

# NEUROBLASTOM

Aktuelle Therapiekonzepte in Europa

SIOPEN - Group

Univ. Doz. Dr. R. Ladenstein

# Diagnostik

- **Tumormarker**  
Harn CAT (VMS, HVS , Dopamin),  
LDH, NSE, Ferritin
- **Bildgebung**  
US, MRT, mIBG
- **Biologie**  
MycN (1p del, 11q-, 17q+, Ploidie)
- **Histologie**  
Shimada – günstig/ungünstig, INPC

**Surgical risk factors in primary surgery  
for localized neuroblastoma: the LNESG1 study  
of the European International Society of Pediatric  
Oncology Neuroblastoma Group.**

**J. Clin Oncol. 2005 Nov 20;23(33):8483-9**

**Cecchetto G, Mosseri V, De Bernardi B, Helardot P, Monclair T,  
Costa E, Horcher E, Neuenschwander S, Toma P, Rizzo A,  
Michon J, Holmes K.**

- An effort to develop guidelines on the bases of defined surgical risk factors (SRFs) based on the imaging characteristics.

- **PATIENTS:**  
905 patients in 10 European countries (1995 to 1999)
- **RESULTS:**  
Information on SRFs in 719 patients;  
367 without and 352 with SRFs.
- **CONCLUSION:**  
The adoption of SRFs as predictors of adverse surgical outcome was validated because their presence was associated with lower complete resection rate and greater risk of surgery-related complications. Additional studies aiming to better define the surgical approach to localized neuroblastoma are warranted.

# INRG

## International Neuroblastoma Risk Grouping

- Initial tumour extent for risk grouping at diagnosis instead of post-surgical INSS.
- Focused on imaging. The new “INRG Staging System” is to a large extent based on the
- “Surgical Risk Factors” as they have been developed for the E-SIOP protocols during the last ten years.
  
- **INRG Stage L1:** Localised disease without surgical risk factors
- **INRG Stage L2:** Localised disease with presence of one or more surgical risk factors
- **INRG Stage M:** Distant metastatic disease (except Stage Ms)
- **INRG Stage Ms:** Distant metastatic disease confined to liver and/or skin and/or BM

# Risk Factors Related to Localisation

- **Neck**
  - Tumour encasing vertebral and/or carotid artery
  - Tumour encasing brachial plexus roots
  - Tumour crossing the midline
- **Thorax**
  - Tumour encasing the trachea or principal bronchus
  - Tumour encasing the origin and branches of the subclavian vessels
  - Thoraco-abdominal tumour, peri-aortic fusiform tumour
  - Lower left mediastinal tumour, infiltrating the costo-vertebral junction between T9 and T12
- **Abdomen**
  - Adrenal tumour infiltrating the porta hepatis
  - Suprarenal tumour infiltrating the branches of the superior mesenteric artery at the mesenteric root
  - Suprarenal tumour surrounding the origin of the coeliac axis, and of the superior mesenteric artery
  - Tumour invading one or both renal pedicles
  - Fusiform tumour surrounding the infrarenal aorta
  - Tumour encasing the iliac vessels
  - Pelvic tumour crossing the sciatic notch

# LNESG2 STUDY

## Background LNESG1

- majority of patients with localized, resectable, *MYCN* negative NB are cured with surgery alone
- operation in spite of risk factors leads to more frequent postoperative complications and macroscopic residual disease
- risk factors
  - Shimada and INPC pathological classification,
  - LDH at diagnosis
  - 1p deletion

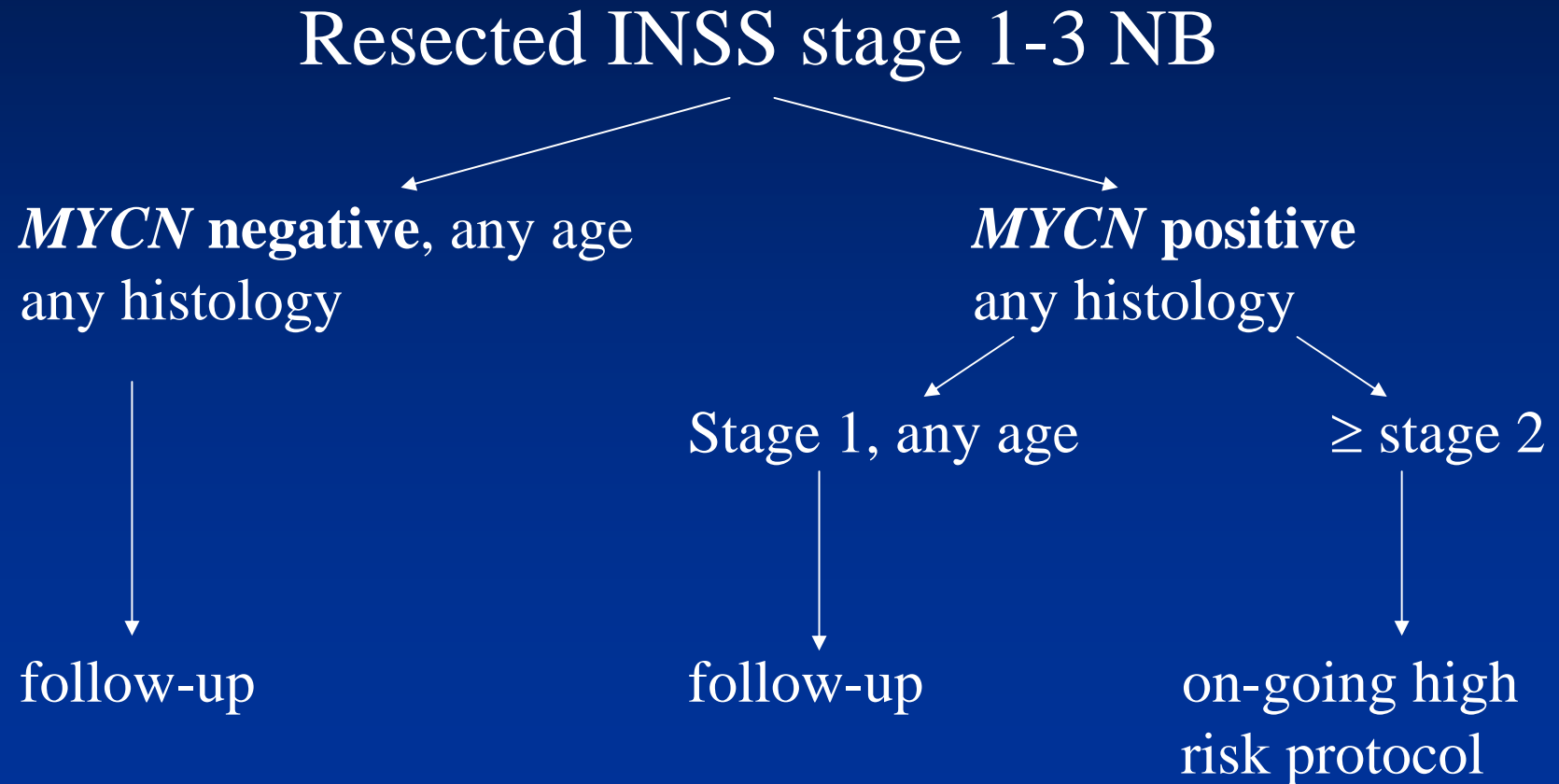
# LNESG2 STUDY

## **Aim:**

**To expand LNESG1 experience in localized neuroblastoma,  
Focus on preoperative LDH, 1pdel and histology**

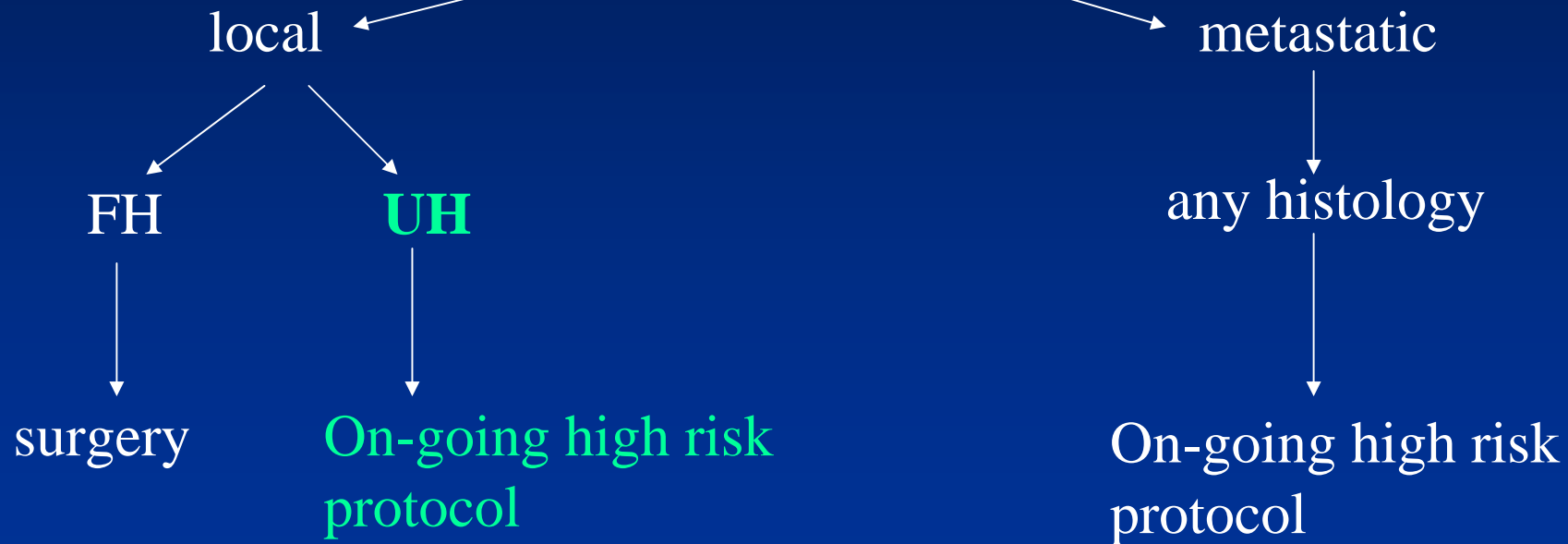
- age between 0 to 18 years
- **resectable INSS stage 1 to 3 NB, no *MYCN* amplification**
- **resectable INSS stage 1 NB, with *MYCN* amplification**
- **biological assessment:** *MYCN* amplification, 1p deletion
- **histological assessment:** review - INPC classification
- preoperative LDH
- **full metastatic work-up** (including MIBG at diagnosis)
- registration within 6 weeks of surgery
- secure local or national banking of tumour material

# Treatment guidelines at diagnosis



# Treatment at relapse (1)

Resected stage 1-3 patients, *MYCN* negative



# Treatment at relapse (2)

Resected stage 1 patients, *MYCN* positive



local or metastatic, any age



On-going high-risk protocol

***Treatment of Children Over the Age of 1 Year  
with Unresectable Localised Neuroblastoma  
without MYCN Amplification***

## **Primary Aims**

To determine the outcome, in particular the local control, event-free survival and overall survival, for children over the age of one year with Stage 2 and Stage 3 unresectable neuroblastoma without MYCN amplification. Unresectable (at diagnosis) means not resectable without risk (see 9.6 risk factors). The chemotherapy regimen will represent a reduction in therapy compared with most current European protocols.

The aim is a 3 year event free survival rate of 80% and a 3 year overall survival rate of 85%.

## **Secondary Aims**

To treat all children presenting to members of the cooperative groups in a uniform manner and collect the data centrally.

To collect validated biological data on all cases so that the value of other prognostic markers can be established.

**STUDY DESIGN**

**Unresectable Localised neuroblastoma**



**Biopsy**



**Carboplatin/Etoposide (1)**



**CADO (2)**



**Re-assessment  
(progression off study)** →

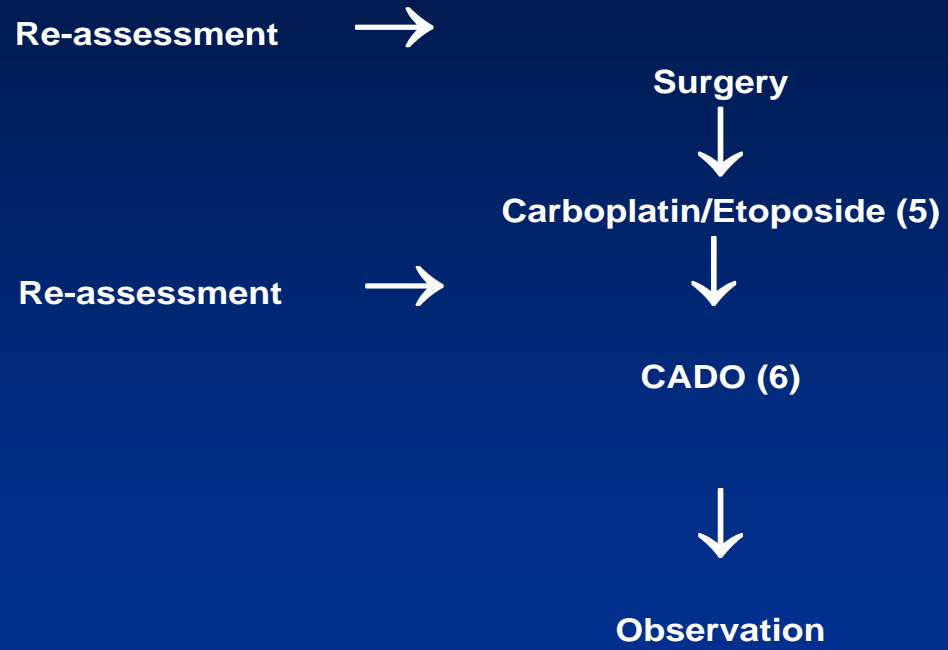
**Carboplatin/Etoposide (3)**



**CADO (4)**



**STUDY DESIGN**



# *NEW Strategy for INES*

INFANTS

# Background I

- General knowledge on infant neuroblastoma
  - More « goodies » (results of screening studies) in Infants, and may be over one till 2 years?
  - Regression in
    - Stage 4S : Infant 99.2 trial : 60% did not receive CT
    - Stage 2-3 GPOH : 2/3 of pts regression are observed
- Less chemotherapy is allowing to observe more progression
- Is surgery preventing from progression?

# Background II

- Very little knowledge on factors predicting
  - Spontaneous regression
  - Local progression versus in metastatic sites
- Chemotherapy may lead to
  - Acute and late toxicity
  - tumor profile change
- Surgery with no risk does not exist but risks can be minimized

# General strategy for suspected Neuroblastoma in Infants

## Suspected NB in Infant



**Revealed by Screening method  
+ No Symptoms  
+ Neonate (or below the age of 2 mo)**

**Registered in INES II « 0 »  
Follow-up without  
diagnostic Investigation**

**All other situations**

**Procedure**

- Allowing the Diagnostic of NB
- Assessing
  - Resectability
  - Re-evaluation of symptoms
  - Stage using INSS criteria
  - Biology of the tumour

# Strategy in confirmed Infant Neuroblastoma

**Localised NB**  
**Primary resectable**

All Stage 1  
Stage 2 MYCN not Amplified

**Eligible for LNESG II**

**MYCN not Amplified**  
**Non Stage 1-2**



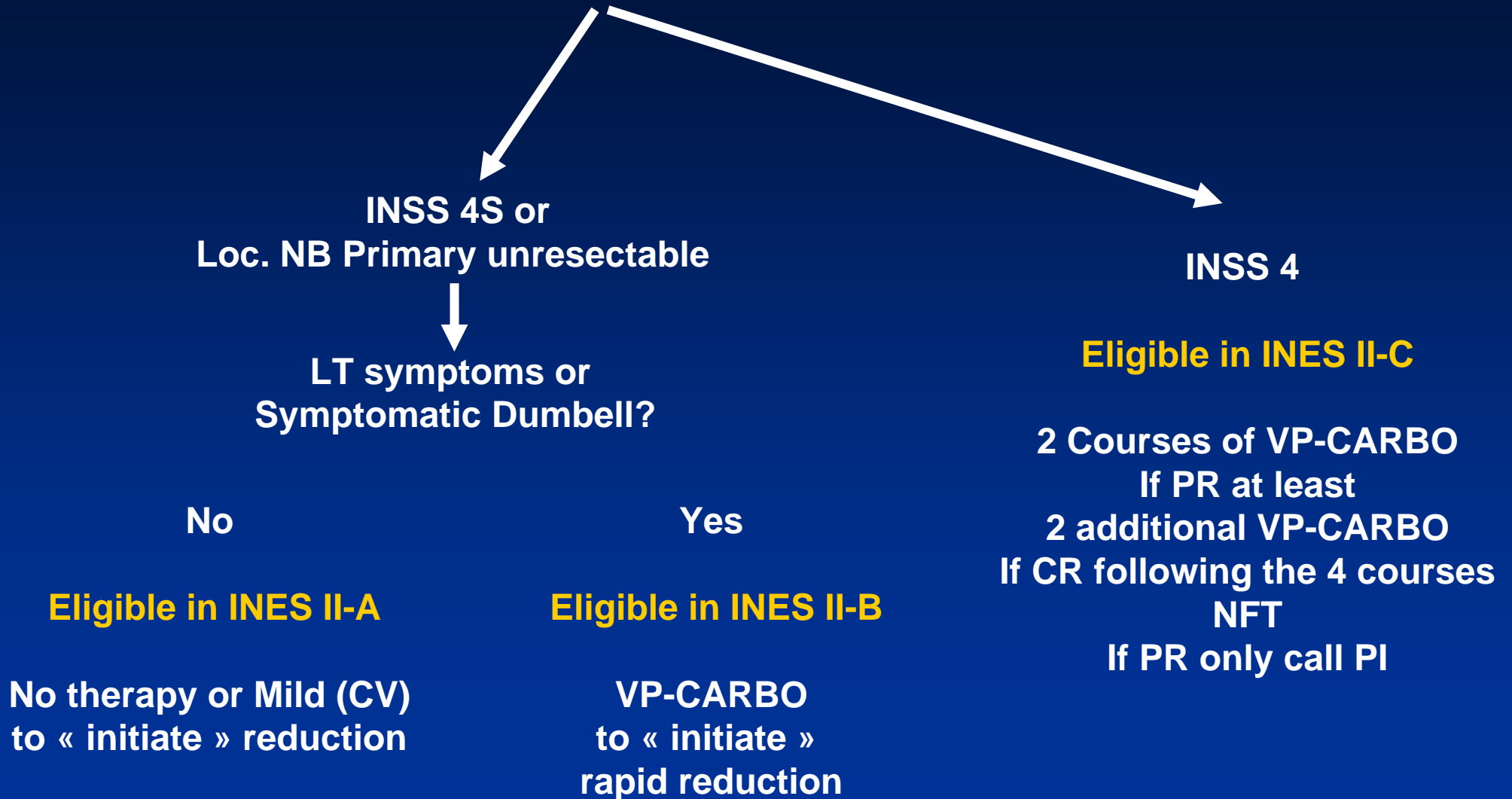
**Eligible for INES II**  
**approaches**

**Stage 2-4 NB**  
**MYCN Amplified**



**Eligible for the**  
**current High-Risk**  
**Infant approach**

# INES II Strategies



# INES II-A Scheme

Eligible Patients with UR St 2-3 or Stage 4S



**UR St 2-3**

**2 courses of CV**

**To initiate Regression**

**Stage 4S**

**Carefull Observation**

Monthly evaluation of Symptoms

Bimestrial evaluation of US or CXR

Semestrial evaluation of MIBG

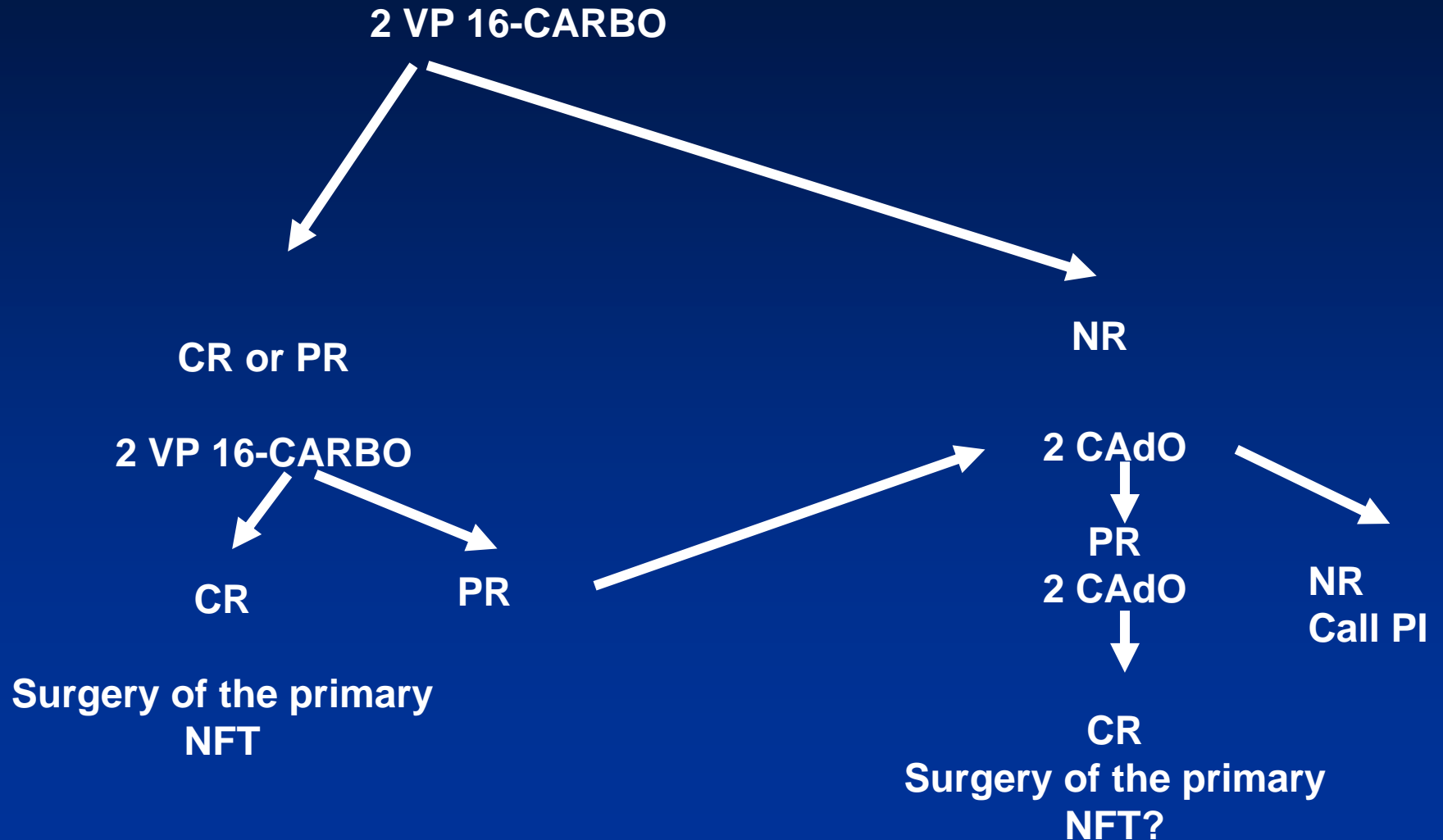
# INES II-A Scheme Contd

**Eligible Patients with UR St 2-3 or Stage 4S**



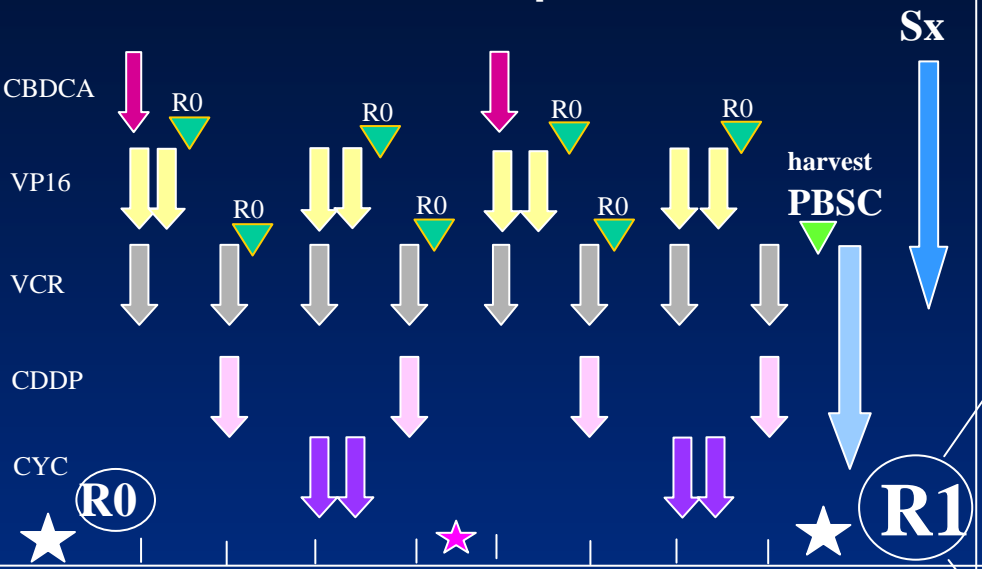
**Consider Surgery after one year if no unacceptable risk  
And tumor still detectable**

# INES II-C strategy



# HR-NBL-1 / ESIOP FLOWSHEET

## INDUCTION: Rapid COJEC



Day 0 10 20 30 40 50 60 70 90 95  
 A B C B A B C B Course

★ **Staging** local MRI / CT / US, mIBG, BM (aspirate/biopsy)  
 ★ BM aspirates only / local ultrasound  
 ★ local MRI / CT only post surgery

▽ **G-CSF**  
 Supportive Care: R0  
 Neupogen® 5µg/kg

A ↓ **CBDCA** 750 mg/m<sup>2</sup>  
 ↓ **VP16** 175 mg/m<sup>2</sup>  
 ↓ **VCR** 1.5 mg/m<sup>2</sup>

B ↓ **CDDP** 80 mg/m<sup>2</sup>  
 ↓ **VCR** 1.5 mg/m<sup>2</sup>

C ↓ **CYC** 1050 mg/m<sup>2</sup>  
 ↓ **VP16** 175 mg/m<sup>2</sup>  
 ↓ **VCR** 1.5 mg/m<sup>2</sup>

## MGT/PBSC

**BU**  
 4x150mg/m<sup>2</sup>/d p.o.  
**L-PAM**  
 140mg/m<sup>2</sup>/d short i.v.

**BuMel**

**CEM**

**CBDCA**  
 4x ctn iv 425mg/m<sup>2</sup>  
**VP16**  
 4x ctn iv 338mg/m<sup>2</sup>  
**L-PAM**  
 3x short iv 70mg/m<sup>2</sup>

## R<sub>x</sub>

21Gy

21Gy

21Gy

## MRD Treatment

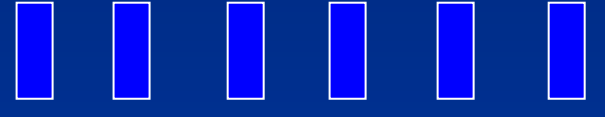
**Ch 14.18 anti GD2 AB iv**  
 20mg/m<sup>2</sup>/day x 5 days  
 every 4 weeks



**R2B**  
 Not **ACTIVATED**  
 Days after Start of 13 cis RA

0 28 56 84 112 140

**R2A**



**13 cis retinoic acid po**  
 160mg/m<sup>2</sup>/day x 14 days  
 every 4 weeks

# Recruitment

