



# PLEUROPULMONARY BLASTOMA IN CHILDREN AND ADOLESCENTS

## STANDARD CLINICAL PRACTICE RECOMMENDATIONS

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**TITLE: PLEUROPULMONARY BLASTOMA IN CHILDREN AND ADOLESCENTS**

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**This document has been developed by EXPeRT** as part of the EU funded PARTNER project:

PARTNER aims to create a European Registry dedicated to children and adolescents with very rare tumors (VRT) linking existing national registries and to provide a registry for those countries not already having a registry for VRT in place. The European Registry will be an essential part of the activity of the VRT subnetwork part of the ERN PaedCan. The possibility to link the registry with a virtual consultation system and the elaboration of diagnostic/treatment recommendations will create a platform that can be easily accessed by EU Health care providers. The increasing expertise in VRT based on the data collected in the European registry will increase the capacity to provide international consultation and define standard of treatment recommendations. This will ultimately result in improved patients' care and reduce currently existing inequalities in cancer outcome across EU member states.

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## 1. BACKGROUND AND RATIONALE

### 1.1 Summary

Pleuropulmonary blastoma (PPB) is a rare cancer occurring mainly during early childhood and often associated with germline *DICER1* mutations. It is classified by the macroscopic appearance into 3 interrelated clinico-pathologic entities on a developmental continuum. Complete tumor resection is a main prognostic factor and can be performed at diagnosis or after a neo-adjuvant treatment that includes chemotherapy, and in some cases radiotherapy. Optimal modalities of neo- or adjuvant treatments can be challenging taking into account potential long-term toxicities in this young population. This document presents the recommendations for the diagnosis and treatment of children and adolescents with PPB elaborated by the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) within the EU-funded project PARTNER (Paediatric Rare Tumours Network - European Registry).

### 1.2 Background

Pleuropulmonary blastoma (PPB) is a very rare neoplasm arising in the lungs and presenting in early childhood, with most cases diagnosed in children less than 6 years of age. It is a dysembryonic malignancy believed to arise from the pleuropulmonary mesenchyme. PPB is classified according to its macroscopic appearance into 3 interrelated clinico-pathologic entities which represent a developmental continuum: Type I (cystic), Type II (solid and cystic), and Type III (solid). The solid component of both type II and III may show a mixed-pattern including high grade sarcoma elements [1-3]. Type I cystic PPB may progress to the aggressive Type II and Type III PPB but may also regress to Type Ir, where r stands for regressed/regressing [4, 5] and no malignant cells are present. Types II-III PPB should be considered aggressive tumors. PPB is distinct from adult-type pulmonary blastoma and infantile pulmonary teratoid tumor. Microscopically, PPB is characterized by blastemata islands with high mitotic activity associated with areas of spindle cells that can be undifferentiated or in various stages of malignant differentiation (rhabdomyosarcoma, chondrosarcoma, liposarcoma). This tumor is the seminal disease of the spectrum of the *DICER1*-related tumors which also includes ovarian sex cord-stromal tumors, nodular hyperplasia of the thyroid gland and thyroid carcinoma, cystic nephroma, pineoblastoma, pituitary blastoma, uterine cervical rhabdomyosarcoma, ciliary-body medulloepithelioma and nasal chondromesenchymal hamartoma [6-8]. Multimodality treatment has increased the possibility of survival, and approximately > 90% of children with Type I, > 70% with Type II and > 50% with Type III PPB can be cured [9, 10].

**2. METHODOLOGY**

According to the Consensus Conference Standard Operating Procedure methodology, the levels of evidence can be classified from Level I to V and the grades of recommendation A to E (*Table 1*).

<b>Levels of evidence</b>	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
<b>Grades of recommendation</b>	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

**Table 1.** Levels of evidence and grades of recommendation (adapted from the Infectious Disease Society of America-United States Public Health Service Grading System)

EXPeRT/PARTN-ER members recognized that due to the rarity of this tumor, no evidence of Level I to II exists. Therefore, recommendations for VRTs are developed based on the evidence collected from some published prospective studies (Level III), but more frequently retrospective series (Level IV), case reports (Level V) and personal expertise (Level V). In addition, the “strength” of recommendations will be categorized by additional grading (Grade A to E).

To identify tumors that need shared recommendations, PARTN-ER members designed the following procedure:

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- Identification of the tumor of interest on the base of its relevance, and previous PARTN-ER experience, (i.e., data analysis and publication). Tumors should be classified as VRT (i.e. < 2/100000/inhabitants/y),

- Designation of two main coordinators for each VRT on the basis of their experience (data analysis, publications, personal experience).

Coordinators have to:

- Analyze the medical literature and select the relevant papers.

- Propose a series of recommendation in a form of a first draft of recommendations.

- Identify the main diagnostic and therapeutic problems for the designated VRT. The first drafts will be shared and discussed, along with the relevant publications, into a selected expert group of PARTN-ER members and annotated.

- Produce a draft version of recommendations, taking into account proposals from the group of selected PARTN-ER members.

- Propose a mature version of the recommendations to external experts identified by the coordinators based on a recognized experience on the tumor (pediatricians, medical oncologist, radiation oncologist, surgeon...).

- The final version has to be validated by the whole PARTN-ER group. In case of remaining disagreements, a vote has to be done, during a consensus meeting, to agree on in a final recommendation.

- The final version should be submitted for publication to a peer-reviewed journal.

The final document including recommendations will be available on the EXPeRT website:

<https://www.raretumors-children.eu/>.

**NB:** These guidelines may change over time according to new data available. Local clinicians remain responsible for the care of his patient. The EXPeRT/PARTN-ER members are not responsible for results or complications related to their use. If necessary, medical discussions are possible with EXPeRT members of these groups via the group's consultation platform and virtual tumor board:  
**<https://vrt.cineca.it>**



### 3. PATIENT GROUP

#### 3.1 Diagnostic Criteria

PPB should be suspected when a young child presents with a pulmonary lesion that can be completely cystic, cystic with a solid component or completely solid. A PPB diagnosis could be challenging in case of pure cystic lesions that need to be differentiated from other congenital cystic pulmonary lesions. Similarly, a solid lesion needs to be distinguished from other pediatric tumors.

PPB in children is characterized by symptoms often mistaken for respiratory infection, pneumothorax, or lung malformation [20, 21]. The tumor is usually located in the lung, but it may extend to the mediastinum, diaphragm and/or parietal pleura. Type I PPB is a localized tumor, but Types II or III PPB may be associated with metastasis at diagnosis, during treatment or after completion of therapy. The most common metastatic sites are within the thorax or CNS although bone, liver and lymph nodes may also be involved. [17, 22].

##### 3.1.1 Imaging

All types of PPB need Computed Tomography (CT) of the chest. In addition, Type II and III need abdominal CT or MRI. The primary tumor and its loco-regional extension must be evaluated by Chest CT with contrast enhancement [Level IV; Grade A]. This is necessary for evaluation of lymph nodes, mediastinum, cardiac and pericardial involvement, and possible extension of the tumor to the diaphragm and liver [Level IV; Grade B]. In Types II and III PPB, thoracic MRI may help to define regional tumor extension [Level IV; Grade C].

Evaluation for distant metastasis in Type II or III PPB should include brain MRI and radionuclide bone scan [Level IV; Grade B]. There are no data regarding the use of Positron emission tomography (PET)/CT but, as in other solid tumors, it is expected to eventually replace bone scan [Level IV; Grade C]. An echocardiography is also required to identify vascular invasion and intra-cardiac involvement [Level IV; Grade B]. There are currently no tumor markers available [Level IV; Grade E]. Clinical work-up at diagnosis and during follow-up should include a search for synchronous *DICER1*-related disorders.

##### 3.1.2 Histopathology

When a Type II or III PPB is suspected, a histological diagnosis through a surgical procedure or core needle biopsy (16-18 Gauge) must be obtained (see Surgery section). Histology is mandatory and pathologists should pay attention to distinguishing PPB from benign conditions (congenital cystic adenomatoid malformations, pulmonary sequestration and peripheral bronchogenic cysts, lung cysts) and other tumors (i.e., rhabdomyosarcoma, inflammatory myofibroblastic tumor) [23] [Level IV; Grade A]. A revision of the histological slides by a pathologist with experience in pediatric tumors and especially in PPB and/or pediatric sarcoma is highly recommended [Level IV; Grade A]. Percutaneous biopsy may be safer when respiratory distress and/or mediastinal compression make general anaesthesia risky

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[Level IV; Grade B]. Nevertheless, biopsy should be large enough to ensure adequate diagnosis, noting the pleomorphic appearance of PPB could be difficult to diagnose by a small inadequate biopsy.

### 3.1.3 Molecular pathology

Tumor tissue should be evaluated for *DICER1* mutation, and if positive, a search for germline *DICER1* mutation should be initiated, along with genetic counselling and thereafter screening of the family [Level IV; Grade A].

### 3.1.4 Other

In children with *DICER1* mutation additional evaluation should be considered to look for synchronous *DICER1*-related disorders [Level IV; Grade A].

## 4. TREATMENT DETAILS

### General considerations:

Due to the rarity of PPB and the necessary multidisciplinary treatment, a tumor board discussion is highly recommended at diagnosis and during therapy [Level V; Grade A]. The enrolment of patients in a prospective trial, if available, and data collection in national or international databases should be proposed to patients and families [14] [Level IV; Grade A]. Even if many aspects of PPB treatment could not be fully supported by evidence-based medicine, EXPeRT group proposes a possible overall strategy in order to help physicians to treat patients. This therapeutic strategy should nevertheless be debated locally during multidisciplinary team discussions. Having the limited evidence in mind, the authors nevertheless considered it useful to elaborate a more precise treatment proposal, to facilitate planning and stratification of therapy in these rare tumors. Nevertheless, this concept should not be mandatory (for example different chemotherapy regimens may have similar efficacy) but more an attempt to offer clinicians and patients a homogenous approach that can also allow us to accumulate greater experience (Appendix 1).

## 4.1 Treatment

### 4.1.1 Surgery

A surgical procedure is necessary to obtain a tumor sample and to establish the diagnosis of PPB. Different series, although with a limited number of patients, have shown that complete tumor resection is a major prognostic factor [16, 17, 22-24]. Therefore, surgery is fundamental for the diagnosis and treatment in children with PPB [Level IV; Grade A]. The optimal surgical procedure for a given situation

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should be planned considering the radiological assessment and the respiratory difficulties with which patients with PPB often present [Level V; Grade A]. Special attention is required if mediastinal compression is present and general anaesthesia is needed [Level V; Grade A]. When pneumothorax and/or pleural effusion is present, needle aspiration may be mandatory to relieve respiratory distress [Level V; Grade A]. In some patients with respiratory distress, chest tube can be lifesaving. However, chest tube placement should be avoided, if possible, to minimize the contamination of the pleura [Level V; Grade B].

#### 4.1.1.1 Type I PPB surgery

Type I PPB should be suspected when a cystic pulmonary lesion is evident (especially if there is a known familial history of *DICER1* disease) [25-27]. In this case, a total tumor resection with a conservative intent should be planned [Level IV; Grade A]. Therefore, a total pneumonectomy is not recommended for Type I PPB [Level IV; Grade E]. When the number and localization of cysts preclude a complete resection, the largest cysts should be removed, and the remaining should be followed up closely [Level IV; Grade B]. There is insufficient data to define the risk of pleural tumor spread after core needle biopsy (< 18 G) or fine needle aspiration, or in case of initial intra-thoracic cyst puncture or drainage [Level IV; Grade D]. Even if the impact of tumor spillage during initial surgery on outcome is not totally clear, aim of the surgery is to obtain an *en-bloc* R0 resection [Level IV; Grade B] [9]. There are not clear data to guide the treatment in case of microscopically incomplete surgery (R1). We propose to consider a re-excision; if an R0 resection is still not deemed feasible with the second surgery, chemotherapy should be considered [Level IV; Grade C]. In the case of initial macroscopically incomplete surgery (R2 resection), a new resection should be planned, whenever feasible, to obtain negative margins [Level V; Grade C]. If an R0 resection is still not deemed feasible with the second surgery, chemotherapy should be considered [Level IV; Grade C].

Thoracotomy is the recommended surgical approach while thoracoscopic procedures are discouraged, except if the lesion is well delineated and R0/R1 should be obtained as anticipated in open procedure [Level IV; Grade B]. The surgical report should mention any mediastinal, diaphragmatic, or pleural extension, clearly state the resection status and any rupture of the lesion [Level IV; Grade B].

#### 4.1.1.2 Types II-III PPB surgery

Type II and III PPB usually present as a large pulmonary mass, in some cases with cystic changes. Primary tumor resection should be considered if a complete macroscopic resection (R0/R1) is achievable with minimal risk, and if there is no clear radiological evidence of lymph node or metastatic disease [Level IV; Grade B]. Before any treatment, histological, biological, and genetic tests are mandatory and require enough tumor material. Core-needle (18 or 16 Gauge) or open surgical biopsies are both possible options [Level IV; Grade B]. Cytology of pleural fluid cannot be used for diagnosis [Level V; Grade C]. In all other cases, tumor resection should be considered after neo-adjuvant

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chemotherapy [Level IV; Grade A]. Pneumonectomy to obtain radical tumor resection at diagnosis is discouraged [Level IV; Grade E]. When PPB causes a life-threatening situation, an immediate debulking surgery may be considered [Level V; Grade C].

After neo-adjuvant chemotherapy, additional surgery to attain complete resection is highly recommended [Level IV; Grade A]. Even if CT scan after neoadjuvant chemotherapy is not able to identify a residual lesion, delayed surgery or thoracoscopy is advised to confirm the absence of residual viable cells and to evaluate the need for adjuvant radiotherapy [Level V; Grade B]. During surgery, the pleural cavity and the pulmonary parenchyma should be carefully analyzed and pleural fluid collected for cytological analysis, but the negativity of this last analysis is not sufficient to exclude initial pleural spread [Level V; Grade B]. All remaining pleural or lung nodules should be resected or biopsied (the positioning of clips or tattoo by an interventional radiologist before the operation may be helpful for the surgeon) [Level V; Grade B]. Surgery could imply non-anatomical lung resection or lobectomy and associated removal of infiltrated pericardium and/or diaphragm and/or parietal pleura [Level V; Grade B]. All resected tissues should be annotated and histologically analyzed to define the adjuvant radiotherapy fields [Level V; Grade A]. If resection of the remaining lesions after neoadjuvant chemotherapy requires a total pneumonectomy or pleuro-pneumonectomy, it should be balanced with the possibilities of local treatment with radiotherapy [Level V; Grade C]. Total pleuro-pneumonectomy could be considered in the absence of tumor regression after chemotherapy [Level V; Grade C]. In case of microscopic or macroscopic residual viable tumor, after neo-adjuvant chemotherapy and surgery, a pneumonectomy or a lung irradiation should be discussed and decided balancing the long-term effects of the two procedures [Level V; Grade C]. If a complete pneumonectomy is chosen, a complete parietal pleurectomy should be performed simultaneously in case of pleural extension [Level V; Grade B].

There are no data to indicate the best timing for secondary surgery. It is recommended to discuss the timing of the local treatment in a multidisciplinary board, and we generally advise to plan the operation after 3 to 6 cycles of neo-adjuvant chemotherapy.

#### 4.1.2 Chemotherapy

##### 4.1.2.1 PPB Type I schedule

Data to support the use of adjuvant chemotherapy in patients with PPB Type I are controversial. Published series report long-term survivors treated with surgery alone or followed by different multi-agent chemotherapy regimen including Vincristine, Actinomycin-D, Ifosfamide and/or Cyclophosphamide [Level IV; Grade C] (Appendix 2). In the case of R0 resection (i.e., microscopically complete resection), adjuvant chemotherapy might be discussed with the aim to avoid relapse and progression to Types II or III PPB [Level V; Grade C]. In the case of R1 resection (i.e., microscopic residue), chemotherapy can be discussed if R0 resection cannot be achieved with a repeated surgery [Level V; Grade C]. In children younger than 12 months, the decision for adjuvant chemotherapy in the

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case of suspected spillage or residual tumor after best feasible surgery should be therefore made on an individual basis with doses adapted due to patient age [Level V; Grade C].

#### 4.1.2.2 PPB types II-III schedule

In these types, chemotherapy is mandatory for any chance of cure of patients with Type II-III [Level IV; Grade A]. Different multidrug regimens with evidence of tumor response have been described. They are similar to those used for the treatment of rhabdomyosarcoma: IVA (Ifosfamide, Vincristine, Actinomycin-D), IVA with the addition of Doxorubicin (VAIA or IVADo) or with Cyclophosphamide replacing Ifosfamide (VAC). Some data seem to support the use of a Doxorubicin-containing regimen but evidence is limited [17, 18]. Besides, superimposing cardiotoxicity should carefully be considered when both radiotherapy and doxorubicin are planned. There are no data regarding the optimal duration of chemotherapy; most regimens range from 21 to 45 weeks. In consideration of the higher risk of cardiac, hepatic, and renal toxicity, drug doses should be adapted in infants [Level V; Grade B] (Appendix 2).

#### 4.1.3 Radiotherapy

The role of radiotherapy is unclear in PPB. Radiotherapy is not recommended for PPB type I [Level IV; Grade E]. We recommend radiotherapy only in the case of residual viable tumor after chemotherapy and second look surgery in PPB type II-III. In this case, the advantages and risks of the external radiotherapy should be balanced against a total pleuro-pneumectomy [Level IV; Grade C]. No data exist on the optimal dose of radiotherapy. A soft tissue sarcoma approach may be adopted. Total dosage should be between 45 Gy (R1 margins) to 54 Gy (R2 margins), with 1.8 Gy daily fractions [Level V; Grade C]. Fields should therefore be focused and restricted to residual tumor volume after chemotherapy [28]. In the case of malignant pleural effusion at diagnosis, irradiation of the hemi-thorax may be avoided if secondary surgery demonstrated no evidence of remaining pleural tumor cells after chemotherapy [Level IV; Grade C]. Specific attention should be paid to potential long-term side effects of myocardial irradiation after anthracycline exposure [Level IV; Grade B].

## 4.2 Special focus

### 4.2.1 Metastatic PPB strategy

We recommend intensive chemotherapy, surgery (including neurosurgery for CNS metastasis), followed by radiotherapy to the primary tumor and metastatic site if feasible [Level V; Grade B] [9, 28].

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#### 4.2.2 Poorly responding tumors strategy

The experience on the therapy of these patients is very limited. Different regimens should be tested, including anthracyclines if not used during the first line chemotherapy [Level V; Grade B]. Wherever possible, tumor tissue should be evaluated for novel molecular therapeutic targets [Level V; Grade C].

#### 4.2.3 Relapsed PPB strategy

According to the literature, local or metastatic relapse (mainly CNS) occur in about 41-63% of cases. Survival for these patients is very poor [9, 29]. No specific second line treatment is supported by literature data. Antineoplastic agents that have been reported in the literature include Etoposide, Cisplatin or Carboplatin [29]. Overall, the same drugs used for rhabdomyosarcoma, including Irinotecan, may be considered [Level V; Grade C]. Local treatment of relapse should be discussed (i.e., surgery and/or radiotherapy of relapsed sites) [Level V; Grade C] [29]. Wherever possible, tumor tissue should be evaluated for novel molecular therapeutic targets [Level V; Grade C].

### 4.3 Assessments

Patients should undergo clinical and radiological evaluation during and after the end of treatment. CT scan with contrast enhancement is usually adopted. Assessment should be performed to evaluate response to initial chemotherapy after 2 to 3 cycles, before surgery to plan the operation and after surgery to evaluate the possible residuals and decide for radiotherapy.

The role of PET has not been assessed in PPB.

In the case of initial metastatic disease, imaging evaluation should include all known metastatic sites, every 3 courses. Other imaging studies should be considered depending on clinical evaluation.

Specific follow-up in the case of *DICER1* predisposition is detailed in *Chapter 4.7*.

**4.4 Summary of known adverse events associated with treatment recommendation**

Type of treatment	Main side effects
Surgery (depending on the extent of the surgical procedure)	<p>Short-term side effects: post-operative pain, persistent air leak, atelectasis, hemorrhage, infection, bronchopleural fistula.</p> <p>Long-term side effects: mediastinal deviation, thoracogenic scoliosis, respiratory insufficiency (amputation of lung parenchyma).</p>
Chemotherapy (depending on chemotherapeutic agents used)	<ul style="list-style-type: none"> <li>- General side effects: fatigue, risk of infection, nausea and vomiting, hair loss, loss of appetite, hematological side effect...</li> <li>- Vincristine: constipation, peripheral neuropathy...</li> <li>- Actinomycin: hepatic toxicity...</li> <li>- Ifosfamide: renal and bladder toxicities (tubulopathy, hemorrhagic cystitis), central neurotoxicity, gonadotoxicity, cardiotoxicity...</li> <li>- Doxorubicin: cardiotoxicity...</li> <li>- Cyclophosphamide: bladder toxicity, second malignancy, gonadotoxicity</li> </ul>
Radiotherapy (depending on dose and volume of irradiation)	<ul style="list-style-type: none"> <li>- Acute side effects, that may persist for a long time: pain, mucositis, fatigue, hematological side effect (low blood counts), skin reactions.</li> <li>- Late side effects, which may arise after a long delay from treatment completion: musculoskeletal growth retardation, osteoradionecrosis and fractures, pulmonary sequelae (lung fibrosis), cardiotoxicity (especially in the case of irradiation after anthracycline exposure), hypothyroidism, and second cancer.</li> </ul>

**4.5 Dose Modifications and delays**

See *Appendix 2* for dose modifications in chemotherapy regimen according to the age and weight.

## 4.6 Supportive Treatment

After surgery, general supportive post-operative treatment (i.e., scar nursing, analgesic therapy...) are recommended [Level V; Grade A].

In the case where chemotherapy is needed, central venous access insertion should be considered and is strongly recommended before chemotherapy administration [Level V; Grade B]. Anti-emetic treatment is administered in addition to chemotherapeutic agents. Early nutritional status evaluation +/- supportive care if needed are recommended. Hyper-hydration and Uromitexan to prevent bladder toxicity is required with Ifosfamide/cyclophosphamide administration [Level V; Grade A].

In the case where RT is considered, other supportive treatment may be necessary depending on the potential acute side effects (analgesic therapy, skin care, nutritional support ...) [Level V; Grade A].

Pneumocystis prophylaxis should be proposed according to local procedures.

## 4.7 Genetic considerations

Germline *DICER1* pathogenic variant have been reported in approximately 2/3 of analysed patients with PPB [13, 30, 31]. All PPB cases should be referred for genetic consultation with screening for *DICER1* mutation [Level IV; Grade A]. If positive, patients should be enrolled into a surveillance programme to identify other *DICER1* related diseases. Therefore, we recommend a careful follow-up and active surveillance of children and adolescents carrying the germline *DICER1* pathogenic variant, as proposed by Schultz et al., with the aim to discover pulmonary lesions and other *DICER1*-associated disorders at an earlier stage [Level IV; Grade A] [32]. Surveillance of the lungs may prevent the transformation of Type I to Type II or III PPB, and/or allow discovery of smaller lesions more easily amenable to a complete resection. It must be kept in mind that germline *DICER1* pathogenic variants increase the risk for other lesions, not only PPB [21]. In particular, abdominal ultrasound is recommended to exclude cystic nephroma and ovarian tumors [Level IV; Grade B]. Evaluation for other family members for *DICER1* pathogenic variation is strongly encouraged [Level IV; Grade B].

## 4.8 Patient Follow Up

Due to the possibility of long-term toxicities in survivors after invasive surgery, chemotherapy or radiotherapy, a follow-up more than 5 years is highly recommended. Surveillance should focus on both the risk of recurrence (locoregional and/or metastatic), which may occur even after several years, and potential long-term side effects, including surgical complications, chemotherapeutic late toxicities (such as cardiac toxicity after anthracycline-based regimens) and radiation-related effects depending on the dose and volume of irradiation [Level IV; Grade A].

Early local relapses may occur. Patients should thus undergo a clinical and imaging evaluation after the surgical procedure, then every 3 chemotherapeutic courses and/or 1 month after the end of irradiation if required, then every 3 to 4 months for 2 to 3 years after the end of treatment, and every 6 months for



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3 years. Imaging studies include chest CT scan during the 2-3 first years and then at least chest X ray *[Level V; Grade C]*.

Metastatic relapse, primarily CNS metastases, only concern type II and III PPB, and may occur even after a long time from the end of treatment. Routine cerebral imaging, as well as bone scintigraphy, are not systematically recommended, but advised for type II-III of PPB according to clinical symptoms *[Level V; Grade C]*.

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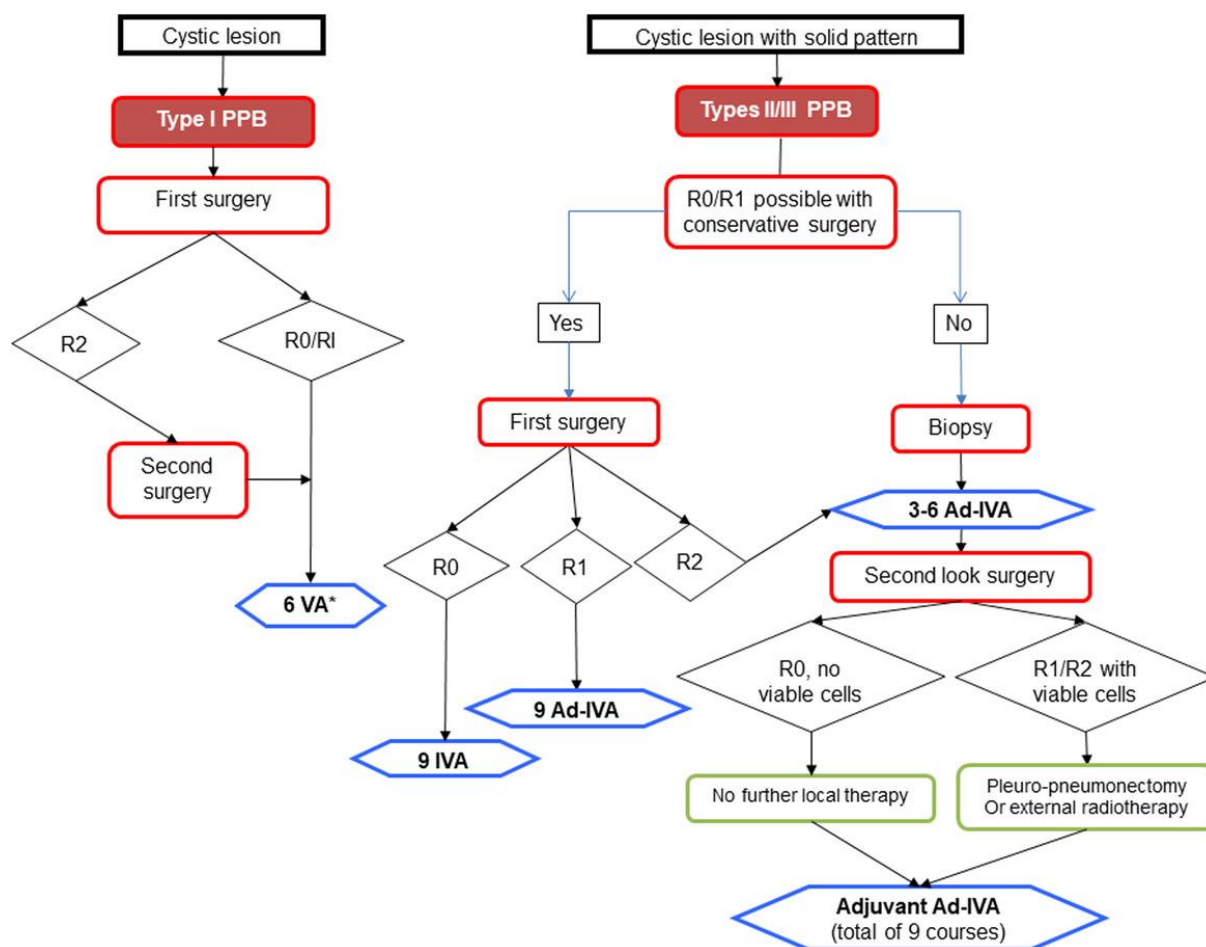
**5. REFERENCE LIST**

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APPENDIX 1 - THERAPEUTIC FLOWCHART, THE PARTN-ER PROPOSAL



Abbreviations: R0, microscopic complete surgery; R1, microscopic incomplete surgery; R2, macroscopic incomplete surgery; Ad-IVA: IVADo/IVA or VAIA regimens.

\* The decision for chemotherapy versus observation after surgery for Type I PPB depends on a variety of factors. See text for details.

**APPENDIX 2 – CHEMOTHERAPY SCHEDULES**

There is a 3-weeks interval between cycles for all the regimens described below. See details for dose modifications for young patients.

**VA regimen**

Vincristine, Actinomycin-D:

	V	V	V	V	V	V	V	V	V	V	V	V
	A		A		A		A		A		A	
	—————→											
Week	1		4		7		10		13		16...	
Cycle	1		2		3		4		5		6...	

**(V) Vincristine:** 1.5 mg/m<sup>2</sup> on day 1, 8, 15, 21 (max 2 mg per dose); bolus injection, in 10 ml 0.9% NaCl.

**(A) Actinomycin-D:** 1.5 mg/m<sup>2</sup> on day 1 and day 21; IV in 10 ml G5% dextrose.

**Total number of cycles:** 6 cycles.

**IVA regimen**

	V		V		V		V		V		V		V	
	A				A				A				A	
	I				I				I				I	
	—————→													
Week	1				4				7				10...	
Cycle	1				2				3				4...	

**(I) Ifosfamide:** 3 g/m<sup>2</sup>/day on day 1 and 2; IV 3 hours (total: 6 g/m<sup>2</sup>/course).

**(V) Vincristine:** 1.5 mg/m<sup>2</sup> on day 1 (+ day 8 and day 15 for the 2 first courses) (max 2 mg per dose); bolus injection, in 10 ml 0.9% NaCl.

**(A) Actinomycin-D:** 1.5 mg/m<sup>2</sup> on day 1; IV in 10 ml G5% dextrose.

**Total number of cycles:** 9 cycles.

A central line is essential and mandatory for the administration of hydration and Uromitexan.

Hyper-hydration (3 L/m<sup>2</sup>/day) and diuresis (75% of intake) should be strictly followed at diagnosis in the context of a respiratory distress with compressive pleural effusions.

**IVADo regimen**

	I VVV A Do	I VVV A Do	I V A Do	I V A Do	I V A		I V A	I V A	I V A
Week	1	4	7	10	13	16	19	22	25
Cycle	1	2	3	4	5	6	7	8	9

**(I) Ifosfamide:** 3 g/m<sup>2</sup>/day on day 1 and 2; IV 3 hours (total: 6 g/m<sup>2</sup>/course).

**(V) Vincristine:** 1.5 mg/m<sup>2</sup> on day 1 (+ day 8 and day 15 for the 2 first courses) (max 2 mg per dose); bolus injection, in 10 ml 0.9% NaCl.

**(A) Actinomycin-D:** 1.5 mg/m<sup>2</sup> on day 1; IV in 10 ml G5% dextrose.

**(Do) Doxorubicin:** 30 mg/m<sup>2</sup>/day on day 1 and 2; IV 4 hours in 0.9% NaCl (max 4 cycles).

**Total number of cycles:** 9 cycles.

A central line is essential for the administration of hydration and Uromitexan and Doxorubicin. Hyper-hydration (3 L/m<sup>2</sup>/day) and diuresis (75% of intake) should be strictly followed at diagnosis in the context of a respiratory distress with compressive pleural effusions.

**VAIA regimen**

	I VVV Ad	I VVV A	I V Ad	I V Ad	I V A	I V Ad		I V A	I V A	I V A
Week	1	4	7	10	13	16	19	22	25	
Cycle	1	2	3	4	5	6	7	8	9	

**(I) Ifosfamide:** 3 g/m<sup>2</sup>/day on day 1 and 2; IV 3 hours (total: 6 g/m<sup>2</sup>/course).

**(V) Vincristine:** 1.5 mg/m<sup>2</sup> on day 1 (+ day 8 and day 15 for the 2 first courses) (max 2 mg per dose); bolus injection, in 10 ml 0.9% NaCl.

**(A) Actinomycin-D:** 1.5 mg/m<sup>2</sup> on day 1; IV in 10 ml G5% dextrose.

**(Ad) Doxorubicin:** 40 mg/m<sup>2</sup>/day on day 1 and 2; IV 4 hours in 0.9% NaCl (max 4 cycles).

**Total number of cycles:** 9 cycles.

A central line is essential for the administration of hydration and Uromitexan and Doxorubicin. Hyper-hydration (3 L/m<sup>2</sup>/day) and diuresis (75% of intake) should be strictly followed at diagnosis in the context of a respiratory distress with compressive pleural effusions.

**Modification by age and weight****Vincristine and Actinomycin-D**

- For children < 3 months or < 5 kg: 25 µg/kg/injection for the 2 first cycles (4 injections) then if good tolerance **33 µg/kg/injection** for further injections and 50 µg/kg/injection only when age > 6 months and weight > 8 kg.

- For children 3-6 months and 5-8 kg: 33 µg/kg/injection for the 2 first cycles (4 injections) then if good tolerance **40 µg/kg/injection** for further injections and 50 µg/kg/injection only when age > 6 months and weight > 8 kg.

- For children 6-12 months and 8-10 kg: 40 µg/kg/injection for the 2 first cycles (4 injections) then if good tolerance **50 µg/kg/injection** for further injections until age > 12 months and weight > 10 kg.

**Ifosfamide**

- For children < 1 month: no alkylating agent.

- For children 1-3 months or < 5 kg: 40 mg/kg/injection/day for the 2 first cycles (2 injections) then if good tolerance **60 mg/kg/injection/day** for further injections and 80 mg/kg/injection/day only when age > 6 months and weight > 8 kg.

- For children 3-6 months and 5-8 kg: 60 mg/kg/injection/day for the 2 first cycles (2 injections) then if good tolerance **80 mg/kg/injection/day** for further injections and 100 mg/kg/injection/day only when age > 6 months and weight > 8 kg.

- For children 6-12 months and 8-10 kg: 80 mg/kg/injection/day for the 2 first cycles (2 injections) then if good tolerance **100 mg/kg/injection/day** for further injections until age > 12 months and weight > 10 kg.

- For children > 12 months and > 10 kg: **3000 mg/m<sup>2</sup>/injection/day**.

**Doxorubicin (in IVADo regimen)**

- For children < 3 months or < 5 kg: no doxorubicin.

- For children 3-6 months and 5-8 kg: 0.6 mg/kg/injection for the 2 first cycles (2 injections) then if good tolerance **0.8 mg/kg/injection** for further injections and 1 mg/kg/injection only when age > 6 months and weight > 8 kg.

- For children 6-12 months and 8-10 kg: 0.8 mg/kg/injection for the 2 first cycles (2 injections) then if good tolerance **1 mg/kg/injection** for further injections until age > 12 months and weight > 10 kg.

- For children > 12 months and > 10 kg: **30 mg/m<sup>2</sup>/injection/day**.

**Doxorubicin (in VAIA regimen)**

- For children < 3 months or < 5 kg: no doxorubicin.

- For children 3-6 months and 5-8 kg: 0.85 mg/kg/injection for the 2 first cycles (2 injections) then if good tolerance **1 mg/kg/injection** for further injections and 1 mg/kg/injection only when age > 6 months and weight > 8 kg.

- For children 6-12 months and 8-10 kg: 1 mg/kg/injection for the 2 first cycles (2 injections) then if good tolerance **1.33 mg/kg/injection** for further injections until age > 12 months and weight > 10 kg.

- For children > 12 months and > 10 kg: **40 mg/m<sup>2</sup>/injection/day**.



**VAC/VA regimen** (for type I PPB, international PPB registry)

	Drug	Age	Dose
V	Vincristine	≥ 3 years	1.5 mg/m <sup>2</sup> IV x 1 (maximum dose 2 mg)
		≥ 1 year and < 3 years	0.05 mg/kg IV x 1 (maximum dose 2 mg)
		< 1 year	0.025 mg/kg IV x 1
A	Actinomycin D	≥ 3 year	0.045 mg/kg (maximum dose 2.5 mg) IV X 1
		< 1 year	0.025 mg/kg IV x 1
C	Cyclophosphamide	≥ 3 year	1200 mg/m <sup>2</sup> /dose IV as 1 hr infusion with IV fluids and MESNA, day 0 of weeks 1, 4, 7, 10
		< 3 years	40 mg/kg/dose IV
M	MESNA	Use of Mesna with this dose of cyclophosphamide is the decision of the treating physician and institution	

Week of therapy:	1	2	3	4	5	6	7	8	9	10	11	12
Vincristine:	V	V	V	V	V	V	V	V	V			
Actinomycin D:	A			A			A			A		
Cyclophosphamide:	C			C			C			C		
Mesna*:	M*			M*			M*			M*		
Week of therapy:	13	14	15	16	17	18	19	20	21	22	23	
Vincristine:	V	V	V	V	V	V	V	V	V		End of Therapy Evaluation	
Actinomycin D:	A			A			A			A		

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**APPENDIX 3 – MAIN OPEN QUESTIONS REMAINING**

- Role of adjuvant chemotherapy in Type I PPB
- Role of Doxorubicin in Type II and III PPB
- Place for radiotherapy in patients with Type II or III PPB with residual disease after surgery, its indications and dose
- Optimal strategy for poor responding, metastatic and relapsed tumors
- Efficacy and place of new drugs for PPB patients.