European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

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HIGH-RISK NEUROBLASTOMA: STANDARD CLINICAL PRACTICE RECOMMENDATIONS

Moderation: Ruth Ladenstein

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SIOPEN R-NET
GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS
SIOP Europe the European Society for Paediatric Oncology
St. Anna Kinderkrebs Forschung

COI declaration

- I have no conflit of interest to disclose

High-risk neuroblastoma

High-risk neuroblastoma (HR-NBL) defined as:

- Stage M neuroblastoma above 365 days of age at diagnosis (no upper age limit), any MYC status;
- L2, M or Ms neuroblastoma with MYC amplification, any age

HR-NBL strategy

4 main treatment phases

- Induction Phase
- Consolidation Phase
- Local Treatment Phase
- Maintenance Phase

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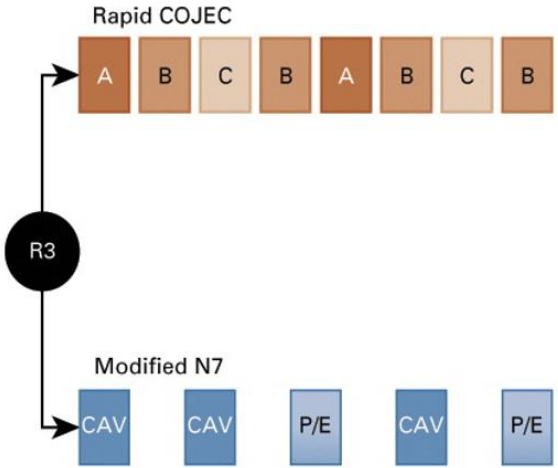
Background and rational: induction

The metastatic response after induction chemotherapy has been identified as a prognostic factor in patients with high-risk neuroblastoma

Different induction regimens has been used:

- The SIOPEN used Rapid COJEC in their standard practice *(Pearson et al. Lancet Oncol 2008)*
- The Memorial Sloan Kettering Cancer Center (MSKCC) investigated the effect of two non–cross-resistant drug combinations (N7 regimen), then adopted as the standard induction CT by the COG *(Kushner et al. JCO 1994)*

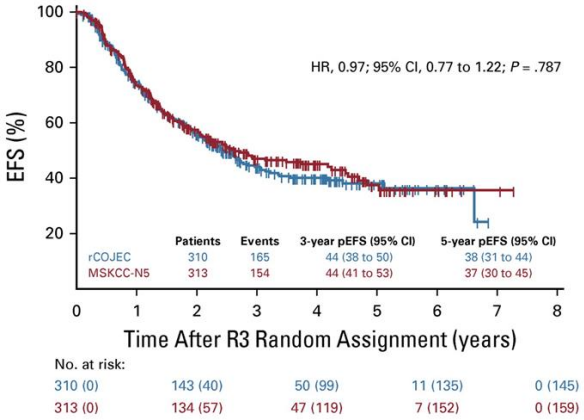
Randomization of 2 induction regimens in HR-NBL1 trial

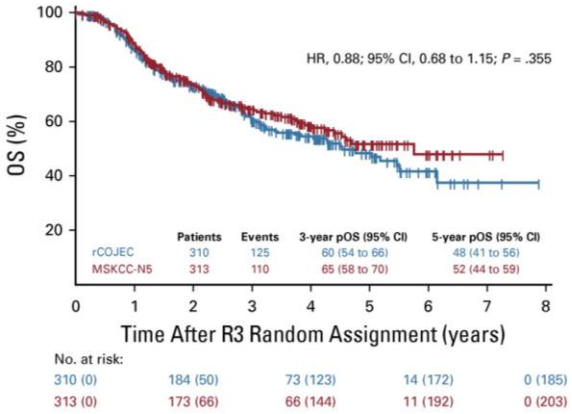


Rapid COJEC	A	Course A	**Vincristine** **Carboplatin** **Etoposide**	1.5 mg/m^2 (maximum dose 2 mg) × 1 day 750 mg/m^2 × 1 day 175 mg/m^2 × 2 days
	B	Course B	**Vincristine** **Cisplatin**	1.5 mg/m^2 (maximum dose 2 mg) × 1 day 80 mg/m^2/ctn over 24 hours × 1 day
	C	Course C	**Vincristine** **Etoposide** **Cyclophosphamide**	Vincristine 1.5 mg/m^2 (maximum dose 2 mg) × 1 day 175 mg/m^2 × 2 days 1,050 mg/m^2 × 2 days
Mod N7	CAV	Course CAV	**Cyclophosphamide** **Doxorubicin** **Vincristine**	70 mg/kg × 2 days 25 mg/m^2 × 3 days 0.022 mg/kg × 3 days
	P/E	Course P/E	**Cisplatin** **Etoposide**	50 mg/m^2 × 4 days 200 mg/m^2 on 3 days

Adapted from Garaventa et al. JCO 2021

Results of Induction Randomization





Garaventa et al. JCO 2021

Rapid Cojec is confirmed as the SIOPEN standard of care

No significant difference in survival
Toxicity: Rapid COJEC < mod N7

Rapid COJEC

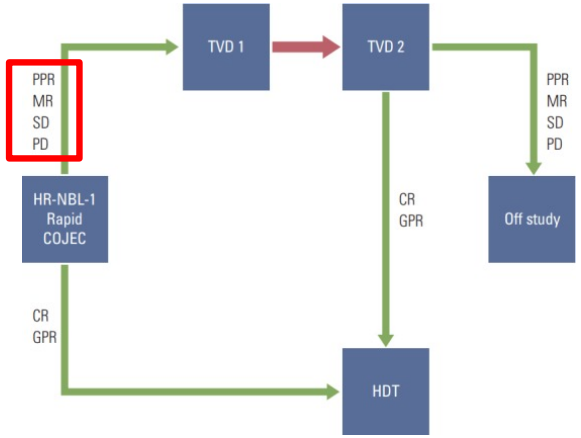
Disease evaluation Disease evaluation

Day	0	10	20	30	40	50	60	70
Course	A	B	C	B	A	B	C	B
VINCRISTINE	↓	↓	↓	↓	↓	↓	↓	↓
CARBOPLATIN	↓				↓			
ETOPOSIDE	⇊		⇊		⇊		⇊	
CISPLATIN		←		←		←		←
CYCLOPHOSPHAMIDE			⇊				⇊	
G-CSF (days of administration)	3→8	12→18	23→28	32→38	43→48	52→58	63→68	72→76 or until harvest

- G-CSF administration
- Timing is important (>>> MYC amplified)
- Careful monitoring of renal and ototoxicity

Is survival better with a prolonged induction phase ?

Additional 2 **TVD courses** if no metastatic CR



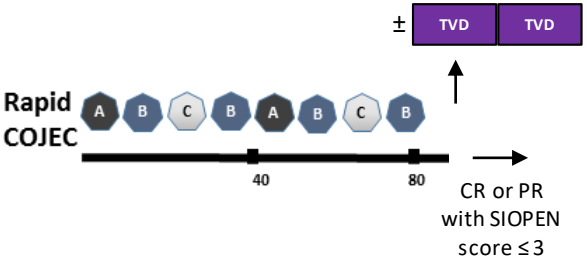
TVD: topotecan, vincristine, doxorubicine

Site of metastatic disease		Metastatic response after TVD					
		Eligible to HDT		Not eligible to HDT			
		CR	PR ≤ 3 mIBG spots and negative bone marrow	PR > 3 mIBG spots and negative bone marrow	MR	SD	PD
Bone marrow only	10	7 (70.0)[a]	0	0	0	3 (30.0)	0
Skeleton only	25	5 (20.0)[b]	6 (24.0)	4 (16.0)	0	10 (40.0)	0
Combined bone marrow and skeleton	27	5 (18.5)[a],[b]	0	5 (18.5)[a]	16 (59.3)	0	1 (3.7)
Liver	1	0	0	0	0	1 (100)	0
Total	63	17 (27.0)	6 (9.5)	9 (14.3)	16 (25.4)	14 (22.2)	1 (1.6)

Amoroso et al. Cancer Res Treat 2018

- **Effective in improving the response rate**
- **No significant impact on survival**

Current standard SIOPEN treatment for HR-NBL



HR-NBL strategy

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Consolidation phase: eligibility

Localized disease (MYC amplified) at diagnosis:

- Patients may proceed to consolidation following the front-line induction provided that there is no evidence of progression and the other eligibility criteria are met

Metastatic disease at diagnosis:

- Patients may proceed to consolidation after the front-line induction (RAPID COJEC +/- TVD) provided that a sufficient metastatic response has been achieved
- For patients with metastatic disease not fulfilling the response criteria after induction, an Expert's advice is highly recommended (= *refractory disease*)
- For patients **12-18 months old** with stage M **non-MYC amplified**, and with **numerical chromosomal** alterations only, in case of metastatic **complete response**, the treatment will be completed by surgery only

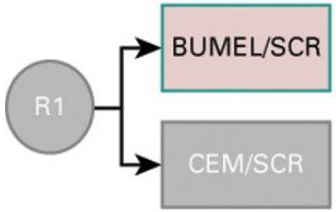
Background and rational: consolidation

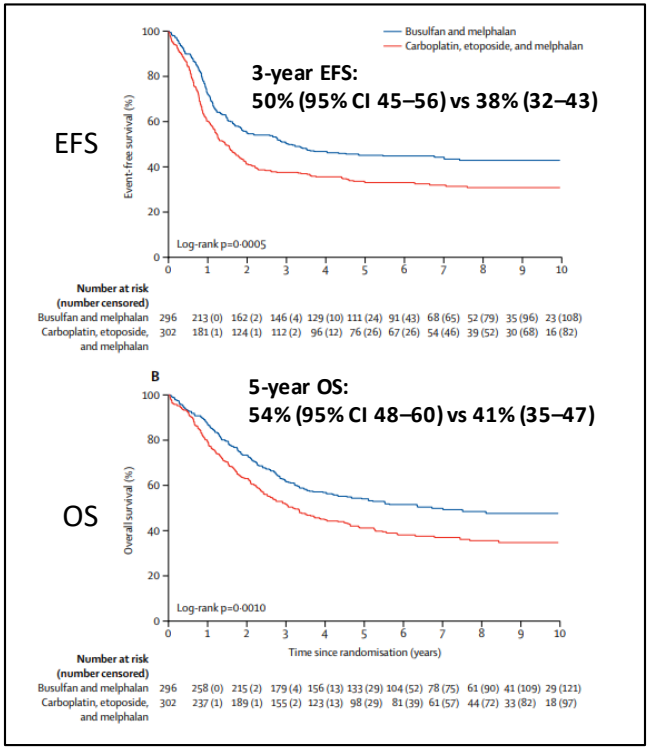
- Three randomized trials had shown that HDC improves EFS compared with treatment not including HDC in patients with high-risk neuroblastoma

- Different high-dose treatment regimens had been used:
  - The International Society of Pediatric Oncology European Neuroblastoma Group (SIOPEN) used busulfan and melphalan **(Bu-Mel)** as the HDC regimen in their standard practice;
  - The Children's Oncology Group (COG) developed carboplatin, etoposide, and melphalan **(CEM)** as HDC regimen

Results of Consolidation Randomization

Randomization of 2 HDC regimens in HR-NBL1 trial





Ladenstein et al. Lancet Onc 2017

BU-MEL confirmed as the SIOPEN HDC standard of care

Peripheral blood stem cells (PBSC) harvest

- Pediatric apheresis procedure should be performed by an accredited stem cell transplantation programs and conducted by an **experienced pediatric team**.

- Timing: following the end of the induction, preferably prior to surgery:
  - after the last chemotherapy cycle (**G-CSF 5 µg/kg/day** until harvest, to be increased to 10 µg/kg/day if needed)
  - out of steady state mobilization (**G-CSF 10 µg/kg/day** until harvest)
  - in case of mobilization failure with G-CSF, the use of **plerixafor** is allowed according to local practice.

- The aim is to obtain a total harvest of at least 3 x 10^6/kg CD34+ cells, to be stored in <u>at least 2 separate bags</u>.

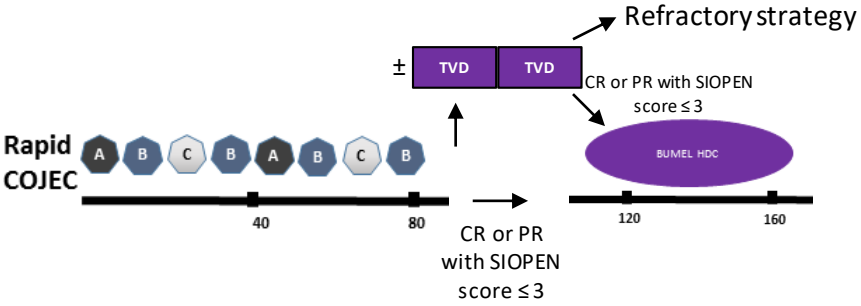
- CD34+ positive selection or other purging techniques are not recommended.

Busulfan-Melphalan iv

HD Bu-Mel (days)		- 6	- 5	- 4	- 3	- 2	- 1	Day 0
DRUG	**DOSE**							
Busulfan	< 9kg: 1.0 mg/kg/dose 9 kg to < 16 kg : 1.2 mg/kg/dose 16 kg to 23 kg : 1.1 mg/kg/dose >23 kg to 34 kg: 0.95 mg/kg/dose >34 kg: 0.8 mg/kg/dose **Infusion IV over 2 hours** **Administration every 6 hours** **for a total of 16 doses**	•	•	•	•	•		
Melphalan	140 mg/m²/dose IV short infusion (15'), **at least** 24 h after the last busulfan dose						▲	
Hydration	3L/m²/day = 125 ml/m²/h	Continuous until Day 0 (24 h after Melphalan), then 1.5 ml/m²/day						
Clonazepam	0.025 – 0.1 mg/kg/day Total dose i.v as continuous infusion or divided in 3 oral doses/day	Continuous infusion from 12 hours before the first dose of Bu until Day +0 If the child is excessively drowsy then reduce dose						
PBSC rescue	Minimum 3X10⁶/kg CD34+ i.v, **at least** 24 hours after the last dose of Melphalan							◆

- Anti-emetics:
  - not needed during busulfan
  - given i.v. approximately 30 minutes prior to the melphalan, for a minimum of 24 hours
- Adequate hydration is crucial.
- Pre-medication with anticonvulsants (Bu-related seizures).
- **Sinusoidal occlusive syndrome** (SOS) may occur. Prophylaxis for SOS might be performed according to institutional policy.
- Prophylactic antibiotics and antifungal treatment with ketoconazole, itraconazole or fluconazole should not be used (increased risk of SOS).

Current standard SIOPEN treatment for HR-NBL



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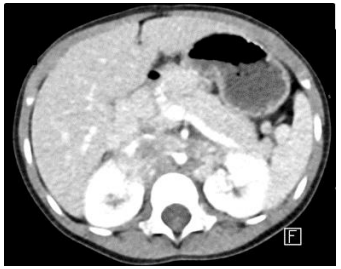
Surgery

- There is no place for surgery before induction chemotherapy other than biopsy.
- The surgery will be performed **after the end of induction**, ideally after peripheral stem cell harvest.
- The aim of surgery is to achieve complete excision of the tumor with minimal morbidity to improve local control.

- Reasons to postpone surgery:
  - encasement of celiac axis AND/OR
  - encasement of superior mesenteric artery AND/OR
  - encasement of both renal pedicles

to be discussed first with national/international Experts



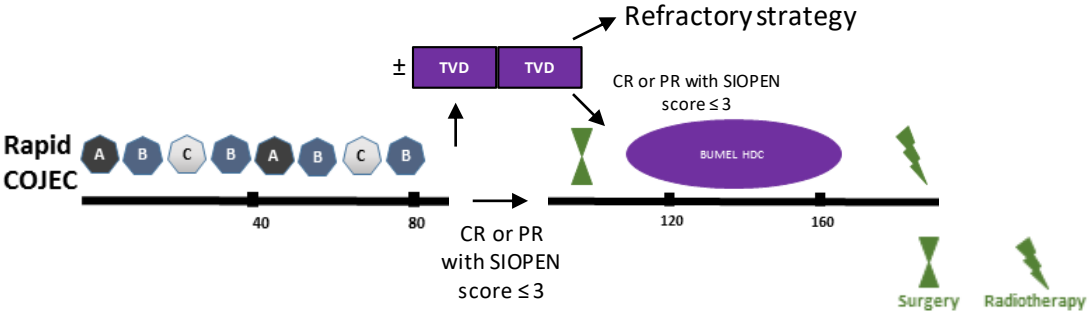
The risk of removal a kidney is <u>not</u> a sufficient reason to postpone surgery until after HDC although everything must be done to save the kidney during surgery.

Local radiotherapy

- All patients will receive 21.6 Gy-radiotherapy to the primary tumor site after HDC/ASCR

- Local radiotherapy will be given after HDC/ASCR and prior to the maintenance treatment.
- After HD Bu-Mel, the interval between ASCR and radiotherapy must be greater than 60 days, due to the risk of busulfan-enhanced radiotoxicity and ideally not greater than 90 days. However, if more than 90 days are needed to allow hematological recovery, radiotherapy should still be given.

Current standard SIOPEN treatment for HR-NBL



HR-NBL strategy

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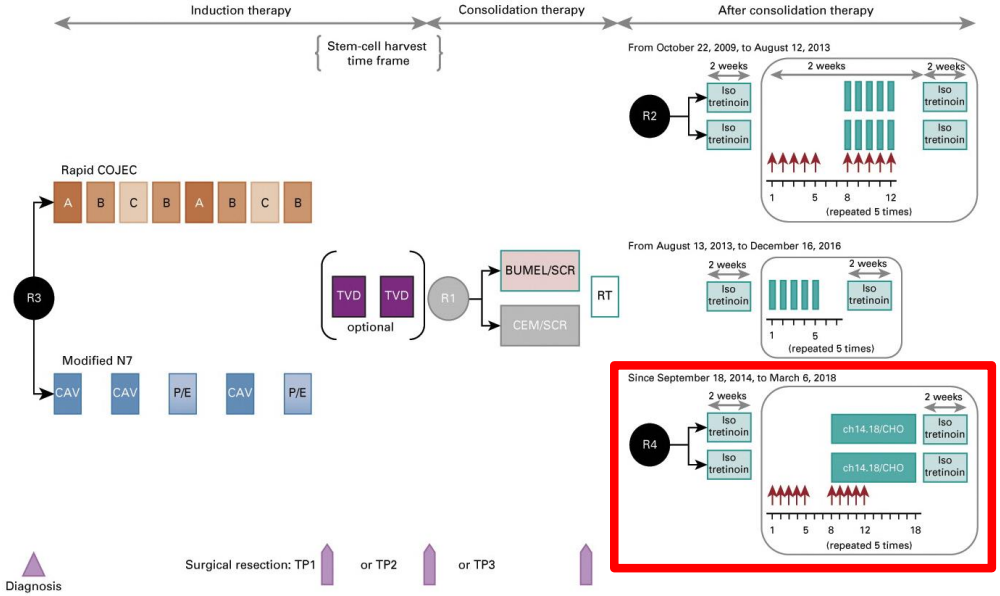
Background and rational: Maintenance

- **COG 2010**
  - **Dinutuximab (ch14.18/SP2/0)** in combination with cytokines (IL2 and GM-CSF) showed benefit in HR-NBL with 2y EFS 66%±5%, *(Yu et al., NEJM, 2010).* The role of cytokines in this context remains unclear.

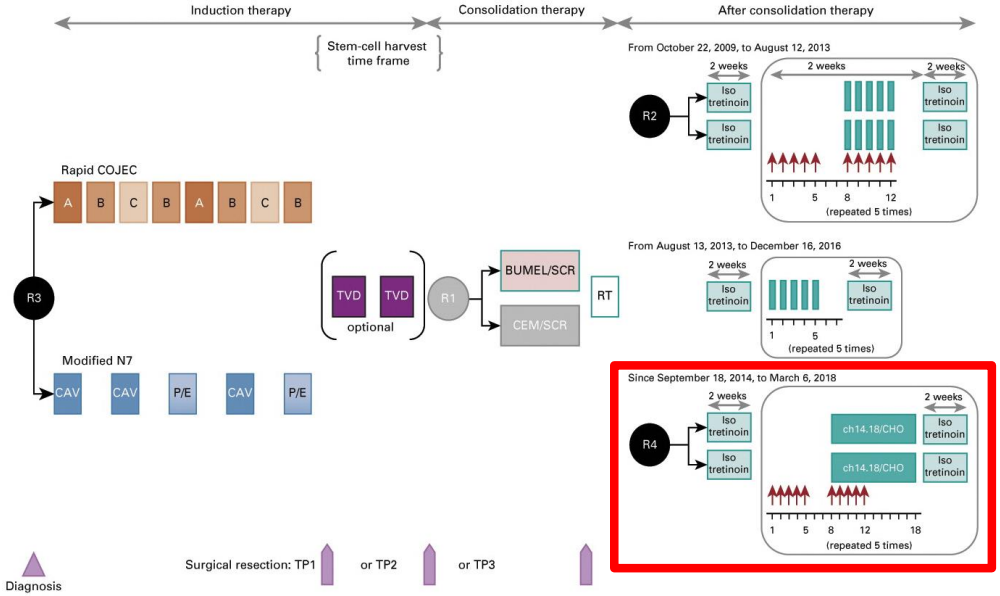
- **SIOPEN (randomization R2)**
  - Combination of **Dinutuximab beta (ch14.18/CHO)** as short 8h infusion (TD: 100mg/m²/cycle) with 6 x 10E6 IU/m2/day s.c.IL2 twice per cycle and 2 weeks standard oral isotretinoin.
  - No EFS benefit for the combination with IL2 was detected, but higher toxicity *(Ladenstein et al., Lancet Oncol 2018)*

HR-NBL1 protocol: R4 Maintenance



Adapted from Garaventa et al. JCO 2021

HR-NBL1 protocol: R4 Maintenance



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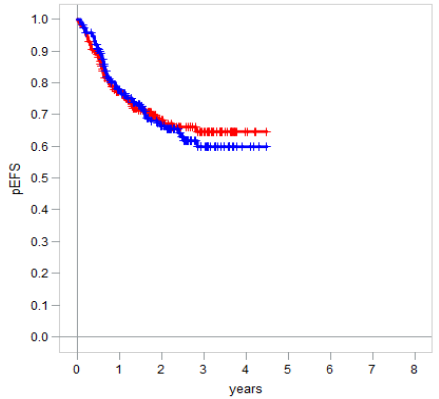


	Patients	Events	3-yrs pEFS	p-value
w/o IL2	200	61	0.65±0.04	0.796
with IL2	191	61	0.60±0.04	

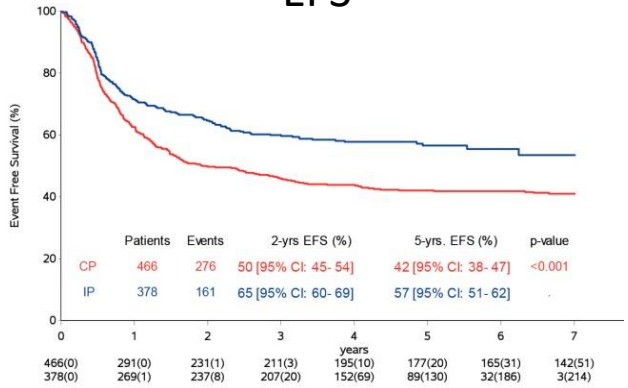
Courtesy of U. Pötschger

Role of Dinutuximab Beta-based Immunotherapy in the SIOPEN HR-NBL1

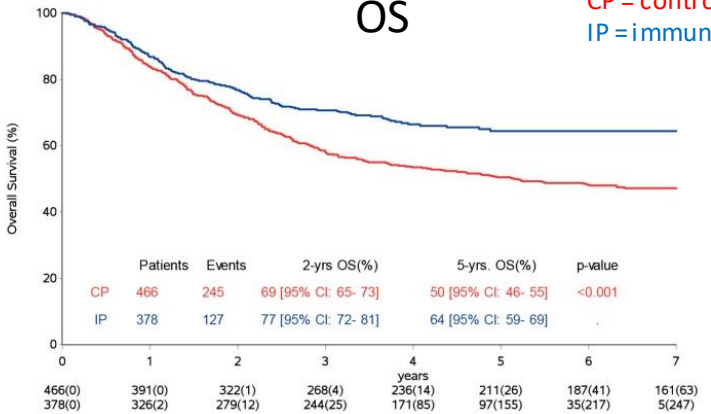
European Reference Network for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

CP = control population
IP = immunotherapy population

EFS



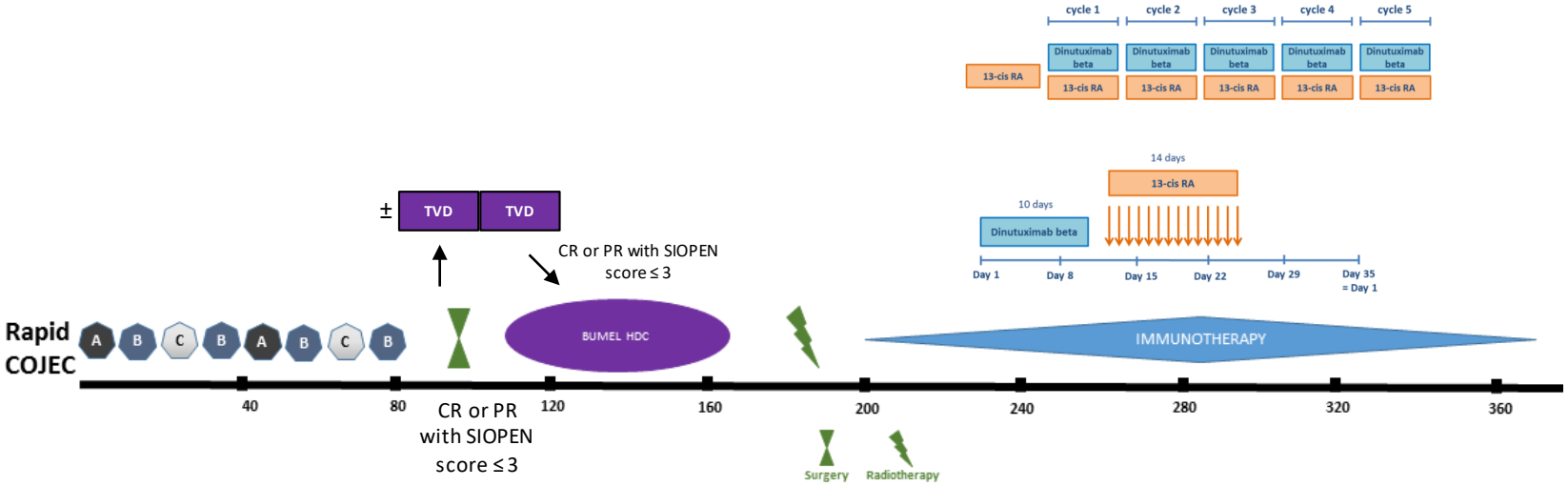
OS



A multivariate analysis identified **absence of immunotherapy** (p = 0.0002, hazard ratio (HR) 1.573); type of HDT (*p* = 0.0029, HR 1.431); less than complete response prior to maintenance therapy (*p* = 0.0043, HR 1.494) and >1 metastatic compartment at diagnosis (*p* < 0.001, HR 2.665) **as risk factors for relapse or progression**

Ladenstein et al. Cancers 2020

Current standard SIOPEN treatment for HR-NBL



Expected 3-year EFS = 49%

Follow-up

Clinical examination + ultrasound of the primary site + urinary CA

No mandatory MIBG (or PET) scan

No mandatory bone marrow evaluation

The schedule for mandatory evaluation is as follows:

- Year 1 after the end of treatment : Every 3 months
- Year 2 and 3 after the end of treatment: Every 4 months
- Year 4 and 5 after the end of treatment: Every 6 months
- Then, patients will enter into **long-term follow-up** (cardiac/ thyroid/gonadal/lung function, growth, neurocognitive development)

Ideal world *vs* reality

Ideal world

Diagnosis → End of treatment

Reality

Diagnosis → End of treatment

If any doubt, please share and ask for advice!

Thanks to SIOP EUROPE Neuroblastoma Group

Patients, their Families and Care Teams in all current Member Countries:
clinicians, surgeons, pathologists, biologists, radiation therapists, nuclear medicines specialists, nursing and supportive care staff

Austria
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