomarkers. Analyses should be iterative, and clinical data from studies in adults or pediatric patients and early observations, for example, 11q loss in neuroblastoma, should inform future prospective biomarker selection for trial eligibility. One approach could be to use an adaptive clinical trial platform design that uses a Bayesian statistical model, monitoring response and enriching for the relevant biomarkers as the trial progresses, as has been done in the I-SPY trials.¹³² Optimal biomarkers may vary according to the combination of agents and disease subtypes. The adaptive clinical trial platform could be within a master protocol (basket trial). Trials of single ATRi with multiple combination agents are proposed. One of the many strengths of an industry-supported, academic-sponsored platform trial is that assets from different pharmaceutical companies can be included. The platform trial would be conducted to very high-quality standards with intent to file, that is, fit for filling a pediatric investigation plan and early input sought from regulators. It is important to design a complex clinical trial around its primary objective, which should be initially exploratory and hypothesis-generating. Once the trial has generated data, there should be further discussions with regulators on the necessary data needed toward confirmatory evidence (fit for market authorization).¹³³ With the same eligibility criteria, end points, and methods of patient monitoring, contemporaneous nonrandomized arms can serve as controls.

The current challenge is that despite there are many potential biomarkers, there is difficulty in defining the optimal pediatric screening assay. From an industry viewpoint, defining the population is a critical decision that is often made early. There is a concern that if the approach is too broad, a meaningful response may be diluted. One potential approach is to commence with narrower populations and, if results are encouraging, allow inclusion to become broader. Another strategy is a tissue-agnostic multilayered approach including (1) ATM loss defined by immunochemistry or 11q loss, (2) gene fusions, and (3) ALT by ATRX loss or c-circle assay. However, these groupings are not mutually exclusive as biomarkers might overlap, for example, *ATRX* and 11q loss. In addition, combinations designed to elicit synthetic lethality or enhance exogenous DNA damage are different mechanistically and will probably have different biomarkers. The major challenge with a histology-agnostic approach is the current lack of established biomarkers. The key will be to evaluate a biomarker both in biomarker-positive and

biomarker-negative populations and then revise the biomarker hypothesis. As such, an industry-supported, academic-sponsored international platform trial that provides clinical trial data that can be used for licensing purposes—fit for filing—would be a highly efficient approach to evaluate ATRi in the pediatric population. These concepts were discussed and endorsed at a recent meeting in the Childhood Cancer Academic-Industry Collaborative: Platform Trials of the Multi-Regional Clinical Trials Center (MRCT Center), Brigham, and Women's Hospital and Harvard University, in Boston.¹³³

OVERALL PLAN FOR DEVELOPMENT

In very rare patient populations, overlap of clinical studies evaluating similar drugs for the same clinical indications needs to be avoided; otherwise, the same hypothesis will be addressed repeatedly, knowledge will not be advanced, and trials will fail to recruit. Clinical trials, driven by regulatory requirements, should fulfill patient needs.¹³⁴⁻¹³⁶ A coordinated and integrated drug development strategy is required when developing multiple products of the same class in a rare group of children.¹³⁴⁻¹³⁶ One approach is to encourage industry partners to develop different products within the same class for different indications. For example, there is strong preclinical evidence for combinations of ATRi with PARP, ALK, and aurora kinase A inhibitors in neuroblastoma. One proposal is that the academic early phase cooperative groups help guide companies to potential nonoverlapping indications. For example cooperative groups, suggest one company evaluates a combination with PARPi, another a combination with an ALK inhibitor and a further with an aurora A kinase inhibitor. Another approach is a focused and sequential development. For this approach to work, there should be agreement by all involved (industry and academia) through external agencies, on which product(s) based on current evidence should be advanced first for regulatory approval, without delay. The sequence (based on scientific arguments) for other available or emerging products should be agreed upon, and as soon as the development of the first product is completed (either because of futility or efficacy), other products should already be prepared to be evaluated.^{18,135} Academic-sponsored platform trials, such as ESMART, ComboMATCH, and Global Study of Novel Agents in Paediatric and Adolescent Relapsed and Refractory B-cell Non-Hodgkin Lymphoma (Glo-BNHL),^{69,71,128,137-139} can evaluate different combinations of different products from different companies.

Despite recent or impending major regulatory developments, the challenge remains that pediatric drug development is driven by adult indications. There is reluctance for companies to evaluate a new class of medicinal products in pediatrics until they have identified an adult indication and started the process to submit a New Drug Application or Biologics License Application with a route forward to market authorization. Given the legislative mandate for pediatric evaluation of compounds directed at a molecular target

which is relevant to the growth or progression of a pediatric cancer, regulators should be encouraged when there is intense investigator interest based on evidence to entertain discussions with industry sponsors about possible pediatric investigation as early as possible in the development timeline of appropriate molecules, rather than limiting pediatric discussion plans contingent upon a decision for the adult indication for which they plan to seek approval. Importantly, proof of concept from adult studies may not be relevant to pediatric studies as the mechanism of action may be different. Currently, this is the situation with ATRi. For example, there are a strong mechanism of action and pre-clinical evidence supporting combining ATRi with ALK inhibitors in *ALK/MYCN*-aberrant neuroblastoma, where there is an unmet need for new therapies. Yet, companies are reluctant to provide ATRi for these trials as there is no adult indication for a market authorization. To enhance the early evaluation and development of ATRi in children and make this attractive to industry, early phase investigation clinical trials should be conducted in regulatory-approved, academic-sponsored, industry-supported, platform trials, which have been designed so that data produced can be used for regulatory purposes. In Europe, the European Medicines Agency (EMA) supports this via scientific advice, and such a platform can be used in a pediatric investigation plan to generate evidence supporting clinical proof of concept

(eg, early go/no go decision making) such that only the most promising product(s) move toward evidence generation, supporting a registration.¹⁴⁰ An example is the Glo-BNHL study where the EMA, not part of Glo-BNHL, provided qualification advice with a letter of support on its website on the methodological and scientific aspects, endorsing the trial. This has facilitated the development of products for B-cell lymphoma, and companies have used the platform for regulatory purposes. Such a platform could provide benefits and efficiencies to industry, with a clear value proposition supporting development efforts.

To rapidly advance knowledge, protect patients, and avoid redundancy (which can hinder enrollment because of scarcity of patients), global coordination of early development and late development programs across multiple agents in the same class is necessary. The objective is to drive timely pediatric development through scientific, data-driven approaches that maximize the potential to address unmet medical needs, generate robust clinical evidence, and elucidate a biomarker hypothesis. Class, product and combination prioritization are needed to ensure that patients enrolling in trials have the best chance of benefiting from investigational treatment. A framework to support integrated development strategies of new products like the ATRi across sponsors would be very beneficial.

AFFILIATIONS

¹Department of Cancer and Genomic Sciences, School of Medical Sciences, College of Medicine and Health, University of Birmingham, Birmingham, United Kingdom

²Department of Paediatric Oncology, Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom

³Memorial Sloan Kettering Cancer Centre, New York, NY

⁴ACCELERATE, Brussels, Belgium

⁵Genentech, A Member of the Roche Group, South San Francisco, CA

⁶Institute of Cancer Research, Sutton, United Kingdom

⁷Newcastle University Centre for Cancer, Newcastle-upon-Tyne, United Kingdom

⁸Department of Paediatrics, The Hospital for Sick Children, University of Toronto, Ontario, Canada

⁹Bayer HealthCare Pharmaceuticals, Inc, Whippany, NJ

¹⁰Department of Biomolecular Medicine, Ghent University, Ghent, Belgium

¹¹Cancer Research Institute Ghent (CRIG), Ghent, Belgium

¹²Department of Oncology, St Jude Children's Research Hospital, Memphis, TN

¹³The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

¹⁴Merck Serono Ltd, Feltham, United Kingdom, an affiliate of Merck KGaA, Darmstadt, Germany

¹⁵Charité—Universitätsmedizin, Berlin, Germany

¹⁶Princess Máxima Center for Pediatric oncology, Utrecht, the Netherlands

¹⁷University Medical Center Utrecht (UMCU), Utrecht, the Netherlands

¹⁸Hopp Children's Cancer Center (KITZ), Heidelberg, Germany

¹⁹German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany

²⁰AstraZeneca, Cambridge, United Kingdom

²¹Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

²²EMD Serono, Billerica, MA

²³Hopp Children's Cancer Center Heidelberg (KITZ)/Division of Pediatric Neurooncology, DKFZ/KITZ, Clinical Trial Unit and Childhood Brain Tumors, National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany

²⁴National Cancer Institute, Bethesda, MD

²⁵Gustave Roussy Cancer Centre, Paris, France

CORRESPONDING AUTHOR

Andrew D.J. Pearson, MBBS, MD, DCH; e-mail: andy1pearson@btinternet.com.

DISCLAIMER

Andrew McDonough B+ Foundation for financial support of ACCELERATE.

EQUAL CONTRIBUTION

S.A.G., J.G.-B., A.D.J.P., and M.V.O. are joint first authors.

AUTHOR CONTRIBUTIONS

Conception and design: Susanne A. Gatz, Julia Glade-Bender, Andrew D.J. Pearson, Michael V. Ortiz, Sarah Cohen-Gogo, Esther De La Cuesta, Teresa de Rojas, Elizabeth Fox, Ioannis Gounaris, Anton George

Henssen, Alberto Pappo, Gregory K. Pennock, Emily K. Slotkin, Malcolm Smith, Brenda J. Weigel, Gilles Vassal

Administrative support: Alberto Pappo

Provision of study materials or patients: Lou Chesler, Alan Lau, Frank Speleman

Collection and assembly of data: Andrew D.J. Pearson, Michael V. Ortiz, Ronald Bernardi, Sarah Cohen-Gogo, Teresa de Rojas, Kaat Durinck, Anton George Henssen, Meredith Irwin, Alan Lau, Frank Speleman

Data analysis and interpretation: Susanne A. Gatz, Julia Glade-Bender, Andrew D.J. Pearson, Michael V. Ortiz, Ronald Bernardi, Lou Chesler, Steve Clifford, Sarah Cohen-Gogo, Teresa de Rojas, Kaat Durinck, Sara Federico, Elizabeth Fox, Sally George, Ioannis Gounaris, Anton George Henssen, Meredith Irwin, Marcel Kool, Karsten Nysom, Stefan M. Pfister, Nicole Scobie, Frank Speleman, Elizabeth A. Stewart, Brenda J. Weigel

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Susanne A. Gatz

Consulting or Advisory Role: Amgen, Gilead Sciences, AstraZeneca

Research Funding: AstraZeneca (Inst), GlaxoSmithKline (Inst), Bayer (Inst), AstraZeneca (Inst)

Julia Glade-Bender

Consulting or Advisory Role: Jazz Pharmaceuticals

Research Funding: Eisai (Inst), Lilly (Inst), Loxo (Inst), Roche/Genentech (Inst), Bayer (Inst), Jazz Pharmaceuticals (Inst), Jazz Pharmaceuticals (Inst), Merck (Inst)

Patents, Royalties, Other Intellectual Property: Patent on a T lymphoblastic lymphoma cell line, CUTLL1

Travel, Accommodations, Expenses: Amgen (Inst), Eisai (Inst)

Uncompensated Relationships: SpringWorks Therapeutics, Bristol Myers Squibb, Merck, Eisai, Pfizer

Open Payments Link: <https://openpaymentsdata.cms.gov/physician/708514>

Andrew D.J. Pearson

Honoraria: Norgine

Consulting or Advisory Role: Norgine

Ronald Bernardi

Employment: Genentech/Roche, Exelixis

Stock and Other Ownership Interests: Roche/Genentech, Exelixis

Lou Chesler

Consulting or Advisory Role: Abbvie

Esther De La Cuesta

Employment: Bayer

Stock and Other Ownership Interests: Bayer

Travel, Accommodations, Expenses: Bayer

Sally George

Travel, Accommodations, Expenses: Recordati

Ioannis Gounaris

Employment: Merck Serono

Stock and Other Ownership Interests: Novartis, Alcon, Sandoz

Anton George Henssen

Stock and Other Ownership Interests: Econic Biosciences

Consulting or Advisory Role: Econic Biosciences

Research Funding: Bayer

Alan Lau

Employment: AstraZeneca

Stock and Other Ownership Interests: AstraZeneca

Patents, Royalties, Other Intellectual Property: I am named on patents filed by AstraZeneca plc., but do not receive royalties

Karsten Nysom

Consulting or Advisory Role: Lilly, Ipsen

Alberto Pappo

Honoraria: Bayer, Roche, Lilly, Pfizer

Consulting or Advisory Role: Merck, Loxo/Bayer, EUSA Pharma, Debbio, Lilly, Pfizer

Gregory K. Pennock

Employment: EMD Serono

Stefan M. Pfister

Leadership: PMC, University Hospital Essen Westdeutsches Tumorzentrum

Stock and Other Ownership Interests: Heidelberg Epignostix

Consulting or Advisory Role: BioSkrub

Research Funding: Lilly (Inst), Bayer (Inst), Roche (Inst), PharmaMar (Inst), Pfizer (Inst), AstraZeneca (Inst), Janssen & Janssen (Inst), Servier (Inst), Sanofi (Inst), Amgen (Inst)

Patents, Royalties, Other Intellectual Property: Patent on utilizing DNA methylation profiling for tumor classification, patent using nanopore sequencing for rapid tumor diagnostics, Rapid comprehensive adaptive nanopore-sequencing of CNS tumors, a proof of concept study, Method for the detection of a premalignant lesion in a subject

Emily K. Slotkin

Consulting or Advisory Role: Guidepoint Global, Inhibrx

Research Funding: Lilly (Inst), Esperas Pharma

Gilles Vassal

Consulting or Advisory Role: AstraZeneca, Pfizer, Abbvie, Merck, Daiichi Sankyo/Astra Zeneca, SERVIER

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

We very gratefully acknowledge Andrea Demadonna and Beatriz Martinez for their dedication, efficiency, enthusiasm, and very substantial work and Gynette Cook for preparation of the manuscript.

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