International Pleuropulmonary Blastoma Registry for PPB, DICER1 and Associated Conditions

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ABSTRACT

Background: Pleuropulmonary blastoma (PPB) is a rare malignant neoplasm of the lung presenting in early childhood. Four pathologic “Types” are recognized. The Types are manifestations of one disease along a time spectrum from birth to age ~72 months (7% of cases occur after age 72 months). Type I PPB is an air-filled purely cystic neoplasm (median diagnosis age 10 months) for which treatment is surgery with or without adjuvant chemotherapy. Type II PPB (cystic/solid) and Type III PPB (solid) are aggressive sarcomas (median diagnosis ages 33 and 44 months, respectively) for which treatments are surgery and multi-agent chemotherapy with or without radiation therapy. Type Ir (regressed) PPB is a unique, purely cystic tumor which lacks a primitive cell component. Type Ir PPB has varied in age at diagnosis from 7 months to 45 years of age (median 46.5 months).1

The International Pleuropulmonary Blastoma Registry: The International Pleuropulmonary Blastoma Registry (IPPBR) (www.ppbregistry.org) was formed in 1987.

PPB has strong genetic implications with a unique set of associated neoplasia and dysplasia in the patient or family occurring mostly in childhood and adolescence. The International PPB Registry (IPPBR) first reported the germline loss-of-function mutations in the gene Dicer1 in PPB patients and family members.2,3 Conditions associated with PPB include: ovarian sex cord-stromal tumors including Sertoli-Leydig cell tumor (SLCT) and gynandroblastoma4,5, lung cysts, cystic nephroma (CN) and renal sarcoma, Wilms tumor6-8, pineoblastoma9-11, pituitary blastoma11-13, multinodular goiter and thyroid carcinoma14,15, nasal chondromesenchymal hamartoma16,17, ciliary body medulloepithelioma18, embryonal rhabdomyosarcoma19 and undifferentiated sarcoma20. Dicer1 mutations may also be associated with macrocephaly21 and an overgrowth syndrome22.

The IPPBR estimates that 30-50 cases of Type I PPB and 40-60 cases of Types II and III PPB are diagnosed annually worldwide. In 2009 the IPPBR began a prospective study to collect treatment data on patients for whom therapy decisions are made by each institution. Due to the rarity of the PPB, this study will build on the previous “Treatment and Biology Registry” protocol, continuing collection of data on patients. This study builds off of the 2009 study and will also seek to enroll individuals with Dicer1-associated conditions, some of whom may present only with the Dicer1 gene mutation, which will allow the IPPBR to Dicer1-associated conditions.

PPB therapy choices and screening tests are the decision of each institution. This International PPB Registry for PPB, Dicer1 and Associated Conditions presents surgery and chemotherapy guidelines. Through this Registry, it is anticipated that analysis of a group of similarly treated children with PPB will advance the knowledge of effective ways to treat PPB.

The International PPB Registry for PPB, Dicer1 and Associated Conditions Design and Goals:

- Type I and Type Ir PPB: Type I PPB is an early manifestation of this malignant disease, cured in some cases by surgery. Surgical guidelines are presented. It is unknown whether adjuvant chemotherapy improves cure rates for Type I PPB.
patients. If the treating physicians select adjuvant chemotherapy treatment, the Registry guideline is a 22-week regimen: 4 courses of vincristine, actinomycin D and cyclophosphamide (VAC) followed by 3 courses of vincristine and actinomycin D (VA). Therapy decisions are the responsibility of the treating institution.

- **Types II and III PPB:** Types II and III PPB are aggressive sarcomas. Surgery and chemotherapy are necessary in all cases. Surgical guidelines are presented. The Registry chemotherapy guideline is a single-arm multi-agent chemotherapy neo-adjuvant/adjuvant regimen of vincristine, actinomycin, ifosfamide, doxorubicin (“IVADo”) for 36 weeks. Second and possible 3rd look surgery may be considered for local control. Radiation therapy may be considered, particularly for unresectable focal disease. Specific therapy decisions are the responsibility of the treating institution.

- **PPB-Associated Conditions:** An unusual feature of PPB is that in a large number of cases, the PPB patient or other young family members have a mutation in the *DICER1* gene which puts them at risk for other tumors or malformations. The International PPB Registry for PPB, *DICER1* and Associated Conditions will use standard procedures to collect information on these cases.

- Diagnostic pathology consultation is strongly encouraged, but enrollment in this Registry relies on local diagnosis. Retrospective central pathology review is required.

- The International PPB Registry for PPB, *DICER1* and Associated Conditions will generate overall and event-free survival data (a) for Type II and Type III PPB patients, where pathology is confirmed by central review and (b) for Type I PPB patients where pathology is confirmed by central review, comparing those who received or did not receive chemotherapy. Results will be compared to historical controls to provide the basis for future studies for this disease.

- Collection of tumor samples or normal tissue when removed for a clinical indication, as well as collection of germline DNA and plasma and serum samples, are also included in this protocol to allow further research into the biology of PPB and optimal treatment of *DICER1*-associated conditions. In the rare instance in which spinal fluid is collected for clinical purposes, an additional 1 ml may be processed for biomarker analysis.

Patient (or parental) consent for data and specimen collection by the Registry is required for all enrollees (also HIPAA in the USA).

### 1.0 SPECIFIC AIMS

1.1 To enroll and follow Type Ir and I PPB patients for disease-free survival (DFS) and overall survival (OS), progression, and recurrence. Use of chemotherapy will be decided by the treating physician/institution.
1.2 To enroll and follow Types II and III PPB patients for DFS and OS, progression and recurrence. Maximum attempts at surgical resection are suggested. A single-arm neoadjuvant/adjuvant chemotherapy regimen is the chemotherapy guideline in this Registry. Radiation therapy for unresectable focal residual is determined by the treating institution.

1.3 To provide surgical guidelines for Types Ir, I, II and III PPB.

1.4 To enroll and follow patients who have the DICER1 gene mutation or conditions associated with PPB, but who do not have PPB.

1.5 To establish an annotated DICER1 biorepository for research use which includes clinical and family history data, germline DNA and plasma/serum specimens as well as fresh, frozen and preserved tumor or tissue samples or other samples from individuals with PPB or DICER1-associated conditions when removed for a clinical indication (See §).

2.0 BACKGROUND AND RATIONALE

2.1 General Considerations

PPB Overview: PPB is a rare and unique childhood malignancy, first described in 1988. PPB is a dysembryonic malignancy believed to arise from pleuropulmonary mesenchyme. It is recognized as the pulmonary analog of more common childhood developmental neoplasms such as Wilms tumor of kidney (nephroblastoma), hepatoblastoma, neuroblastoma, embryonal rhabdomyosarcoma and medulloblastoma. Like these, most cases of PPB (93%) are diagnosed in children less than 6 years of age.

The International Pleuropulmonary Blastoma Registry: The IPPBR is a collaboration between the Department of Cancer and Blood Disorders at Children’s Minnesota, Minneapolis, MN, USA; the Department of Pathology, Children’s National Medical Center and ResourcePath, Washington, DC, USA, and the departments of Surgical Pathology and Cancer Genetics at Washington University Medical Center, St. Louis, MO, USA. These institutions have also collaborated on genetic and molecular studies of PPB.

Approximately 900 cases of PPB have been recorded since the initial description, comprised of 508 pathology-confirmed IPPBR cases (Oct. 2016) and approximately 400 other cases between cases in the medical literature and informal inquiries to the IPPBR. Children with PPB had been treated diversely according to local therapy decisions until the first IPPBR treatment and biology study opened in 2009 with suggested treatment guidelines. The cohort of children treated since the opening of the 2009 PPB Treatment and Biology Registry represent the largest cohort of individuals with PPB or DICER1- associated conditions.

2.2 Pleuropulmonary Blastoma (PPB)
2.2.1 PPB Pathologic “Type” Definitions

PPB is divided into three pathologic subtypes representing a progression of the disease along an age-related biologic continuum from birth to age ~72 months (93% of cases).

Type I PPB is an air-filled entirely cystic neoplasm occurring generally in peripheral lung parenchyma or visceral pleura. Type I PPB is a subtle malignancy with typically scattered malignant cells beneath a benign epithelial cyst lining. (see Pathology description §2.2.1)

Type Ir PPB is a newly-recognized cystic manifestation of PPB. It is not considered malignant. It is rare and found usually, but not exclusively, in relatives of PPB patients. Type Ir cysts may also rarely be found in a PPB patient’s lung separate from the frank manifestations of Types I, II, or III PPB. The “Ir” designation represents Type I “regressed”. (Type Ir diagnosis is highly specialized; consultation with IPPBR pathologists is suggested.)

Type I PPB with features of regression is a judgment by experienced PPB pathologists that the particular Type I case may, over time, become a Type Ir PPB. Because there is uncertainty whether chemotherapy should be used for any Type I PPB, the IPPBR specifically suggests to clinicians that chemotherapy not be used for cases interpreted as “Type I PPB with features of regression.” Real-time referral of Type I PPB cases is strongly encouraged to evaluate this possibility.

Type II PPB is a cystic and solid neoplasm. Cystic portions are identical to Type I PPB. The solid elements are an aggressive mixed-pattern sarcoma. It also occurs generally in peripheral lung parenchyma or visceral pleura. (see Pathology description §2.2.1).

Type III PPB is an entirely solid aggressive mixed-pattern sarcoma. It occurs in lung parenchyma, visceral pleura and parietal pleura. (See Pathology description §2.2.1).

2.2.2 PPB Biology and Genetics

PPB biology is unique among pediatric malignancies with its age-related cystic, cystic/solid and solid expressions. There is strong evidence that Types I, II and III PPB are related on a time spectrum from the neonate though early childhood. Approximately 95% of T-I, T-II and T-III cases are diagnosed by 30, 82, and 64 months respectively, although diagnosis of each Type and progression may rarely be discovered up to approximately age 20 years. Evidence for the potential for progression of Type I to Type II to Type III PPB includes: 1) PPB Type is correlated with age; 2) PPB not eradicated at one stage has been shown in some specific cases to evolve into more advanced disease; 3) histologic complexity and malignancy increases as Type progresses; 4) prognosis worsens as Type progresses, 5) likelihood of metastasis increases with Type).

PPB is a strongly genetic disease. A wide and unusual set of dysplasia and neoplasms, known as the DICER1 syndrome, are found in the PPB patient or the family in ~40% of IPPBR cases. Several families with multiple PPB cases are known. Particularly common in these children and kindreds are multifocal and/or bilateral lung cysts and cystic nephroma (found in 9-10% of IPPBR cases of PPB). The complete phenotype for this syndrome continues to
In April 2009 the IPPBR and colleagues at Washington University St. Louis first reported germline, loss-of-function mutations in the gene *DICER1*. Additional studies to explore the role of *DICER1* are ongoing. The IPPBR continues actively to explore the implications of this finding through current protocol, the PPB genetic study and collaboration with the National Institutes of Health’s *DICER1*-Related Pleuropulmonary Blastoma Cancer Predisposition Syndrome: A Natural History Study (http://ppbcancer.org).

### 2.2.3 PPB Clinical Manifestations

**Type I PPB**: In the IPPBR historical experience, Type I PPB occurs from birth through age 114 months, but typically in the first 3 years of life; the median diagnosis age is 8 months. Patients may present with the cyst as an incidental finding on radiograph or with respiratory distress from a large cyst or pneumothorax. Type I PPB cannot be distinguished radiographically from benign congenital lung cysts, although pneumothorax and the presence of multifocal or bilateral cysts suggests PPB. Also, the presence in the patient or family of any disease associated with PPB strongly suggests a cyst is PPB.

**Types II and III PPB**: Type II PPB may present like Type I PPB as an incidental finding or with respiratory distress from cyst or pneumothorax. More commonly, Types II and III PPB present as “pneumonia” with an ill child: fever, lethargy, cough, an opaque finding on chest radiograph. The child does not improve on antibiotics and further investigation (usually chest CT scan) reveals a mass. Type II and especially Type III PPB are typically extensive tumors, often involving an entire hemithorax. The median diagnosis age for Type II is 35 months; and 41 months for Type III.

**Metastasis in PPB**: Metastasis of Type I PPB has not been reported. PPB can recur and/or have metastatic disease. In addition to local recurrence, metastatic disease has primarily been found in central nervous system (CNS), bone, and rarely, liver. In a recent look at 425 IPPBR cases of PPB a total of 107 patients relapsed. The majority of these relapses (48%) were isolated chest relapse. There was also 27% with isolated CNS metastatic disease and 25% with other relapse.

### 2.2.4 PPB Pathologic Diagnosis

**Type I PPB**: Type I PPB, occurring in the youngest children, is an entirely cystic tumor. Pre-operatively, malignancy is rarely suspected. The cyst is usually a multilocular cyst in peripheral lung.

Microscopically, the cystic structure of Type I PPB may appear unicystic in the gross examination but has a characteristic multilocular architecture with delicate septa at low magnification. A diagnostic population of small primitive mesenchymal cells is found in the stroma beneath the benign epithelial lining; these cells may be a localized single focus, several foci or a diffuse proliferation resembling the cambium layer effect of a sarcoma botryoides. The primitive small cells may display rhabdomyomatous differentiation as seen in an embryonal rhabdomyosarcoma. When there is rhabdomyoblastic differentiation, cells with prominent eosinophilic cytoplasm may be present. Small nodules of immature cartilage
may be found in the septa and are not necessarily accompanied by the small primitive cells. Because the small primitive cells or nodules of cartilage are present only focally in some cases, it may be necessary to submit an entire cyst specimen for microscopic examination. Anaplastic cells are rarely found in Type I PPB.

Type Ir PPB is a more recently recognized cystic manifestation of PPB. It is not considered malignant. It is rare and found usually, but not exclusively, in relatives of PPB patients. Type Ir cysts may also rarely be found in a PPB patient’s lung separate from the frank manifestations of Types I, II, or III PPB. The “Ir” designation represents Type I “regressed”. Type Ir diagnosis is highly specialized; consultation with IPPBR pathologists is suggested.

Type I PPB with features of regression is newly recognized by IPPBR pathologists. It is a judgment by experienced PPB pathologists that the particular Type I case may, over time, become a Type Ir PPB. This has implications for the clinicians’ decision whether to use chemotherapy for Type I cases. Real-time referral of Type I PPB cases is strongly encouraged to evaluate this possibility.

Types II and III PPB: The cystic portions of Type II PPB are similar to Type I PPB. The histologic findings in the solid portions of Types II and III PPB are typically those of a mixed pattern aggressive sarcoma including embryonal rhabdomyosarcoma, chondrosarcoma, fibrosarcoma-like areas, undifferentiated blastema, anaplasia, and occasional other sarcoma subtypes. Necrosis is common. Apparent “cysts” resulting from necrosis are “pseudocysts” and are not diagnostic of the epithelial lined cysts required for a designation of Type II cystic/solid disease. Anaplasia, similar to anaplasia in Wilms tumor, occurs in 75% of Type II and 85% of Type III PPB. Lymph node involvement is very rare. The cytology of pleural effusions is rarely diagnostic.

2.2.5 PPB Historical Treatments and Prognosis

Until the IPPBR opened the initial PPB Treatment and Biology Registry protocol in 2009 there had been no large prospective studies of PPB treatment nor any large collections of PPB patients treated consistently. While treatment for each patient was decided by the local physician, the 2009 protocol did suggest a chemotherapy regimen of vincristine (V), actinomycin (A), cyclophosphamide (C) treatment for T-I PPB. Ifosfamide (I), vincristine (V), actinomycin (A), doxorubicin (Do) was suggested for patients with T-II or T-III PPB. Outcome was not yet available from the original IPPBR protocol from 2009 – 2016 when this study was designed.

2.2.5.1 Type I PPB: Historical Treatments and Prognosis

Historically, Type I PPB treatment has consisted of surgery with or without adjuvant chemotherapy. While treatment has always been ultimately determined by the local physician, the IPPBR protocol opened in 2009 offered a chemotherapy treatment schema and roadmaps outlining a 41-week regimen of vincristine (V), actinomycin (A), cyclophosphamide (C).

One Children’s Oncology Group (COG) ARST0331 study enrolled patients with low-risk embryonal rhabdomyosarcoma (stage I) on an arm where patients received surgery followed
by just 22 weeks of vincristine (V) and dactinomycin (A) chemotherapy with favorable outcome.40

In 2011 the IPPBR analyzed 91 Type I PPB cases. There were 31 patients with surgery alone, 31 with surgery plus adjuvant chemotherapy, and unknown therapy for 28 patients.41 The surgery alone group had 6 patients develop disease progression; and the surgery + chemotherapy group had only 2 individuals with progression, suggesting a benefit to adjuvant chemotherapy. An alternative to managing Type I PPB with surgery plus adjuvant chemotherapy is to perform complete resection with negative margins and frequent surveillance for early recurrence.

2.2.5.2 Types II and III PPB: Historical Treatments and Prognosis

Historically, Types II and III PPB have been treated as sarcomas similar to rhabdomyosarcoma. For many years, attempted surgical extirpation was followed by various adjuvant therapies. More recently, because many PPBs are very large and because neo-adjuvant chemotherapy can reduce the volume of other tumors, PPB has been approached with biopsy, neo-adjuvant chemotherapy, extirpative surgery and further adjuvant therapies. In “biopsy-first” cases, chemotherapy may result in >90% volume reduction. Responses are seen after the first 2-4 courses of neo-adjuvant therapy though may not be sustained; anaplastic cells may be or may become resistant to chemotherapy. Surgery should be performed after 2-4 courses of neo-adjuvant therapy (unpublished IPPBR observations). No data is available to compare cure or metastasis outcomes for initial biopsy versus initial resection strategies.

In the United States, chemotherapy treatments for PPB have typically involved vincristine (V), dactinomycin (A), cyclophosphamide (C), often with the addition of doxorubicin (Adriamycin®) (Ad) and/or cisplatin (Plat).42,43 Typical regimens have been VA, VAC, VACA (= VACAd = VAC alternating with VAdC), or VAC/PlatAd (VAC alternating with PlatAd). In Europe, the tendency has been to use ifosfamide (I) more than C, epirubicin (Ep) or Ad, carboplatinum (Carbo) instead of Plat, and in some regimens to add etoposide (Et). Typical regimens in Europe have been denoted VA, VAI, “VAIA” (= VAIAd = VAI alternating with VAdI), “EVAIA” (= EtVAIAd, and “CEVAIE” (= CarboEpVAIE = alternating VAI, CarboEpV and VIEt). “ICE” (= ICARboEt) has also been used. Radiation therapy has been typically reserved for residual foci of disease not amenable to resection.

In a 1997 report of 50 cases, treated from approximately 1975 to 1995 using the typical agents listed above used in the United States, overall 2-yr survival for Types II and III PPB was 73% and 48%, respectively.42 The 5-yr overall survival for Types II and III was approximately 45% and 35%, respectively. These differences did not reach statistical significance. No specific chemotherapy agent or regimen could be shown to be especially effective.

The Italian Rare Tumor Group (AIEOP-TREP) has published 22 PPB cases accessioned from 1982 to 2005, including 3 Type I, 6 Type II, 12 Type III cases (one Type unknown).44 Type II and III patients were treated with VAIAd or CarboEpVAIEt with radiation in three cases, including 9 patients entered prospectively after 1998 who received VAIAd (VAI alternating...
with VAdI). Overall Kaplan-Meier 5-yr survival, including the three Type I cases, was 49%.

The German Soft Tissue Sarcoma Group has described in abstract form 19 Type II and III PPB cases accessioned from 1981 to 2007.45,46 Treatments were VACAd, VIA, VAIAd, EtVAIAd, or CarboEpVAIAd with radiation in 5 cases. Overall Kaplan-Meier 5-yr survival was 70%. It is not clear why this series has notably better survival than the two series noted above. The German Soft Tissue Sarcoma Group advocates extirpative surgery, “VAIA” (“VAIAd”) chemotherapy and consideration of focal radiotherapy for unresectable residual for Types II and III PPB (Kirsch/Koscielniak personal communication).

In an unpublished 2006 analysis by the IPPBR, the chemotherapy of 137 Types II and III PPB patients was evaluated. This case population was comprised of 102 pathology-reviewed IPPBR cases, 16 cases reported by Kirsch, which were not differentiated as to Type II vs. III,45 and 19 cases reported by Indolfi.44 There were 64 Type II cases, 52 Type III cases and 21 Type II/III NOS cases. This analysis suggests that vincristine, dactinomycin, ifosfamide and doxorubicin are more active in PPB than other agents.

2.2.6 Arms

2.2.6.1 Arms for the International PPB Registry for PPB, DICER1 and Associated Conditions

Patients may be eligible for one of 4 arms:

2.2.6.2 Arm A: Type I PPB

2.2.6.2.1 Enrollment: Type I PPB patients will be enrolled in this study and followed.

2.2.6.2.2 Surgical Guidelines: (see §4.1). Complete surgical excision of Type I cystic lesions is recommended if at all possible, but it is recognized that some children have such extensive multifocal and/or bilateral cystic change that complete removal of cysts is not possible.

2.2.6.2.3 Chemotherapy Guidelines- Type I PPB: The decision whether to use chemotherapy for Type I PPB will be made at the local institution. Because of the tendency for PPB to progress over time, the pathology of “late” Type I PPB merges with “early” Type II PPB.23 Therefore, before a final decision on use of chemotherapy, real-time pathology consultation with IPPBR pathologists for Type I cases is encouraged. (see Background sections on Pathology (see §2.4)

If an institution elects to use chemotherapy for Type I PPB, the International PPB Registry for PPB, DICER1 and Associated Conditions provides a treatment guideline which includes 22-week regimen (VAC/VA): 4 courses of vincristine, actinomycin D and cyclophosphamide (VAC) followed by 3 courses of vincristine and actinomycin D (VA). This recommendation is based on recent low- and
moderate-risk rhabdomyosarcoma regimens. Neo-adjuvant low-risk regimens limiting cyclophosphamide have been complicated by early on-therapy recurrence; although there is no directly comparable experience with Type I PPB; recurrences of Type I PPB have been advanced Type II and III PPB. Treating providers may also wish to consider the use of full VAC (previously provided as a recommended regimen from the International PPB Registry) or VA alone. No data is available as to the efficacy of VA alone for Type I PPB.

Surveillance Recommendations for Type I PPB are offered in this International PPB Registry for PPB, DICER1 and Associated Conditions based on time to recurrence/progression data.

### 2.2.6.3 Arm B: Types II and III PPB

Because the number of PPB patients worldwide is small and because there is insufficient data for stratification by prognostic group, representatives agreed that PPB Types II as III should be treated with a single-arm chemotherapy regimen. The IVADo regimen for 36 weeks was chosen because of the four chemotherapy agents involved and because the up-front dose intensity of IVADo may be especially useful in neo-adjuvant setting.

Since February 2007, when contacted by physicians treating PPB, the IPPBR has recommended IVADo therapy for Types II and III PPB patients. The results are preliminary but responses and outcome so far suggest that IVADo is associated with improved outcomes compared to heterogeneously-treated historical controls.48

#### 2.2.6.3.1 Enrollment: Types II and III PPB patients will be enrolled in this International PPB Registry for PPB, DICER1 and Associated Conditions and followed.

#### 2.2.6.3.2 Surgical Guidelines: Surgical (and biopsy) Guidelines are presented. Local disease control with 2nd and if necessary 3rd look surgical procedures is suggested by this International PPB Registry for PPB, DICER1 and Associated Conditions. (§4.1)

#### 2.2.6.3.3 Chemotherapy Guidelines - Types II and III PPB: Treating physicians will decide locally what therapy to use for Types II and III PPB. The International PPB Registry for PPB, DICER1 and Associated Conditions chemotherapy guideline is a single-arm chemotherapy regimen: “IVADo” for 36-weeks (neo-adjuvant/adjuvant chemotherapy when biopsy is chosen for initial diagnosis).

#### 2.2.6.3.4 Radiation Therapy: Whether to use radiation therapy for focal unresectable residual disease or other indications will be decided by local institutions.

Therapy for recurrence after Types II and III PPB is not included in this study, but patients will be followed for outcome and institutional choices will be collected.

### 2.2.6.4 Arm C: Type Ir PPB
2.2.6.4.1 **Enrollment:** Type Ir PPB patients will be enrolled in this International PPB Registry for PPB, *DICER1* and Associated Conditions and followed.

2.2.6.4.2 **Surgical Guidelines:** Surgical (and biopsy) Guidelines are presented. (§4.1)

2.2.6.4 **Arm D: *DICER1* Gene Mutation or Condition Associated with PPB or the *DICER1* Gene Mutation**

Germline heterozygous *DICER1* mutation was identified in 72.6% of children with PPB.31 Particularly common in these children and kindreds are multifocal and/or bilateral lung cysts and cystic nephroma (found in ~10% of IPPBR cases of PPB).6,23 Previous work has shown that judicious genetic screening can lead to diagnosis in PPB in family members in its earliest and most curable form.49 and IPPBR unpublished observations

This study includes collection of family medical histories and biologic specimens on patients (see §2.2.2) for research into the biology of PPB.

Because PPB and the associated conditions found in PPB families suggest a familial tendency to formation of tumors, this International PPB Registry for PPB, *DICER1* and Associated Conditions study will collect information on the diagnosis and treatment of PPB and *DICER1*- associated conditions and individuals with germline *DICER1* mutations on the “associated conditions” arm of this study.

2.3 **PPB Type versus IRS Clinical Group versus TNM staging**

In evaluating patients for outcome, the IPPBR and most other investigators have evaluated PPB cases according to PPB Types I vs. II vs. III. The IPPBR has not used the Intergroup Rhabdomyosarcoma Study (IRS) “clinical group” classifications (Ia and b, IIa and b, IIIa and b, and IV50), which are assigned after complete radiological staging, initial surgery and pathological examination.

Establishing an “IRS-type” clinical grouping system for PPB is a challenge because PPB is very different from most rhabdomyosarcomas originating in specific muscle sites. Difficulties are as follows:

- Precise anatomic localization of PPB primary site is often difficult or impossible: lung, visceral pleura, parietal pleura.
- How does one integrate Types I, II, and III PPB into “groups”?
- PPB often involves an entire hemithorax and CT does not yield details of radiographic staging in the way that MRI can define extent of involvement of muscle planes for typical rhabdomyosarcomas.
- How are multifocal cysts and/or bilateral cysts, which are a unique part of PPB biology, factored into the grouping?
- How does one classify tumor spill? Pleural Effusion? Involvement of a contiguous lobe? Involvement of parietal pleura?
- Nodes are almost never involved with PPB and are difficult to image intrathoracically.
- Will detailed grouping of some PPB cases be useful if many cases are only biopsied?
Notwithstanding these difficulties, it is reasonable for a prospective study of PPB treatment to attempt consistent staging procedures and to compare PPB-adapted IRS-type clinical grouping to PPB Types for prognostic importance. The IPPBR will continue to classify cases retrospectively for research purposes using a PPB-adapted clinical group-TNM staging system, however, the clinical utility of this staging system is uncertain. The system being used is presented in the Appendix I.

2.4 Central Pathology Review and Biology Studies

2.4.1 Central Pathology Review
The International PPB Registry for PPB, DICER1 and Associated Conditions Registry enrollment will be based on local diagnosis, but central pathology review is required in all instances of biopsy or surgical intervention. Central review is critical for correct identification and classification of PPB, for the standardization of future protocols that base treatment strategies on PPB Type classification, for cataloging diseases identified as being associated with PPB, and for research studies which may correlate novel prognostic markers with clinical and pathologic data. Central review of post-chemotherapy resection tissue and metastatic tissue is strongly encouraged. (For submission details, see Appendix II).

2.4.2 PPB Biology Studies (research objective separate from patient care)
To better understand the molecular pathogenesis and optimal surveillance and treatment of PPB and other DICER1 related tumors, this study will collect, annotate and bank tumor samples, serum/plasma, germline DNA and adjacent normal tissue when removed for a clinical indication. In the rare instance that CSF is obtained for clinical purposes, an additional 1 ml will be processed for research purposes. Additionally, samples may be used for generation of preclinical models including cell lines and patient-derived xenograft models as well as identification of novel biomarkers of DICER1-related conditions.

Primary goals of this biology research are (1) to identify new clinical, pathological and molecular factors that predict outcome and (2) to define biomarkers for use in future clinical surveillance and (3) to establish a collection of biologic specimens for both PPB and PPB-associated conditions for future research by Registry and other researchers.
Table of biomarker times points based on diagnosis.

<table>
<thead>
<tr>
<th>Arm</th>
<th>Condition</th>
<th>Timepoints</th>
<th>Approximate samples expected per patient over total duration of treatment and followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Type I or Ir PPB</td>
<td>Diagnosis, after definitive surgery and with each chest CT for first 2 years of followup</td>
<td>Approximately 4</td>
</tr>
<tr>
<td>A2</td>
<td>Types II or III PPB</td>
<td>Diagnosis, after surgery, every week during first month of therapy, q3 months during therapy, after definitive surgery, at completion of therapy and q3 months during followup</td>
<td>Approximately 10</td>
</tr>
<tr>
<td>B</td>
<td>DICER1-related cancer (not PPB)</td>
<td>Diagnosis, q3 months during treatment and followup</td>
<td>Approximately 6</td>
</tr>
<tr>
<td>C</td>
<td>Healthy DICER1 carrier</td>
<td>Routine surveillance, generally with CT scan at 3 months of age and 2.5 years of age; adult carriers having routine venipuncture for clinical care or genetic testing</td>
<td>Approximately 2</td>
</tr>
</tbody>
</table>

2.5 Analysis of Late Effects

We hypothesize cardio respiratory outcomes and quality of life for individuals with PPB will remain within acceptable limits and similar to survivors of other childhood cancers but will be lower than healthy controls. Assessments of cardiopulmonary function will occur at standard intervals per Children’s Oncology Group Long Term Follow up Guidelines (www.survivorshipguidelines.org). These include echocardiogram and pulmonary function testing. In addition, due to the potential for extensive pulmonary surgery in children with PPB/DICER1 mutations, pulmonary function testing when clinically feasible, should be considered annually once the patient is old enough to comply with pulmonary function testing.

2.5.1 Ability to Assess Quality of Life for PPB Patients (research objective separate from clinical care)

Chemotherapy and surgery may have adverse effects on quality of life (QOL) outcomes. PPB patients and their parents represent a specific sup-group of cancer patients whose quality of life can be significantly impacted by cancer and treatment related side effects and complications. This study is designed to allow the International PPB Registry for PPB, DICER1 and Associated Conditions to determine the quality of life (QOL) outcomes based on QOL assessments in patients and their parents or legal guardians. The QOL design will allow for assessment at the same points across countries for English- and Spanish-speaking participants. Outcomes in individuals will be assessed by a neuropsychologist with extensive experience in assessment of neuropsychology and QOL outcomes in childhood cancer survivors and their parents. The use measures have standardization of data flow, and the quality measures been validated for various age groups and will allow more global concerns to be addressed. Analyzing this data across different time points will allow for a better understanding of the diagnosis and treatment and allow us to determine predictors of poor outcome so that interventions can be developed.

The Pediatric Quality of Life Inventory Measurement System (PedsQL) will be used to measure health-related quality of life (HRQOL) and fatigue beginning within the first 6 months of enrollment and re-administered every other year to monitor changes over time. The PedsQL is a widely used system for measuring HRQOL in childhood cancer patients and other
chronic illnesses of childhood.\textsuperscript{51,52} Parent proxy report versions will be used for children ages 2-18 years of age to assess parent perceptions of child HRQOL. The adult self-report version will be used for those over 18 years of age. Items comprising each of the forms are essentially identical, differing only in developmentally appropriate language, or first or third person tense. The instructions for the standard version asks the rater to determine how much of a problem each item has been during the past 1 month on a 5-point Likert scale (with 0 being never and 4 being almost always). Items are reverse scored and linearly transformed to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0) such that higher PedsQL scores indicate better HRQOL (fewer symptoms). Spanish language versions are available and will be used with Spanish-speaking families.

The following PedsQL scales will be used, with total completion time expected to be no more than 10 minutes, based on survey developers’ estimates. The PedsQL 4.0 Generic Scale consists of 23 items measuring the core physical, mental, and social health dimensions as delineated by the World Health Organization, as well as school functioning. The PedsQL Multidimensional Fatigue Scale consists of 18-items which encompass 3 subscales tapping 1) General Fatigue, 2) Sleep/Rest Fatigue, and 3) Cognitive Fatigue\textsuperscript{53}. All scales have acceptable internal consistency reliability (child- and parent-report alphas .89 to .93 for the Generic and Fatigue Modules) and have been shown to distinguish healthy children and children with cancer as a group, and among children with cancer who are on and off treatment.

### 2.6 Cardiac Outcomes
#### 2.6.1 Cardiac Assessment
Cardiotoxicity is associated with anthracycline medications and may impact quality of life outcomes.\textsuperscript{54} For the first time, this study will allow the IPPBR to assess these outcomes in individuals with \textit{DICER1}-associated tumors and will compare outcomes to those in individuals with more common childhood cancers. Echocardiograms will be obtained consistent with good clinical care in individuals who received cardiotoxic chemotherapy or thoracic radiation at routine clinical time points per Children’s Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers (http://www.survivorshopguidelines.org). Reports will specifically be requested and analyzes in conjunction with pulmonary data below.

### 2.7 Pulmonary Function Outcomes
#### 2.7.1 Assessment of Pulmonary Function
Childhood cancer survivors in general are at increased risk for pulmonary-related morbidity and mortality.\textsuperscript{55} This may be compounded the \textit{DICER1} specific risks which include history of PPB with one or more thoracic surgeries, intensive chemotherapy and/or radiation and theoretical concern for pulmonary development in individuals harboring a \textit{DICER1} mutation. Some individuals with PPB undergo multiple lobectomies or pneumonectomy. Also, as surveillance allows detection of asymptomatic lung cysts, only some of which are destined to progress to Type II or III PPB, we must carefully assess the impact of subsequent resections on ultimate pulmonary function. Thus, in concordance with good clinical practice, the
Registry suggests consideration of annual pulmonary function testing for individuals who have a history of PPB or undergo thoracic surgery.

This study will determine the prevalence of pulmonary function abnormalities in a pediatric survivor cohort and assess the pulmonary outcomes and quality of life for individuals with PPB and determine whether they are within acceptable limits and/or similar to survivors of other childhood cancers.

2.8 Biomarker analysis (research objective separate from clinical care)

PPB is most curable when found in its earliest form. Likewise, other DICER1 conditions including Sertoli-Leydig cell tumor and Wilms tumor are most curable when found as Stage I. Individuals with early stage disease often require less intensive therapy and have lower likelihood of acute and chronic toxicities. Thus, early diagnosis is a high priority. Current research efforts focus on evaluation of potential biomarkers. Blood samples for biomarker research are drawn at times of clinically indicated venipuncture. Urine samples will also be collected at these time points for biomarker research. For health individuals with DICER1 testing, the blood will be drawn at times of IV placement for surveillance CT scans, currently recommended at 3-6 months of age and 2.5-3.5 years of age. Serum biomarkers may also be drawn when venipuncture is performed for another purpose such as evaluation of tumor markers in an individual with an ovarian mass seen by screening ultrasound. When feasible, a voided urine specimen will also be obtained at the time of each blood draw.

In children with Type I PPB, samples are collected prior to surgery, post operatively and with surveillance CT scans. In individuals with Types II and III PPB, samples are collected at diagnosis, post surgery and during chemotherapy at times of CT scans or other evaluations requiring IV placement or port access. Following therapy for PPB, samples are collected with surveillance imaging time points.

Blood draw volumes: Blood draws include two 5 ml blood collection tubes. In small children or individuals with moderate to severe anemia, smaller volumes are recommended not to exceed 3 ml/kg per time point or 7 ml/kg per 6 week interval. Typical blood volumes are expected to be less than these volumes.

Urine collection volumes: Collect between 15 – 50 cc of urine.

The consent form provides a specific “opt out” area for collection of these specimens for biomarkers analysis.

2.9 Fresh Tissue/Preclinical Models (research objective separate from patient care)
Efforts are underway to develop more effective and less toxic therapies for PPB and *DICER1*-related conditions. Cell lines and preclinical models including patient derived xenograft murine models are key to development of novel therapeutics. PPBs and *DICER1*-related tumors are often large and complete resection is often attempted. When sufficient tissue is available from a clinically indicated procedure, the Registry requests fresh tissue be sent for RESEARCH purposes (See Appendix A-II: 1.3). Fresh/frozen tissue is not required for participation and should not be sent if in the judgment of the treating physician or pathologist would negatively impact patient care.

Tissue and blood samples obtained at autopsy may also assist in research. Contribution of such tissue is possible for patients/families who wish to contribute such samples for research. Please contact the study team directly for further information regarding sample processing if applicable.

Fresh tissues are used for generation of cell lines and patient derived xenograft preclinical models. PDX preclinical models are desirable because they provide renewable tissue specimens derived from human tumors implanted prior to culturing of the cells in vitro (therefore reducing artifacts associated with growth in cell culture). Further, PDX models, which have been used for pre-clinical drug testing and identification of cancer biomarkers and provide excellent systems to test novel and combination therapeutics for treatment of these rare tumors. **The use of these preclinical models has been reviewed: IACUC number 00030413; Animal assurance number for Children’s Research Institute - A3338-01**

### 3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

#### 3.1 Approval by Human Subjects Committee (Institutional Review Boards, Helsinki Committees)

Because PPB is rare, many institutions will not prospectively review a study of PPB therapy. In addition, differences between countries make formation of an international treatment trial very difficult. Formulating this project as the International PPB Registry for PPB, *DICER1* and Associated Conditions as has been done in previous iterations of this protocol provides flexibility in collecting cases from institutions with differing regulatory environments or review-board practices. Parental consent is required. Assent is required where applicable. In the United States, HIPAA consent is also required. Many institutions will allow direct parental consent for enrollment. Some institutions will require Human Subjects Committee, Institutional Review Board or Helsinki Committee approval in addition to parental consent. Therefore, several scenarios leading to case participation in the International PPB Registry for PPB, *DICER1* and Associated Conditions are possible – see Appendix III. The International PPB Registry for PPB, *DICER1* and Associated Conditions consent forms, including an “Assent” form (for older children), and HIPAA consent are in Appendix IV.
3.2 Patient Enrollment
To enroll a patient, complete the enrollment form found in Appendix III, then contact the International PPB Registry for PPB, DICER1 and Associated Conditions office via email PPBinfo@childrensmin.org, phone, 612-812-7121, or fax, 612-813-7108. A unique study patient identifier number will be assigned after the registration process.

Also, parents may enroll their child by sending to the Registry office (fax or pdf or mail) a signed Consent Form (Appendix IV). The Registry will then contact the treating institution for further information.

Patients enrolled under the age of legal consent by a parent or guardian will be invited to ‘re-consent’ to in the International PPB Registry for PPB, DICER1 and Associated Conditions study once legal age to consent is reached.

3.3 Eligibility Criteria
3.3.1 Age
Patients of any age will be included in the International PPB Registry for PPB, DICER1 and Associated Conditions study.

3.3.2 Prior Therapy
There are no prior therapy restrictions for enrollment on the International PPB Registry for PPB, DICER1 and Associated Conditions study.

4.0 TREATMENT GUIDELINES

| Children with PPB should receive care at pediatric oncology specialty centers. The following represent conscientiously collected guidance for surgery, chemotherapy, and radiation therapy; however, all treatment decisions remain the responsibility of the treating institution. |

4.1 PPB Biopsy/Surgical Guidelines:
Surgical Principles: (1) Primary resection is preferred, but adequate biopsy (see below) followed by neo-adjuvant chemotherapy and delayed complete resection is acceptable.
(2) Complete surgical removal, whether in primary or subsequent surgeries, is highly recommended.
(3) Specimens should be submitted fresh to the Pathology Laboratory for molecular studies and snap-freezing for biology studies (see Appendix II).
(4) See section for information regarding Type Ir PPB.
4.1.1 Predominantly CYSTIC Lesions (Type I PPB; Type II PPB with minimal solid elements)

4.1.1.1 Anatomic Considerations
Type I PPB is a purely cystic pulmonary/pleural lesion with no gross evidence of cyst-wall thickening or solid nodules suggesting malignancy. Early Type II PPB grossly may appear purely cystic. The clinical and radiographic presentation of Type I and very early Type II PPB are not suspicious for malignancy, however, when possible, a “cancer operation” is should be performed when feasible and safe. Intra-operative pathological examination and frozen sections will rarely indicate the diagnosis. When there is evidence in the patient or family history for a DICER1-associated condition, a lung cyst should be considered PPB until proven otherwise and a “cancer operation” should be planned.

Type I PPB or early Type II PPB is most often multilocular cysts occurring in the periphery of lung adjacent to and/or involving visceral pleura. The cysts of PPB are usually air filled. Pneumothorax is a common presentation. Radiographically, the lesions are diagnosed as blebs, bullae, “congenital emphysema” or “congenital cystic adenomatoid malformation” (CCAM). These lesions may be 5 – 10 cm in diameter. Rarely these tumors are unilocular cysts and rarely are completely within lung parenchyma. Predominantly cystic PPB may be exophytic and present on the visceral pleural surface, or it may substantially distort or replace lung parenchyma. The cysts may be adjacent to parietal pleura, may lie within lobar fissures and may arise near the lung hilum. Predominantly cystic PPB usually involves one segment or one lobe of the lung, but it may involve a contiguous lobe or may be multifocal and bilateral. Cystic PPB can be highly unsymmetrical, such as very large multilocular cysts in one lobe and scattered small cysts elsewhere. Occasional cystic PPB patients have marked multifocal or bilateral disease making complete resection is impossible; such patients should have the largest cyst(s) removed for diagnostic pathology (see §4.1). In Type I PPB, residual normal lung is typically markedly compressed by cysts or pneumothorax and routinely expands following resection of the diseased lung.

Outcomes following resection of Type I PPB are excellent. Most children have been followed by observation after complete resection and have not shown progression. In an IPPBR analysis of 33 individuals with Type I PPB who underwent surgery alone, 1 individual developed a second cystic PPB and 2 individuals progressed to Types II/III PPB (ASCO, . The risk for progression in an individual patient may be age-related and discussion with IPPBR staff is encouraged.

4.1.1.2 Recommended Surgery
This study recommends thoracotomy for predominantly cystic lesions. However, because pre-operative evaluation of predominantly cystic lesions is unlikely to suggest malignancy, thorascopic resections may be undertaken.

4.1.1.2.1 THORACOSCOPIC RESECTIONS
4.1.1.2.1.1 Major Cystic Structures
When thorascopic resection is performed, cystic elements should be removed as completely as possible. Cystectomy is recommended for exophytic tumors. Segmentectomy or lobectomy is recommended to the extent that lung parenchyma is replaced by cyst formation. The cysts are mostly air filled and the specimen is likely to collapse. The resection margin of the specimen should be identified for the pathologist. Fresh tissue should be submitted to the laboratory as a fresh or frozen section and for biology studies.

4.1.1.2.1.2 Additional Minor Cystic Structures
Some children present because of one large multilocular cyst but also have multifocal cysts involving diverse regions of one or both lungs. These additional cysts are often small (1 – 2 cm diameter). It is not recommended that all such cysts be removed.

4.1.1.2.1.3 Re-operation after Thorascopic Resections
Following thorascopic resection and after pathologic interpretation, an open thoracotomy to achieve a complete resection should be considered in two situations: (1) when the tumor is determined to be Type II PPB and the thorascopic resection margin is positive and/or (2) when post-operative CT scan in either Type I or early Type II PPB reveals that portions of a major cystic structure remain.

4.1.1.2.2 THORACOTOMY RESECTIONS

4.1.1.2.2.1 Major Cystic Structures
If open thoracotomy is the initial procedure, cystic elements should be removed as completely as possible. The extent of resection is dictated by the extent of the cystic defacement of lung parenchyma. Cystectomy is recommended for exophytic tumors. Segmentectomy or lobectomy is recommended depending on the extent that lung parenchyma is replaced by cyst formation. The surgical margin should be noted for the pathologist. Fresh tissue should be submitted to the laboratory as a fresh or frozen section and for biology studies.

4.1.1.2.2.2 Additional Minor Cystic Structures
Some children present because of one large multilocular cyst but also have extensive multifocal cysts involving diverse regions of one or both lungs. These additional cysts are often small (1 – 2 cm diameter). It is not recommended that all such cysts be removed unless they are obvious intra-operatively.

4.1.1.2.2.3 Re-operation after Thoracotomy Resections
If the pathologic diagnosis of predominantly cystic lesions is Type II PPB and the surgical margins are positive, a further open resection is recommended to achieve clear margins.

4.1.2 Predominantly or Completely SOLID Lesions (Types II and III PPB)

4.1.2.1 Anatomic Considerations
Types II and III PPB are thoracic masses either in lung parenchyma or in parietal pleura. Pleural effusion is present in some cases and may be considered empyema; it is rarely cytologically positive and cannot be relied upon for accurate diagnosis.
Type II PPB has gross or microscopic evidence of air-filled epithelial-lined cysts in addition to solid elements.

Type III PPB is entirely solid.

Types II and III PPB usually arise within one lobe of the lung but often invade adjacent structures: another lobe, parietal pleura, diaphragm, chest wall (rare), or mediastinum (rare). They usually destroy the lobe in which they originate. Rarely solid PPB arises in parietal pleura and lung is only compressed. These tumors often fill the hemithorax with marked mediastinal shift. Very rarely, patients require ventilator support until surgery or chemotherapy shrinkage. Tumor measurements of 10 cm x 8 cm x 12 cm are common in children aged 3 - 5 years. Types II and III tumors may be encapsulated but more often have no defining margin. Extensive parietal pleural involvement with studding or sheets of disease occurs. Types II and III PPB may be very necrotic with pre- or intra-operative rupture/spillage. Uninvolved lung may be completely effaced but is usually viable and expands promptly.

Rarely will Types II or III PPB grossly invade major thoracic vessels (as seen in cavoatrial extension of Wilms tumor). Unlike Wilms, PPB may affect right or left circulations with extension to right or left cardiac chambers. Systemic embolization may occur. Any suggestion of vascular involvement (facial plethora, vena cava syndrome, cardiac murmur) should be investigated with vascular ultrasound. Biopsy followed by chemotherapy is recommended for such cases.

4.1.2.2 Recommended Surgery
This study recommends attempted initial tumor resection if it can be accomplished. When this is not deemed possible, open biopsy is recommended. Multiple core needle biopsies may replace open biopsy. Fine-needle aspiration for cytology is not adequate.

4.1.2.2.1 Primary Resection (Recommended)
When predominantly solid PPB is of moderate size, thoracotomy resections are recommended. Lobectomy or bilobectomy is recommended. Pre- or intra-operative rupture/spillage may occur, requiring piecemeal resection. Usually one lobe is unaffected and re-expands. Surgical margins should be sampled and marked for the pathologist. Sites of unresectable residual disease should be titanium clipped for radiographic and possible radiotherapy. Fresh tissue should be submitted to the laboratory as a fresh or frozen section and for biology studies. For very large lesions, pneumonectomy occasionally has been performed. Major nodular involvement of parietal pleura should be excised. Rarely excision of one or two ribs has been utilized, but chest wall invasion is rare. Diaphragmatic involvement may require excision of a portion of the diaphragm and use of a Gortex patch.

4.1.2.2.2 Initial Open Biopsy (Recommended)
If resection is not done, adequate biopsy sampling is essential. PPB is characterized by diverse histologic morphologies which must be sampled. Open biopsy should be used. Fresh tissue should be submitted to the laboratory as a fresh or frozen section and for biology studies.
4.1.2.2.3 Initial Core Needle Biopsy (Not Preferred)
Adequate biopsy sampling is essential. PPB is characterized by diverse histologic morphologies which must be sampled. If used, multiple core biopsies must be obtained. Fresh tissue should be submitted to the laboratory as a fresh or frozen section and for biology studies.

4.1.2.2.4 Fine Needle Aspiration Cytology (FNAC) (Not Adequate)
Fine needle aspiration cytology is not typically adequate for diagnosis.

4.1.2.2.5 Delayed Resection after Biopsy and Chemotherapy (Recommended)
Although initial biopsy patients receiving chemotherapy may have dramatic tumor reduction, surgical resection is still required. An early chemotherapy response may be transient, and thoracotomy resection should be planned for Week 10, following hematologic recovery after the first three courses of chemotherapy (§4.1).

Delayed resection should be as complete as possible following the same guidelines for initial resection described above (§4.1). Tumor margins should be sampled and clipped if questionable for residual disease. Fresh tissue should be submitted to the laboratory to assess chemotherapy effect and for diagnostic and biology studies.

4.1.2.2.6 “2nd” and “3rd” Look Thoracotomies (Recommended)
For several reasons, strong consideration should be given to surgical control of the primary thoracic disease site:

First, pathology of lesions following neo-adjuvant chemotherapy suggests that anaplastic PPB is less sensitive to chemotherapy than other histologic subtypes. (Anaplasia is common: 75% of Type II PPB and 85% of Type III PPB.¹³) Therefore chemotherapy alone is unlikely to eradicate PPB.

Second, there are no studies or case reports suggesting that PPB is particularly sensitive to radiation therapy.

Third, sarcoma radiation doses (3,500-4,000 cGy) may be difficult to deliver to some thoracic locations in young children. High doses to residual disease to the chest wall or lateral aspects of the diaphragm may be possible. But, especially because of anthracycline chemotherapy, high doses to locations along the medial diaphragm, mediastinum and pericardium may not be possible. Wide fields to lung parenchyma must be limited to ~1,800-2,000 cGy and may not be therapeutic for PPB.

Therefore, this study recommends early attempts at surgical control of the primary disease site: at diagnosis or at ~week 10 after three cycles of chemotherapy. See Treatment Schema (Appendix A-V: 2.0).

If disease remains after week 10, consideration should be given to repeat thoracotomy (“3rd look”) and attempted complete resection after 2-3 further courses of chemotherapy. This study recommends up to three thoracotomies to attempt complete resection. Attempted
resection times would be approximately Week 0, Week 10, and Week 19. See Treatment Schema ([Appendix A-V: 2.0]).

4.1.3 Surgery for Type Ir (regressed) PPB
Outcomes following resection of Type Ir PPB are excellent. Most children have been followed by observation after complete resection and have not shown progression. In an IPPBR analysis of 33 individuals with Type Ir PPB who underwent surgery alone, 1 individual developed a second cystic PPB and 2 individuals progressed to Types II/III PPB. The risk for progression in an individual patient may be age-related and discussion with IPPBR staff is encouraged.

4.1.4 Surgery for Metastasis
4.1.4.1 Intracerebral Metastases
Brain parenchyma is the most common metastatic site for PPB. Resection according to general principles of neurosurgery is strongly suggested for intracranial mass lesion(s). Several patients with cerebral PPB metastases have been cured. Because PPB is associated with other dysplastic and neoplastic diseases cerebral disease in a PPB patient cannot be assumed to be PPB. Glioblastoma multiforme, medulloblastoma, and medulloepithelioma have been discovered in PPB children and their kindred. Cerebrospinal fluid involvement in PPB is rare.

4.1.4.2 Other Metastatic sites
After brain parenchyma, bone and liver are the most common sites of distant PPB metastasis. Biopsy for diagnosis is recommended, but therapeutic resection is rarely indicated.

Because PPB can be associated with several other dysplastic and neoplastic diseases, sites of new disease in PPB patients cannot be assumed to be PPB and must be investigated. Many PPB children have had additional primary tumors. For example, a child with co-occurring PPB and bladder rhabdomyosarcoma has been observed. Sertoli Leydig cell tumor, gynandroblastoma and Wilms tumor are all more common in individuals with DICER1 mutations. Contralateral lung involvement may also represent a second primary disease.

4.2 Chemotherapy Guidelines
Chemotherapy administration, chemotherapy doses, dose modifications for toxicity, and supportive care decisions should conform to local practice guidelines. The following are the recommended Guidelines of this International PPB Registry for PPB, DICER1 and Associated Conditions.
Outcomes following resection of Type Ir PPB are excellent. Most children have been followed by observation after complete resection and have not shown progression. The risk for progression in an individual patient may be age related and discussion with IPPBR staff is welcomed.
4.2.1 Type I Chemotherapy Decision and Guidelines

Whether to use chemotherapy for Type I PPB is a decision to be made by the patient’s physician and local institution. If the decision is to use chemotherapy, the International PPB Registry for PPB, *DICER1* and Associated Conditions treatment schema and roadmaps, and hydration guidelines, for the recommended therapy are provided in Appendix V.

International PPB Registry for PPB, *DICER1* and Associated Conditions recommended VAC/VA regimen is as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>≥ 3 years</td>
<td>1.5 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>≥ 1 year and &lt; 3 years</td>
<td>0.05 mg/kg IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 year</td>
<td>0.025 mg/kg IV x 1</td>
</tr>
<tr>
<td>A</td>
<td>≥ 3 year</td>
<td>0.045 mg/kg (maximum dose 2.5 mg) IV x 1</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 year</td>
<td>0.025 mg/kg IV x 1</td>
</tr>
<tr>
<td>C</td>
<td>≥ 3 year</td>
<td>1200 mg/m²/dose IV as 1 hr infusion with IV fluids and MESNA, day 0 of weeks 1, 4, 7, 10</td>
</tr>
<tr>
<td></td>
<td>&lt; 3 years</td>
<td>40 mg/kg/dose IV</td>
</tr>
<tr>
<td>M</td>
<td>Use of Mesna with this dose of cyclophosphamide is the decision of the treating physician and institution</td>
<td></td>
</tr>
</tbody>
</table>
### 4.2.2 Types II and III Chemotherapy Guidelines

Treatment of Type II and Type III PPB is determined by the patient’s physician and local institution. Guidance, including treatment schemas and roadmaps, and hydration guidelines, for IVADo therapy are provided in the Appendix V.

1. **I²VADo²** courses (courses #1, #2, #3, #4)
   Criteria to start next course: ANC ≥ 750/μL and platelet count ≥ 75,000/μL

<table>
<thead>
<tr>
<th>I²VADo² Doses</th>
<th>Drug</th>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V</strong> Vincristine</td>
<td>≥ 12 months</td>
<td>1.5 mg/m² IV x 1 (maximum dose 2 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>1 mg/m² IV x 1 (maximum dose 2 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>0.75 mg/m² IV x 1 (maximum dose 2 mg)</td>
<td></td>
</tr>
<tr>
<td><strong>A</strong> Actinomycin</td>
<td>≥ 12 months</td>
<td>1.5 mg/m² IV x 1 (maximum dose 2 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>1 mg/m² IV x 1 (maximum dose 2 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>0.75 mg/m² IV x 1 (maximum dose 2 mg)</td>
<td></td>
</tr>
<tr>
<td><strong>I</strong> Ifosfamide</td>
<td>≥ 12 months</td>
<td>3 g/m²/dose IV over 3 hours on Days 1, 2, (6 g/m²/cycle) with MESNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>2 g/m²/dose IV over 3 hours on Days 1, 2, (4 g/m²/cycle) with MESNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>1.5 g/m²/dose IV over 3 hours on Days 1, 2, (3 g/m²/cycle) with MESNA</td>
<td></td>
</tr>
<tr>
<td><strong>M</strong> MESNA</td>
<td>≥ 12 months</td>
<td>600 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>400 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>300 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.</td>
<td></td>
</tr>
<tr>
<td><strong>D</strong> Doxorubicin</td>
<td>≥ 12 months</td>
<td>30 mg/m²/dose IV over 30 min, Days 1, 2 (60 mg/m²/cycle), If BSA &gt; 2 m², maximum dose 75 mg/day (150 mg/cycle).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>20 mg/m²/dose IV over 30 min, Days 1, 2 (40 mg/m²/cycle)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>15 mg/m²/dose IV over 30 min, Days 1, 2 (30 mg/m²/cycle)</td>
<td></td>
</tr>
</tbody>
</table>

* Substitute CPM for IFOS for all subsequent cycles if significant Fanconi syndrome occurs. see Appendix VI for CPM, and Mesna with CPM, doses.
2. IVA Courses (courses #5 through #12)  
Criteria to start each course: ANC ≥ 750/μL and platelet count ≥ 75,000/μL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
</table>
| V     | Vincristine          | ≥ 3 years: 1.5 mg/m² IV x 1 (maximum dose 2 mg)  
6 – 12 mo of age: 1 mg/m² IV x 1 (maximum dose 2 mg)  
< 6 mo of age: 0.75 mg/m² IV x 1 (maximum dose 2 mg) |
| A     | Actinomycin          | ≥ 3 years: 1.5 mg/m² IV x 1 (maximum dose 2 mg)  
6 – 12 mo of age: 1 mg/m² IV x 1 (maximum dose 2 mg)  
< 6 mo of age: 0.75 mg/m² IV x 1 (maximum dose 2 mg) |
| I     | Ifosfamide           | Courses 1 - 4: 3 g/m²/dose IV over 3 hours on Days 1, 2, (6 g/m²/cycle) with MESNA  
Courses 5 - 12: 3 g/m²/dose IV over 3 hours on Day 1 (3 g/m²/cycle) with MESNA  
6 – 12 mo of age: Courses 1 - 4: 2 g/m²/dose IV over 3 hours on Days 1, 2, (4 g/m²/cycle) with MESNA  
Courses 5 - 12: 2 g/m²/dose IV over 3 hours on Day 1 (2 g/m²/cycle) with MESNA  
< 6 mo of age: Courses 1 - 4: 1.5 g/m²/dose IV over 3 hours on Days 1, 2, (1.5 g/m²/cycle) with MESNA  
Courses 5 - 12: 1.5 g/m²/dose IV over 3 hours on Day 1 (1.5 g/m²/cycle) with MESNA |
| M     | MESNA                | ≥ 1 year: 600 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.  
6 – 12 mo of age: 400 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.  
< 6 mo of age: 300 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7. |

* Substitute CPM for IFOS for all subsequent cycles if significant Fanconi syndrome occurs. see Appendix VI – 1.2 for CPM, and Mesna with CPM, doses.

4.3 Radiation Therapy Guidelines

Although there are no specific studies or case reports specifically supporting a curative role for radiation therapy in PPB radiation therapy should be considered for known, unresectable residual primary disease, after chemotherapy and aggressive attempts at surgical resection.

4.3.1 Residual Primary Thoracic Disease

Focal boosts to childhood soft-tissue sarcoma doses should be considered where anatomic site allows (e.g., lateral diaphragm or thoracic cage). Typical limitations to radiation of lung parenchyma must be followed.

The timing of radiation to residual chest disease is suggested in the study schema (Appendix V: 2.0). Use of radiation is a decision of the treating institution and physicians. When radiation therapy is utilized, copies of planning and documentation of radiation administered are requested to aid in future analyses.

4.3.2 Metastatic Disease

Cerebral Metastasis

Radiation therapy is specifically recommended for control of cerebral metastasis following attempted surgical resection. Several children with cerebral metastases have been cured. Physicians may contact the International PPB Registry for PPB, DICER1 and Associated Conditions for details of therapy in cured cerebral metastasis cases.
Other Metastatic Sites
The treating physician will determine therapy including surgery, radiation and chemotherapy modalities.

5.0 CHEMOTHERAPY ADMINISTRATION, DOSE MODIFICATIONS FOR TOXICITY, AND SUPPORTIVE CARE GUIDELINES

All aspects of chemotherapy administration (including, for example, hydration, use of uroprotective agents, dose modifications for toxicity, use of hematopoietic stimulants) are the responsibility of the treating physician and institution. Local supportive care practices should be followed.

The following guidelines are included in the appendices:
- Hydration guidelines for Type I PPB (Appendix A-V:1.1.3)
- Hydration guidelines for Types II and III PPB (Appendix A-V:2.1.3)
- Dose modifications for toxicity and supportive care guidelines (Appendix A-VI:1.0)

6.0 OBSERVATION GUIDELINES

6.1 Observation Guidelines for Type I PPB: For Patients with Surgery Only

<table>
<thead>
<tr>
<th>Test-Observation/Time</th>
<th>Diagnosis</th>
<th>Post Surgery/ Baseline</th>
<th>Year 1 after diagnosis</th>
<th>Year 2 after diagnosis</th>
<th>Yearly 3 after diagnosis</th>
<th>Thereafter until age 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx/PE (Ht/Wt), Clinical assessment</td>
<td>X</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray^</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest CT*</td>
<td>X</td>
<td>X</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
<td></td>
</tr>
</tbody>
</table>

^ Additional chest x-rays at the discretion of the treating physician.
*Physicians must recognize that recurrence of chest disease may occur up to 4-5 years after resection of Type I PPB. Furthermore, solid PPB can develop very quickly. It is difficult to perform adequate surveillance for early detection. Modern chest CT scanners with reduced radiation exposures for small children are recommended. Only chest surveillance and routine screening is recommended. Metastasis has not been observed in Type I PPB.
### 6.1.2 Observation Guidelines for Type I PPB: During Treatment, for Patients who Receive Chemotherapy

<table>
<thead>
<tr>
<th>Observation Week</th>
<th>Week 0 Diagnosis</th>
<th>Week of Therapy</th>
<th>Week 24 End of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>H&amp;P, Ht/Wt</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum Collection</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC/Diff/Plt</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Creatinine, SGPT, Alk. Phos, Ca/Phos/Alb</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Electrolytes (Na, K, Cl, CO2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest CT</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MRI</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Retroperitoneum and liver CT</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bone scan</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Consider LP for cytology in individuals at high risk of CNS metastatic disease including individuals with other sites of metastasis or abnormal MRI. If LP performed for clinical indication, consider sending additional 1 ml CSF for biomarker analysis.

** Chest MRI: In general, MRI has limited value in the chest. However, for delineating sarcomatous PPB from other soft tissues in the thorax, for following response to chemotherapy, and for reducing diagnostic radiation exposure, thoracic MRI can be useful in management of Types II and III PPB. For lesions with extensive air-filled cystic components, chest CT is preferred. Because additional air-filled pulmonary cysts can develop or enlarge in children with PPB, chest CT should be done at least annually when MRI is the primary surveillance modality. Consider additional imaging to evaluate sites of known metastatic disease as clinically indicated. Treating providers are also referred to Children’s Oncology Group Long Term Follow up Guidelines for intervals for cardiopulmonary assessments (www.survivorshipguidelines.org). Pulmonary function testing as clinically indicated is also recommended for individuals who have undergone pulmonary resection or radiation.
### 6.1.3 Observation Guidelines for Type I PPB: Post Chemotherapy, for Patients who Received Chemotherapy

<table>
<thead>
<tr>
<th>Test-Observation/Time</th>
<th>Year 1 after diagnosis</th>
<th>Year 2 after diagnosis</th>
<th>Yearly 3 after diagnosis</th>
<th>Thereafter until age 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx/PE (Ht/Wt), Clinical assessment</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Chest x-ray*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest CT</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
<td>Every 6 months</td>
</tr>
</tbody>
</table>

* Additional chest x-rays at the discretion of the treating physician.

*Physicians must recognize that recurrence of chest disease may occur up to 4-5 years after resection of Type I PPB. Furthermore, solid PPB can develop very quickly. It is difficult to perform adequate surveillance for early detection. Modern chest CT scanners with reduced radiation exposures for small children are recommended. For individuals with germline \textit{DICER1} mutations, additional screening may be indicated. Please refer to \textit{DICER1} surveillance guidelines. Metastasis has not been observed in Type I PPB however metachronous conditions may develop. Treating providers are also referred to Children’s Oncology Group Long Term Follow up Guidelines for intervals for cardiopulmonary assessments (www.survivorshipguidelines.org). Pulmonary function testing as clinically indicated is also recommended for individuals who have undergone pulmonary resection.
6.2 Observation Guidelines for Types II and III PPB

6.2.1 Observation Schedule Types II and III PPB - While on Treatment:

<table>
<thead>
<tr>
<th>Observation</th>
<th>Week 0 Diagnosis</th>
<th>Week 0 post surgical baseline, if tumor resected</th>
<th>Week of Therapy</th>
<th>Week 37 End of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy Course</td>
<td>Week 0</td>
<td></td>
<td>1 2 3 4 5 6 7 8 9 10 11 12</td>
<td></td>
</tr>
<tr>
<td>Hx/PE, Ht/Wt</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/Diff/Plt</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Collection</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis, Creatinine, SGPT,</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alk. Phos, Ca/Phos/Alb, Electrolytes (Na, K, Cl, CO2)</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance or GFR</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF cytology*</td>
<td>X</td>
<td></td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest CT (or MRI**)</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen CT</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Scan and/or PET/CT</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac ECHO or MUGA and EKG for cardiac monitoring</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head MRI or enhanced CT</td>
<td>X</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Consider LP for cytology in individuals at high risk of CNS metastatic disease including individuals with other sites of metastasis or abnormal MRI. If LP performed for clinical indication, consider sending additional 1 ml CSF for biomarker analysis.

** Chest MRI: In general, MRI has limited value in the chest. However, for delineating sarcomatous PPB from other soft tissues in the thorax, for following response to chemotherapy, and for reducing diagnostic radiation exposure, thoracic MRI can be useful in management of Types II and III PPB. For lesions with extensive air-filled cystic components, chest CT is preferred. Because additional air-filled pulmonary cysts can develop or enlarge in children with PPB, chest CT should be done at least annually when MRI is the primary surveillance modality. Consider additional imaging to evaluate sites of known metastatic disease as clinically indicated. Treating providers are also referred to Children’s Oncology Group Long Term Follow up Guidelines for intervals for cardiopulmonary assessments (www.survivorshipguidelines.org). Pulmonary function testing as clinically indicated is also recommended for individuals who have undergone pulmonary resection or radiation.

6.2.2 Observation Guidelines Types II and III PPB - Post-Therapy:
<table>
<thead>
<tr>
<th>Test-Observation/Time</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Yearly thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx/PE</td>
<td>monthly</td>
<td>q 3 mo</td>
<td>q 6 mo</td>
<td>X</td>
</tr>
<tr>
<td>CBC &amp; chemistries</td>
<td>monthly</td>
<td>q 3 mo</td>
<td>q 6 mo</td>
<td>X</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>monthly</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Chest &amp; upper abdomen CT (or MRI*)</td>
<td>q 3 mo</td>
<td>q 3 mo</td>
<td>q 6 mo</td>
<td></td>
</tr>
<tr>
<td>Head MRI or enhanced CT</td>
<td>q 3 mo</td>
<td>q 3 mo</td>
<td>q 6 mo</td>
<td></td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
<td></td>
<td>X</td>
<td>q 5 years</td>
</tr>
</tbody>
</table>

* Chest MRI: In general, MRI has limited value in the chest. However, for delineating sarcomatous PPB from other soft tissues in the thorax, for following response to chemotherapy, and for reducing diagnostic radiation exposure, thoracic MRI can be useful in management of Types II and III PPB. For lesions with extensive air-filled cystic components, chest CT is preferred. Because additional air-filled pulmonary cysts can develop or enlarge in children with PPB, chest CT should be done at least annually when MRI is the primary surveillance modality. ** LP with cytology should be considered for individuals with previous CNS metastatic disease or high risk of CNS metastatic disease such as those with abnormalities on brain MRI or those with bone mets.

### 6.3 Followup Guidelines for Arm D: DICER1 and Associated Conditions

Suggested observations for DICER1 related conditions are specific to each condition. Surveillance of individuals with germline DICER1 mutations or mosaicism should be considered.

A request for follow-up to the treating institution and or the patient will be sent on a yearly basis.
7.0 QUALITY OF LIFE OUTCOMES

7.1 Quality of Life Study

This study is designed to allow the International PPB Registry for PPB, DICER1 and Associated Conditions to determine the quality of life (QOL) outcomes based on QOL assessments in patients and their parents or legal guardians. The QOL design will allow for assessment at the same points across countries for English-speaking or Spanish-speaking participants. Outcomes in individuals will be assessed by a neuropsychologist with extensive experience in assessment of neuropsychology and QOL outcomes in childhood cancer survivors and their parents. The use measures have standardization of data flow, and the quality measures been validated for various age groups and will allow more global concerns to be addressed. Comparing the impact between two groups: one of patients, the other of parents, will allow for a better understanding, from each groups’ perspective as to the impact the diagnosis and treatment of PPB has and to try to determine predictors of poor outcome so that interventions can be developed.

7.1.1 Pediatric Quality of Life Inventory System

The Pediatric Quality of Life Inventory Measurement System (PedsQL) will be used to measure health-related quality of life (HRQOL) and fatigue beginning at entry to long-term follow-up (i.e., 2 years after completion of treatment) and re-administered every other year to monitor changes over time. The PedsQL is a widely used system for measuring HRQOL in childhood cancer patients and other chronic illnesses of childhood. Parent proxy report versions will be used for children ages 2-18 years of age to assess parent perceptions of child HRQOL. In addition, child/adolescent self-report versions will be used for those ages 5-18 years of age. The young adult self-report version will be used for those over 18 years of age. Items comprising each of the forms are essentially identical, differing only in developmentally appropriate language, or first or third person tense. The instructions for the standard version asks the rater to determine how much of a problem each item has been during the past 1 month on a 5-point likert scale (with 0 being never and 4 being almost always). Items are reverse scored and linearly transformed to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0) such that higher PedsQL scores indicate better HRQOL (fewer symptoms). Spanish language versions are available and will be used with Spanish-speaking families.

The following PedsQL scales will be used, with total time spent in administration and completion expected to be no more than 10 minutes, and based on survey developers’ estimates:

- The PedsQL 4.0 Generic Scale consists of 23 items measuring the core physical, mental, and social health dimensions as delineated by the World Health Organization, as well as school functioning.
- The PedsQL Multidimensional Fatigue Scale consists of 18-items which encompass 3 subscales tapping 1) General Fatigue, 2) Sleep/Rest Fatigue, and 3) Cognitive Fatigue.

All scales have acceptable internal consistency reliability (child- and parent-report alphas .89 to .93 for the Generic and Fatigue Modules) and have been shown to distinguish healthy children and children with cancer as a group, and among children with cancer who are on and off treatment.

8.0 PATHOLOGY AND BIOLOGY TISSUE SPECIMENS
REQUESTED SPECIMENS

Preparation of Specimens  See Appendix II
Shipping of specimens

9.0 OFF PROTOCOL AND OFF STUDY CRITERIA

This is a registry. Therefore, a child’s treating physician is responsible for deciding whether to use or to continue to use recommended Guideline therapies.

The International PPB Registry for PPB, DICER1 and Associated Conditions will follow outcomes.

10.0 STATISTICS

10.1 Statistical Considerations

The first objective includes estimation of event-free survival (EFS) and overall survival (OS) rates in patients with Type I PPB treated at physician discretion.

The second objective of this study is to estimate EFS and OS rate of patients with Type II/III PPB treated with a prescribed regimen of single-arm chemotherapy.

The third objective is to follow patients with DICER1-associated conditions. A Table with these diseases and other descriptive statistics may be done.

10.1.1 Accrual Rate

The IPPBR enrolled 28 patients with PPB in 2015, with 22 additional patients known to the IPPBR who have had central pathology confirmation by a Registry pathologist, but for whom consents are pending. We anticipate that a minimum of 20 patients with Type II/III PPB will be eligible for this study per year.

10.1.2 Endpoints

The primary endpoints for statistical analysis will be time from start treatment to an event, defined as the occurrence of progression or recurrence of PPB, occurrence of a second malignant neoplasm, or death from any cause that is at least possibly related to the original disease or treatment. Secondary endpoints will be the best overall response to chemotherapy among patients with radiographically measurable tumor following initial surgery or biopsy, and time to death from any cause.

10.1.3 Statistical Methods

Estimates of EFS percent and OS percent will be based on the product-limit (Kaplan Meier) estimate with Greenwood standard errors. Estimates of response rate (CR/PR) will be based on the asymptotic normal approximation to the binomial distribution.

10.1.4 Accrual Target and Statistical Precision

The accrual goal for this study will be based on achieving sufficient precision for estimating 5-year DFS. Data from the IPPBR shows that 5-year DFS rates in 124 Type II patients, 21 Type II/III patients, and 90 Type III patients are 71%, 53%, and 62%, respectively, which suggests 5-year DFS for the combined group of 62%.


Assuming a minimum of 2 years follow-up on the last patient enrolled on this study at the time of final analysis and a 5% loss to follow-up rate overall, enrollment of 120 Type II/III patients over 4 years will provide a standard error for the 5-year EFS estimate of approximately ±5.2%. Similar precision will be achieved for the 5-year OS estimate. Precision of EFS and OS estimates in Type I patients and for response in Type II/III patients will depend on the number of Type I patients enrolled and on the number of Type II/III patients with radiographically measurable tumors.

10.2 Data Management

10.2.1 Patient/Tissue Data
Patient tissue and data will be recorded and maintained by the study office.

10.2.2 Clinical Data
Demographic, clinical data, and pathology data will be abstracted into the database using each patient’s unique study identifier number.

11.0 CRITERIA FOR RESPONSE TO THERAPY

11.1 Radiographic Primary Tumor Response, Volumetric

11.1.1 Type I PPB
The goal for Type I PPB surgery is complete removal of major cystic elements while avoiding rupture, spillage and tumor at surgical margins. This must be assessed with early post-operative chest CT scan (see Surgical Guidelines §4.1). Some small and multifocal cysts cannot all be resected; if major cystic elements are bilateral, bilateral surgery is recommended.

Complete Response/Resection (CR) for Type I PPB is radiographic evidence of removal of all major cystic elements.

Partial response/resection (PR): residual elements of major cystic structures larger than 10% volume of initial cystic volume.

Progressive Disease (PD): At least 40% cyst volume increase compared to the smallest volume obtained since the beginning of therapy.

11.1.2 Types II and III PPB
For Type II and III PPB patients treated with primary surgery or with neoadjuvant chemotherapy and surgery: three-dimension, volumetric measurements are required to measure chemotherapy response. CT and/or MRI are reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest.

- Complete Response (CR): Complete disappearance of the tumor:

  Depending on therapy sequence, CR can be achieved in five ways:
1. following neoadjuvant chemo. (unusual)
2. following neoadjuvant chemo and delayed primary surgery. (common)
3. following neoadjuvant chemo, surgery, and requiring adjuvant chemo. (most common)
4. following primary surgical resection. (unusual)
5. following primary surgical resection and adjuvant chemo. (common)

The way in which CR is achieved will be considered in outcome evaluations.

- Partial Response (PR): At least 65% volume decrease compared to the measurement obtained at diagnosis. This is the minimum tumor volume (maximal response to all therapies) achieved at any time after diagnosis. As in the CR criterion above, any of the above therapy sequences may result in this PR assessment.

- Progressive Disease (PD): At least 40% tumor volume increase compared to the smallest volume obtained since the beginning of therapy.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as a reference the smallest disease volume since treatment started. Assessments which meet these criteria must be >6 weeks apart.

- Neoadjuvant Chemotherapy Response: for children treated with neoadjuvant chemotherapy, the maximal volume decrease before surgical resection will be determined and considered in outcome evaluations.

### 11.2 Metastatic Disease Response Measurements

Responses of metastatic disease at diagnosis will be tabulated and evaluated individually (for example: number of bone lesions and response to chemotherapy and/or radiation).

### 12.0 ADVERSE EVENT REPORTING REQUIREMENTS

#### 12.1 Adverse Event Reporting Purpose

Adverse reporting, as required by regulatory agencies, must meet the specific guidelines of the country where each individual subject is enrolled. Data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

#### 12.2 Determination of Reporting Requirements

Adverse events reporting should be first and foremost follow the guideline of the local institution or country/state requirements.

We encourage notification to the Registry adverse events for any of the agents used in this International PPB Registry for PPB, DICER1 and Associated Conditions, all of which are commercially available agents. Notification should include:

1) The characteristics of the adverse event including the grade (severity).
2) The relationship to the study therapy (attribution).
3) The prior experience (expectedness) of the adverse event.
Determine the prior experience. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current Agent-Specific Adverse Event List; or
- the drug package inserts.

### 12.3 Reporting of Adverse Events for Commercial Agents:

This table outlines the reporting requirements for adverse events experienced by patients on this International PPB Registry for PPB, *DICER1* and Associated Conditions.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexpected</td>
<td>Expected</td>
</tr>
<tr>
<td>Unrelated or Unlikely</td>
<td>Registry Adverse Events Report Required</td>
<td>Registry Adverse Events Report Required</td>
</tr>
<tr>
<td>Possible, Probable, Definite</td>
<td>Registry Adverse Events Report Required</td>
<td>Registry Adverse Events Report Required</td>
</tr>
</tbody>
</table>

This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported to via a Registry Adverse Events Report form.

### 12.4 Reporting Secondary AML/MDS

Although this International PPB Registry for PPB, *DICER1* and Associated Conditions is not an NCI sponsored trial, the IPPB requests that participants use NCI-similar procedures to report all cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on this International PPB Registry for PPB, *DICER1* and Associated Conditions.

Submit the following information within thirty days of an AML/MDS diagnosis occurring after treatment:

- a completed PPB Registry Secondary AML/MDS Report Form (Appendix VIII).
- a copy of the pathology report confirming the AML/MDS; and
- a copy of the cytogenetic report (if available).

Submit the information via fax to:

The International PPB Study Office
Children’s Minnesota
910 East 26th Street, Suite 40-LL10
Minneapolis, MN 55404, USA
Tel: (612) 813-7121
13.0 RECORDS AND REPORTING

13.1 Data Submission

The following data will be provided on every enrolled patient.
(Records may be de-identified at the local institution, replacing all unique identifiers with the Patient Unique Study Identification Number.

- Signed study consent (and assent if required) and HIPAA if patient treated in the U.S.
- Human Subjects Committee, Institutional Review Board or Helsinki Committee study approval letter (if applicable at the patient’s institution)
- Hospital discharge summaries
- Pathology reports on
  - surgical specimens (biopsy, resection, and metastasis)
  - pleural fluid cytology
  - bone marrow
  - spinal fluid
  - molecular studies
  - cytogenetic studies
- Surgical/operative reports
- Radiology reports (x-ray, CT scan, MRI scan, bone scan etc)
- Genetic testing reports
- Digital copies of diagnostic studies (and of selected follow-up studies, when requested)
- Treatment records (chemotherapy, radiation therapy, including chemotherapy roadmaps or Case Report Forms:
  - Type I PPB VAC/VA roadmaps: Appendix V
  - Types II/III PPB IVADo roadmaps: Appendix V
  - Case Report Forms: Appendix IX
- Oncology clinic records
- Consultations
- Family medical history including family medical history diagram, if available

13.1.2 Submission Address

(for Pathology Central Review shipment See Appendix II; for biologic material shipment, see Appendix II).

Send data to the International PPB Registry for PPB, DICER1 and Associated Conditions Office:

The International PPB Study Office
Children’s Minnesota
910 East 26th Street, Suite 40-LL10
Minneapolis, MN 55404, USA
14.0 IMAGING STUDIES

See §6.1 for Type I PPB and §6.2 for Types II/III PPB for the International PPB Registry for PPB, DICER1 and Associated Conditions observation schedule.
## APPENDIX I: PRE-TREATMENT (POST SURG; POST PATH) STS-STYLE GROUP CLASSIFICATION

<table>
<thead>
<tr>
<th>&quot;STS Clinical Group&quot;</th>
<th>PPB Type</th>
<th>Tumor Site Extension/Invasion (if T1 or T2, add modifier)</th>
<th>Size*</th>
<th>Intrathoracic/ Hilar Nodes* (add modifier)</th>
<th>Metastasis</th>
<th>Laterality</th>
<th>Focality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia or b, Ila or b, Ilib or b</td>
<td>I</td>
<td>TX, T1 or T2</td>
<td>a, b or c</td>
<td>N0</td>
<td>M0</td>
<td>u, b</td>
<td>u, m, fx</td>
</tr>
<tr>
<td>(In Type I PPB, subgroups Ib and Ilib probably do not exist)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ia or b, Ila or b, Ilib or b</td>
<td>II</td>
<td>TX, T1 or T2</td>
<td>a, b or c</td>
<td>N0, N1, NX</td>
<td>M0</td>
<td>u, b</td>
<td>u, m, fx</td>
</tr>
<tr>
<td>Ia or b, Ila or b, Ilib or b</td>
<td>III</td>
<td>TX, T1 or T2</td>
<td>a, b or c</td>
<td>N0, N1, NX</td>
<td>M0</td>
<td>u, b</td>
<td>u, m, fx</td>
</tr>
<tr>
<td>IV</td>
<td>II or III</td>
<td>TX, T1 or T2</td>
<td>a, b or c</td>
<td>N0, N1, NX</td>
<td>M1</td>
<td>u, b</td>
<td>u, m, fx</td>
</tr>
</tbody>
</table>

**Group I:** Localized disease, completely resected (documented clear margins preferred)
- (a) confined to lobe (and associated visceral pleura) of origin or to parietal pleura
- (b) contiguous involvement (infiltration to adjacent lobe, diaphragm, mediastinum, parietal pleura, or chest wall beyond pleura).

**Group II:** Gross total resection (GTR) with microscopic residual
- (a) GTR, micro residual, and no known intrathoracic/hilar node involvement
- (b) GTR, micro residual and path pos intrathoracic/hilar nodes

**Group III:** Incomplete resection with gross residual disease
- Biopsy or incomplete resection with macroscopic residual
  - (a) biopsy only
  - (b) gross/macro residual but >50% resection

**Group IV:** Metastatic disease

### Abbreviations:
- **vp** = visceral pleura
- **pp** = parietal pleura
- **TX:** T status uncertain
- **T1:** “Confined to anatomic site of origin” = confined to tissue of origin
- **T1l:** confined to vp + lobe of origin
- **T1pp:** confined to pp of chest wall, mediastinum, or diaphragm
- **T2:** “extension and/or fixation to surrounding tissue” = extends beyond lobe/vp of origin to another lobe or to adjacent intrathoracic structures:
  - **T2l:** invades another lobe/vp of the lung
  - **T2d:** invades diaphragm or assoc pp
  - **T2cw:** invades chest wall or assoc pp
  - **T2m:** invades mediastinum or assoc pp
- **T2** does not include very light adhesions between lobes or between lobes and parietal pleura
- **T2** may involve more than one surrounding structures; code all.

### Size:
- **maximum diameter**:
  - (a) < 5 cm.
  - (b) 5 - 10 cm.
  - (c) > 10 cm.

### Intrathoracic/ Hilar Nodes:
- **N0**: not clinically** involved, not sampled
- **N1**: clinically involved, sampled, path -
  - **N1, sp-:** clinically involved, sampled, path -
  - **N1, sp+:** clinically involved, sampled, path +
- **NX**: status unknown/not assessed, not mentioned

### Metastasis:
- **M0**: no distant metastasis
- **M1**: distant metastasis*

### Laterality:
- **u**: unilateral
- **b**: bilateral
- **m**: multifocal

### Focality:
- **u**: unifocal lesion
- **m**: multifocal lesion
- **fx**: focality not determined

* size does not include pneumothorax
* any nodes outside the thoracic cavity are distant mets
* max diam of: cyst, or cyst + tumor, or tumor
* supraclavicular or intraabdominal nodes are distant metastasis
** "clinically" = noted by radiography or by surgeon at operation

*any nodes outside the thoracic cavity are distant mets
m = multifocal: discrete separate cysts and/or PPB within one or more lobes. (if bilateral, may be multifocal on one side and unifocal on other.)
 u = unifocal: solitary lesions
fx = focality unknown or undetermined (large lesions often obscure residual lung detail)
APPENDIX II: PATHOLOGY AND BIOLOGIC TISSUE SPECIMENS

The International PPB Registry for PPB, DICER1 and Associated Conditions recommends attempted initial tumor resection if it can be accomplished. When this is not deemed possible, open biopsy is recommended. Multiple core needle biopsies may replace open biopsy. Fine-needle aspiration for cytology is not adequate. Once removed, tumor tissues rapidly degrade so it is necessary for biological specimens to be processed directly in the Operating Room under the supervision of the Pathology Department. Tissues should be as sterile as possible. After the necessary tissues are obtained for local institutional diagnosis and research, the remaining tissue should be submitted.

DNA derived from tumor, normal lung, will be appropriately stored indefinitely for future research.

A-II: 1.1 Tissue for Diagnosis - Preparation

Submit solid tissue in as many of the following formats as possible but do so in this order of priority:

A-II: 1.1.1 Histologic Sampling

1. **Incisional biopsy or core needle biopsy** – If primary resection is not used, *incisional biopsy* is recommended. If core needle biopsies are used, several cores should be taken to obtain sufficient tissue for diagnosis and for biology studies. *Fine needle aspiration cytology (FNA)* is not acceptable.

2. **Tumor excision** – Representative tissue from all the varying regions of the tumor mass must be sampled for classification. Adequate sampling requires approximately 1 section per cm diameter of tumor. Include samples of both cystic and solid areas if both are present. Tissue sampling should focus on viable appearing tissue. Tissue margins should be examined histologically to evaluate complete or incomplete tumor resection when applicable.

Consider preserving additional tumor tissue – fresh, snap frozen, paraffin or formalin blocks for the PPB Biology Specimens Reference Bank (§4.1).

A-II: 1.1.2 Recommended Histologic and Microscopic Studies

PPB is a pattern diagnosis made with routine histopathologic and immunologic stains. Microscopically, Type III PPB and the solid areas of Type II PPB show at least one of four basic histologic patterns that may blend into each other: (1) cohesive aggregates of primitive small cells with hyperchromatic nuclei, high ratio of nuclei to cytoplasm, and brisk mitoses resembling the blastoma of a Wilms tumor; (2) spindled, stellate, and small ovoid cells in a variably prominent myxoid stroma resembling embryonal rhabdomyosarcoma; (3) spindle cell sarcoma resembling synovial sarcoma of congenital-infantile fibrosarcoma; or (4) nodules of immature or overtly malignant cartilage. Individual or groupings of large anaplastic cells with highly atypical mitotic figures are present in 75% of Type II and 85% of Type III cases. Eosinophilic hyaline bodies are often seen in association with anaplastic cells. Within any one tumor, not all patterns are equally represented and one or two patterns may dominate the overall microscopic appearance. Occasional cases show other sarcomatous subtypes. Rarely neuroblastic differentiation has been seen.

A-II: 1.1.3 PPB Tumor “Type” Classification

PPB tumors will be classified as Type Ir, Type I, Type II and Type III according to the criteria supplied
Pathologists are advised that Type II and especially Type III PPB can be necrotic with “cysts” not lined by respiratory epithelium. These are “pseudocysts” and do not represent the pulmonary cyst remnants necessary for Type II PPB classification.

A-II: 1.2 Tissue for Biology Studies – Preparation
Specimens from the Pathology Laboratory requested for biology studies include, when available:

- Fresh and frozen tumor tissue (and, when present, normal tissue)
  AND
- Paraffin-embedded tumor tissue (and, when present, normal tissue)
  AND/OR
- Formalin-fixed tumor tissue (and, when present, normal tissue)

A-II: 1.2.1 Preparation of Snap Frozen Primary or Metastatic Tumor and Normal Tissue
Prepare frozen specimens of tumor and non-neoplastic lung or other tissue for Biology Studies as follows:

From several areas of viable tumor, prepare 1 cm³ (1 gram) aliquots of tumor and normal tissue (up to 10 samples if available), wrap in foil, or place in cryopreservation tubes if the tumor is very liquid, and snap freeze in liquid nitrogen or cold isopentane chilled in liquid nitrogen or dry ice. The tissue must be frozen within 15 - 20 minutes after removal, so in most cases it will be necessary to have liquid nitrogen available in the Operating Room.

Place in a sealable plastic bag and label bag:

(a) with the patient’s unique study identifier number
(b) surgical pathology number
(c) “tumor” versus “normal”
(d) tissue site
(e) date obtained

Store in a manner that will preserve the nucleic acids in the specimen (-70 to 80 °C freezer or liquid nitrogen tank). Specimens must be kept below -70° C until shipped. A regular freezer (-20° C) is not adequate. See shipping instructions in Appendix A-II: 1.2.1.

A-II: 1.2.2 Preparation of Paraffin-embedded Primary or Metastatic Tumor and Normal Tissue
When sufficient paraffin-embedded tissue has been dedicated to diagnostic studies, excess primary tumor, metastatic tumor or resected normal tissue is useful for Biology Studies. Paraffin block(s) or a complete set of hematoxylin and eosin-stained slides and 15 unstained paraffin sections on glass sections.

Place the slides in cassettes to prevent breakage, and blocks in paper envelopes. Label envelopes:
(a) with the patient’s unique study identifier number
(b) surgical pathology number
(c) “tumor” versus “normal”
(d) tissue site
(e) date obtained

See shipping instructions in Appendix A-II: 1.2.2.

**A-II: 1.2.3 Preparation of Formalin-fixed Primary or Metastatic Tumor and Normal Tissue**

When sufficient formalin-fixed tissue has been dedicated to diagnostic studies, excess primary tumor, metastatic tumor or resected normal tissue is useful for Biology Studies.

"Cassette-sized” aliquots of tumor and adjacent normal tissue (when available) should be placed in appropriately-labeled formalin jars. Stretch the Parafilm around the jar lids after the lids are attached to the jars. Using a waterproof marker, label the jars:

(a) with the patient’s unique study identifier number
(b) surgical pathology number
(c) “tumor” versus “normal”
(d) tissue site
(e) date obtained

These should be shipped as soon as convenient since excessive fixation reduces the usefulness of the tissue. See shipping instructions in Appendix A-II: 1.2.3.

**A-II: 1.3 Biology Studies**

See separate Standardized Protocol for Specimen Processing

**A-II: 1.3.1 Preserved tissue for Biology Studies**

**A-II: 1.3.1.1 Paraffin-embedded tissue** (primary or metastatic tumor or normal tissue)
When sufficient paraffin-embedded tissue has been dedicated to diagnostic studies, excess primary tumor, metastatic tumor or resected normal tissue will be submitted for International PPB Registry for PPB, **DICER1** and Associated Conditions biology studies.

See shipping instructions in Appendix A-II: 1.5.

**Formalin-fixed tissue** (primary or metastatic tumor or normal tissue)
See shipping instructions in Appendix A-II: 1.2.3.

**Frozen tumor tissue** (and, when present, normal tissue).
See shipping instructions in Appendix A-II: 1.2.1.

**Fresh tumor tissue** (and, when present, normal tissue).
Contact PPB Registry pathologist Dr. D. Ashley Hill (ph: 202-476-2815; email: dashill@cnmc.org) for
A-II: 1.4  **Shipment of Specimens for Central Pathology Review**  
(Required for the International PPB Registry for PPB, *DICER1* and Associated Conditions enrollment)

The International PPB Registry for PPB, *DICER1* and Associated Conditions enrollment is based on local pathology diagnosis. However, pathology material and pathology reports are sent to the International PPB Registry for PPB, *DICER1* and Associated Conditions office for central pathology review. Any discrepancies in the diagnostic interpretation will be discussed directly with the submitting pathologist or clinician. If the central-review diagnosis is not considered PPB, the referring physician will be notified promptly. Cases which are not PPB will be removed from the study unless the diagnosis makes the case eligible for the associated diseases arm of the International PPB Registry for PPB, *DICER1* and Associated Conditions.

**Required materials:**
- Label all materials with the patient’s unique study identifier number.
- Call or email the Study Office (612-813-7121 or PPBinfo@childrensmn.org) to notify the study of the shipment. Shipping account number is available to cover shipping cost.
  (A) 1 H&E section of all available blocks, and
  (B) 1 or 2 representative paraffin blocks from excess tumor tissue

  OR

  (C) Prepare from 2 representative paraffin blocks:
  - 2 H&E slides from the same blocks and
  - 10 unstained sections (on plus-charged, polarized slides) for immunoperoxidase studies,

Include with the blocks or slides:
1. Institutional Pathology Report
2. Institutional Operative Report
3. Study Specimen Transmittal Form
4. Gross photographs are encouraged (digital format preferred)

**Send all central pathology review materials to:**

International PPB Registry  
Children’s Minnesota  
910 East 26th Street  
Suite 40-L110  
Minneapolis, MN 55404  
USA

Telephone: 612-813-7121  
E-mail: PPBinfo@childrensmn.org  
Fax: 612-813-7108
A-II: 1.5 Shipment of Biologic Specimens
(Requested)

Biologic specimens requested in the International PPB Registry for PPB, *DICER1* and Associated Conditions include, when available:

- Fresh or frozen tumor tissue (and, when present, adjacent normal tissue) from biopsy, resection and/or metastasis
- Paraffin-embedded tumor tissue (and, when present, adjacent normal tissue) from biopsy, resection and/or metastasis
- Formalin-fixed tumor tissue (and, when present, adjacent normal tissue) from biopsy, resection and/or metastasis

NOTE: All shipments MUST be arranged in advance to ensure delivery on weekdays and preservation of tissue during transit. All necessary collection containers, shipping materials, address labels, biohazard labels, and courier billing forms will be provided by the International PPB Registry for PPB, *DICER1* and Associated Conditions for fresh or frozen tissue samples. Pathology blocks or slides do not need to be packaged or shipped together.

To obtain collection and shipping materials, or to schedule shipments, contact the Study Office:

Phone: 612 813 7121
Email: PPBinfo@childrensmn.org
Fax: 612-813-7108
APPENDIX III: STUDY ENROLLMENT AND PATIENT ELIGIBILITY

Several scenarios may occur leading to enrollment:

- An institution, perhaps with a coordinating cooperative oncology group, approves this Registry for
  International Registry for PPB, DICER1 and Associated Conditions in advance of a particular child’s
  diagnosis. This may include approval of therapy guidelines offered by the Registry. If a child with PPB,
  DICER1 mutation or associated condition is diagnosed in such an institution, parental consent for
  Registry enrollment is obtained and therapy is initiated. Medical records and/or biologic specimens are
  sent to the Registry.

- A child is diagnosed with PPB, a DICER1 mutation or an associated condition. Because of its rarity, the
  institution has not approved in advance therapy for or the International PPB Registry for PPB, DICER1
  and Associated Conditions. The institution decides upon and initiates the child’s therapy. The institution
  decides whether to participate in the International PPB Registry for PPB, DICER1 and Associated
  Conditions. The institution obtains all regulatory approval to participate and enroll patients on the
  International PPB Registry for PPB, DICER1 and Associated Conditions. Parental consent for Registry
  enrollment is obtained. Medical records and/or biologic specimens are sent to the Registry.

- A child is diagnosed with PPB. Because of its rarity, the institution has not approved in advance therapy
  for or study of PPB. The institution decides upon and initiates the child’s therapy. The institution allows
  the parents to act independently and to agree directly with the International PPB Registry for PPB,
  DICER1 and Associated Conditions to share their child’s medical record and/or to provide biologic
  specimens. The institution complies with the parents’ wishes.

- The above study enrollment and eligibility steps are also followed for individuals diagnosed with a
  condition associated with PPB.
PATIENT AND FAMILY MEDICAL HISTORY QUESTIONNAIRE

Patient Name ___________________________ Date Form Completed ________________
Patient Gender  □ Male  □ Female

Section I: Patient’s Racial Ethnicity (check all that apply):

- Black, or African American
- Asian
- American Indian, incl. Aleutian, Eskimo
- Arab
- White
- Indian Subcontinent
- Hispanic or Latino, incl. Mexican, Puerto Rican, Cuban, Cen. or S. American
- Other, Specify: ___________________________

Section II: Patient’s History (Circle yes or no):

1. Does the patient have any other major illnesses? Yes / No
2. Has the patient had a chest x-ray or chest CT prior to the current situation? Yes / No
3. Has the patient or a patient’s birth parent had previous genetic testing? Yes / No

If you answered Yes to any of the above questions, please provide details here:
__________________________________________________________

Section III: Past history for the patient and all family members

Is there a history of any of the following? (Check all that apply):

- collapsed lung (pneumothorax)
- nasal or sinus tumors
- lung cysts
- pituitary tumors or “adenomas”
- kidney cysts
- any eye tumors?
- cancer of cervix of uterus
- intestinal polyps or intestinal surgery
- Endometriosis
- ovarian or testicular tumors
- any childhood brain tumors
- thyroid nodules, “goiter” or cancer
- any childhood cancer (including leukemia and lymphoma)
- Syndromes/other conditions (such as VACTERL, Fragile X, NF1, etc.) or Birthmarks (such as ‘strawberry’ hemangiomas, ‘port-wine’ stains, etc.)

If you checked any of the above, please provide details here:
__________________________________________________________

__________________________________________________________

__________________________________________________________
APPENDIX V: PPB Treatment Schema, Roadmaps, and Hydration Guidelines

A-V: 1.1 Type I PPB Treatment Schema, Roadmaps, and Hydration Guidelines

Whether to use chemotherapy for Type I PPB is a decision to be made by the patient’s physician and local institution. Provided here are the International PPB Registry for PPB, DICER1 and Associated Conditions schema, roadmaps and hydration guidelines for the recommended VAC therapy.

A-V: 1.1.1 Schema

<table>
<thead>
<tr>
<th>Week of therapy:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vincristine:</strong></td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
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<tr>
<td><strong>Actinomycin D:</strong></td>
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<td><strong>Cyclophosphamide:</strong></td>
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<td>C</td>
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<tr>
<td><strong>Mesna</strong>:</td>
<td>M*</td>
<td>M*</td>
<td>M*</td>
<td>M*</td>
<td>M*</td>
<td>M*</td>
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</tbody>
</table>

*Use of Mesna with this dose of cyclophosphamide is the decision of the treating physician and institution.

A-V: 1.1.2 Type I PPB Treatment Roadmaps
### International PPB Registry for PPB, *DICER1* and Associated Conditions

#### Type I PPB Roadmap  Weeks 1 – 12

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>DOSAGE(^{\text{a}})</th>
<th>DIRECTIONS</th>
</tr>
</thead>
</table>
| Vincristine (VCR)     | IV    | Infants < 1 yr: 0.025 mg/kg/dose  
                     |       | Children ≥ 1yr to 3 yrs: 0.05 mg/kg/dose  
                     |       | Children ≥ 3 yrs: 1.5 mg/m²/dose  | IV push over 1 minute day 1 of weeks 1-9 (max. dose 2 mg).  
| Dactinomycin (DACT)*  | IV    | Infants < 1 yr: 0.025 mg/kg/dose  
                     |       | Children ≥ 1 yr: 0.045 mg/kg/dose  | Slow IV push over 1-5 minutes day 1 of weeks 1, 4, 7, 10 (max. dose 2.5 mg).  
| Cyclophosphamide (CPM)| IV    | Infants and children < 3 yrs: 40 mg/kg/dose  
                     |       | Children ≥ 3 yrs: 1200 mg/m²/dose  | IV over 30-60 minutes day 1 of weeks 1, 4, 7, 10 with Mesna*.  
| Mesna*                | IV    | ~60 % of the daily cyclophosphamide dose | IV day 1 of weeks 1, 4, 7, 10.  

\(^{\text{a}}\)Dosing rules: use current age and size at start of each course

*Use of Mesna with this dose of cyclophosphamide is the decision of the treating physician and institution*

---

### Measurements

- **Week 1:** Ht _______ cm  
  Wt _______ kg  
  BSA______m²
- **Week 4:** Ht _______ cm  
  Wt _______ kg  
  BSA______m²
- **Week 7:** Ht _______ cm  
  Wt _______ kg  
  BSA______m²
- **Week 10:** Ht _______ cm  
  Wt _______ kg  
  BSA______m²

### Treatment Schedule

<table>
<thead>
<tr>
<th>Date Due</th>
<th>Date Given</th>
<th>Week</th>
<th>Day</th>
<th>VCR _____mg</th>
<th>DACT* _____mg</th>
<th>CPM _____mg</th>
<th>Mesna* _____mg</th>
<th>Comments (Include any held dose, or dose medications with date)</th>
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<td>_____mg</td>
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Use Patient Label

**OR**

Patient Name:_______________________________________

MRN:_____________________ DOB:____________________
# International PPB Registry for PPB, DICER1 and Associated Conditions

## Type I PPB Roadmap  Weeks 13 - 23

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>DOSAGE*</th>
<th>DIRECTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine (VCR)</td>
<td>IV</td>
<td>Infants &lt; 1 yr: 0.025 mg/kg/dose</td>
<td>IV push over 1 minute day 1 of weeks 13-21 (max. dose 2 mg).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children ≥ 1yr to 3 yrs: 0.05 mg/kg/dose</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Children ≥ 3 yrs: 1.5 mg/m²/dose</td>
<td></td>
</tr>
<tr>
<td>Dactinomycin (DACT)</td>
<td>IV</td>
<td>Infants &lt; 1 yr: 0.025 mg/kg/dose</td>
<td>Slow IV push over 1-5 minutes day 1 of weeks 13, 16, 19, 22 (max dose 2.5 mg).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children ≥ 1 yr: 0.045 mg/kg/dose</td>
<td></td>
</tr>
</tbody>
</table>

*Dosing rules: use current age and size at start of each course*

Week 13: Ht _______cm  Wt ______kg  BSA______m²  
Week 16: Ht _______cm  Wt ______kg  BSA______m²  
Week 19: Ht _______cm  Wt ______kg  BSA______m²  
Week 22: Ht _______cm  Wt ______kg  BSA______m²  

<table>
<thead>
<tr>
<th>Date Due</th>
<th>Date Given</th>
<th>Week</th>
<th>Day</th>
<th>VCR _____mg</th>
<th>DACT _____mg</th>
<th>Comments (Include any held dose, or dose medications with date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
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<td>13</td>
<td>1</td>
<td>______mg</td>
<td>__________</td>
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<tr>
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<td>14</td>
<td>1</td>
<td>______mg</td>
<td>__________</td>
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<tr>
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<td>15</td>
<td>1</td>
<td>______mg</td>
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<tr>
<td>23</td>
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<td>23</td>
<td>1</td>
<td>______mg</td>
<td>__________</td>
<td>End of reporting period.</td>
</tr>
</tbody>
</table>

Use Patient Label

**OR**

Patient Name: ____________________________  
MRN: ____________________________  DOB: ____________________________
A-V: 1.1.3 Type I PPB Hydration Guidelines

A-V: 1.1.3.1 Pre-hydration, all courses:

D5½NS IV at 200 mL/m²/hour, until patient is adequately hydrated (urine output exceeds 2 cc/kg/hr).

A-V: 1.1.3.2 Post-hydration, all courses:

Suggested hydration after Cyclophosphamide dose is D5½NS IV at 3L/ m²/hour over 24 hours.
How to treat a patient with Type II or Type III PPB is a decision to be made by the patient’s physician and local institution. Provided here are the International PPB Registry for PPB, DICER1 and Associated Conditions schema, roadmaps and hydration guidelines for the recommended IVADo therapy.

### A-V: 2.1.1 Types II and III PPB I²VADo² Schema

<table>
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<tr>
<th><em>Dosing for age &gt; 12 months:</em></th>
<th>#1</th>
<th>#2</th>
<th>#3</th>
<th>#4</th>
<th>#5</th>
<th>#6</th>
<th>#7</th>
<th>#8</th>
<th>#9</th>
<th>#10</th>
<th>#11</th>
<th>#12</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFO 3 g/m²/d x 1 or 2 d</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
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<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VCR 1.5 mg/m²/d x 1 d</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>AMD 1.5 mg/m²/d x 1 d</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<td>↓</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td>DOXO 30 mg/m²/d x 2 d</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>MESNA 600 mg/m²/d x 1 d</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
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<td>↓</td>
</tr>
</tbody>
</table>

**Recommended radiographic evaluations of chest**
- Week 1: CXR
- Week 2: CXR
- Week 3: CXR
- Week 4: CXR
- Week 5: CXR
- Week 6: CXR
- Week 7: CT
- Week 8: CT
- Week 9: CT
- Week 10: CT
- Week 11: CT
- Week 12: CT
- Week 13: CT
- Week 14: CT
- Week 15: CT
- Week 16: CT
- Week 17: CT
- Week 18: CT
- Week 19: CT
- Week 20: CT
- Week 21: CT
- Week 22: CT
- Week 23: CT
- Week 24: CT
- Week 25: CT
- Week 26: CT
- Week 27: CT
- Week 28: CT
- Week 29: CT
- Week 30: CT
- Week 31: CT
- Week 32: CT
- Week 33: CT
- Week 34: CT
- Week 35: CT
- Week 36: CT

**Recommended surgical intervention**
- Week 1: Complete resection, if possible.
- Week 2: at week 10, depending on response. Attempt complete resection if not done at diagnosis.
- Week 3: at week 19. Attempt a complete resection if not done at #1 and #2.

**Focal radiation therapy, if needed** (Actino and/or Doxo will be held).

**Dose Modifications:**

<table>
<thead>
<tr>
<th></th>
<th>VCR:</th>
<th>IFOS:</th>
<th>DACT:</th>
<th>DOXO:</th>
<th>Mesna:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 months</td>
<td>0.75 mg/m²</td>
<td>1.5 gm/m²</td>
<td>0.75 mg/m²</td>
<td>15 mg/m²</td>
<td>300 mg/m²</td>
</tr>
<tr>
<td>6 months - 12 months</td>
<td>1 mg/m²</td>
<td>2 gm/m²</td>
<td>1 mg/m²</td>
<td>20 mg/m²</td>
<td>400 mg/m²</td>
</tr>
</tbody>
</table>

### A-V: 2.1.2 Type II & Type III PPB I²VADo² Treatment Roadmaps
### International PPB Registry for PPB, Dicer1 and Associated Conditions

**Types II & III Treatment Roadmap: i^2^VA^2^ ** **Weeks 1-12**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>DOSAGE^</th>
<th>DIRECTIONS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine (VCR)</td>
<td>IV</td>
<td>Infants &lt; 6 mos: 0.75 mg/m^2^/dose</td>
<td>IV push over 1 minute day 1 weeks 1-7, 10. (Max. dose 2 mg.)</td>
<td>^ Dosing rules: use current age and size at start of each course.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children ≥ 6 mos - 1yr: 1 mg/m^2^/dose</td>
<td></td>
<td>* Substitute CPM for IFOS for all subsequent cycles if significant Fanconi syndrome occurs. See Protocol Appendix A-VII: 2.0 for CPM, and Mesna with CPM, doses.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children ≥ 1 yr: 1.5 mg/m^2^/dose</td>
<td></td>
<td>^Begin next course when Plt. Ct. &gt;100k and ANC &gt; 1,000.</td>
</tr>
<tr>
<td>Ifosfamide* (IFOS)</td>
<td>IV</td>
<td>Infants &lt; 6 mos: 0.75 mg/m^2^/dose</td>
<td>IV push over 3 hours day 1 and 2 weeks 1, 4, 7, 10. Given with Mesna and hydration.</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>Children ≥ 6 mos - 1yr: 2000 mg/m^2^/dose</td>
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<td>Children ≥ 1 yr: 3000 mg/m^2^/dose</td>
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<tr>
<td>Dactinomycin (DACT)</td>
<td>IV</td>
<td>Infants &lt; 6 mos: 0.75 mg/m^2^/dose</td>
<td>IV push over 1-5 minutes day 1 weeks 1, 4, 7, 10. (Max. dose 2.0 mg.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children ≥ 6 mos - 1yr: 1 mg/m^2^/dose</td>
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<tr>
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<td>Children ≥ 1 yr: 1.5 mg/m^2^/dose</td>
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</tr>
<tr>
<td>Doxorubicin (DOXO)</td>
<td>IV</td>
<td>Infants &lt; 6 mos: 15 mg/m^2^/dose</td>
<td>IV over 30 minutes days 1 and 2 weeks 1, 4, 7, 10.</td>
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<td>Children ≥ 6 mos - 1yr: 20 mg/m^2^/dose</td>
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<td>Children ≥ 1 yr: 30 mg/m^2^/dose</td>
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<tr>
<td>Mesna (M)</td>
<td>IV</td>
<td>Infants &lt; 6 mos: 300 mg/m^2^/dose</td>
<td>IV with IFOS* over 1 hour; doses 2 and 3 over 3-5 minutes at hours 3 and 7 on</td>
<td></td>
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<tr>
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<td>Children ≥ 6 mos - 1yr: 400 mg/m^2^/dose</td>
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<td>Children ≥ 1 yr: 600 mg/m^2^/dose</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Date Due</th>
<th>Date Given</th>
<th>Week</th>
<th>Day</th>
<th>VCR mg</th>
<th>IFOS* mg</th>
<th>DACT mg</th>
<th>DOXO mg</th>
<th>Mesna dose mg</th>
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<td></td>
<td>mg</td>
<td>* mg</td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>10*</td>
<td>2</td>
<td></td>
<td></td>
<td>mg</td>
<td>* mg</td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
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</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mg</td>
<td>mg</td>
<td>mg</td>
<td>--No Chemotherapy--</td>
</tr>
<tr>
<td>12*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mg</td>
<td>mg</td>
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<td></td>
</tr>
</tbody>
</table>
### International PPB Registry for PPB, *DICER1* and Associated Conditions

#### Types II & III Treatment Roadmap: I²VAĐo² Weeks 13-36

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ROUTE</th>
<th>DOSAGE^</th>
<th>DIRECTIONS</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vincristine (VCR)</strong></td>
<td>IV</td>
<td>Infants &lt; 6 mos: 0.75 mg/m²/dose</td>
<td>IV push on day 1 of weeks 13, 16,19,22,25,28,31,34. (Max. dose 2 mg).</td>
<td>^Dosing rules: use current age and size at start of each course.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children 6 mos ≥ 1yr: 1 mg/m²/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children 1 yrs ≥: 1.5 mg/m²/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>Ifosfamide</em> (IFOS)</em>*</td>
<td>IV</td>
<td>Infants &lt; 6 mos: 1500 mg/m²/dose</td>
<td>IV push over 3 hours on day 1 of weeks 13,16,19,22,25,28,31,34. Give with Mesna and hydration.</td>
<td>*Substitute CPM for IFOS for all subsequent cycles if significant Fanconi syndrome occurs. See Protocol Appendix A-VII: 2.0 for CPM, and Mesna with CPM, doses.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children 6 mos ≥ 1yr: 2000 mg/m²/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children 1 yrs ≥: 3000 mg/m²/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dactinomycin (DACT)</strong></td>
<td>IV</td>
<td>Infants &lt; 6 mos: 0.75 mg/m²/dose</td>
<td>IV push on day 1 of weeks 13, 16,19,22,25,28,31,34.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children 6 mos ≥ 1yr: 1 mg/m²/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children 1 yrs ≥: 1.5 mg/m²/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mesna (M)</strong></td>
<td>IV</td>
<td>Infants &lt; 6 mos: 300 mg/m²/dose</td>
<td>IV with IFSO* over 1 hour; doses 2 and 3 over 3-5 minutes at hours 3 and 7 on day 1 of weeks 13,16,19,22,25,28,31,34</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children 6 mos ≥ 1yr: 400 mg/m²/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children 1 yrs ≥: 600 mg/m²/dose</td>
<td></td>
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</tbody>
</table>

**Week 13:** Ht _______cm   Wt ______kg  BSA______m²

**Week 19:** Ht _______cm   Wt ______kg  BSA______m²

**Week 28:** Ht _______cm   Wt ______kg  BSA______m²

**Week 34:** Ht _______cm   Wt ______kg  BSA______m²

<table>
<thead>
<tr>
<th>Date Due</th>
<th>Date Given</th>
<th>Week</th>
<th>Day</th>
<th>VCR ____mg</th>
<th>IFOS* ____mg</th>
<th>DACT ____mg</th>
<th>Mesna ____mg</th>
<th>Comments (Include any held dose, or dose medications with date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>1</td>
<td>1</td>
<td></td>
<td>mg</td>
<td>* mg</td>
<td>mg</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>1</td>
<td></td>
<td>mg</td>
<td>* mg</td>
<td>mg</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>1</td>
<td>1</td>
<td></td>
<td>mg</td>
<td>* mg</td>
<td>mg</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>1</td>
<td></td>
<td>mg</td>
<td>* mg</td>
<td>mg</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>1</td>
<td>1</td>
<td></td>
<td>mg</td>
<td>* mg</td>
<td>mg</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>1</td>
<td>1</td>
<td></td>
<td>mg</td>
<td>* mg</td>
<td>mg</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>1</td>
<td>1</td>
<td></td>
<td>mg</td>
<td>* mg</td>
<td>mg</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>1</td>
<td>1</td>
<td></td>
<td>mg</td>
<td>* mg</td>
<td>mg</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>1</td>
<td></td>
<td></td>
<td>End of therapy, begin follow up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Use Patient Label

OR

**Patient Name:** _______________________________________

**MRN:** _____________________  **DOB:** _______________
A-V: 2.1.3 Hydration for l²VAĐo² courses

A-V: 2.1.3.1 Pre-hydration for IVADo courses (courses #1, #2, #3, #4):

D5½NS IV at 200 mL/m²/hour, until patient is adequately hydrated (urine output exceeds 2 cc/kg/hr).

Chemotherapy:
- Vincristine IV push day 1, then weekly until (including) week 7 then every 3 weeks.
- Actinomycin IV push day 1.
- Ifosfamide (I) IV over 3 hours, days 1, 2.
- MESNA with Ifosfamide and then 3, 6, and 9 hours after the start of the Ifosfamide dose.
- Doxorubicin IV over 30 min, days 1, 2.

A-V: 2.1.3.2 Pre-hydration for IVA courses (Courses #5, #6, #7, #8, #9, #10, #11, #12):

D5½NS IV at 200 mL/m²/hour, until patient is adequately hydrated (urine output exceeds 2 cc/kg/hr).

Chemotherapy:
- Vincristine IV push day 1.
- Actinomycin IV push day 1.
- Ifosfamide (I) IV over 3 hours, day 1.
- MESNA with Ifosfamide and then 3, 6, and 9 hours after the start of the Ifosfamide dose.

A-V: 2.1.3.3 Post-hydration, all courses:

D5½NS + 10 mEq KCl/L IV at 125 mL/m²/hour beginning immediately after Ifosfamide and continuing until next Ifosfamide dose or until 24 hours after last dose.
APPENDIX VI: GUIDELINES FOR TOXICITY MODIFICATIONS AND FOR SUPPORTIVE CARE

A-VI: 1.0 Dose Modifications for Toxicities

For intolerable or unexpected toxicity, or if a patient is removed from protocol therapy for toxicity, notify the International Pleuropulmonary Blastoma Registry for PPB, DICER1 and Associated Conditions office (telephone: 612-813-7121; E-mail: PPBinfo@childrensmin.org).

A-VI: 1.1 Slow Blood Count Recovery

A-VI: 1.1.1 Neutrophils and Platelets

The growth factors G-CSF or GM-CSF may be used at the treating physician’s discretion and must be noted on the Therapy Delivery Maps. If at the time scheduled therapy, the absolute neutrophil count (ANC) has not recovered to ≥750/μL or the platelet count < 75,000/μL, further therapy should be delayed until ANC is ≥ 750/μL and platelets ≥ 75,000/μL.

A-VI: 1.1.2 Anemia

Erythropoietic growth factors (e.g. erythropoietin) may be used at the treating physician’s discretion and must be noted on the Therapy Delivery Maps.

A-VI: 1.2 Fanconi Syndrome/Renal Toxicity

Elements of Fanconi Syndrome include:
1. Renal phosphorus wasting with hypophosphatemia.
2. Renal bicarbonate wasting with acidosis.
3. Renal potassium wasting with hypokalemia (< 3.0 mEq/L).
4. 1+ glycosuria with serum glucose < 150 mg/dL.
5. Proteinuria: a ratio of urine protein:urine creatinine > 0.2 occurring in the absence of significant malnutrition and acidosis due to sepsis/infection.
6. Decreased GFR.

If significant Fanconi syndrome occurs modify therapy as follows:
- Cyclophosphamide replaces Ifosphamide:
  - Delete ifosfamide from all subsequent cycles and substitute cyclophosphamide at the dose of 700mg/m2 (23mg/kg if <3 years) x 2 days for I^2VADO^2 courses and 700mg/m2 (23mg/kg if <3 years) x 1 day for the IVA courses with MESNA uroprotection. Dose Mesna at 60% of the daily Cyclophosphamide dose, divided into 3 doses. The first dose is given with CPM, doses 2 and 3 are given 3 and 7 hours after the start of CPM.

Future cycles of chemotherapy should include cyclophosphamide instead of ifosfamide.

A-VI: 1.3 Hyperbilirubinemia

Dose modifications for patients with hyperbilirubinemia secondary to biliary obstruction due to tumor and other situations with elevated bilirubin (NOTE: elevated total bilirubin without elevation of direct [conjugated] bilirubin is not associated with increased chemotherapy toxicity.)
<table>
<thead>
<tr>
<th>Total bilirubin &lt; 2.1 mg/dL</th>
<th>Full doses of vincristine, dactinomycin.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin 2.1 – 4.0 mg/dL</td>
<td>50% doses of vincristine and dactinomycin (for example, if the full vincristine dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose; if the full dactinomycin dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose).</td>
</tr>
<tr>
<td>Total bilirubin 4.1 – 6.0 mg/dL</td>
<td>25% dose of vincristine, 50% dose of dactinomycin, (for example, if the full vincristine dose is 1.5 mg, then administer 0.4 mg for a 25% dose; if the full dactinomycin dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose).</td>
</tr>
<tr>
<td>Total bilirubin &gt; 6.0 mg/dL</td>
<td>Do not give vincristine; give 50% dose of dactinomycin (for example, if the full dactinomycin dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose).</td>
</tr>
</tbody>
</table>

If the bilirubin falls prior to subsequent cycles, increase the doses as indicated above in the next cycle.

**A-VI: 1.4 Veno-occlusive Disease (VOD) of the Liver (Hepatopathy)**

VOD graded as below and Dactinomycin dose modifications:

| | MILD | MODERATE | SEVERE |
|-----------------------------|-----------------------------|-----------------------------|
| Bilirubin | < 6 mg/dL | >6 and < 20 mg/dL | > 20 mg/dL |
| Weight Gain | < 5% of baseline of noncardiac origin | > 5% of baseline of noncardiac origin | |
| Ascites | None | Clinical or radiologic documentation | Compromising respiratory function |
| Hepatic Dysfunction | Reversible | Reversible | Hepatic encephalopathy |
| Chemotherapy modifications: Dactinomycin | 50% dactinomycin dose for the next cycle and then resume 100% dose if tolerated. | Discontinue dactinomycin | Discontinue chemotherapy and then proceed as per moderate VOD without dactinomycin if all clinical and laboratory parameters return to normal |

**A-VI: 1.5 Cardiac Toxicity**

If prolongation of the QTc interval (> 0.44 sec), or a decrease in the shortening fraction to < 27 percent, or a decrease in the ejection fraction to < 45 percent are observed, the doxorubicin containing chemotherapy should be postponed one week, any existing malnutrition corrected and the tests repeated.

If the abnormalities persist, doxorubicin should be PERMANENTLY DISCONTINUED.

**A-VI: 1.6 Neurological Toxicity**

Neurological toxicity can result from vincristine and ifosfamide.

**A-VI: 1.6.1 Vincristine Neuropathy (severe peripheral neuritis or paralytic ileus)**

Vincristine should be stopped until normal bowel movements are re-established and the signs of vocal cord paralysis have disappeared, etc. Then vincristine should be restarted at 50% dosage. If problems persist or recur, the drug should be further decreased by 50% decrements. Mild to moderate constipation (lasting < 4 days) and depression of deep tendon reflexes are not indications for interrupting vincristine. If jaw pain develops, analgesics should be used.
A-VI: 1.6.2 Ifosfamide Neurotoxicity
This is an organic brain syndrome, which ranges from mild confusion and disorientation to seizures, ataxia, and coma. It may be aggravated by impaired renal function. It usually, but does not always, resolve spontaneously, and it may or may not recur with subsequent doses.

A-VI: 1.7 Hematuria or Hemorrhagic Cystitis

Ifosfamide dose modifications for Hematuria: Withhold ifosfamide in the presence of significant hematuria (> 50 RBCs/HPF). Restart drug after hematuria has been clear for at least 1 week at 50% dosage and increase to 100% (full dose) if tolerated. Give MESNA by continuous infusion. The total daily MESNA dose is equal to at least 60% of the daily ifosfamide dose. Urine specific gravity should be < 1.010 and bladder emptied every 2 hours x 3 after starting ifosfamide.

APPENDIX VII: Supportive Care Guidelines

A-VII: 1.1 Pneumocystis Carinii Prophylaxis
Pneumocystis Carinii prophylaxis should be given per institutional standard. Alternatively, Trimethoprim/sulfamethoxazole prophylaxis should be given to all patients (TMP 5 mg/kg/day divided bid, 2 consecutive days per week). If allergic or intolerant, use pentamidine or dapsone.

A-VII: 1.2 G-CSF/GM-CSF
G-CSF or GM-CSF can be used at the discretion of the treating physician. Note Regarding PEG-filgrastim (Neulasta): the use of PEG-filgrastim in children is still under investigation.

A-VII: 1.3 Erythropoietin
Erythropoietin may be used with supplemental iron.

A-VII: 1.4 Blood Products Irradiation
Blood products should be irradiated.
## APPENDIX IX: Reporting Schedule and Case Report Forms

* INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY OFFICE (MINNEAPOLIS, MN)

<table>
<thead>
<tr>
<th>Required Materials</th>
<th>Send to:</th>
<th>At time of Enrollment</th>
<th>End of RT</th>
<th>End of each phase*</th>
<th>At relapse/progression/secondary malignancy</th>
<th>At time of each surgery</th>
<th>During follow-up</th>
<th>At death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment Form</td>
<td>IPPBTKRO *</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representative Formalin-Fixed Paraffin Blocks of Tumor Material (A)</td>
<td>IPPBTKRO</td>
<td>X (A)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathology Report</td>
<td>IPPBTKRO</td>
<td>X</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patient and Family History Form</td>
<td>IPPBTKRO</td>
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</tr>
<tr>
<td>Imaging Reports and Electronic Digital Images</td>
<td>IPPBTKRO</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>RT Treatment Summary*</td>
<td>IPPBTKRO</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

(A) If blocks absolutely cannot be sent, then send: (a) 1 H&E section of all available blocks, and (b) 10 unstained sections (on plus-charged, polarized slides) for immunoperoxidase studies from 2 representative blocks, and (3) 2 H&E slides from the same blocks. See protocol Appendix VII
Patient Questions:

Are there any other major illnesses in the patient?:

Has this child ever had a chest x-ray or chest CT prior to the current situation?:

Has this child ever had a pneumothorax?:

Has this child had any lung cysts diagnosed prior to PPB?:

Has this child had any kidney cysts?: (cystic nephroma or undiagnosed renal cysts)

Has this child had any thyroid nodules/surgery?:

Does this child have birth defects/syndromes/or other conditions (such as VACTERL, Fragile X, etc etc)?:

If you answered YES to any of the above questions, please provide details below:

Family Questions:

Has any brother, sister, parent, relative had any of the following:

Pneumothorax?:

Kidney cysts?: (esp. cystic nephroma)

Lung cysts?:

Thyroid nodules or tumors?:

Ovarian Tumors; testicular tumors?: (esp. Sertoli-Leydig ovarian tumors; testicular seminomas, ovarian dygerminomas)

Childhood Cancers?: (any childhood cancer)

If you answered YES to any of the above questions, please provide details below:

Has this child’s mother or father had previous marriages?

Are there any “half-siblings” of the patient?:

Are there any of the above findings in any half-siblings?: If YES, please provide details above.

* The questions in this survey emphasize medical conditions found in the PPB Family Tumor Susceptibility Syndrome
REFERENCES

34. DICER1-related Pleuropulmonary Blastoma Cancer Predisposition Syndrome: A Natural History Study, ClinicalTrials.gov
52. Varni JW, Seid M, Kurtin PS: PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 39:800-12, 2001