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Treatment of children with favorable histology Wilms tumor with extrapulmonary metastases: A report from the COG studies AREN0533 and AREN03B2 and NWTSG study NWTS-5

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Carly R. Varela, MD, reports full time employment by Janssen Research and Development at the time of submission, however affiliation at the time of the work for this manuscript was as indicated in above affiliations; Pediatric Specialists of Virginia, Children's National Hospital, and Inova Fairfax Hospital.

Brett Tornwall reports full time employment by Glaukos Corp at the time of submission, however affiliation at the time of the work was Children's Oncology Group Statistics and Data Center.

Eric Gratias, MD, reports full time employment by eviCore healthcare.

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Abstract

Background: Patients with Stage IV Favorable Histology Wilms Tumor (FHWT) with extrapulmonary metastases (EPM) constitute a small subset of FHWT patients. Due to their rarity and heterogeneity, optimal treatment is not well understood. COG protocol AREN0533 assigned patients with FHWT and EPM to intensified chemotherapy, Regimen M, after initial DD-4A chemotherapy. To improve understanding of prognostic factors and best therapies, we reviewed experiences of patients with EPM on AREN0533, as well as on protocols AREN03B2 and NWTS-5.

Methods—Combined outcomes for patients with EPM from NWTS-5, AREN0533 and AREN03B2 were determined. Those treated on AREN0533 were compared to those treated on NWTS-5. Prognostic factors were explored in the pooled cohort.

Results—Forty-seven FHWT patients with EPM enrolled on AREN0533, 37 enrolled on NWTS-5, and 64 were followed only on AREN03B2. The pooled cohort of all 148 patients demonstrated a 4-year EFS of 77.3% (95% CI: 70.8%, 84.4%) and 4-year OS of 88.9% (95% CI: 83.9%, 94.2%). Four-year EFS of patients with EPM treated on AREN0533 was 76.0% (95% CI: 64.6%, 89.4%) vs 64.9% (95% CI: 51.7%, 82.2%) on NWTS-5; HR=0.64, p=0.26; no difference in OS was observed. Increasing linear age and slow incomplete lung response were associated with worse EFS in a pooled cohort.

Conclusions—Outcomes for patients with EPM are among the lowest for children with FHWT. Further trials with standardized surgical and radiation treatment to metastatic sites, and prospectively collected biologic and treatment details are needed.

Precis:

Pooled outcomes across three studies of patients with FHWT and EPM revealed 4-year EFS of 77.3% and OS of 88.9%, with no statistical differences seen between patients on AREN0533 as compared to those on NWTS-5. Missing details on local management of metastatic sites informs a critical need for better data capture in future studies to optimize local control strategies and chemotherapy regimens for this higher-risk FHWT patient group.

Keywords

Extrapulmonary metastases; Wilms tumor; Metastatic Wilms

INTRODUCTION

Outcomes for most patients with newly diagnosed Favorable Histology Wilms Tumor (FHWT) are excellent. Studies conducted by the National Wilms Tumor Study Group (NWTSG) identified patients that were at higher risk of relapse, based on stage and tumor biology.[1,2] The Children's Oncology Group (COG) study AREN0533 prospectively studied patients with "Higher-Risk" FHWT, including all patients with stage IV disease. The outcomes of patients with lung-only metastases, and those with combined LOH of 1p and 16q treated on AREN0533 have already been reported elsewhere.[3,4]

Among FHWT patients with stage IV disease, the majority present with pulmonary metastases alone. For patients with lung-only metastases enrolled on AREN0533 (treated with response-based therapy of either DD-4A without lung irradiation or initial DD-4A followed by chemotherapeutic intensification to Regimen M with lung irradiation), 4-year event-free survival (EFS) was 85.4%.[4]

The remaining stage IV FHWT patients present with extrapulmonary metastases (EPM) with or without lung involvement. Due to their relative rarity, heterogeneity of metastatic sites, and variation in local control techniques, the prognosis and optimal treatment of patients with EPM is less well characterized. Differences in classification, treatment, and outcome

reporting between European (SIOP) and North American (NWTSG/COG) groups makes direct comparison of outcomes challenging.[5] Furthermore, prior reports on patients with EPM focus predominantly on those with liver metastases, while outcomes and treatment of patients with other sites of EPM have not been consistently examined.

An analysis of patients on NWTS-4 and −5 studies showed no significant difference in EFS between stage IV FHWT patients with liver metastases (with or without lung metastases) (n= 96) vs lung-only metastases (n= 513).[6] Five-year EFS by metastatic site were as follows: lung only, 76% (95% CI: 72%, 80%) (513 patients); liver, not lung, 76% (95% CI: 58%, 87%) (34 patients), liver and lung, 70% (95% CI:57%, 80%) (62 patients), and other sites 64% (95% CI: 42%, 79%) (25 patients). Data from SIOP 93-01/GPOH and SIOP 2001/GPOH suggest that Wilms Tumor patients with hepatic metastases fare worse than patients with lung-only metastases. Szavay et al. reported a five-year overall survival (OS) of 62.6% among 29 patients with hepatic metastases (with or without other sites),[7] compared to 83.3% reported by Warmann et al. for 210 patients with lung-only metastases.[8] Both analyses included patients with high-risk histologies (diffuse anaplasia and blastemal type), limiting comparison to the NWTS studies, which excluded patients with anaplasia but not those with post-chemotherapy blastemal predominant histology. A retrospective review of research records from the NWTS 1-5 database identified 9 patients with bone metastases at initial diagnosis and either anaplastic or FHWT.[9] Four of the 9 (44%) survived, but the limited numbers precluded conclusions about prognostic factors or optimal treatment.

In developing the AREN“0” trials, the COG Renal Tumor Committee sought to augment therapy for patient subgroups with historical EFS estimates <75 to 80%.[10] On AREN0533, patients with EPM were assigned to intensified treatment with Regimen M (following two initial cycles of DD-4A). Herein we review and compare patient characteristics, treatments, and outcomes of children with FHWT with EPM, with or without lung metastases, on consecutive collaborative group studies, NWTS-5, AREN0533 and AREN03B2.

PATIENTS AND METHODS

EPM Trial Cohorts

The National Cancer Institute Central Institutional Review Board (CIRB) and local IRBs approved the protocols. Local research ethics boards provided approval for institutions without CIRB agreements. All participants or their legally authorized guardians provided written consent at the time of enrollment.

AREN0533.—Patients enrolled on AREN0533 between February 2007 and May 2013 after first undergoing required central review and risk assignment on AREN03B2 as previously described.[4] Patients with EPM (with or without lung metastases) were initially assigned to treatment with six weeks of induction DD-4A therapy (vincristine, dactinomycin, and doxorubicin), followed by treatment with Regimen M (adding four cycles of cyclophosphamide and etoposide to a modified DD-4A backbone) during weeks 7-33.[4] Protocol recommended radiation therapy included radiation to metastatic sites, and flank or whole abdominal radiation for patients with local stage 3 disease. Liver radiation was indicated for all patients with liver metastases except those with a solitary liver

lesion resected with negative margins prior to chemotherapy. All patients with EPM and lung metastases received whole lung irradiation. Surgical guidelines for intra-abdominal metastases included biopsy or resection of any suspicious site in the abdomen or liver at the time of initial, upfront exploration to assess for primary tumor operability. If residual intra-abdominal metastatic disease remained at the time of disease re-evaluation at the 6 week evaluation time point, resection was recommended where complete resection was feasible. Otherwise, feasibility of resection was to be reassessed at the completion of therapy.

AREN03B2-Only.—AREN03B2 provided a mechanism for specimen banking and central imaging, pathology, and surgical review of patients who were potentially eligible for COG renal therapeutic protocols. For patients who enrolled onto AREN03B2 between March 2006 and August 2019, not subsequently enrolled onto a therapeutic protocol, participating sites were required to submit additional data including treatment received and long-term outcomes. Here, we include “AREN03B2-only” patients confirmed by central review to have FHWT with EPM in our overall pooled outcome analyses and evaluations of potential prognostic factors, restricted to those whose reporting forms indicated treatment with either DD-4A or Regimen M, and for whom outcome data were available. Lung response data (complete vs incomplete response to initial cycles of DD-4A) were not available for patients with EPM and lung metastases enrolled on AREN03B2-only.

NWTS-5.—Patients enrolled onto the NWTS-5 between July 1995 and June 2002. We report here the outcomes of FHWT patients with EPM enrolled on NWTS-5. All patients on NWTS-5 were confirmed to have been treated with DD-4A. Radiation indications mirrored AREN0533, except liver radiation could be omitted for those with multiple resected metastases provided that margins were negative.

Statistical Methods

Eligibility and Endpoints.—FHWT patients with EPM who enrolled on NWTS-5, AREN0533, or AREN03B2 as described above were included in pooled analyses for EFS, OS, and prognostic factors. Patients found ineligible for their respective studies or who were found to have non-FHWT histology (e.g., anaplasia upon delayed nephrectomy) were excluded.

The primary endpoint analyzed was EFS, defined as the time from enrollment (NWTS-5) or initial diagnostic biopsy or nephrectomy (AREN0533 or AREN03B2-only) to the earliest of disease progression, relapse, secondary malignancy, or death due to any cause. OS was defined as the time from enrollment to death due to any cause. For each endpoint, patients who did not experience an event of interest were right-censored at the time of their last known disease status (EFS) or vital status (OS).

Descriptive Analyses.—Patient characteristics were summarized with means, standard deviations, and ranges for continuous variables and relative frequencies for categorical variables, both overall and separately by trial cohort. Differences in the means of continuous patient features (e.g., age at diagnosis) across the three trial cohorts were tested using analysis of variance (ANOVA) when approximate normality could reasonably be assumed.

Otherwise, the Kruskal-Wallis tests were employed. Differences in the distributions of categorical patient characteristics were tested using Fisher Exact tests. Descriptive statistics were also tabled to compare Stage IV patients with EPM vs patients with lung-only metastases who enrolled on either AREN0533 or AREN03B2-only.

Analyses of EFS and OS

Kaplan-Meier estimates of EFS and OS were calculated with 95% confidence bands and reported for the pooled EPM cohort (NWTS-5, AREN0533, AREN03B2). The same statistics were reported by therapeutic study (NWTS-5 vs AREN0533), which were additionally compared using log-rank tests and Cox proportional models.

Analyses of Prognostic Factors.—Univariable Cox proportional hazards models for EFS by pre-selected patient and disease characteristics were fit to the overall pooled cohort; hazard ratios (HRs) and 95% CIs were computed. Except where otherwise specified, these models were stratified by a study-by-treatment variable to allow for different levels of background study or treatment-associated baseline risk while isolating the effect of each prognostic factor of interest. Due to the relatively low number of EFS events anticipated and size of the overall cohort, multivariable models for EFS and modeling for OS were not pre-specified and not performed.

Analyses of Radiation and Surgical Intervention for Liver Metastases.—As the liver is the most common site of EPM, patients from AREN0533 with liver metastases were pooled and categorized by whether they received liver surgery, radiation, both, or neither. Whether and where patients in this cohort relapsed were then tabled for each intervention category. All analyses were performed using R.[11]

RESULTS

Descriptive Statistics

The pooled EPM analysis cohort included 37 patients from NWTS-5, 47 patients from AREN0533, and 64 patients from AREN03B2-only (27 treated with DD-4A only and 37 treated with Regimen M); patient selection diagrams are shown in Figure 1.

Descriptive statistics are presented for the pooled EPM cohort in Table 1, both overall and by contributing study. Patient and disease features were largely similar, except patients on AREN0533 were more likely to be White (86%) than on NWTS-5 (54%) or AREN03B2 (68%) (p=0.003), fewer patients on NWTS-5 had local stage III disease (85%) than on AREN03B2 (97%) or AREN0533 (98%) (p=0.038), more patients on NWTS-5 had liver-only EPM (86%) compared to AREN03B2 (80%) and AREN0533 (79%) (p=0.038), and more patients on NWTS-5 had upfront nephrectomy as a diagnostic procedure (41%) compared to AREN03B2 (28%) or AREN0533 (30%) (p=0.043). We note that some variables were not collected on all studies (e.g., ethnicity for NWTS-5).

Sites of EPM included Liver only (n=120), Liver and “Other” (n=7), and “Other”-only (n=21). Across studies, locations of “Other” EPM included: bone metastases (n=10), mediastinal metastases (n=2), pulmonary artery metastases (n=2), and 1 patient each with

the following: brain; testes; bone+epidural; mediastinum and supraclavicular lymph nodes; psoas muscle wall, cervical lymph nodes, pelvis, mediastinum and vascular invasion into IVC with pleural disease; cytology positive pleural effusion; L2 vertebral body; and lymph nodes to the paraspinal region.

Patient and disease features for FHWT patients with EPM vs patients with lung-only metastases enrolled on AREN0533 or AREN03B2-only are shown in Supplemental Table 1. Compared to patients with lung-only metastases, those with EPM were older (mean= 6.0 vs 5.1 years; p<0.001), were more likely to have left-sided tumors (64% vs 52%; p=0.021), be diagnosed by renal biopsy (59% vs 33%; p<0.001), have a delayed nephrectomy (68% vs 34%; p<0.001), and have local stage 3 disease (97% vs 80%; p<0.001).

Pooled Outcomes of Patients with EPM

In the pooled cohort of 148 FHWT patients with EPM including those with early progression, as of May 9th, 2023, the median length of follow-up among patients without an EFS event was 5 years (corresponding to the protocol-specified maximum follow-up duration for AREN03B2-only patients). Overall, 4-year EFS was 77.3% (95% CI: 70.8%, 84.4%) and 4-year OS was 88.9% (95% CI: 83.9%, 94.2%) (Figure 2). Twelve of 47 AREN0533 patients had EFS events (8 relapses/progressions, 2 second malignancies (1 papillary carcinoma of the thyroid diagnosed 8.5 years after AREN0533 enrollment, and 1 renal cell carcinoma diagnosed 2.4 years after enrollment), 2 deaths from other causes); 13 of 37 NWTS-5 patients had EFS events (all relapses/progressions); and 11 of 64 AREN03B2-only patients had EFS events (10 relapses/progressions and 1 death from other cause). The most common site of relapse was the lungs; all sites of relapse and documented reasons for deaths from other causes are in Appendix 1.

Comparison of Outcomes by Study

Although numerically higher, EFS among patients with EPM treated on AREN0533 vs NWTS-5, did not reach statistical significance (4-year EFS= 76.0% (95% CI: 64.6%, 89.4%) vs 64.9% (95% CI: 51.7%, 82.2%); HR= 0.64; p=0.26; Figure 3A), nor was a statistical difference in OS found (4-year OS= 89.1% (95% CI: 80.6%, 98.6%) for AREN0533 vs 86.5% (95% CI: 76.1%, 98.2%) for NWTS-5; HR= 0.90; p=0.86; Figure 3B). Three patients from each study went off protocol therapy prior to cycle 3 for reasons including disease progression or physician/family choice (Figure 1 footnotes); these patients are included in this comparison despite the AREN0533 patients never receiving Regimen M (which began with cycle 3) as this analysis was planned to compare outcomes based on treatment approach of the different studies.

Pooled Analyses of Prognostic Factors and Biomarkers

The potential association of selected patient and disease characteristics and biomarkers with EFS among patients with EPM is shown in Table 2. The effect of age was confirmed to be linear on the log relative hazard scale and was therefore treated as such in the Cox proportional hazards model presented. Factors significantly associated with EFS across the three studies included age at diagnosis (one-year increase in age corresponding to HR = 1.11; p = 0.03) and, for patients on AREN0533 or NWTS-5, lung response following initial

cycles of DD-4A (6 weeks for those on AREN0533, 10 weeks on NWTS-5) among those with lung metastases at diagnosis (HR = 3.87 for incomplete vs complete responders; p = 0.019). Statistically significant differences in EFS were not found in prospectively planned analyses of subgroups with blastemal predominant histology at delayed nephrectomy, with 1q gain, and with combined LOH of 1p and 16q; notably these data were only available in 55% (combined LOH status) and 36% (1q status and post-chemotherapy histology; non-overlapping) of patients.

Description of Liver Interventions and Relapse

Rates and locations of relapse among AREN0533 patients with liver metastases (with or without other sites) are shown in Table 3, including whether patients received liver radiation *with* surgical resection, liver radiation *without* surgical resection, or no liver radiation or surgical resection. Of 39 patients, 25 (64.1%) had documented liver radiation without surgical resection, and among them, 22/25 remained relapse free, while 3/25 relapsed to non-liver sites including the lung, spine, and renal vein. Two patients (5.1%) received both liver radiation and liver lesion resection, and neither relapsed. Twelve patients (30.8%) received neither liver radiation nor liver resection; 10 were relapse-free at last follow-up: one relapsed to the liver, and one relapsed to the liver and a non-liver EPM site. Total doses of liver radiation among patients with liver metastases ranged from 900 to 2550 cGy (median 1980 cGy).

DISCUSSION

The current analysis examined the outcomes and characteristics of FHWT patients with EPM treated or followed on studies AREN0533, AREN03B2 and NWTS-5. Pooling the three study cohorts revealed that patients with EPM have inferior outcomes (observed 4-year EFS of 77.3%) compared to the 85.4% seen for lung-only patients treated with the AREN0533 treatment strategy.[4]

When comparing characteristics of patients with EPM vs lung-only metastases, patients with EPM are older, more often have left-sided tumors, undergo delayed nephrectomy, and have higher local stage tumors, factors which may contribute to the difference in prognosis. An increase in left vs right-sided tumors has been reported in the NWTS-4/-5 cohort of patients with liver metastases.[6] While increased age is associated with adverse outcomes in FHWT,[12] confirmed here via pooled univariate analysis, the prognostic impact of advanced local stage in overall stage IV patients is unclear. In the COG context, patients undergoing delayed nephrectomy do not appear to have adverse outcomes, at least in patients without metastases.[13] Given that some reasons for having local stage III are prognostically relevant in other FHWT cohorts, it will be important to collect the reason for local stage III determinations on future studies. It is noteworthy that SIOP identified pathological stage III FHWT at delayed nephrectomy as prognostic in patients with lung metastases.[14] Exploration of this finding within the COG therapeutic strategy would be of interest.

Patients with EPM and lung metastases had improved EFS when a complete response of lung metastases to the initial weeks of DD-4A chemotherapy was observed, consistent with NWTSG and SIOP studies that prompted the response-based treatment strategy on

AREN0533 for patients with lung-only metastases.[4] This finding warrants validation prior to consideration of risk-stratification for patients with EPM.

Multiple known adverse biologic variables in FHWT were examined for prognostic impact in patients with EPM, however no observed differences in EFS reached statistical significance. Patients with combined LOH of 1p and 16q, previously shown to have prognostic importance in FHWT,[2,15] and those with 1q gain, associated with inferior outcomes in COG/NWTSG[4,16,17] and SIOP[18,19] cohorts, had inferior EFS that was not statistically significant. Patients with blastemal predominant histology at delayed nephrectomy, recently shown in COG analyses to have inferior outcomes,[13,20] similar to inferior outcomes in SIOP's blastemal-type patients,[21–24] had reduced EFS that did not reach significance. The sample size and limited percentage of patients with known biomarker status limits conclusions about these biologic variables. Alternatively, novel prognostic biomarkers may be more impactful in EPM; investigation of which is warranted on future prospective studies.

Liver metastases remained the most common site of EPM on AREN0533 and AREN03B2, consistent with prior studies. COG/NWTSG and SIOP studies have revealed contradictory results on the prognostic impact of liver metastases. On NWTS-4/-5, FHWT patients with liver metastases did not have worse outcomes than those without liver metastases,[6] however SIOP has reported a worse prognosis for patients with liver metastases.[7] Our analyses did not reveal a differential outcome between patients with liver vs non-liver EPM. The increased number of non-liver EPM seen on AREN03B2 and AREN0533 (although not statistically significant) may reflect differences in patient inclusion or data collection between NWTS-5 and AREN-era studies, highlighting a need for more detailed and consistent annotation of clinical and biologic data for patients with EPM on future therapeutic studies.

We examined the impact of surgery, radiation, or both on local recurrence. Data from SIOP suggest that complete resection of liver metastases may lead to improved outcomes.[25] While EFS was higher for those who underwent upfront resection of liver metastases on NWTS-4/-5, this was not statistically significant.[6] Both cohorts were small and with possible biases. Of the 39 patients on AREN0533 with liver metastases, only two were reported to have resection of liver metastases (both of whom also received liver radiation), therefore the role of surgical resection remains unclear. No patient who received liver radiation (27 of 39) relapsed in the liver.

A major treatment difference for patients with EPM between AREN0533 and NWTS-5 was the planned intensification of chemotherapy to Regimen M on AREN0533. This intensification strategy improved outcomes for stage IV patients with lung-only metastases and higher-risk features – combined LOH or incomplete lung response.[4] While we observed no statistical differences in EFS or OS of patients with EPM treated on AREN0533 compared to those on NWTS-5, several factors confound assessment of the role of Regimen M. Three events occurred in patients who had disease progression prior to switching to Regimen M, and two events were deaths not attributed to the treatment regimen. Moreover, chemotherapy remains just one facet of the overall treatment of patients with EPM. Patients

with EPM are heterogeneous, and patients with solitary liver metastasis and those with extensive mediastinal, pleural or bone metastases likely differ in clinically meaningful ways. Reflecting this heterogeneity, local control is highly individualized, and local control details were not uniformly prescribed or recorded in the presented trials, precluding conclusions about the impact of any treatment variable on outcomes.

The major strength of our study is the large reported pooled cohort of patients with EPM, allowing us to look at prognostic factors within this unique FHWT population. Nonetheless, our study has limitations that impact the conclusions that can be made about the optimal therapy for FHWT patients with EPM. First, patients with EPM constitute a diverse group, including highly-varied location and number of metastases. It will be difficult to determine a single best management strategy for a group that includes patients whose solitary metastatic lesions may resolve with chemotherapy alone, and others whose EPM (such as brain metastases) undergo resection and/or radiation. This heterogeneity, occurring within a group that is already small (compared to lung-only patients), may introduce confounding variables that cannot be statistically accounted for, such as as-yet undetermined biologic differences that influence response to chemotherapy.

Second, shifts in staging definitions occurred between NWTS-5 and AREN03B2/AREN0533. For example, it was possible to be classified as Stage II on NWTS-5 with “controlled spill”, or with pre-nephrectomy biopsy performed during the same procedure as upfront nephrectomy. Either strategy resulted in a Stage III determination for patients on AREN03B2/AREN0533, yielding a staging difference that would translate into different therapeutic approach around radiation. Additionally, chest CT was mandated on NWTS-5 but not centrally reviewed, and treatment of CT-only lung nodules was at the discretion of the investigator,[26] whereas CT was mandated on AREN03B2/AREN0533, and central reviewer determination of the presence or absence of lung metastases dictated chemotherapy and radiation management. These differences in staging and their therapeutic implications may influence our comparison of trial strategies in a way that we cannot determine or adjust for.

Third, shifts in overall study approaches to EPM introduced variability into the treatment of these patients. On NWTS-5, patients with EPM were treated with identical chemotherapy as other stage IV patients, while on AREN0533 they were assigned the same therapy as higher-risk lung-only patients. Neither NWTS-5 or AREN0533 included stringent protocol-specified guidelines or data collection regarding the management of EPM sites (NWTS-5 and AREN03B2-only cohorts lacked sufficient levels of surgical and RT data, respectively). There was no protocol-mandated surgical approach to liver metastases on either study, with NWTS-5 lacking any guidance, and AREN0533 including recommendations only. Indications for radiation to liver metastases also differed between studies. As a result, local control strategies for patients with EPM were highly individualized. Neither study collected potentially relevant data, including number of liver lesions and liver lesion response to chemotherapy, that might allow for detailed analysis of the largest EPM site cohort. Additionally, presence of EPM on AREN0533 was deferred to the treating site, and not determined by central radiologic review. Future studies, featuring consistent definitions and central review of EPM, more prescriptive, protocol-specified local treatments, and enhanced

prospective data collection may help to inform optimal treatment strategies for this patient population.

We also recognize a potential impact of differences in patient characteristics between those treated on AREN0533 and NWTS-5, such as higher rates of local stage III tumors in those enrolled on AREN0533. In both trials, rates of missing or unavailable data for known prognostic factors in FHWT (1q status and post-chemotherapy histology) limit our ability to draw conclusions about the impact of treatment differences.

In conclusion, EFS for FHWT patients with EPM remains suboptimal. While the success of Regimen M for other higher-risk FHWT groups is established, a benefit has not been demonstrated in patients with EPM. How to improve outcomes for patients with EPM remains to be determined. Future research, including prospective collection of all relevant data, is needed to define local control strategies and optimize chemotherapy for this higher-risk FHWT patient group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

Clinical data for the patients included in this analysis is available from the NCTN Data Archive or upon request from Children's Oncology Group: https://childrensoncologygroup.org/data-sharing

Appendix

NWTS-5 Patient Classifiers

FINSTAT	N
FOLLOWED: BIOLOGY ONLY	1
FOLLOWED: CLINICAL ONLY	10
FOLLOWED: OTHER	2

FINSTAT	N
STUDIED	24

Sites of Relapse or Progression

Study	Relapse Site	N
AREN03B2 Only	Brain	1
AREN03B2 Only	Liver	1
AREN03B2 Only	Lung	6
AREN03B2 Only	Other	1
AREN03B2 Only	Pelvis	1
AREN0533	Liver	1
AREN0533	Liver Lung Bone	1
AREN0533	Liver Other	1
AREN0533	Lung	2
AREN0533	Lung Other	2
AREN0533	Other	1
NWTS 5	Abdomen	1
NWTS 5	Brain	1
NWTS 5	Chest and Abdomen	1
NWTS 5	Liver	4
NWTS 5	Liver and Lung	1
NWTS 5	Liver, lung, and abdomen	1
NWTS 5	Lung	2
NWTS 5	Multiple Sites Progressed	1
NWTS 5	Pelvis	1

First Event Types by Study

Study	First Event Type	N
AREN03B2 Only	Death	1
AREN03B2 Only	Relapse/Progression	10
AREN0533	Death	2
AREN0533	Relapse/Progression	8
AREN0533	SMN	2
NWTS 5	Relapse/Progression	13

Median Follow Up Time (calculated as median EFS time for patients who did not have an event)

Median Follow Up Time by Study

Study	Median Follow Up Time
AREN03B2 Only	5.442847
AREN0533	8.465435
NWTS 5	9.434634

Median Follow Up Time All Studies Grouped

Median Follow Up Time
5.7577

Death Attributions for Patients with Death as First Event

Study	Comments
AREN03B2 Only	Patient had a sudden desaturation event with persistent saturations in the 60's despite holding CPAP.
AREN0533	Uncontrollable bleeding during surgery for tumor resection.
AREN0533	Autopsy was performed but report did not provide any additional information on cause of death.

Abbreviations Key:

COG	Children's Oncology Group
EPM	Extrapulmonary metastases
FHWT	Favorable Histology Wilms Tumor
EFS	Event-Free Survival
IRB	Institutional Review Board
LOH	Loss of Heterozygosity
NWTSG	National Wilms Tumor Study Group
OS	Overall Survival

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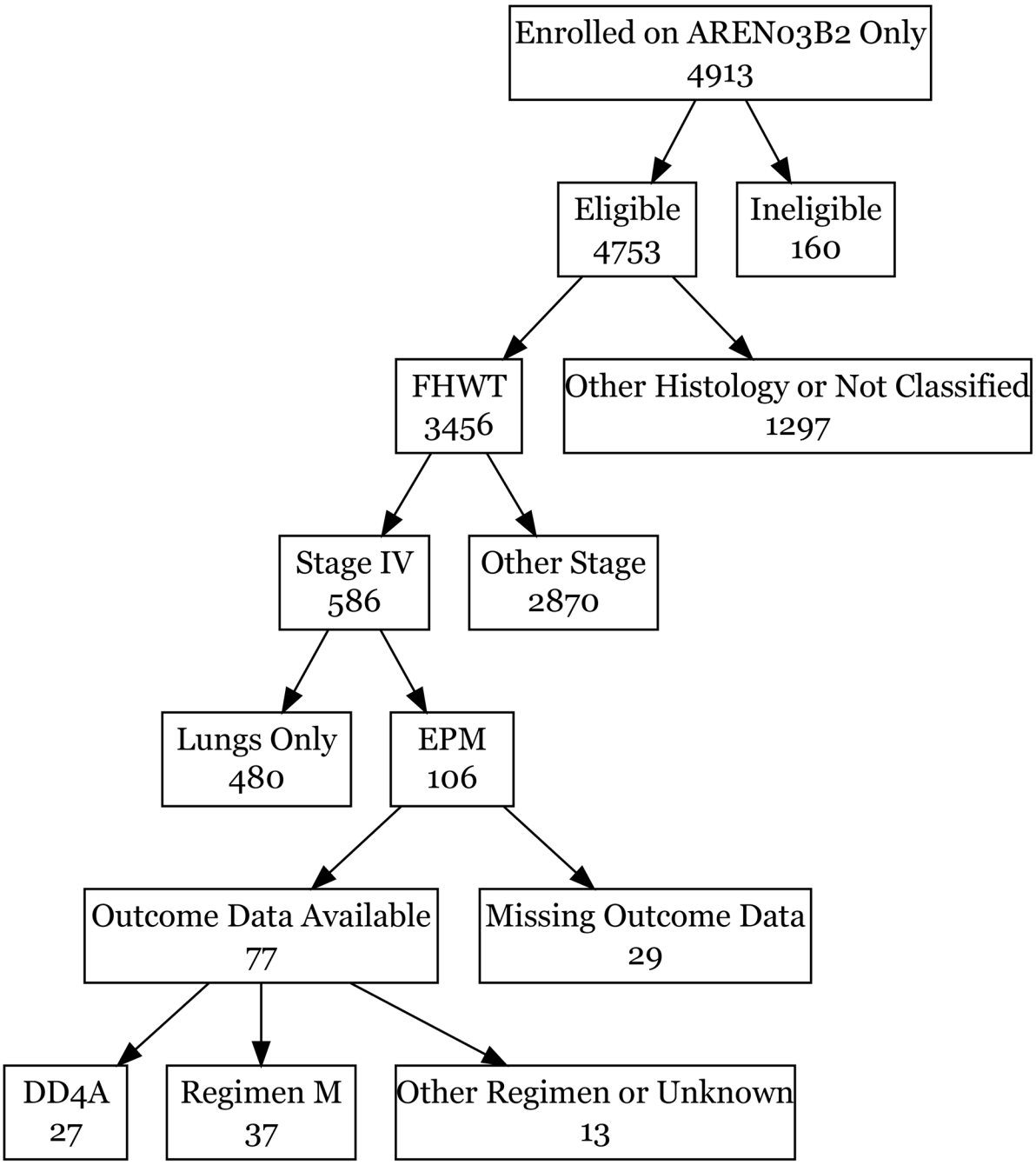
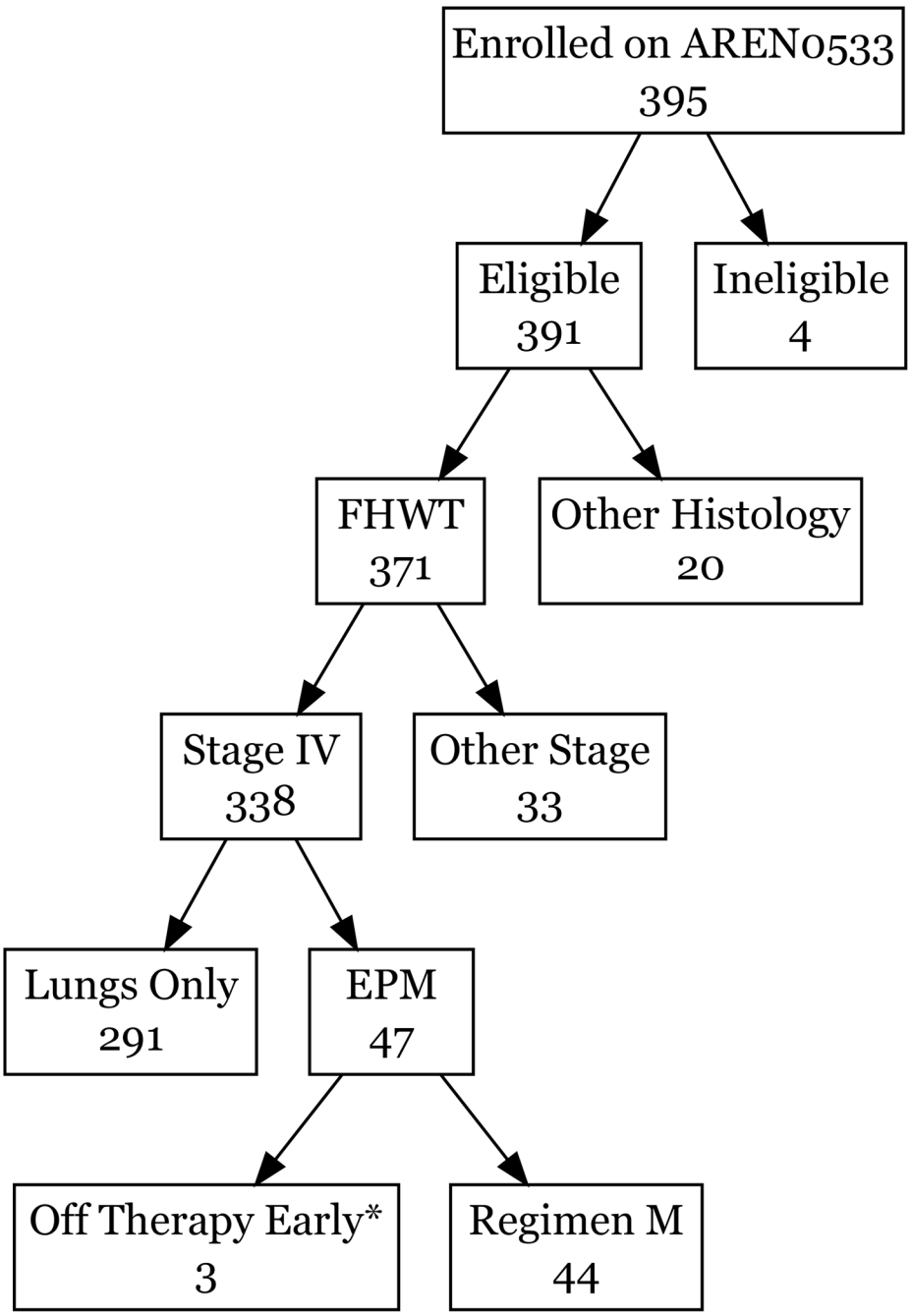




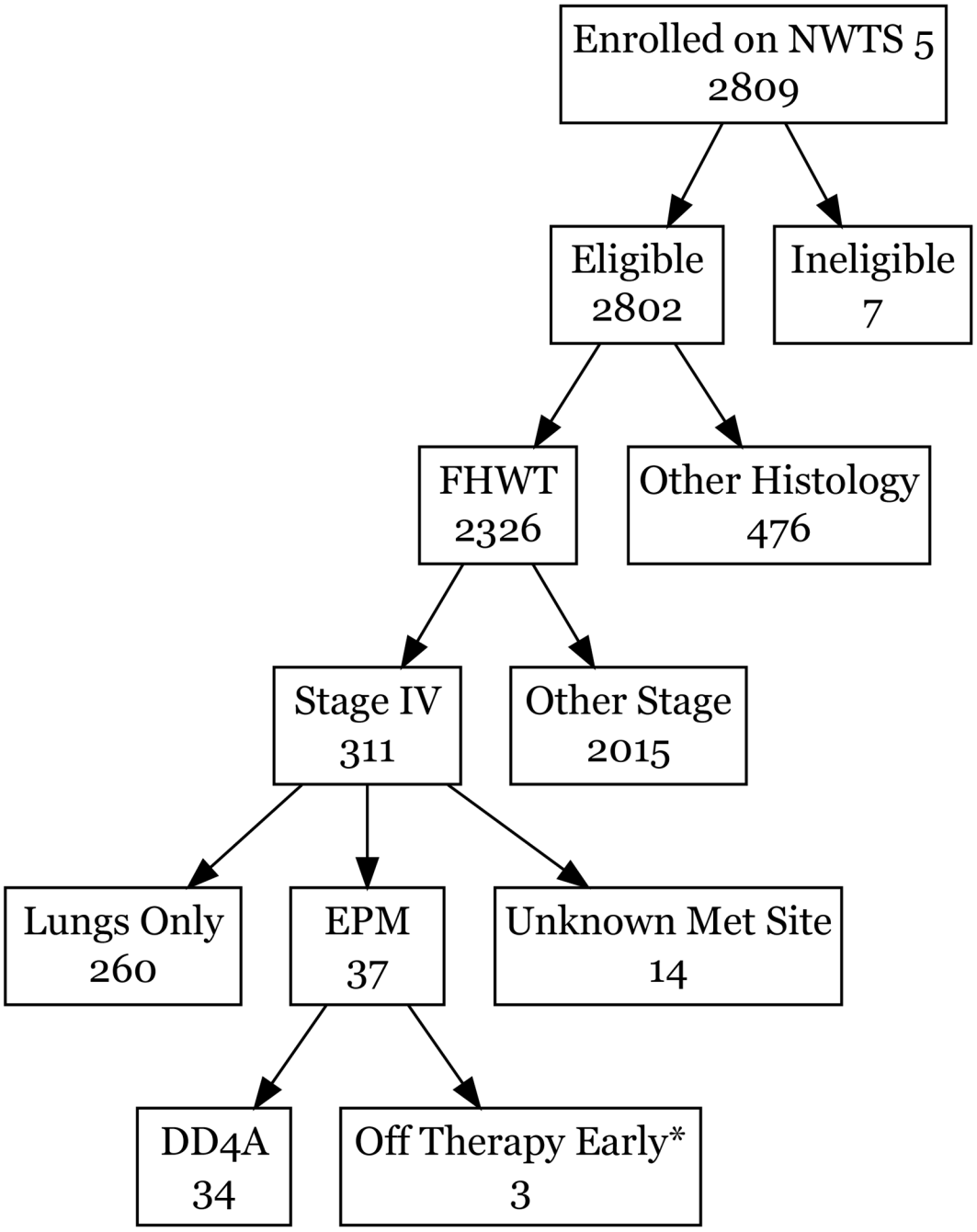


Figure 1.

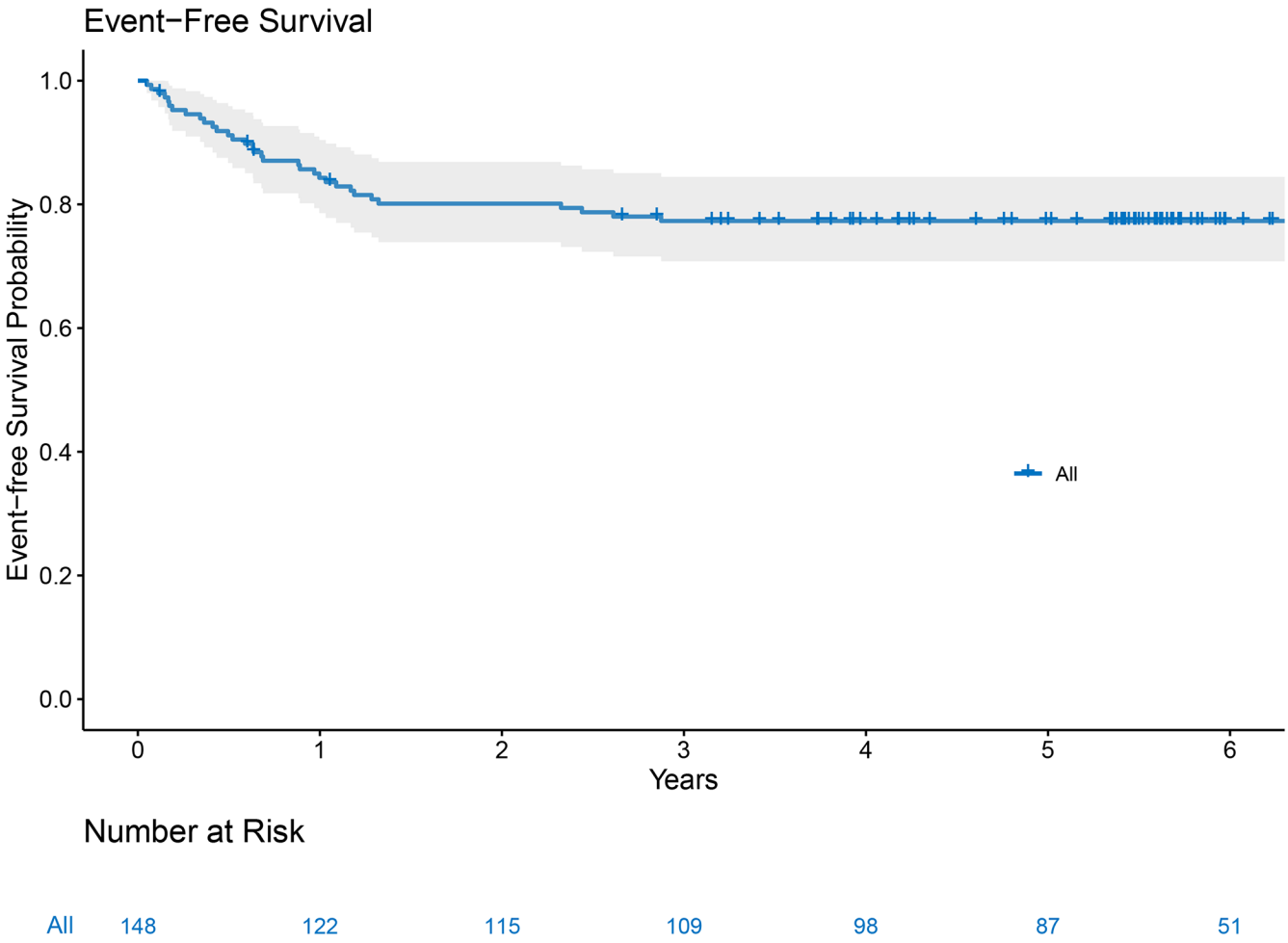
A. AREN0533 Consort Diagram.

*Patients progressed or withdrew from planned protocol theraepy while still receiving DD-4A and thus nevere received Regimen M (1 death, 1 progression, 1 withdrew consent)

B. NWTS-5 Consort Diagram

*Three patients progressed within 8 weeks of study enrollment.

C. AREN03B2-Only Consort Diagram



Number at Risk

All	148	122	115	109	98	87	51

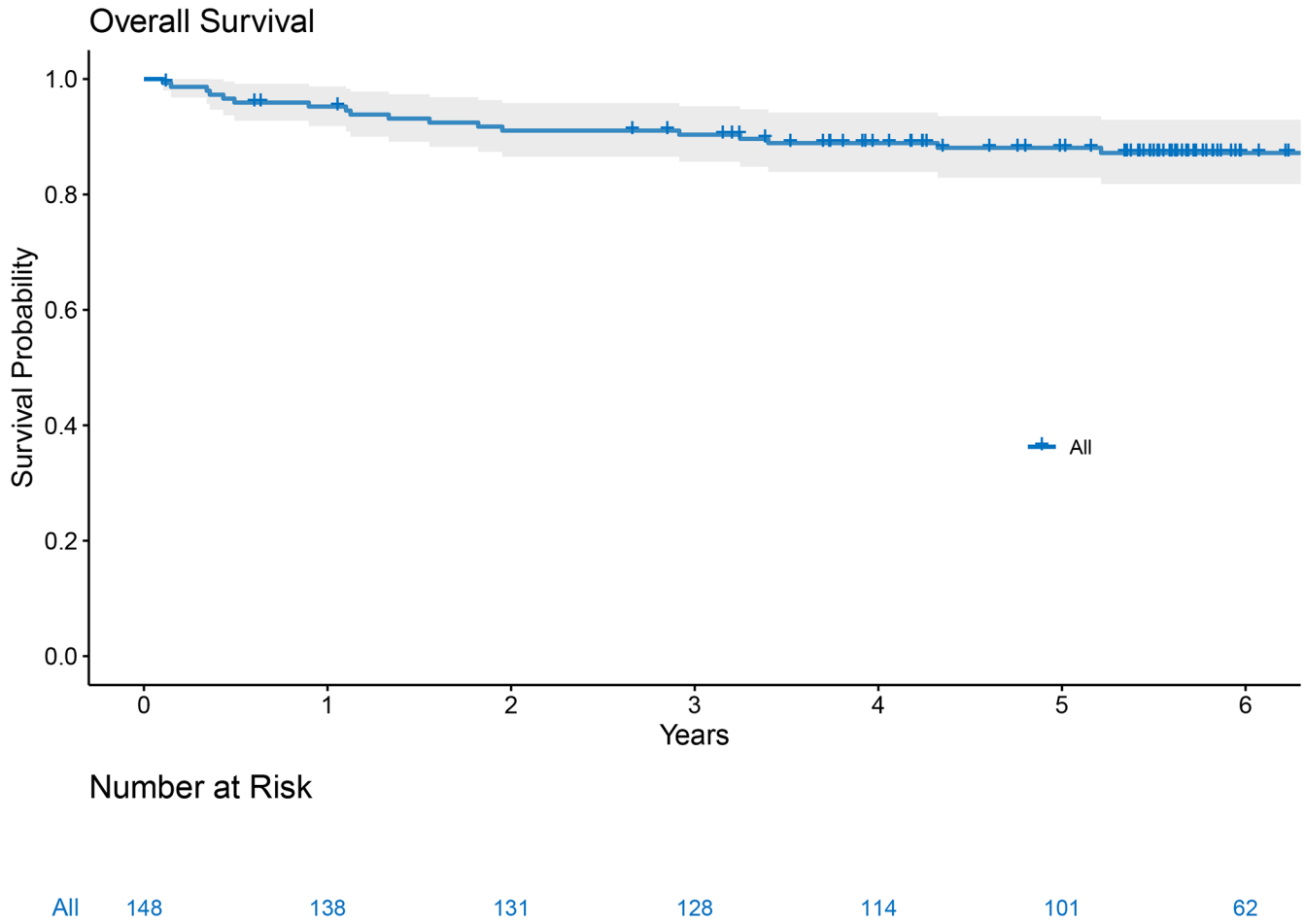
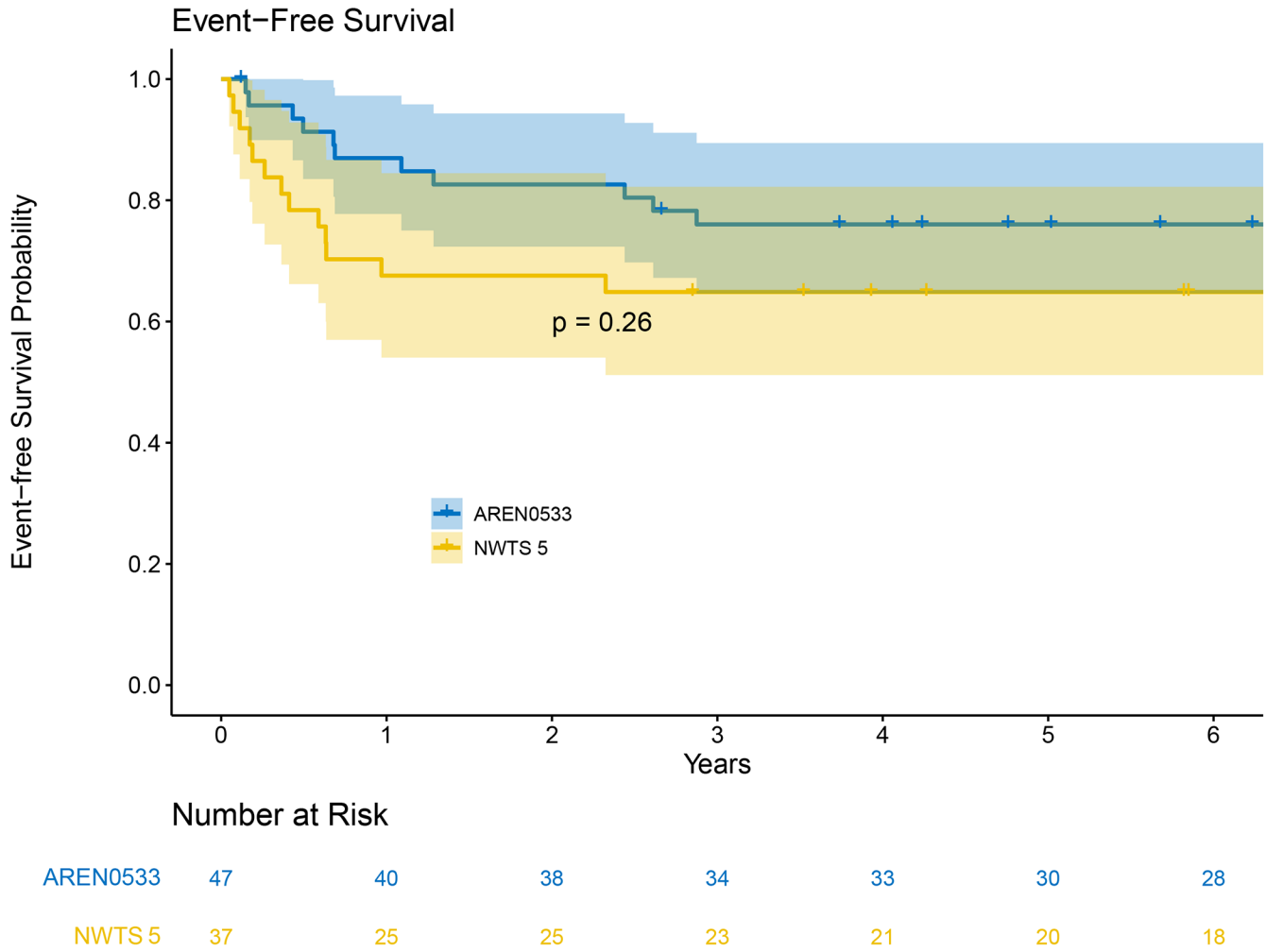


Figure 2.

A. Event-Free Survival of Pooled EPM Cohort

B. Overall Survival of Pooled EPM Cohort



Number at Risk

AREN0533	47	40	38	34	33	30	28
NWTS 5	37	25	25	23	21	20	18

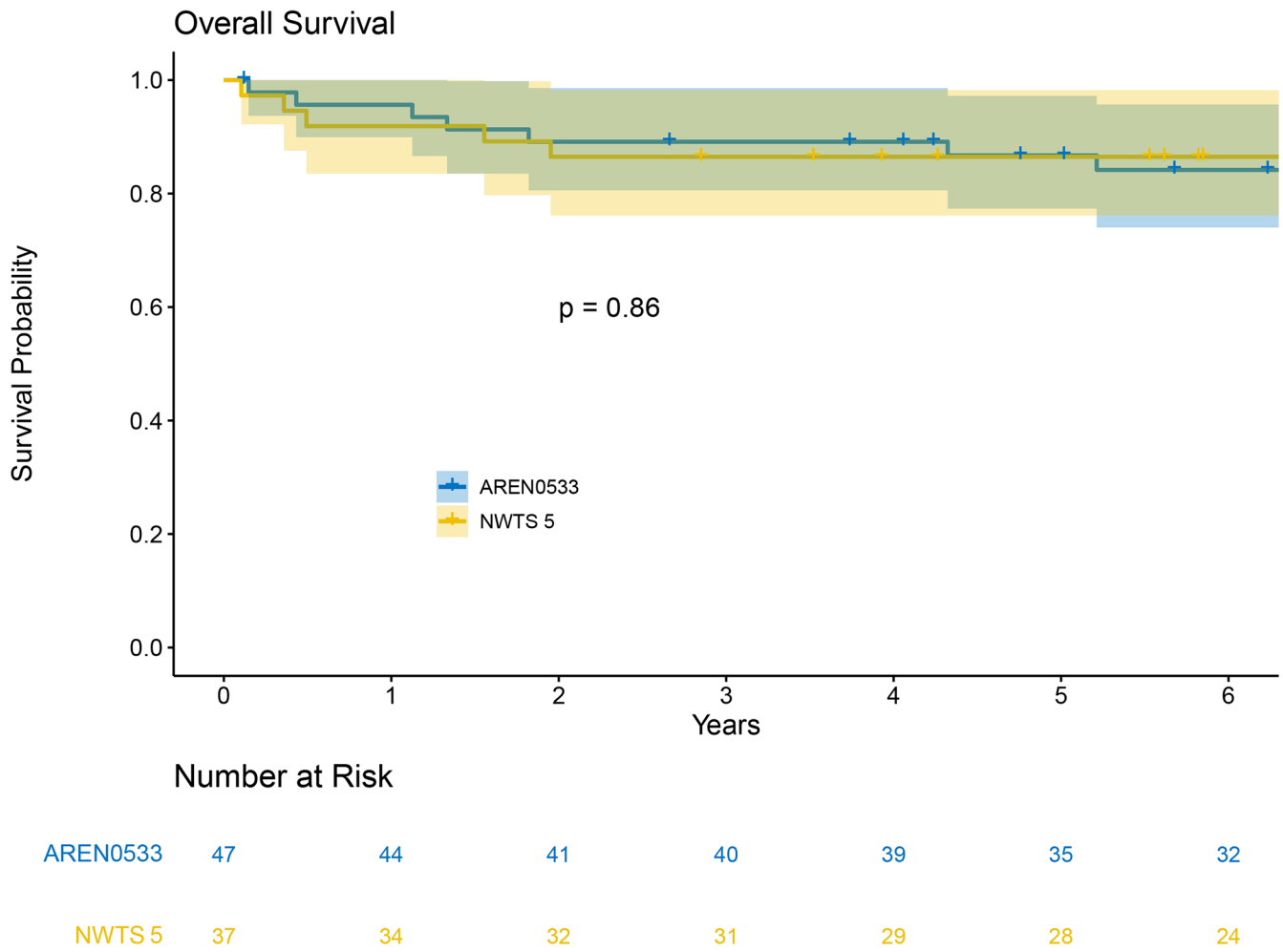


Figure 3.

A. Event-Free Survival AREN0533 vs. NWTS-5

B. Overall Survival AREN0533 vs. NWTS-5

Table 1.

Descriptive Statistics: EPM Patients by Study

	AREN03B2 Only (N=64)	AREN0533 (N=47)	NWTS 5 (N=37)	Total (N=148)	p value
Age (Years)					0.576[1]
Mean (SD)	6.0 (2.7)	5.9 (3.3)	6.4 (3.6)	6.1 (3.1)	
Range	1.3 - 14.1	1.2 - 19.4	0.8 - 20.6	0.8 - 20.6	
Gender					0.867[2]
Female	38 (59%)	29 (62%)	21 (57%)	88 (59%)	
Male	26 (41%)	18 (38%)	16 (43%)	60 (41%)	
Race					0.003[2]
Black or African American	16 (32%)	4 (10%)	14 (40%)	34 (27%)	
White	34 (68%)	36 (86%)	19 (54%)	89 (70%)	
Other	0 (0%)	2 (5%)	2 (6%)	4 (3%)	
Missing/Unknown	14	5	2	21	
Ethnicity					0.628[2]
Hispanic or Latino	11 (18%)	10 (22%)	0	21 (20%)	
Not Hispanic or Latino	50 (82%)	35 (78%)	0	85 (80%)	
Missing/Unknown	3	2	37	42	
Primary Tumor Laterality					0.366[2]
Horseshoe	0 (0%)	0 (0%)	1 (3%)	1 (1%)	
Left	39 (61%)	32 (68%)	20 (54%)	91 (61%)	
Right	25 (39%)	15 (32%)	16 (43%)	56 (38%)	
Initial Procedure Type					0.043[2]
Nephrectomy	18 (28%)	14 (30%)	15 (41%)	47 (32%)	
Renal Biopsy	35 (55%)	30 (64%)	22 (59%)	87 (59%)	
Other Biopsy	11 (17%)	3 (6%)	0 (0%)	14 (9%)	
Nephrectomy Timing*					0.923[2]
Upfront	20 (31%)	15 (32%)	12 (35%)	47 (32%)	
Delayed	44 (69%)	32 (68%)	22 (65%)	98 (68%)	
Missing/Unknown	0	0	3	3	
Delayed Nephrectomy Timing (Weeks)					0.480[1]
Mean (SD)	9.5 (3.3)	8.6 (3.0)	NA	9.0 (3.1)	
Range	5.7 - 15.6	5.7 - 16.1	NA	5.7 - 16.1	
Missing/Unknown	38	16	37	91	
Local Stage					0.038[2]
Stage 2	2 (3%)	1 (2%)	5 (15%)	8 (6%)	
Stage 3	59 (97%)	46 (98%)	28 (85%)	133 (94%)	
Missing/Unknown	3	0	4	7	
Delayed Nephrectomy Risk Classification					0.292[2]
Low risk (completely necrotic)	5 (20%)	5 (17%)	0	10 (19%)	

	AREN03B2 Only (N=64)	AREN0533 (N=47)	NWTS 5 (N=37)	Total (N=148)	p value
Intermediate risk	16 (64%)	23 (79%)	0	39 (72%)	
High risk (blastemal predominant)	4 (16%)	1 (3%)	0	5 (9%)	
Missing/Unknown	39	18	37	94	
Metastatic Site(s)					0.388[2]
Lung + EPM	48 (75%)	38 (81%)	25 (68%)	111 (75%)	
EPM Only	16 (25%)	9 (19%)	12 (32%)	37 (25%)	
EPM Site(s)					0.038[2]
Liver Only	51 (80%)	37 (79%)	32 (86%)	120 (81%)	
Liver + Other**	1 (2%)	2 (4%)	4 (11%)	7 (5%)	
Other** Only	12 (19%)	8 (17%)	1 (3%)	21 (14%)	
Lung Response*					0.191[2]
RCR	0	12 (32%)	12 (50%)	24 (39%)	
SIR	0	25 (68%)	12 (50%)	37 (61%)	
Missing/Unknown	64	10	13	87	
LOH 1p					0.879[2]
No	13 (87%)	42 (91%)	18 (90%)	73 (90%)	
Yes	2 (13%)	4 (9%)	2 (10%)	8 (10%)	
Missing/Unknown	49	1	17	67	
LOH 16q					0.432[2]
No	11 (73%)	39 (87%)	18 (90%)	68 (85%)	
Yes	4 (27%)	6 (13%)	2 (10%)	12 (15%)	
Missing/Unknown	49	2	17	68	
LOH 1p and 16q					1.000[2]
No	15 (100%)	44 (96%)	20 (100%)	79 (98%)	
Yes	0 (0%)	2 (4%)	0 (0%)	2 (2%)	
Missing/Unknown	49	1	17	67	
Gain 1q					0.736[2]
No	0	28 (74%)	12 (80%)	40 (75%)	
Yes	0	10 (26%)	3 (20%)	13 (25%)	
Missing/Unknown	64	9	22	95	
Liver XRT Received					0.797[2]
No	0	12 (31%)	9 (26%)	21 (28%)	
Yes	0	27 (69%)	26 (74%)	53 (72%)	
Missing/Unknown	64	8	2	74	
Regimen					
DD-4A	27 (42%)	0 (0%)	34 (92%)	61 (41%)	
Regimen M	37 (58%)	44 (94%)	0 (0%)	81 (55%)	
Off Therapy Early****	0 (0%)	3 (6%)	3 (8%)	(4%)	

[1] Kruskal-Wallis rank sum test

[2] Fisher's Exact Test for Count Data

*For some patients, timing is not definitive based on the available data.

**Locations of “Other” non-liver EPM included (across studies): 10 patients with bone metastases, 2 patients with mediastinum metastases, 2 patients with pulmonary artery metastases, and 1 patient each of the following individual metastases or combinations: brain, testes, bone+epidural, mediastinum and supraclavicular lymph nodes, psoas muscle wall, cervical lymph nodes, pelvis, mediastinum and vascular invasion into IVC with pleural disease, cytology positive pleural effusion, L2 vertebral body, and lymph nodes to the paraspinal region.

***AREN0533 patients were evaluated for lung response at week 6 of treatment and NWTS-5 patients were evaluated at day 70 of treatment.

****AREN0533 patients who went off therapy prior to starting Reg M but after starting DD-4A per AREN0533 protocol or NWTS-5 patients who progressed within 8 weeks of study enrollment.

Table 2.
Univariable Cox Proportional Hazards Modeling.

(all models are stratified by the following classifications AREN0533, NWTS-5, AREN03B2 DD-4A, or AREN03B2 Regimen M except for the Delayed Nephrectomy Risk Classification, and Regimen Received Models)

Factor	N	Levels	HR, 95% CI	p-value
Age (Years)	148	Mean SD	1.11 (1.01-1.21)	p=0.031
Gender	88	Female	-	
	60	Male	0.86 (0.43-1.73)	p=0.677
Primary Tumor Laterality	91	Left	-	
	56	Right	1.38 (0.70-2.74)	p=0.351
Nephrectomy Timing	98	Delayed	-	
	47	Upfront	0.66 (0.31-1.41)	p=0.281
Delayed Nephrectomy Risk Classification	10	Low risk completely necrotic	-	
	39	Intermediate risk	1.37 (0.30-6.18)	p=0.684
	5	High risk blastemal predominant	5.05 (0.82-31.05)	p=0.081
Metastatic Site(s)	111	Lung + EPM	-	
	37	EPM Only	0.71 (0.31-1.64)	p=0.419
EPM Site(s)	120	Liver Only	-	
	7	Liver + Other	0.46 (0.06-3.38)	p=0.443
	21	Other Only	1.13 (0.42-3.05)	p=0.803
Lung Response	24	RCR	-	
	37	SIR	3.87 (1.25-12.02)	p=0.019
LOH 1p	73	No	-	
	8	Yes	0.53 (0.07-3.97)	p=0.535
LOH 16q	68	No	-	
	12	Yes	1.56 (0.45-5.45)	p=0.487
Gain 1q	40	No	-	
	13	Yes	1.91 (0.62-5.88)	p=0.262
LOH 1p and 16q	79	No	-	
	2	Yes	1.78 (0.23-13.79)	p=0.582
Regimen Received *	34	DD-4A	-	
	44	Regimen M	0.67 (0.28-1.62)	p=0.377

*Only includes patients from AREN0533 and NWTS-5 and patients who went off protocol therapy early were excluded

Table 3.

AREN0533 Liver Treatments and Relapse Locations

	Liver Resection and Liver XRT (N=2)	Liver XRT Only (N=25)	None (N=12)	Total (N=39)
Relapse Site(s)				
Liver and Other *	0 (0%)	0 (0%)	1 (8%)	1 (3%)
Liver only	0 (0%)	0 (0%)	1 (8%)	1 (3%)
Other only *	0 (0%)	3 (12%)	0 (0%)	3 (8%)
None	2 (100%)	22 (88%)	10 (83%)	34 (87%)

* Other sites include lung(x1), L1-2 paraspinal mass (x1), lung and lymph nodes(x1), and lung and thrombus within the left renal vein extending into the inferior vena cava increased in size and lung lesions slightly increased is size (x1)