



Published in final edited form as:

Ann Surg. 2017 September ; 266(3): 470–478. doi:10.1097/SLA.0000000000002356.

Results of the first Prospective Multi-Institutional Treatment Study in Children with Bilateral Wilms Tumor (AREN0534): A report from the Children's Oncology Group

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Abstract

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

The authors have NO conflicts of interest

Objective—The Children's Oncology Group (COG) study AREN0534 aimed to improve EFS and OS while preserving renal tissue by intensifying pre-operative chemotherapy, completing definitive surgery by 12 weeks from diagnosis, and modifying post-operative chemotherapy based on histologic response.

Summary Background Data—No prospective therapeutic clinic trials in children with bilateral Wilms tumors (BWT) exist. Historical outcomes for this group were poor and often involved prolonged chemotherapy; on NWTS-5, 4-year event-free-survival (EFS) for all children with bilateral Wilms tumor was 56%.

Methods—Patients were enrolled and imaging studies were centrally reviewed to assess for bilateral renal lesions. They were treated with 3-drug induction chemotherapy (vincristine, dactinomycin and doxorubicin) for 6 or 12 weeks based on radiographic response followed by surgery and further chemotherapy determined by histology. Radiation therapy was provided for post-chemotherapy stage III and IV disease.

Results—189/208 patients were evaluable. 4-year EFS and OS were 82.1% (95% CI: 73.5%-90.8%) and 94.9% (95% CI: 90.1%-99.7%). 23 patients relapsed and 7 had disease progression. After induction chemotherapy 163/189 (84.0%) underwent definitive surgical treatment in at least one kidney by 12 weeks and 39% retained parts of both kidneys. Surgical approaches included: unilateral total nephrectomy with contralateral partial nephrectomy (48%), bilateral partial nephrectomy (35%), unilateral total nephrectomy (10.5%), unilateral partial nephrectomy (4%) and bilateral total nephrectomies (2.5%).

Conclusions—This treatment approach including standardized three-drug preoperative chemotherapy, surgical resection within 12 weeks of diagnosis and response and histology-based post-operative therapy improved EFS and OS and preservation of renal parenchyma compared to historical outcomes for children with BWT.

Introduction

The outcome for patients with unilateral favorable histology Wilms tumor is excellent with event free survival (EFS) greater than 85%.¹⁻⁴ However, patients with bilateral Wilms tumor (BWT) have significantly poorer results. On National Wilms Tumor Study 5 (NWTS-5), the four-year EFS estimates for all patients with BWT was 56% (95% CI: 44.8% -66.6%); for patients with favorable histology, focal anaplastic and diffuse anaplastic BWT, four-year estimates were 65% (with retention of heterozygosity at 1p), 76% and 25%, respectively.⁵⁻⁷ The Société Internationale d'Oncologie Pédiatrique (SIOP) reported a 10-year overall survival (OS) of just 69% for patients with synchronous BWT treated with either preoperative radiotherapy and/or chemotherapy.⁸⁻¹⁰ Both also reported several late deaths from disease recurrence more than 3 years after diagnosis.¹¹

End stage renal disease (ESRD) rates in children with BWT are also higher as compared to those with unilateral tumors.^{12, 13} The 20-year cumulative incidence of ESRD for survivors of unilateral WT was less than 1%; (0.6% in non-syndromic children), whereas the rate in children with BWT was 12% and much higher in children with genetic syndromes such as Denys Drash Syndrome (DDS, 75%) or the Wilms Tumor-Aniridia-Genitourinary Malformation-Mental Retardation Syndrome (WAGR, 50%). In the patients with BWT who

had ESRD within 5 years after treatment the cause was a second nephrectomy in (30/32) 94% whereas it was only 50% of cases in the children who had ESRD after 5 years.¹²

Several factors are thought to contribute to the unfavorable outcomes in patients with BWT.¹⁴⁻¹⁶ These include under-staging resulting in under-treatment, delay in local disease control and increased incidence of anaplasia. Biopsy, both open wedge and core needle methods, often fails to identify focal or diffuse anaplastic histology.¹⁶ This has resulted in some patients being treated for extended periods of time without effect. Shamberger and colleagues showed that children with BWT received chemotherapy regimens that lasted between 37 and 50 weeks exposing them to both acute and long-term toxic events but with no effect on renal preservation or overall treatment outcome.¹⁴ It has also been shown that in some patients a tumor may not change in size on radiographic imaging or may slightly increase after chemotherapy because the tumor had differentiated or undergone rhabdomyomatous changes.¹⁷ While these patients have excellent survival, their tumors will not regress in size with further chemotherapy.

The success in treating unilateral WT has been the direct result of several large controlled trials by the research consortia in North America, the United Kingdom and Europe.³ These studies have defined surgical, radiotherapy and chemotherapy regimens in other stages of WT. However, no prospective clinical trial with defined treatment regimens for BWT has been reported.

To improve outcomes for children with BWT, the Children's Oncology Group (COG) opened study AREN0534 in 2009.¹⁸ The primary aims related to BWT were to improve four-year event-free survival (EFS) to 73% for patients with BWT, to prevent complete removal of at least one kidney in 50% of patients with BWT by using pre-nephrectomy three-drug chemotherapy with vincristine, dactinomycin and doxorubicin, and to have at least 75% of children with BWT undergo definitive surgical treatment by 12 weeks after initiation of chemotherapy. The purpose of this paper is to present the results of these primary aims.

Methods Section

Study

The COG study AREN0534, "*Treatment for Patients with Bilateral, Multi-centric, or Bilaterally-Predisposed Unilateral Wilms Tumor*" had three arms: one for treatment of patients with BWT, one for patients with unilateral tumors at high-risk for metachronous disease or multi-centric tumors, and one for patients with diffuse hyperplastic perilobar nephro blastomatosis (DHPLN).¹⁸ This report presents the results of children with BWT.

Enrollment and Eligibility

Local institutional review board or research ethics board approval of this study was obtained prior to enrolling patients. Patients had to be < 30 years old at the time of initial diagnosis and had to have synchronous bilateral renal masses 1 cm or greater on radiographic imaging. All patients were first enrolled on the COG biology and classification study AREN03B2. Patients could enroll without a diagnostic biopsy (the majority), with a diagnostic biopsy or after definitive surgery. Before enrollment on the therapeutic study AREN0534, real-time

central review of diagnostic imaging, pathology (if obtained) and operative notes confirmed the status of BWT.¹⁹⁻²¹ Enrollment was required within 14 days of diagnosis or 7 days after starting therapy. Due to the difficulty of distinguishing WT from a nephrogenic rest based on imaging studies and percutaneous biopsies, the guideline was established that a child with a single renal lesion 1 cm or greater in size in the contralateral kidney or multiple lesions (of any size) in the contralateral kidney should be treated on the synchronous BWT stratum. Patients with an isolated lesion less than 1 cm in the contralateral kidney should be treated by nephrectomy with post-operative therapy based on the pathologic findings. These patients could have been enrolled in another therapeutic study.^{18, 22}

Staging

Patients with BWT received both a local stage and an overall disease stage. The final local stage was based on the abdominal tumor burden, whereas the disease stage accounted for the presence of distant metastatic disease. The COG and SIOP staging systems have been well described.²³ The highest local stage is III and disease stage is IV. Patients treated with preoperative chemotherapy without undergoing biopsy were staged according to the staging system used by SIOP.²⁴

Treatment

The overall strategy of the study was to administer pre-nephrectomy chemotherapy with the goal to perform bilateral partial nephrectomies. Initial induction therapy included vincristine, dactinomycin and doxorubicin (regimen VAD) for two cycles three weeks per cycle (dosing and regimen in supplemental files). After six weeks, cross-sectional imaging was performed and a tumor response was assigned for each kidney (see response criteria below). If it was deemed feasible by the local institution to perform bilateral partial nephrectomies, surgery was to be undertaken. If the tumors achieved a partial response (PR) but were not yet amendable to bilateral partial nephrectomy, chemotherapy was continued for another two cycles. If tumors in either kidney did not achieve a PR, bilateral open renal biopsies were performed to assess the histologic reason for non-responsiveness. After four cycles of VAD (12 weeks), repeat cross sectional imaging was performed and definitive surgery was required.

Radiology Response Criteria—Criteria used to assess tumor response included reduction in size and the ability to perform a nephron-sparing procedure. Response was based on the Response Evaluation Criteria in Solid Tumor (RECIST 1.1) modified to include 3 lesions per kidney.²⁵ Target lesions were defined as lesions greater than 10 mm within the kidney. If multiple target lesions were present at least three of them were described. Overall response was not modified by extra renal target lesions nor non-target disease. Each kidney was assessed separately. PR was defined as at least a 30% decrease in the sum of the diameters of target lesions (which equals to a 50% decrease in volume), taking as reference the baseline sum diameters. Progressive disease (PD) was defined as at least a 20% increase in the sum of the diameters of target lesions and stable disease (SD) as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Chemotherapy—Adjuvant therapy was based on tumor stage and histologic response after either six or 12 weeks of chemotherapy. Table 1 describes the chemotherapy regimens and table 2(A, B, C) shows the treatment strategy for patients with BWT at initial diagnosis, week 6 and week 12 (dosing in supplemental files). The final risk stratification based on post-surgery and chemotherapy pathology used by SIOP.²³ The details of the chemotherapy regimens have been used in prior studies, however in the recent studies the regimens changed with respect to mg/kg versus mg/m² dosing (VAD, EE4A, DD4A, I and revised UH-1 (supplemental files)).²⁶⁻²⁸ Treatment was based on the kidney with the highest stage. For example, if one kidney was stage I and the other stage III, chemotherapy treatment was based on the stage III.

Radiation Therapy—For favorable histology tumors that were classified as abdominal stage III, flank radiotherapy with 10.8 Gy was utilized (19.8 Gy for 16 years old). A difference from other COG studies for unilateral Wilms tumor was that although needle or biopsies prior to chemotherapy were considered as a criterion for stage III, these patients were not mandated to receive flank radiation therapy if there were no other reasons for stage III designation. Patients requiring whole abdomen irradiation due to preoperative tumor rupture, peritoneal metastases or a large intraoperative tumor spill affecting areas outside the tumor bed as determined by the surgeon received 10.5Gy. A boost of 10.8 Gy was given to patients with residual disease. For patients with stage I-II anaplastic histology, radiation doses were the same as for favorable histology. However, higher doses (19.8 Gy flank or 10.5 Gy whole abdomen with a 9 Gy boost to the flank for patients requiring whole abdomen irradiation) were provided to patients with stage III diffuse anaplastic histology. Patients 12 months old requiring whole abdomen XRT did not receive the boost to the flank. All patients with stage IV disease with pulmonary metastasis received whole lung irradiation to a dose of 12 Gy (10.5 Gy for patients < 12 months old).

Statistical Considerations

The study was monitored by an independent data safety monitoring board. A target accrual of 234 patients was required to enroll a minimum of 115 eligible patients with favorable histology BWT without blastemal features to meet the study's statistical considerations. This minimal sample size provided 80% power (testing [using the two-sample log-rank test] at the 5% level of statistical significance [1-sided]) to detect about a 43% reduction in the risk of failure in non-blastemal, favorable histology BWT (relative failure rate 0.57:1.00, corresponding to an increase in 4-year EFS to about 80%). Interim efficacy monitoring was done at 25%, 50% and 75% of the expected information using an O'Brien-Fleming boundary (truncated at 3 standard deviations).²⁹ The other histological subsets were too small to detect definitively an improvement in their EFS and are presented using descriptive statistics. Statistical methods used included Fisher exact test and Kaplan-Meier estimates of the OS and EFS curves.³⁰

Results

Patient characteristics

The study opened in July 2009 and closed in June 2015. Two hundred and forty-nine patients were enrolled and 7 were declared inevaluable (1 failure to sign proper consent, 2 with incorrect pathology, 4 went off study because of investigator choice). There were 99 males and 143 females. Eighty percent of children presented before 48 months. 21.1% of the patients had a genetic syndrome as an underlying diagnosis. There were nine children with hemi-hypertrophy, 7 Beckwith-Wiedemann Syndrome (BWS), 6 with WAGR syndrome and 3 with DDS and 16 with an isolated anomaly. One hundred and ninety-five enrolled on the BWT strata, of which 163 had non-blastemal type, 13 had blastemal-type and 19 unknown post-chemotherapy histology. Five of 195 were declared inevaluable due to protocol violations related to chemotherapy delivery and one was excluded because the patient had rhabdoid pathology. Median follow-up was 3.75 years. Twenty-six had at least one kidney with anaplasia, 9 had focal anaplasia and 17 had diffuse anaplasia. After induction chemotherapy and surgery, the local stage distribution (based on the kidney with the highest stage) was stage I (37.5%), stage II (14.4%) and stage III (48.1%). Twenty-seven (14.4%) of patients had stage IV disease (pulmonary metastasis in all cases). Thirteen patients had biopsies at time zero.

Tumor Response and Surgical Resection

The tumor response to pre-nephrectomy chemotherapy among 189 patients with BWT using the RECIST criteria for the least responsive tumors was CR (8), PR (121), SD (58) and PD (2). Of the 189 BWT patients, 163 (84.0%) underwent definitive surgical treatment (partial or complete nephrectomy or wedge resection in at least one kidney) by 12 weeks after initiation of chemotherapy (aim 3). Thirty percent of those patients who achieved definitive surgical resection within the 12 week specified aim did so by at the six-week evaluation point. Surgical approaches included: unilateral total nephrectomy with contralateral partial nephrectomy (48%), bilateral partial nephrectomy (35%), unilateral total nephrectomy (10.5%), unilateral partial nephrectomy (4%) and bilateral total nephrectomies (2.5%).

Clinical Outcomes

For the 189 patients with BWT, the 4-year EFS and OS (aim 1) were 82.1% (95% CI: 73.5%-90.8%) and 94.9% (95% CI: 90.1%-99.7%). (Figure 1) There were 23 (12%) relapses with a median time to relapse of 15.21 ± 10.7 (SD) months. 16/167 (9.5%) patients with favorable histology, 7/16 (43%) patients with diffuse anaplastic histology, and 0/7 patients with focal anaplastic histology relapsed. Three relapses occurred at multiple sites, 10 in the remaining kidney(s) alone, seven in the lung alone, one in the liver alone, and two in the abdomen but not the renal fossa. Seven patients progressed on therapy, with one death.

The 4-year EFS and OS according to histology and stage are listed in Table 3. Aim 2 was to prevent complete removal of at least one kidney in 50% of patients with BWT by using pre-nephrectomy 3-drug chemotherapy induction with vincristine, dactinomycin and doxorubicin. Of the 163 who underwent surgery by 12 weeks, 143 had either 6 or 12 weeks of pre-nephrectomy chemotherapy. In this group 61% required complete nephrectomy of at

least one kidney. The 20 other patients either had upfront surgery, surgery due to complications from disease progression or did not tolerate all the cycles of chemotherapy.

Toxicity—There were no grade 5 toxic events reports on the study. There were 4 cases of sinusoidal obstructive syndrome (SOS/VOD) in patients who received regimen DD4A as part of their post nephrectomy therapy. All 4 recovered.

Discussion

The AREN0534 study successfully improved outcomes for patients with BWT, with four-year EFS and OS estimates of 82.1% and 94.16%, as compared to four-year EFS and OS estimates of 56% and 80.8% on NWTS-5.⁷ Several interventions that were implemented on AREN0534 likely contributed to this improvement. First, chemotherapy was tailored according to post-chemotherapy histologic response. Patients with anaplastic and blastemal-type histology received more intensive chemotherapy compared to previous studies. Although the number of patients in each subgroup was small, the results suggest improvement for both favorable and diffuse anaplastic histology. Four-year EFS for favorable histology went from 65% (reported for patients with retention of heterozygosity at chromosome 1p) on NWTS-5 to 84.1% on AREN0534. For diffuse anaplastic histology, four-year EFS went from 25% on NWTS-5 to 58.2% on the current study. The four-year EFS and OS estimates for patients with blastemal-type tumors were 82% and 91%, respectively. Although outcomes in this small group of patients were not assessed on NWTS-5, this result is promising based on the adverse prognostic significance of blastemal type reported on the SIOP studies.³¹ It is possible that the survival estimates on AREN0534 will diminish over time based on observations from prior BWT reports that late relapses were common.¹⁸ However, thus far, the majority of patients relapsed within the first 18 months following diagnosis, which leads us to believe that the excellent outcomes on AREN0534 will persist.

A second intervention implemented on AREN0534 was to decrease the time from diagnosis to surgical resection. Shamberger and colleagues studied 38 patients from NWTS 4 with progressive or non-responsive disease.¹⁴ Preoperative chemotherapy was given for a median of 7 months (range, 2-29 months) before definitive resection. Thirty-six children went on to a second regimen, and of these, 21 children received a third regimen before resection. Ten of the 38 patients lacked histology data and of the remaining 28 patients, 15 had either rhabdomyomatous differentiation, complete necrosis or stromal differentiation. A tumor may also be non-responsive because it has anaplastic histology which may be chemo-insensitive and requires early definitive surgery.¹⁴ Furthermore, a review by the German Society of Pediatric Oncology and Hematology (GPOH) of patients with BWT reported that maximum tumor shrinkage occurred in the first 12 weeks of chemotherapy.³² Based on these considerations, an aim of AREN0534 was for 75% of patients to undergo definitive surgery by 12 weeks. To facilitate earlier surgical resection, all patients received three-drug therapy with vincristine/dactinomycin/doxorubicin rather than starting with just vincristine/dactinomycin and escalating if response was inadequate. The choice to use three drugs was based on data from SIOP studies showing greater tumor shrinkage with three-drug compared to two-drug therapy.²³ Additionally, Paulino et al. found that a three-drug regimen resulted

in a significantly lower relapse rate (8%) compared to a two-drug regimen (42%) in patients with synchronous BWT.³³ AREN0534 exceeded its aim to expedite surgical resection, with 84% of patients having definitive surgical treatment by 12 weeks, with the majority of patients having a PR to chemotherapy.

Compared to patients with unilateral WT, children with BWT have poorer EFS and are at higher risk for later effects such as renal failure.^{11, 12, 34, 35} An overriding goal was to improve EFS balanced with conservation of renal tissue. Our goal was to have at least 50% of patients undergo bilateral nephron-sparing surgery (NSS). We did not reach this threshold, with only 39% successfully treated with bilateral NSS. Davidoff and associates reported a 13-year experience of 42 patients with BWT where he was able to perform bilateral NSS in 92% of patients.³⁶ Comparison of these two study populations without imaging has its limits but the data does suggest that surgeon experience may affect the chance of undergoing NSS. The aim might have been ambitious for a cooperative group-wide study. However, the NSS rate on AREN0534 was greater than what would be expected based on the NSS experience with unilateral WT. Interestingly, the Surveillance, Epidemiology and End Results Program (SEER) from the NCI reports a similar renal sparing rate. SIOP protocols routinely use pre-nephrectomy chemotherapy, with up to 85% of tumors responding to some degree but not necessarily resulting in NSS in unilateral lesions.³⁷⁻³⁹ In the SIOP 2001 study, partial nephrectomies for unilateral WT were permitted if the tumor was polar or non-infiltrating by cross-sectional imaging, but only 3% of the total cases enrolled met these criteria for a partial nephrectomy after pre-nephrectomy chemotherapy.⁴⁰ In patients with bilateral lesions there is an increased effort at renal preservation to avoid renal failure, in contrast with patients with unilateral lesions in which there is much less concern for this issue. A recent technical paper on longitudinal partial nephrectomy by Fuchs to address central renal lesions may also increase the rate of NSS.⁴¹ Other factors that may increase the NSS rates include regionalization of this patients to centers with more experience since these are rare cases and central review that includes technical guidance.

COG renal tumor studies require pathology prior to treatment and study enrollment. This study was an exception because patients could enroll based on imaging alone. The primary reasons to perform a biopsy at initial presentation are to avoid misdiagnosis of Wilms tumor and to detect anaplasia. The rate of misdiagnosis of Wilms tumor is low, between 1.6% to 5.5 % for unilateral renal tumors on SIOP studies.⁴² The rate is estimated to be even lower for bilateral renal tumors because bilateral non-Wilms renal tumors are very uncommon, though rare patients with bilateral rhabdoid tumor and renal cell carcinoma have been reported.⁴³ Regarding the detection of anaplasia, review of data from NWTS 4 showed that needle biopsy failed to detect anaplasia and open biopsy only detected them in 1/3 of cases.¹⁵ On NWTS-5, among 25 patients with bilateral anaplastic Wilms tumor for whom biopsy and nephrectomy histology were available for review, only two (8%) had anaplasia detected in the initial biopsy sample.⁵ Based on these considerations, patients could enroll on AREN0534 based on imaging alone with the caveat that in an unusual clinical situation that may suggest a diagnosis other than Wilms tumor, such as age > 10 years or atypical imaging features obtaining a tissue diagnosis before starting therapy should be considered.

The limitations of the study are inherent in its design. Although the EFS and OS reported here are improved compared to historical reports, this was not a randomized controlled trial and it is therefore difficult to pinpoint which factors played the greatest role in improving outcome. While radiographic criteria were well defined for this study, we cannot be certain that some of the smaller lesions which resolved with neoadjuvant therapy may have been nephrogenic rests. This may have resulted in the inclusion of patients with unilateral WT in the patient cohort. To mitigate this, we excluded patients with lesions less than a centimeter. It is difficult to estimate how this may affect results. In addition, a core or needle biopsy cannot discriminate between a rests ad tumor unless a rim of capsule or normal tissue is included in the sample. Wilms tumors arise from rests that become hyperplastic and can be considered premalignant. We do not feel that the main reason for the improved EFS and OS was that we were treating benign lesions. Second, the study is not yet mature enough to determine the impact of this treatment strategy on late effects such as renal failure or anthracycline toxicity. Patients will be followed for 10 years to track the renal failure rates. Future study will need to also focus on the impact of initial tumor burden to predict response, common factors predicting relapse including biomarkers such as 1q gain or LOH 1p and 16q, impact of novel agents to improve tumor response and directing further strategies toward renal preserving surgery.

The results of AREN0534 indicate that improved EFS and OS for patients with BWT can be achieved with real-time central review of imaging, surgery and pathology, standardized three-drug preoperative chemotherapy, surgical resection within 12 weeks of diagnosis and histology-based post-operative therapy. While the results provide benchmark outcomes for future studies, EFS can be improved and nephron-sparing surgery rates were suboptimal. In future studies, central review incorporating technical guidance for patients with BWT prior to definitive surgical may be useful.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

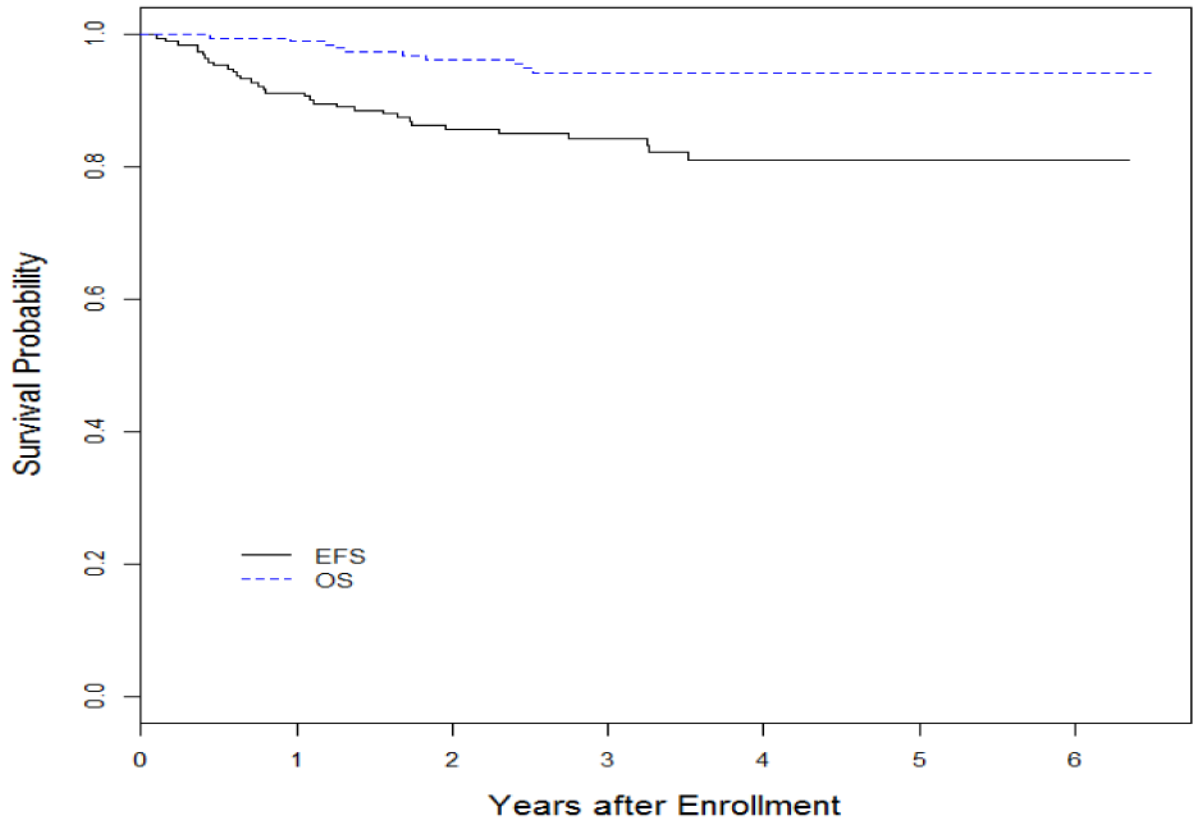
This project was supported by grants CA98543 (Children's Oncology Group Chair's grant) and CA98413 (COG SDC grant) from the National Institutes of Health. U10CA180899

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	4 year EFS	4 year OS
ARENO534	82.1(95% CI: 73.5%-90.8%)	94.9(95% CI: 90.1%-99.7%)

Figure 1. Kaplan Meier Curve ARENO534 Event Free Survival and Overall Survival for all patients and histology

Table 1

Chemotherapy Regimens[~] and Radiation^{*} therapy used for the AREN0534 Bilateral Wilms Tumor Study.

Regimen Name	Chemotherapy Drugs	Duration
VAD (induction therapy only)	Vincristine, dactinomycin, doxorubicin	12 weeks maximum
EE-4A	Vincristine and dactinomycin	19 weeks
DD-4A	Vincristine, dactinomycin, doxorubicin and radiation therapy	25 weeks
Regimen I	Vincristine, dactinomycin doxorubicin cyclophosphamide and etoposide, as well as radiation therapy	28 weeks
Revised UH-1	Vincristine, dactinomycin doxorubicin cyclophosphamide carboplatin, etoposide and radiation	31 weeks

* Flank radiation in most cases.

[~] For specific dosing details please see supplemental files

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Table 2A
Initial Therapy for Bilateral Wilms Tumor at Time of Enrollment

BILATERAL WILMS TUMOR	
	INITIAL REGIMEN
Imaging only (no histology)	VAD
Imaging and biopsy- Reveal favorable histology	VAD
Imaging and biopsy-Reveal diffuse anaplastic Wilms tumor	Revised UH-1
Total or partial nephrectomy at diagnosis Treatment base don the highest assigned risk for either kidney and systemic metastasis	Therapy appropriate for stage and histology

VAD= Vincristine, dactinomycin and doxorubicin

UH-1 = Vincristine, dactinomycin doxorubicin cyclophosphamide carboplatin, and etoposide

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Table 2B
Treatment Regimens for Bilateral Wilms Tumor at Week 6

BWT with COMPLETE RESPONSE AFTER WEEK 6 IMAGING REVIEW		
	Stage	Chemotherapy Regimen
CR by imaging after 6 weeks of chemotherapy, no biopsy done	Localized disease at initial imaging	EE4A
CR by imaging after 6 weeks of chemotherapy	Metastatic disease on initial imaging	DD4A
CR by imaging after 6 weeks of chemotherapy, initial biopsy performed	All Stages	DD-4A for favorable histology Revised UH-1 for anaplastic histology
SURGICAL RESECTION AT 6 WEEKS FURTHER CHEMOTHERAPY IS BASED ON HISTOLOGY OF REMOVED TUMOR AND HIGHEST TUMOR STAGE.		
Histology	Stage	Regimen
Completely necrotic	I-II	EE-4A
Intermediate risk	I	EE-4A
Intermediaterisk	II	DD-4A
Intermediate risk	III-IV	DD-4A+XRT
Blastemal predominant	I	DD-4A
Diffuse anaplastic Wilms tumor	I	DD-4A+XRT
Completely necrotic	III-IV	DD-4A+XRT
Focal anaplastic Wilms tumor	I-III	D-4A+XRT
Blastemal predominant	II	Reg. I
Blastemal predominant	III-IV	Reg. I +XRT
Focal anaplastic Wilms tumor	IV	Revised UH-1+XRT
Diffuse anaplastic Wilms tumor	II-IV	Revised UH-1)+XRT
PARTIAL RESPONSE IN BOTH KIDNEYS BUT BILATERAL PARTIAL NEPHRECTOMY NOT FEASIBLE AT 6 WEEKS. NO SURGERY SHOULD BE PERFORMED. CONTINUE CHEMOTHERAPY.		
Histology	Stage	Regimen
If initial therapy based on imaging only	All stages	6 more weeks of VAD Reevaluate at 12 weeks.
If initial therapy based on imaging and biopsy revealed favorable histology	All stages	6 more weeks of VAD
If initial therapy based on imaging and biopsy revealed anaplastic Wilms tumor	All stages	Continue with Revised UH-1 Reevaluate at 12 weeks.
LESS THAN PARTIAL RESPONSE IN EITHER KIDNEY AT 6 WEEKS. THESE PATIENTS REQUIRE BILATERAL OPEN BIOPSIES.		
6-week biopsy- Reveals anaplasia	All stages	Revised Regimen UH-1 and treat per stage. Reassess at 12 weeks.
6-week biopsy- Reveals blastemal predominant	All stages	Regimen I. Reassess at 12 weeks.
6-week biopsy- All other histology	All stages	Continue VAD for 6 weeks and reassess at 12 weeks.

CR= Complete Response

XRT= Radiation therapy

VAD= Vincristine, dactinomycin and doxorubicin

EE4A= Vincristine and dactinomycin I= Vincristine, dactinomycin, doxorubicin, cyclophosphamide and etoposide

UH-1 = Vincristine, dactinomycin doxorubicin cyclophosphamide carboplatin and etoposide

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Table 2C
Treatment Regimen from Bilateral Wilms Tumor at Week 12

BILATERAL WILMS TUMOR AFTER WEEK 12 IMAGING REVIEW		
	REGIMEN	
IF DEFINITIVE SURGERY HAD OCCURRED AT END OF WEEK 6	Continue with regimen as signed at the end of Week 6.	
AT END OF WEEK 6, THERAPY WAS EITHER CONTINUED CHEMOTHERAPY OR BILATERAL OPEN BIOPSIES WERE PERFORMED. DEFINITIVE SURGERY REQUIRED EITHER PARTIAL OR TOTAL NEPHRECTOMY (UNLESS CR BY IMAGING AT WEEK 12). Treatment will be based on the highest assigned risk for either kidney and systemic metastasis:		
HISTOLOGY	STAGE	REGIMEN
	Complete response	DD-4A
Completely necrotic	I-II	EE-4A(
Completely necrotic	III-IV	DD-4A+XRT
Intermediate risk	I	EE-4A
Intermediate risk	II	DD-4A
Intermediate risk	III-IV	DD-4A+XRT
Blastemal predominant	I	DD-4A
Diffuse anaplastic Wilms tumor	I	DD-4A+XRT
Focal anaplastic Wilms tumor	I-III	DD-4A+XRT
Blastemal predominant	II	Reg. I
Blastemal predominant	III-IV	Reg. I +XRT
Focal anaplastic Wilms tumor	IV	Revised H-1+XRT
Diffuse anaplastic Wilms tumor	II-IV	Revised UH-1+XRT

CR= Complete Response

XRT= Radiation therapy

VAD= Vincristine, dactinomycin and doxorubicin

EE4A= Vincristine and dactinomycin

I= Vincristine, dactinomycin, doxorubicin, cyclophosphamide and etoposide

UH-1 = Vincristine, dactinomycin doxorubicin cyclophosphamide carboplatin and etoposide

Table 3
ARENO534 Outcomes by Post-Surgical Stage and Histology

Histology	N	4-year EFS (95% CI)	4-year OS (95% CI)
FH/FH	163	84.2% (75.2%–93.1%)	97.3% (93.5%–100%)
FH/FH Stage I *	66	85.4% (72.4%–98.5%)	96.87% (90.7%–100%)
FH/FH Stage II *	21	90.23% (69.3%–100%)	100% (100%–100%)
FH/FH Stage III *	59	84.34% (69.7%–99.0%)	97.96% (92.6%–100%)
FH/FH Stage IV *	17	76.5% (34.5%–100%)	94.1% (71.8%–100%)
Both kidneys without blastemal features	140	83.18% (73.2%–92.96%)	977% (93.90%–100%)
At least one kidney with blastemal features	11	81.8% (42.3%–100%)	91% (64.1%–100%)
Anaplasia **			
Diffuse Anaplasia	17	58.2% (15.7%–100%)	68.4% (24.9%–100%)
Focal Anaplasia	8	87.5% (57.18%–100%)	100% (100%–100%)
Stage I *	4	100%	100%
Stage II *	3	No cases	66.67%
Stage III *	15	72.7% (35.5%–100%)	79% (43.2%–100%)
Stage IV *	3	No cases	No cases

* By the highest stage (either favorable histology focal or diffuse anaplasia present)

** In at least one kidney