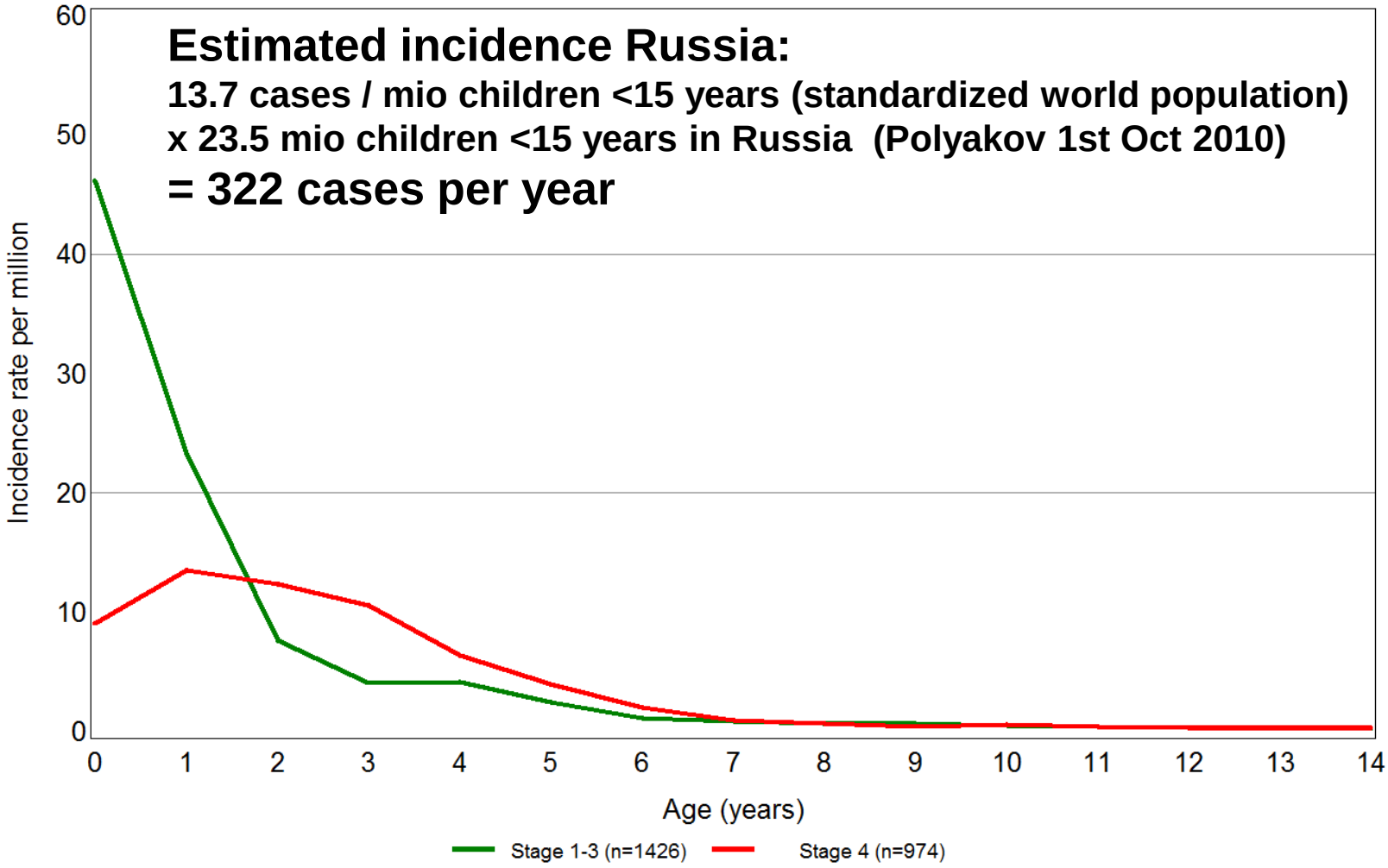
UNIKLINIK KÖLN

Essentials and current options of first and second line treatment in high risk neuroblastoma

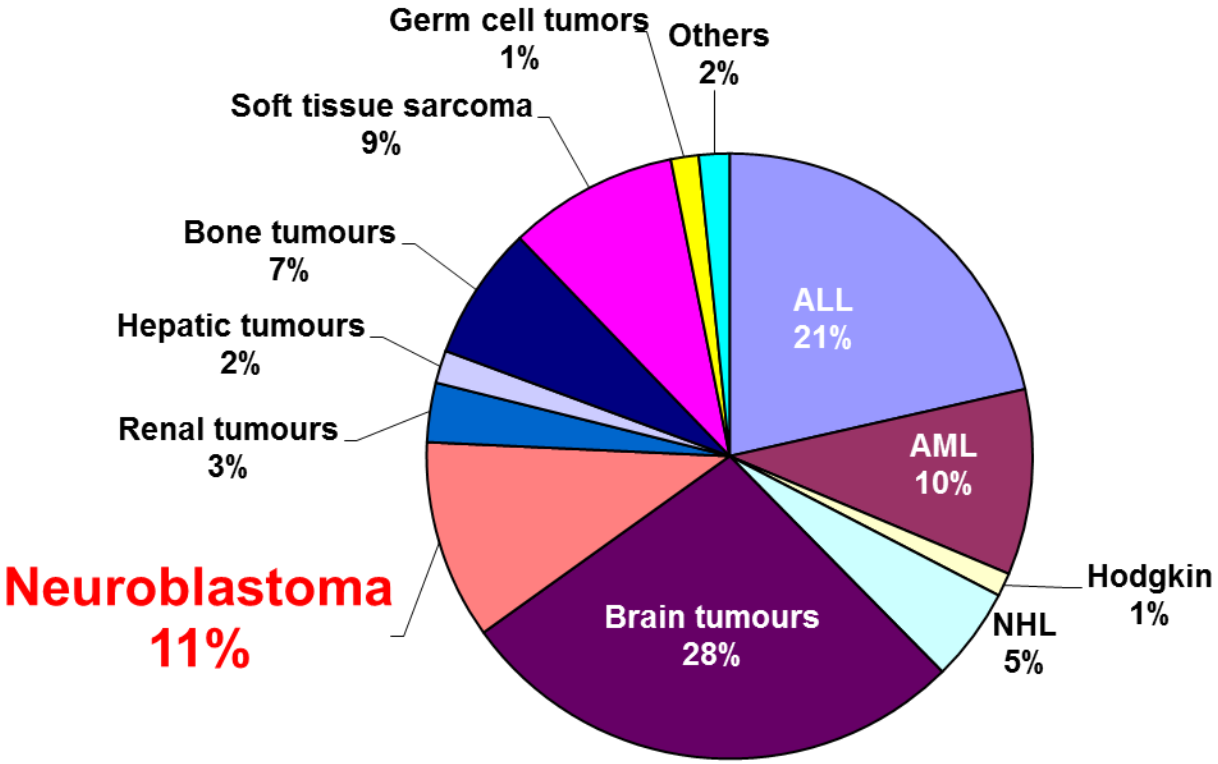
Achievements and Perspectives of Child Oncology
VI Russian Pediatric Oncology Congress
Moscow , 1st-3rd October 2015

Frank Berthold, University of Cologne



Neuroblastoma incidence in Germany by stage (Children‘s Cancer Registry, 01/90-07/15), n=2401

Cancer deaths in childhood
GCCR 1980–2008, n=10,032[1]



US: Cancer deaths in childhood caused by neuroblastoma in children aged <15 years was 11% between 2007 and 2010 as based on Surveillance, Epidemiology, and End Results (SEER) 9 registries[2]

1. Annual reports GCCR: www.kinderkrebsregister.de
2. Smith MA, et al. Cancer. 2014;120:2497–506

Molecular markers to describe HR neuroblastoma*

Non-high risk n= 103	cases	%
TERT-rearrangment	1	1.0 %

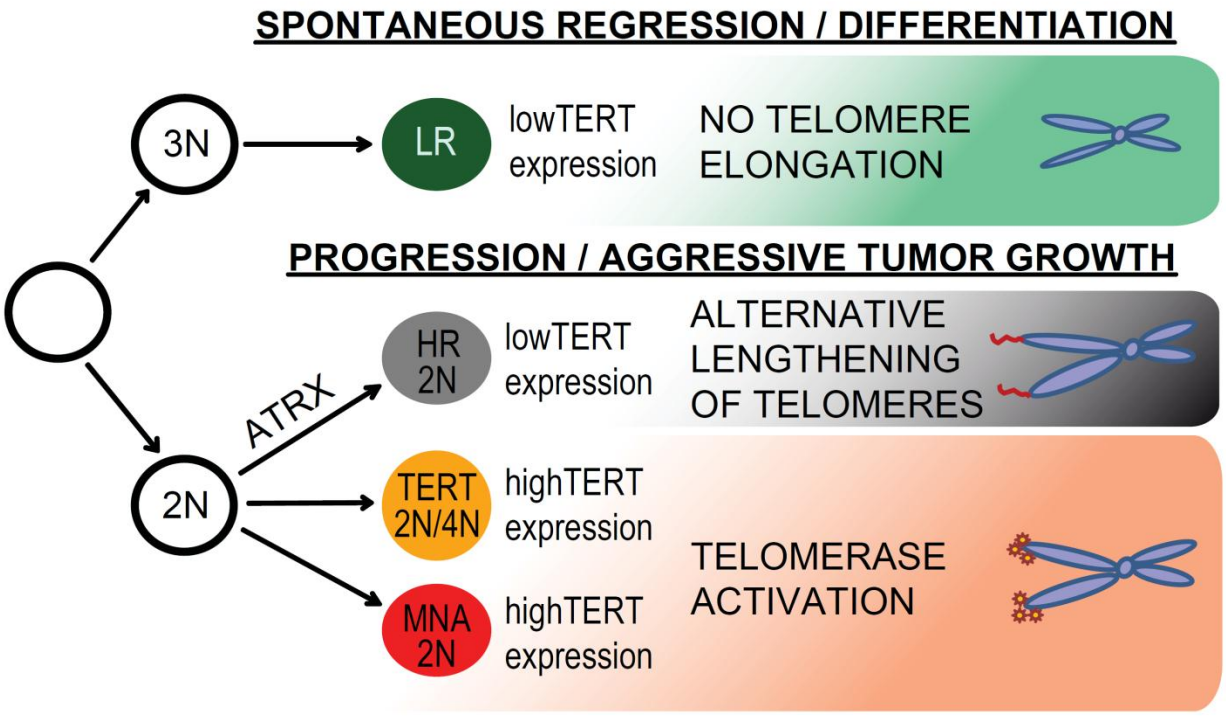
High-Risk n= 114		
MYCN amplification	49	43.0 %
TERT-rearrangment	27	23.7 %
Neither	43	37.7 %

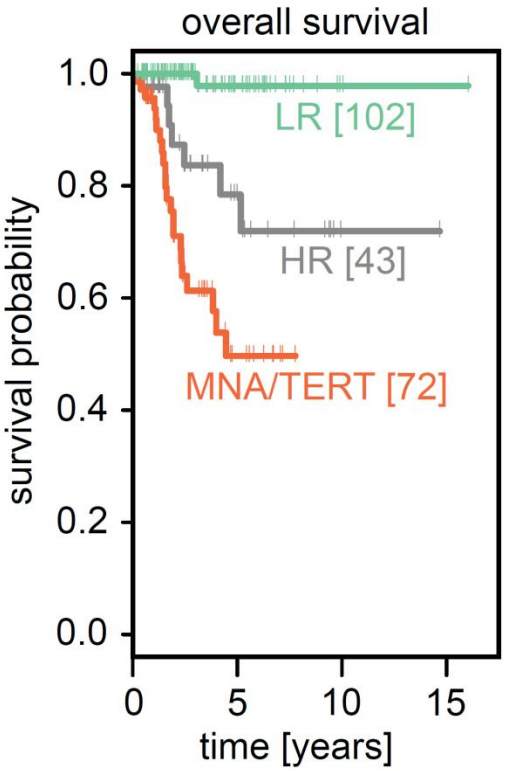
TERT-r and MNA co-occurrence in 4.4% of HR cases

*Peifer M et al: Nature 2015 (in press)

Definition of high-risk neuroblastoma

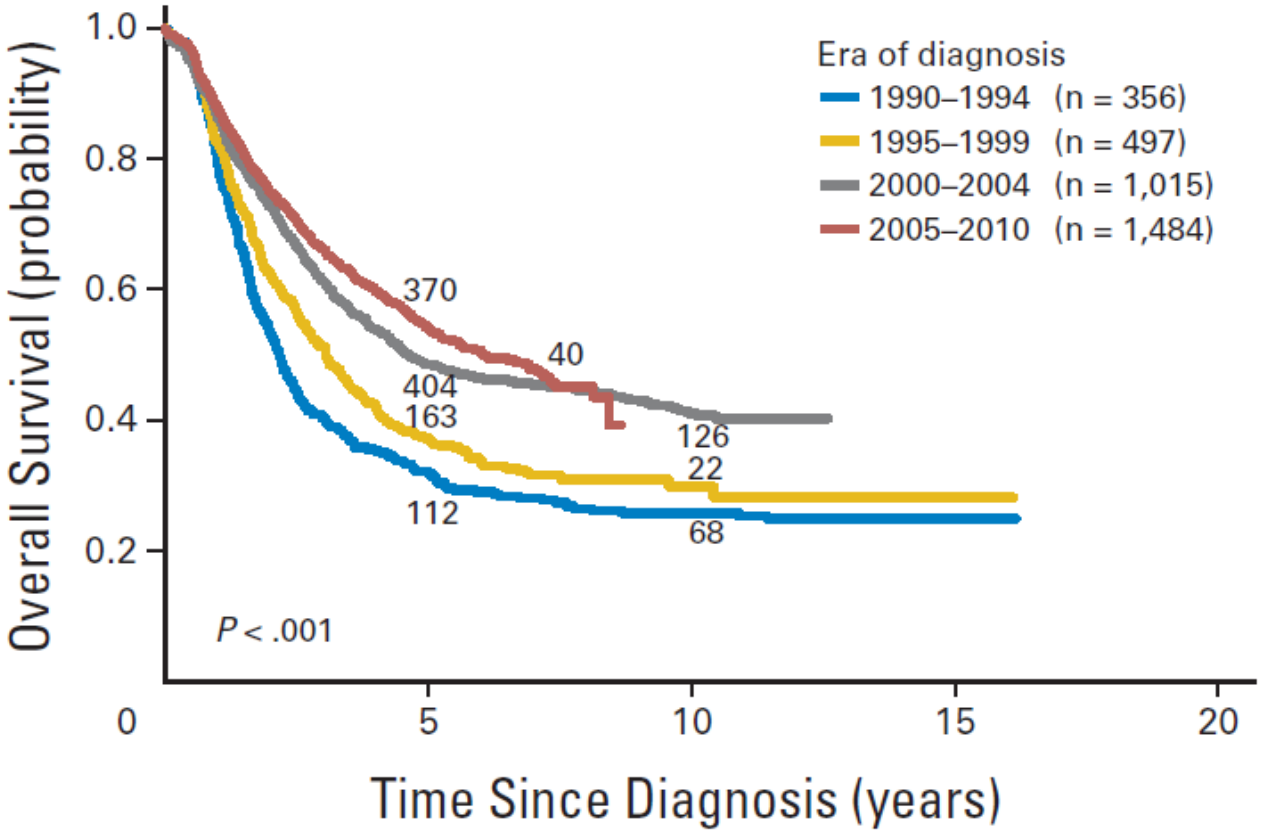
Clinical: stage 4 >18 months, MYCN amplified any stage any age
Molecular: MYCN amplification, TERT rearrangements, ATRX mutations/?*





*Peifer M et al: Nature 2015 (in press)

The 5-year survival rate for neuroblastoma has improved over the last 20 years

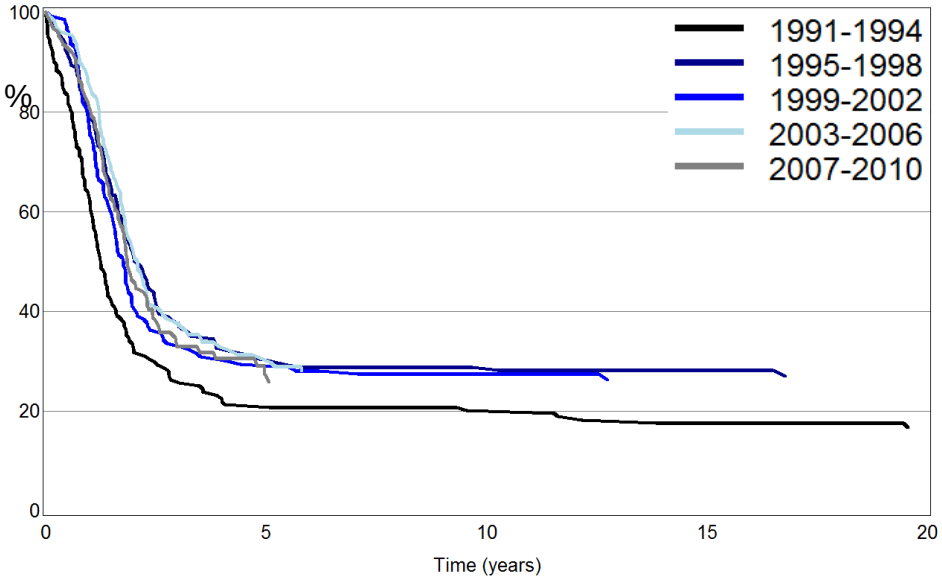


Probability of OS among 3,352 Children's Oncology Group (COG) patients with high-risk neuroblastoma (1990–2010)

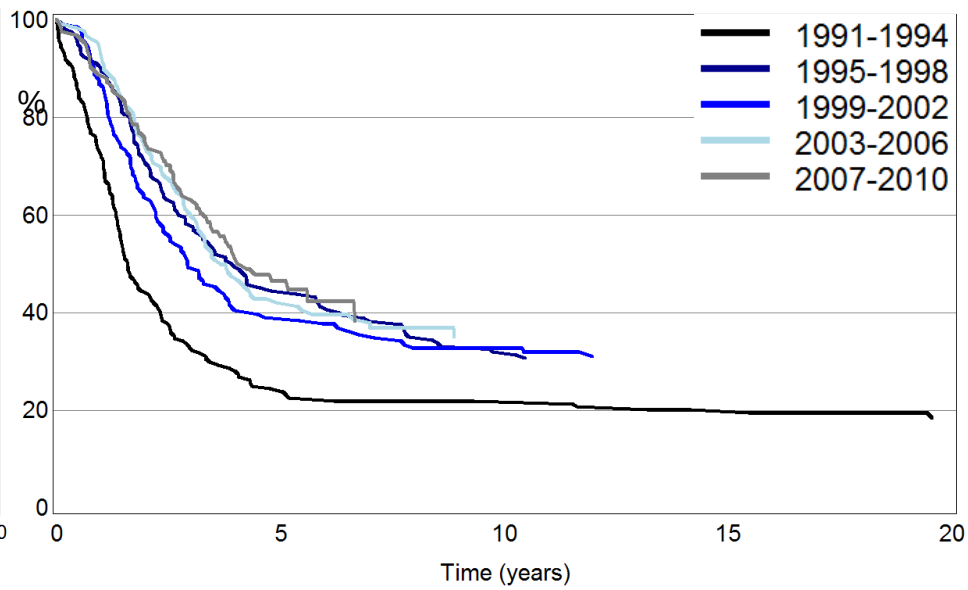
Pinto NR, et al. 2015; J Clin Oncol. 2015 Sep;33:3008–17

However, 5-year survival rates remain unsatisfactory for neuroblastoma stage 4 >18 months

Probability of Event-Free Survival



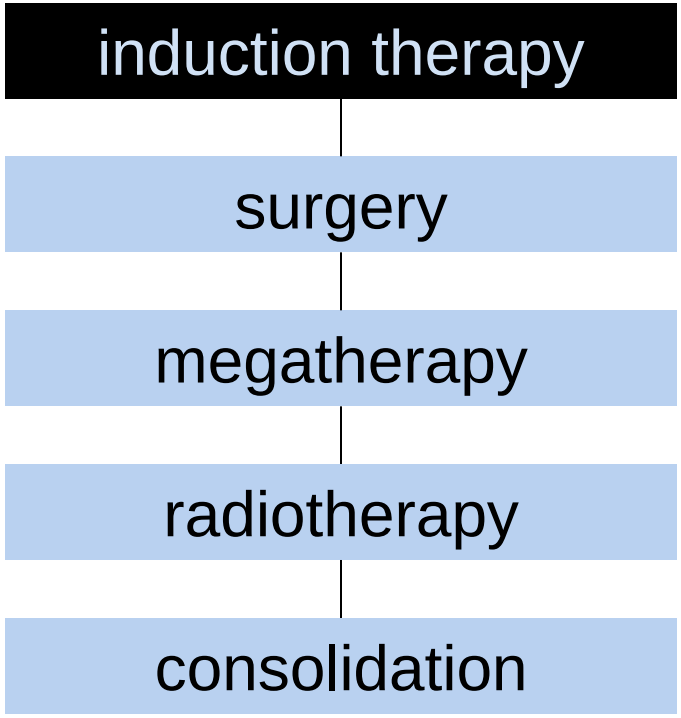
Probability of Overall Survival



Probability of event free and overall survival among 727 patients with <u>stage 4 neuroblastoma, aged >18 months</u> (GPOH, 1991–2010)

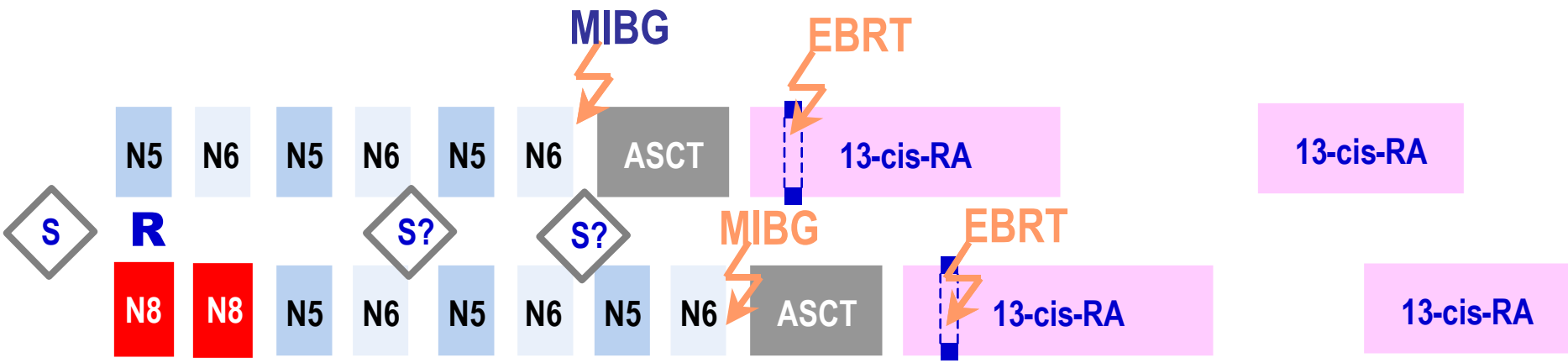
1991–94, n=164; 1995–98, n=161; 1999–2002, n=146; 2003–2006, n=130; 2007–2010, n=126

Therapy in high risk neuroblastoma

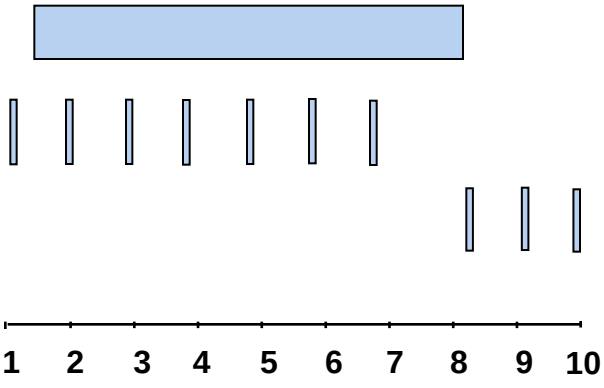


Trial NB2004 – High Risk

stage 4, 1 – 21 years,
presence of MYCN-amplification any stage, age 0.5 - 21 years



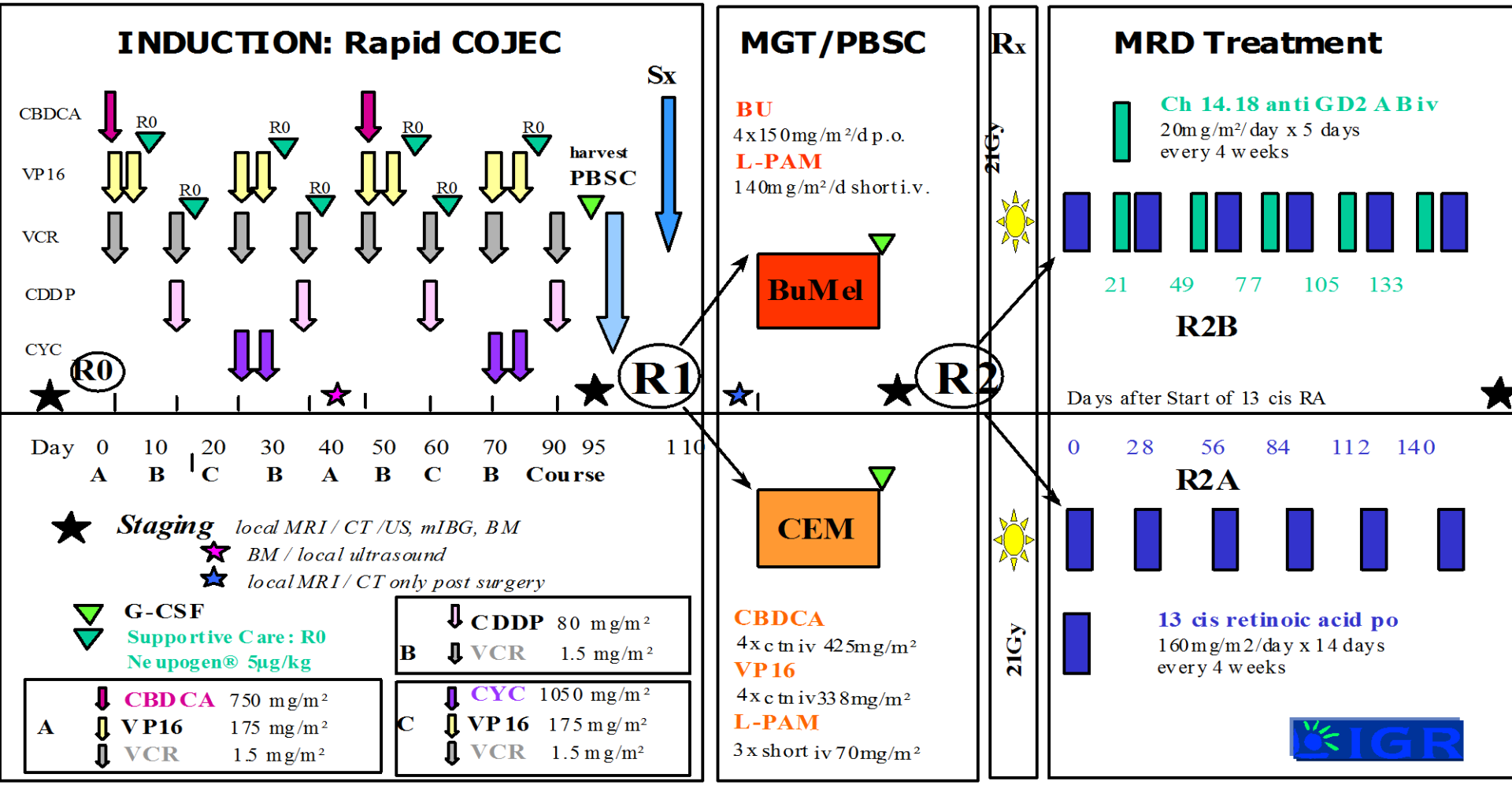
Cycle N8 (TCE)



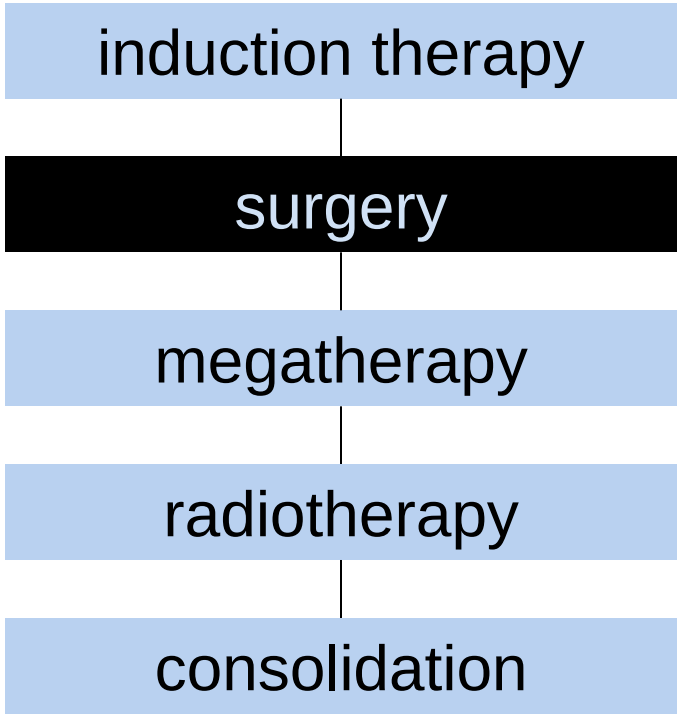
topotecan	1.0 mg/m²xd	d 1 to 7	168 hrs
cyclophosphamide	100 mg/m²xd	d 1 to 7	1 hr
etoposide	100 mg/m²xd	d 1	1 hr

Simon T et al., J Cancer Clin Oncol 2007

HR-NBL-1 / ESIOP FLOWSHEET



Therapy in High Risk Neuroblastoma



Impact of surgery on survival in HR neuroblastoma SIOPEN experience*

Inclusion

Stage 4 >12 mo., stages 2,3,4,4S with MNA

1324 operations

operation related mortality 0.5%

morbidity 10%.

Radicality

Macroscopic complete excision: 76%

Macroscopic incomplete: 23%

Inoperable: 2%

***Holmes K et al; ANR2014 congress, Cologne 13-16th May, 2014; PL012 p107**

Impact of surgery on survival in HR neuroblastoma SIOPEN experience*

all	5 y EFS	5 y OS
Complete (n=1002 pat.)	38%	44%
Incomplete/inoperable	27%	36%
P	0.001	0.013
Stage 4		
Complete (n=895)	33%	27%
Incomplete/inoperable	24%	33%
P	0.006	0.049

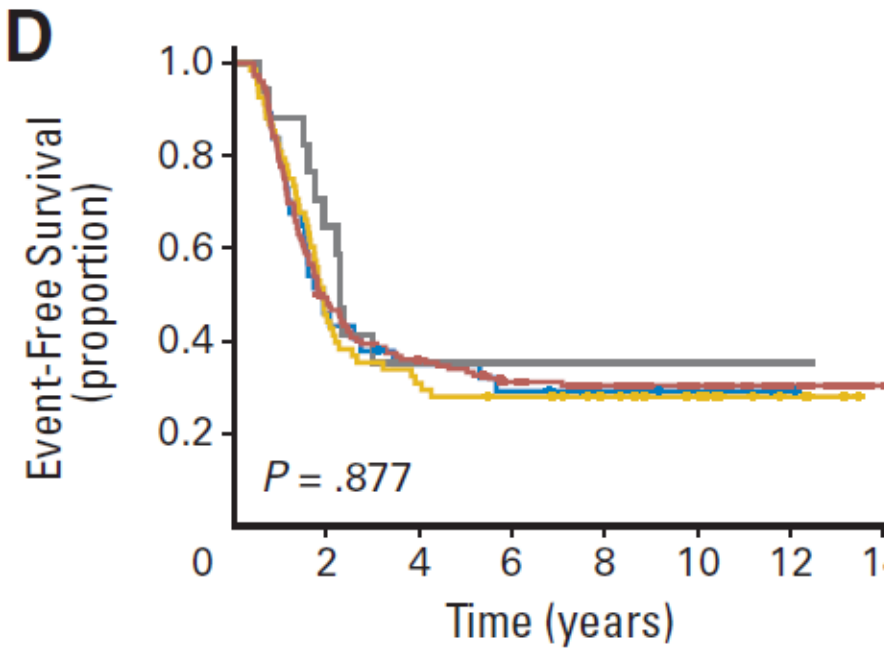
→ macroscopical complete excision is safe and confers a survival advantage

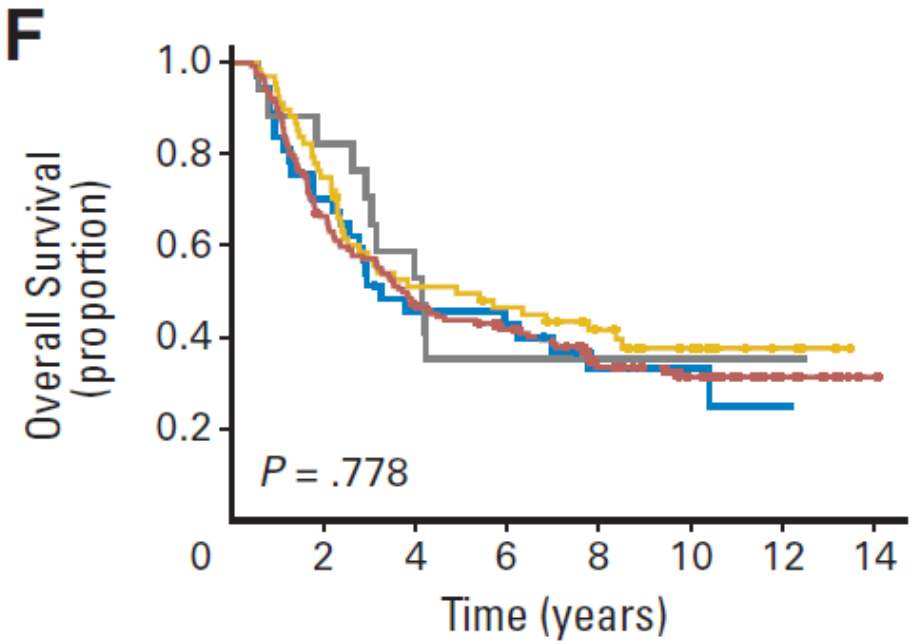
Holmes K et al; ANR2014 congress, Cologne 13-16th May, 2014; PL012 p107

Impact of surgery on survival in HR neuroblastoma GPOH experience*

All 278 patients >18 mo stage 4 by extent of best operation

none + biopsy / 50-90% / >90% / complete



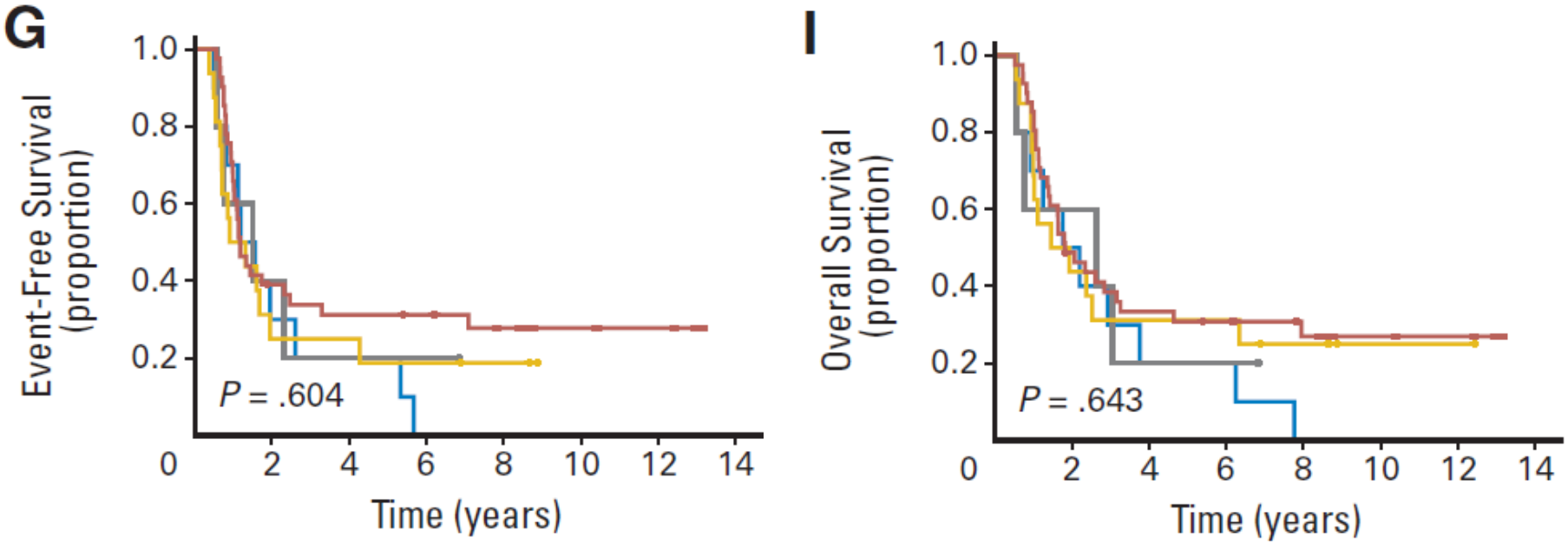


*Simon T et al. (2013) J Clin Oncol 31:752-8

Impact of surgery on survival in HR neuroblastoma GPOH experience*

71 patients with MNA >18 mo. stage 4 by extent of best operation

none + biopsy / 50-90% / >90% / complete



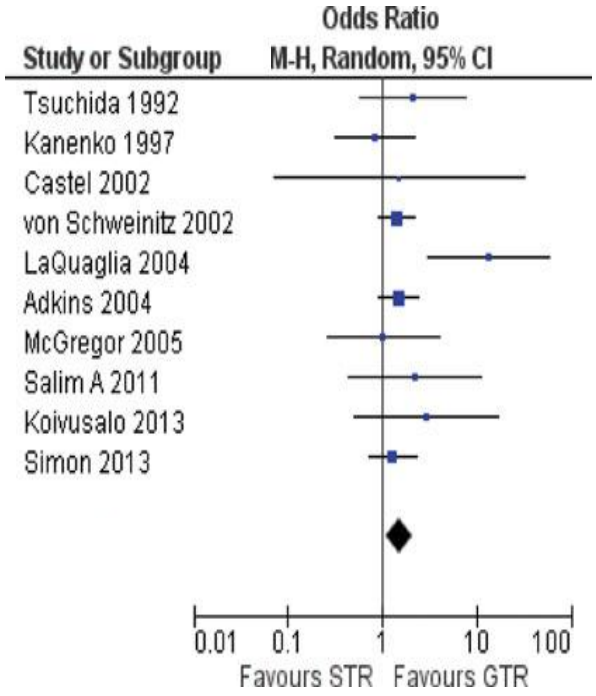
*Simon T et al. (2013) J Clin Oncol 31:752-8

Metaanalysis on the use of aggressive surgical resection in stage 4 neuroblastoma *

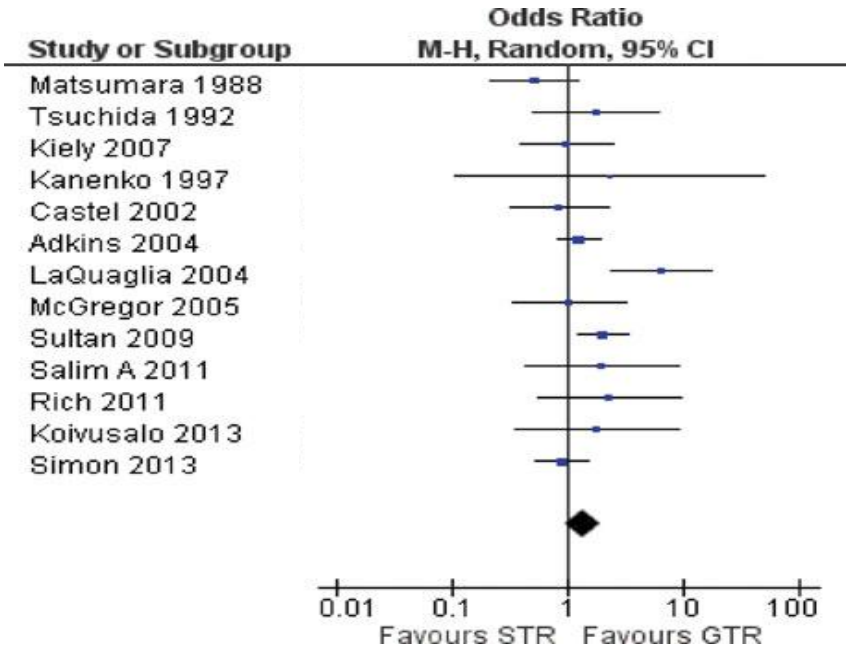
Inclusion criteria: 13 studies

Gross total resection vs. subtotal resection

Pooled Odds ratio 5 y DFS 1.55 (1.12-2.14)



pooled Odds ratio 5 y OS 1.65 (0.96-1.91)

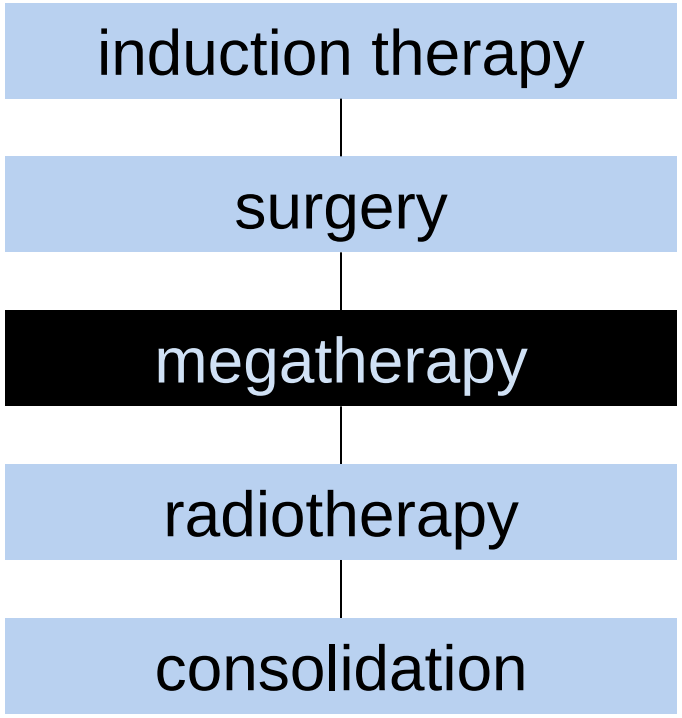


*Mullassery D et al. Pediatr Hematol Oncol (2014) 31:703-16

Differences between the trials to explain the different results and conclusions

- **Different preceding chemotherapy (more-less intensive)**
- **Different use of other local therapies (radiotherapy)**
- **No randomized trial on the impact of surgery available**

Therapy in High Risk Neuroblastoma



Long term results (COG)

Regimen	5 year EFS %	5 year OS %
HR patients		
ABMT (n=190)	30 ± 4	39 ± 4
Chemotherapy (n=189)	19 ± 3	30 ± 4
P	0.043	n.s.
Stage 4 patients:		
ABMT	26 ± 4	37 ± 4
Chemotherapy	16 ± 3	28 ± 4
P	n.s.	n.s.

Matthay KK et al. J Clin Oncol (2009) 27:1007-13 and June 10th, 2014 ; 1862-3

Myeloablative therapy with autologous stem cell transplantation (ASCT) in high risk neuroblastoma

Three randomized trials since 30 years of use

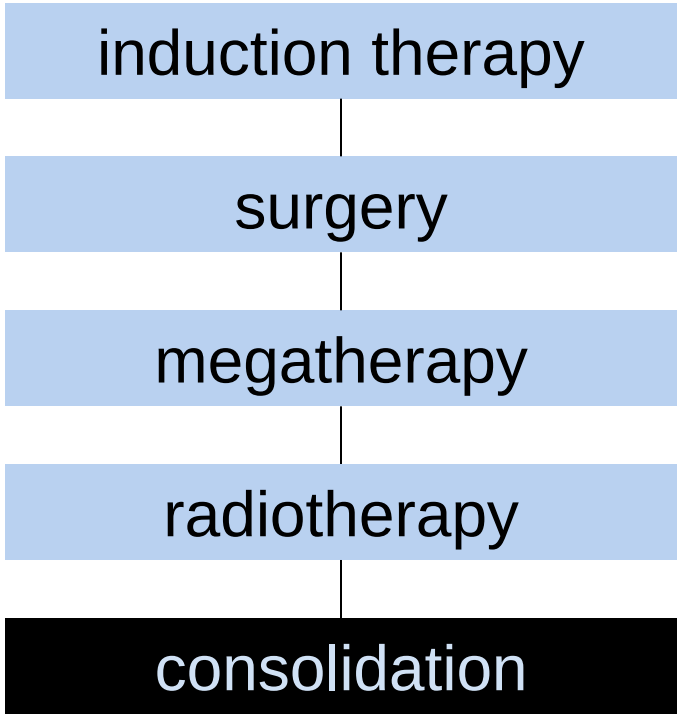
- **Matthay KK et al. N Eng J Med, 1999; 341:1165-73**
- **Pritchard J et al. Pediatr Blood Cancer, 2005; 44: 348-57**
- **Berthold F et al. Lancet Oncol, 2005; 6: 649-58**

=> all in favor of ASCT for EFS

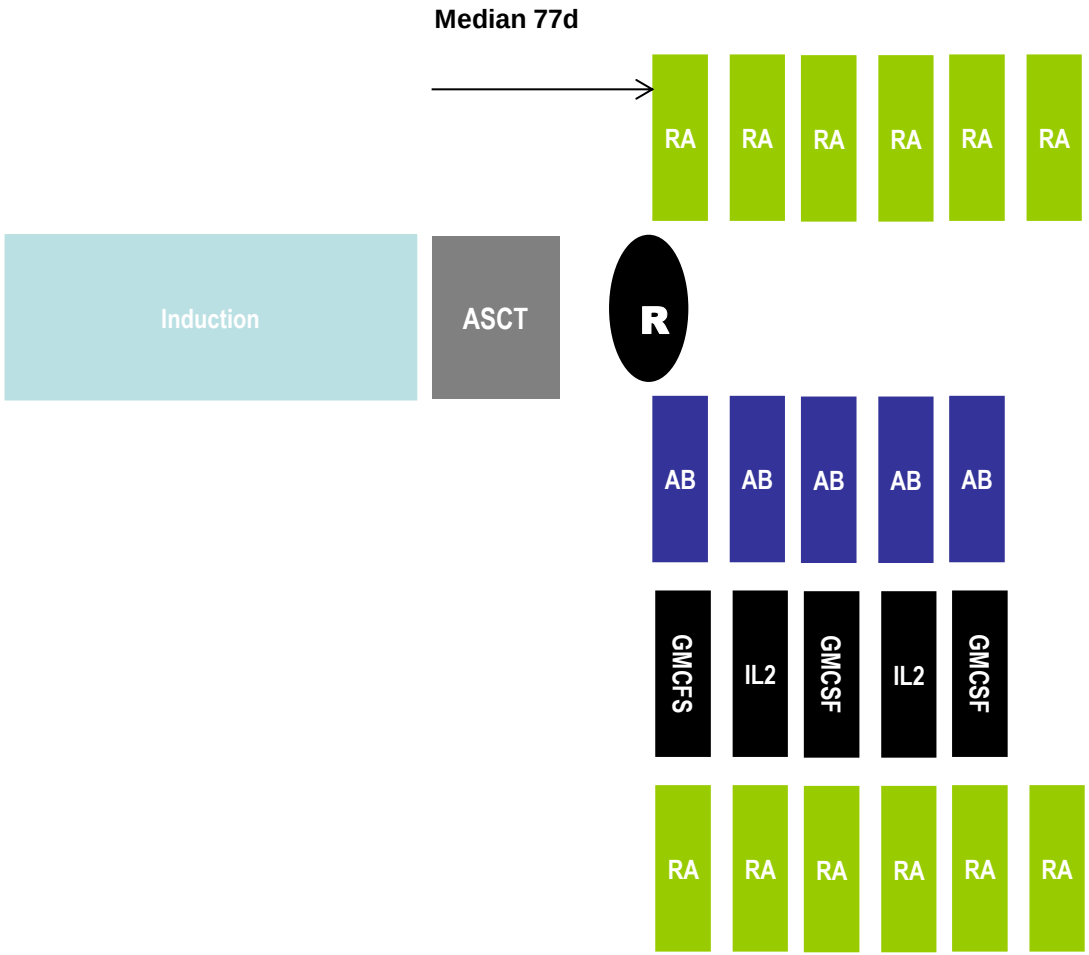
for OS currently no evidence of use (if follow-up data are included)*****

***Yalcin B et al (2013) Cochrane Database Systematic Reviews; DOI:10.1002/14651858**

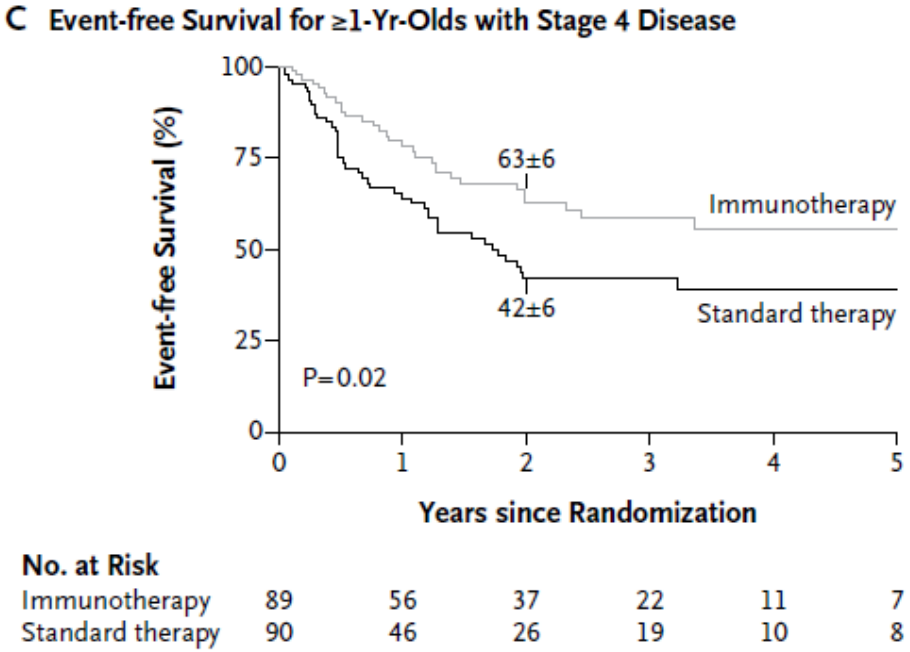
Therapy in High Risk Neuroblastoma



ANBL0032 trial (COG)



ch14.18	25 mg/m²/d	d1-4
GM-CSF	250 µg/m²/d	d1-14
IL2	4,5 Mio IU/m²	d1-7
IL2	3,0 Mio/m²	d8-14
RA	160 mg/m²/d	d1-14



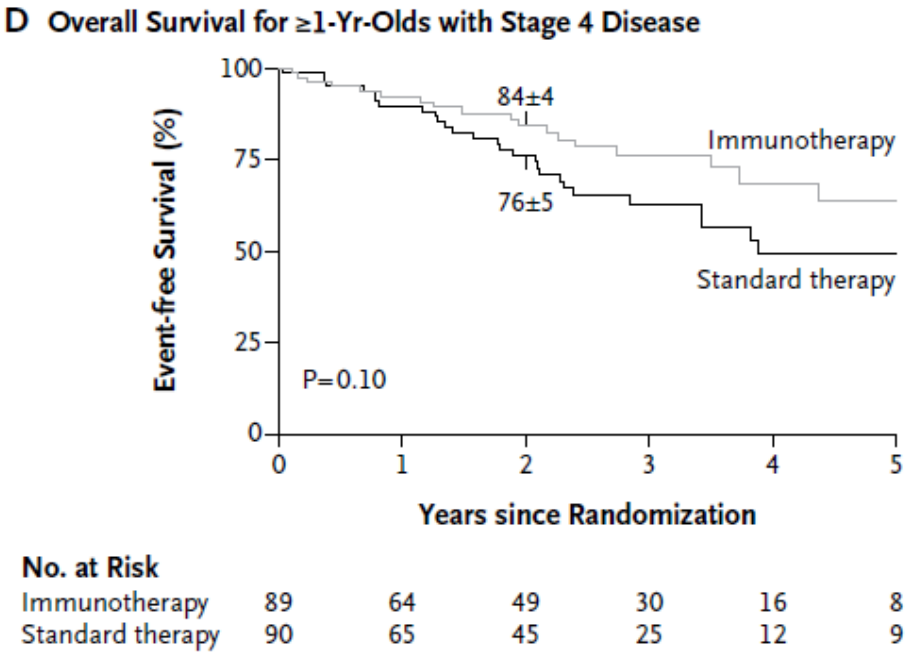


Figure 2. Kaplan–Meier Estimates of Survival among the 226 Study Patients Who Had Been Randomly Assigned, According to Treatment Group.

Data are shown for event-free survival (Panel A) and overall survival (Panel B) for all 226 patients and for event-free survival (Panel C) and overall survival (Panel D) for the 179 patients 1 year of age or older at enrollment. The estimated survival (±SE) at 2 years is indicated in each plot.

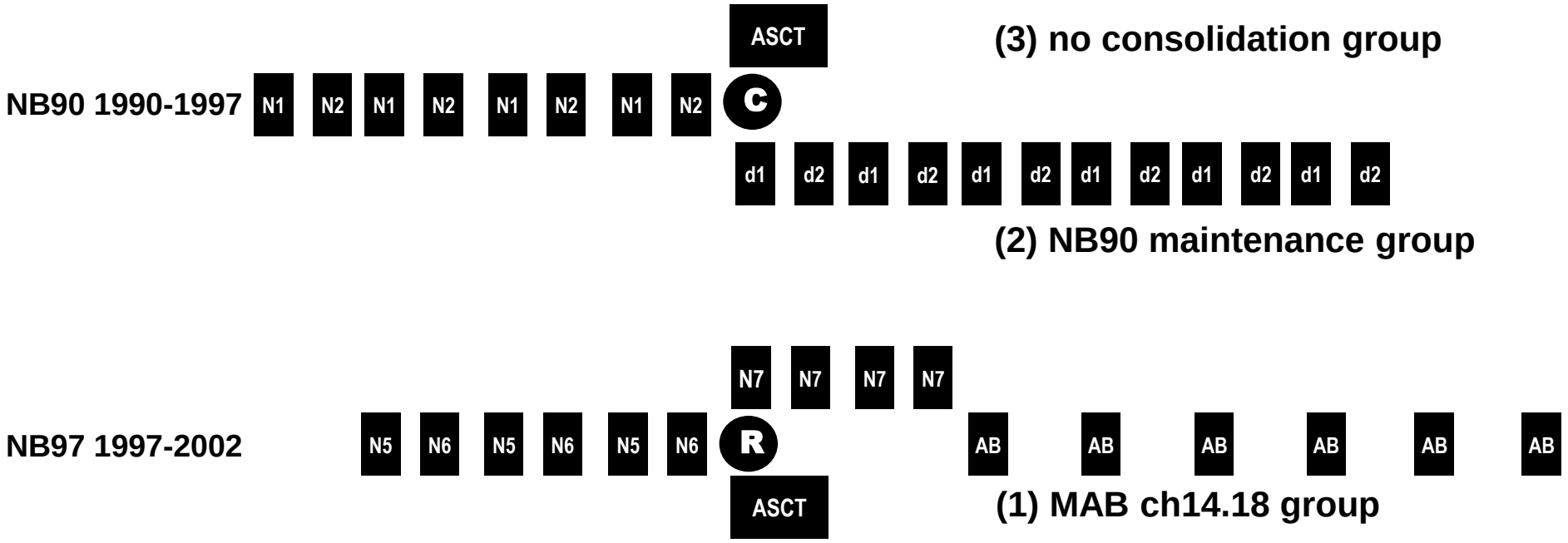
A. Yu et al. N Engl J Med 2010, 363: 1324-34

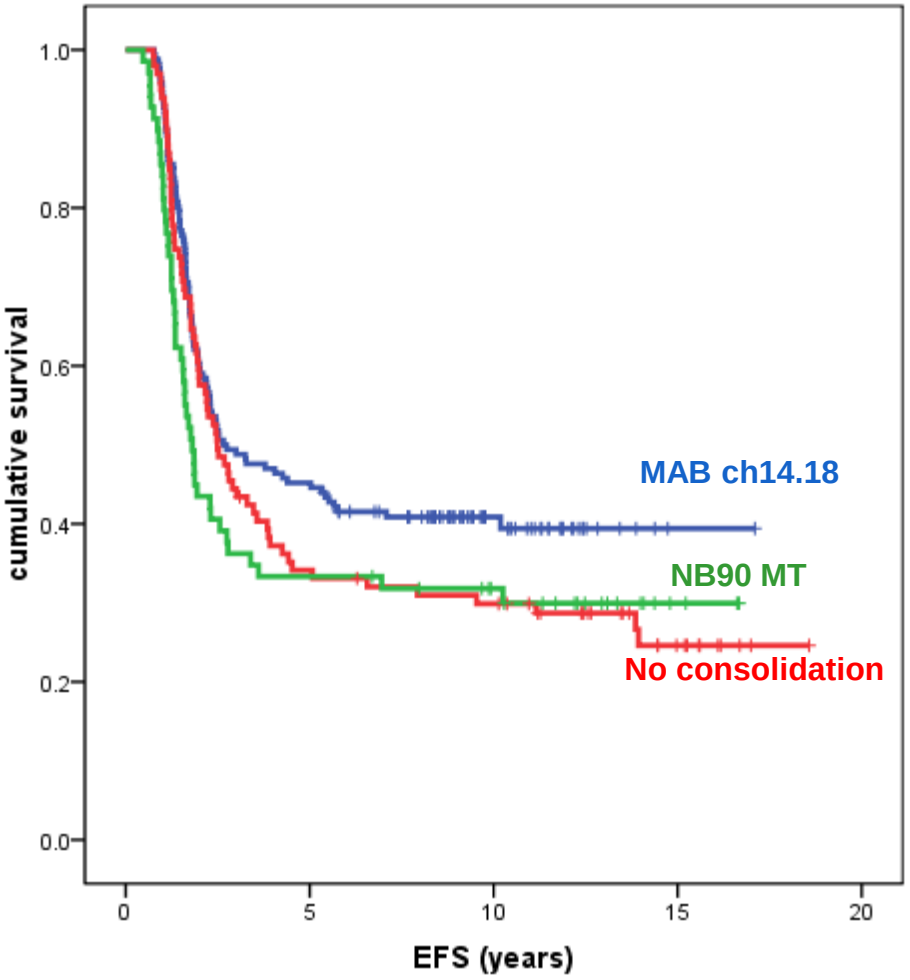
2014 Update immunotherapy COG trial*

	2 year	4 year	p
All patients (n=225)			
EFS immunotherapy	**67 ± 4%**	**59 ± 5%**	
RA alone	**51 ± 5%**	**48 ± 5%**	**0.11**
OS immunotherapy	**83 ± 4%**	**74 ± 5%**	
RA alone	**74 ± 5%**	**59 ± 5%**	**0.02**
Stage 4 patients (n=180)			
EFS immunotherapy	**64 ± 5%**	**54 ± 5%**	
RA alone	**45 ± 5%**	**44 ± 5%**	**0.10**
OS immunotherapy	**83 ± 4%**	**72 ± 5%**	
RA alone	**75 ± 5%**	**56 ± 5%**	**0.02**

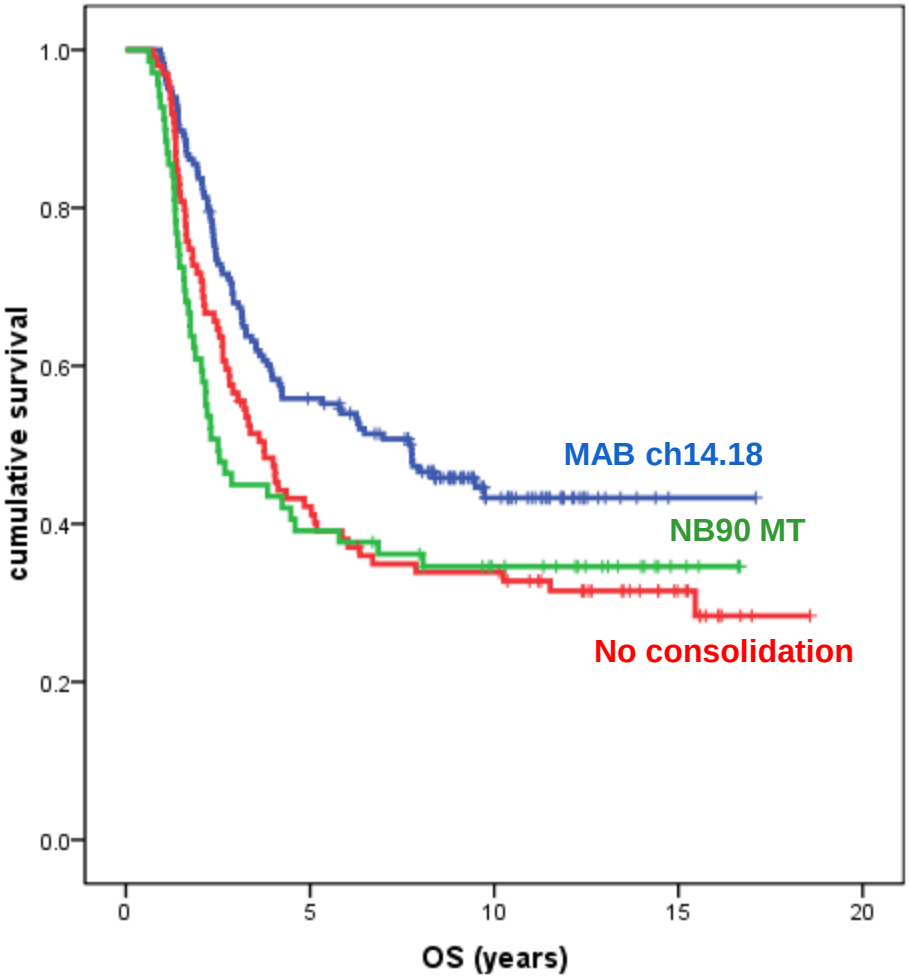
***Yu AL et al. 2014; abstract PL013 Advances in Neuroblastoma Research; Cologne 13.-16th May, 2014, p.108**

GPOH trial


ASCT
(3) no consolidation group
NB90 1990-1997
N1
N2
N1
N2
N1
N2
N1
N2
C
d1
d2
d1
d2
d1
d2
d1
d2
d1
d2
d1
d2
(2) NB90 maintenance group
N7
N7
N7
N7
NB97 1997-2002
N5
N6
N5
N6
N5
N6
R
AB
AB
AB
AB
AB
AB
ASCT
(1) MAB ch14.18 group



MAB vs. no p= 0.038
vs. MT p= 0.147



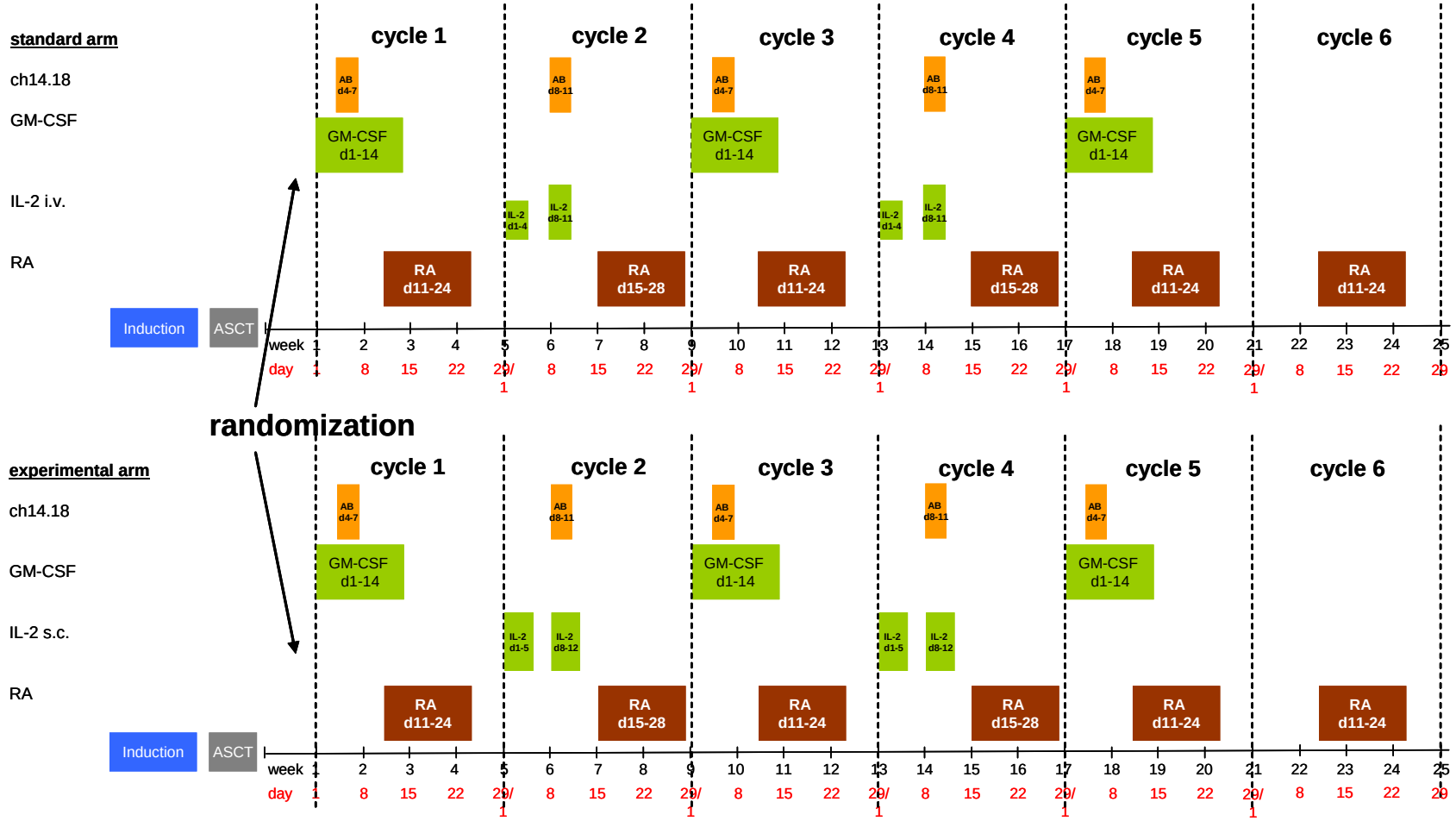
MAB vs. no p= 0.016
vs. MT p= 0.023

Simon T et al. BMC Cancer, 2011; 11(1):21

Side effects
(695 ch14.18 cycles, 151 patients)

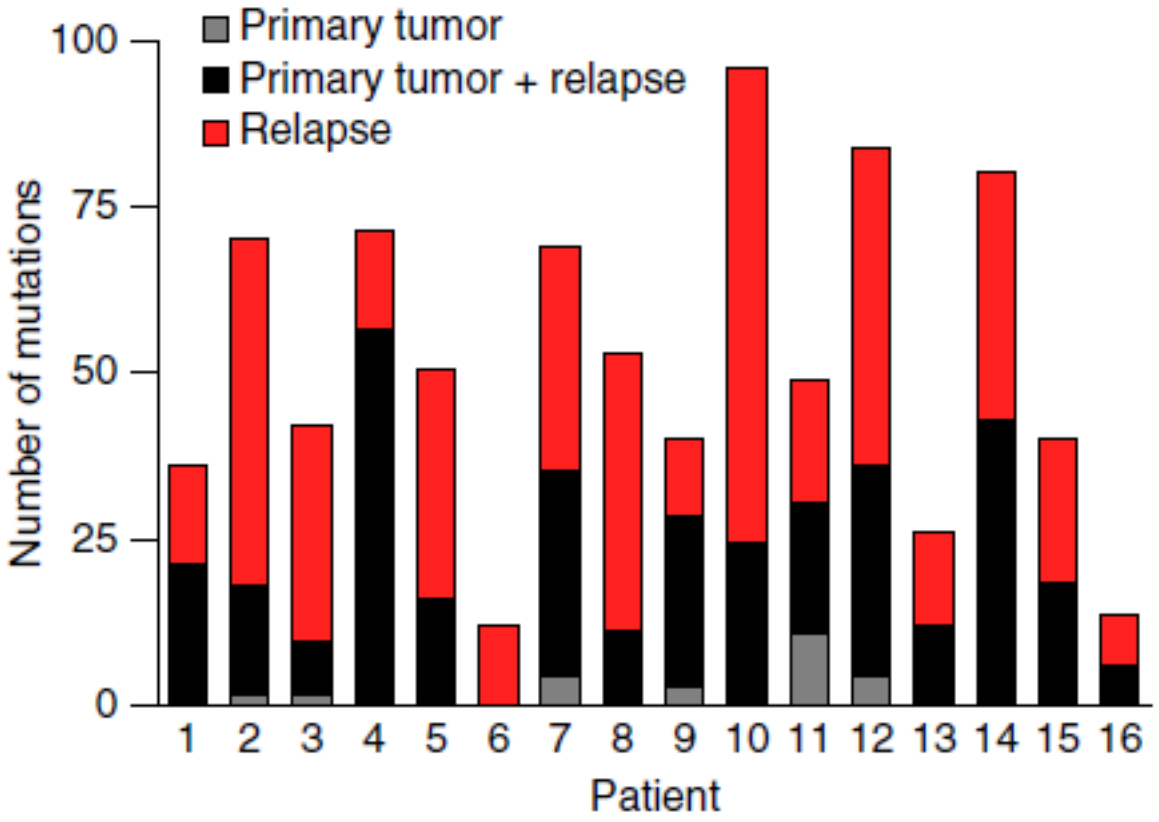
	% of courses	% of patients
Fever	53	82
Elevated CRP	34	57
Cough	24	52
Rash	22	54
Pain despite analgesia	15	31
Itching	8	21
Arterial hypotension	6	13
Abnormal liver enzymes	5	12
Oedema	5	12
Nausea/vomiting	4	15
Pulmonary obstruction	2.2	7.4
Ocular symptoms	1.5	5.1
Oxygen requirement	0.9	4.0
Capillary leak syndrome	0.4	1.7
Febrile convulsions	0.2	1.2
Guillain Barré Syndrome (VZV)	0.1	0.6

NB2013-HR pilot GPOH/DCOG trial



Studies on neuroblastoma recurrences

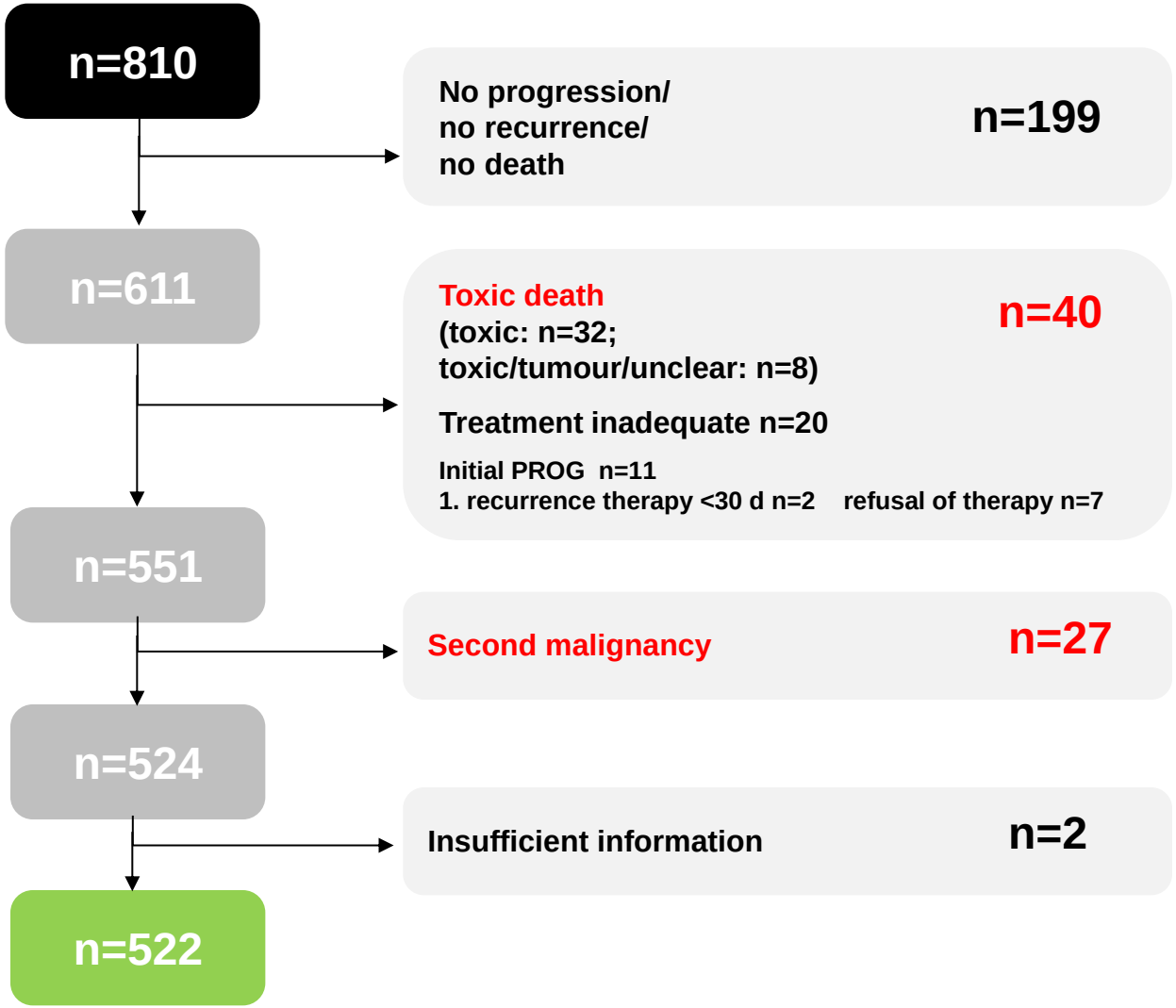
Number of muations in coding regions in matched pretreatment primary and relapse neuroblastomas *



*** Schramm A et al. Nature Genetics 2015; 47 (8); 872-8**

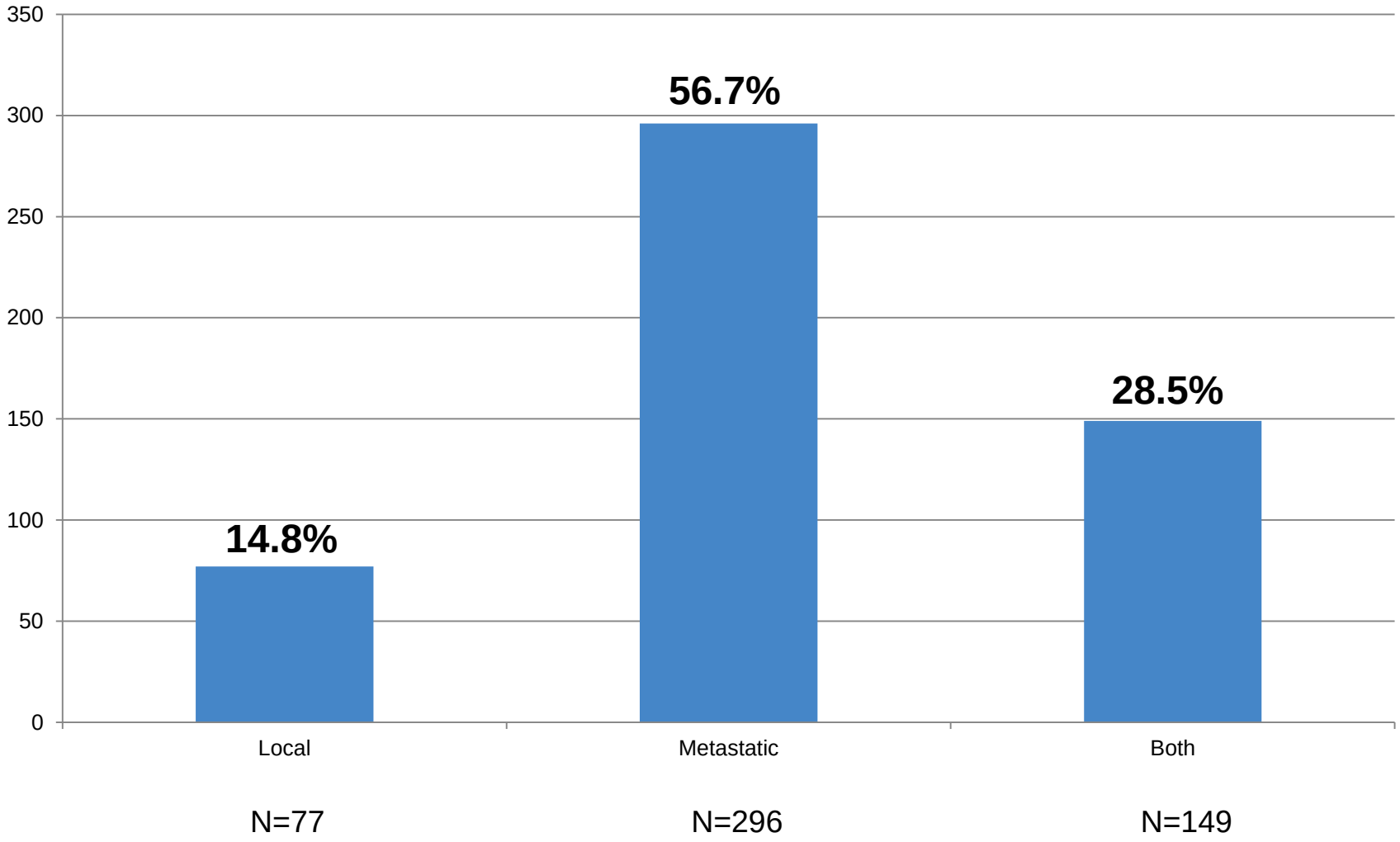
A significant number of high-risk neuroblastoma patients experience relapse

Stage 4 neuroblastoma, aged 1.5 to <21 years at initial diagnosis (1990–2010)

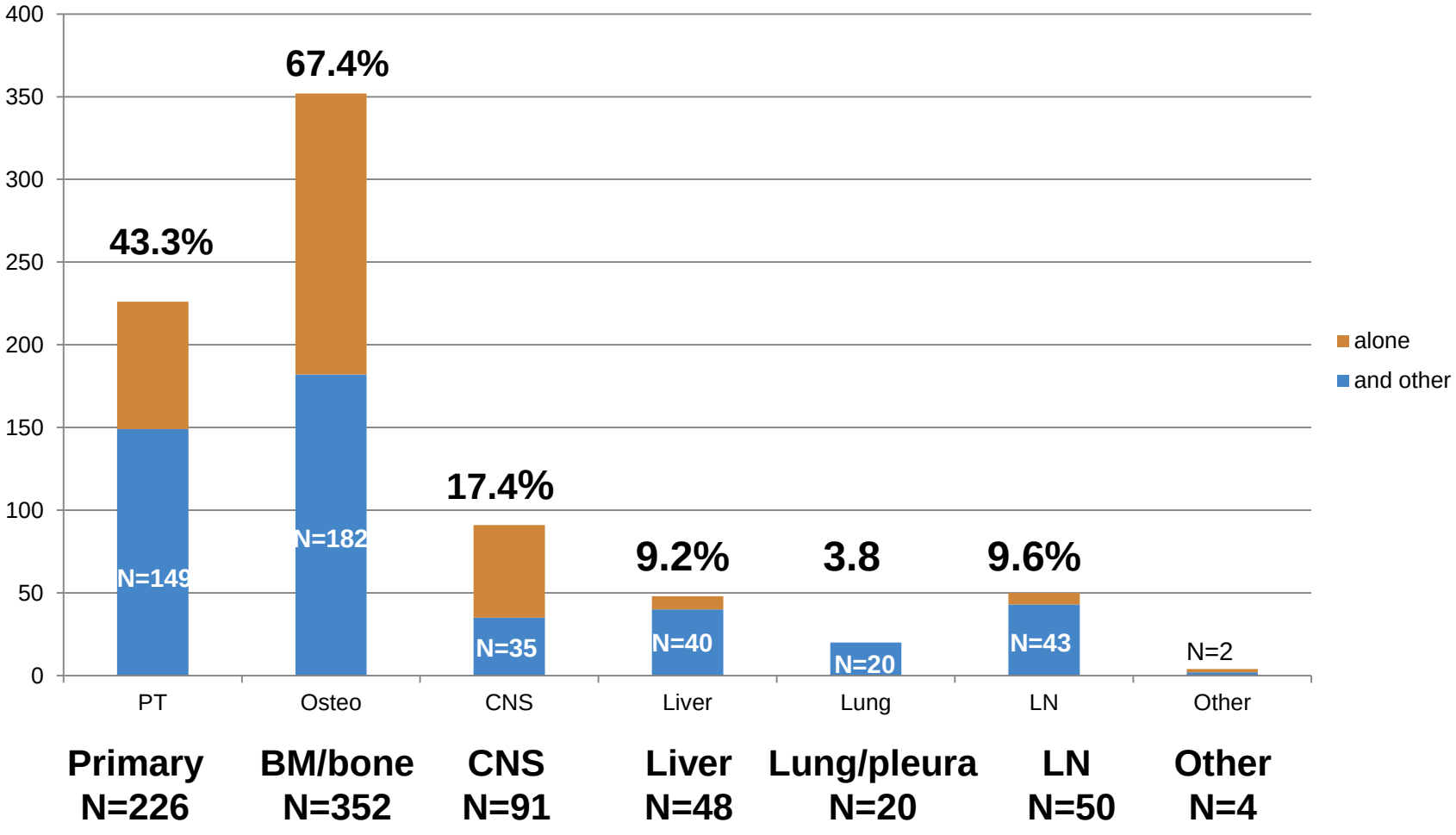


Data unpublished

Local vs. metastatic recurrence in stage 4 neuroblastoma



Frequencies of sites of 1. recurrences in stage 4 neuroblastoma (n=522)



Results

therapy

none/ palliative	35.5 %
chemotherapy	46.3 %
chemotherapy + ASCT	18.2 %
	100.0 %

median time

1. → 2. recurrence	4.1 months
1. recurrence → death of tumor	9.8 months

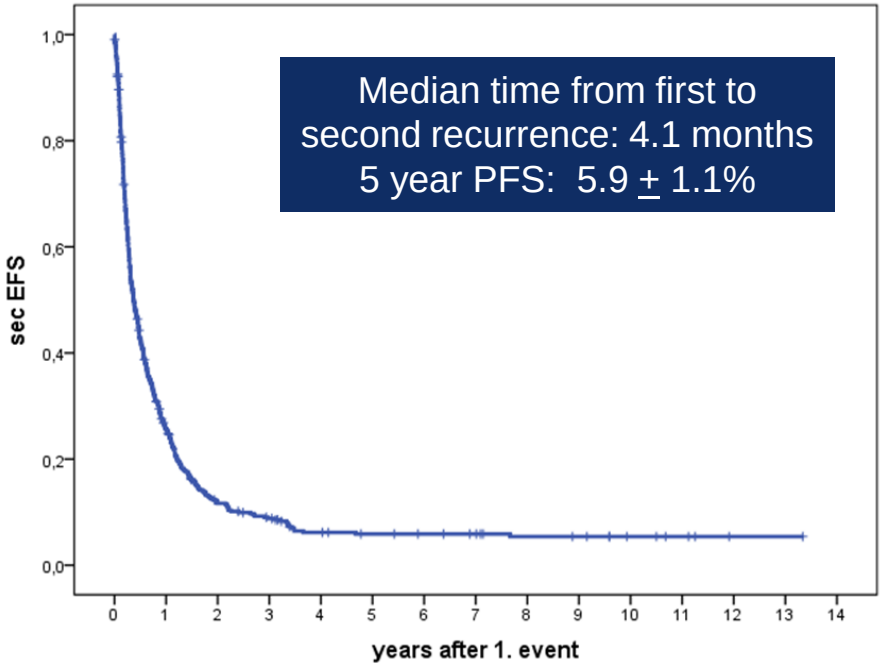
Outcome

5 year EFS	5.9 ± 1.1%
5 year OS	9.8 ± 1.4%

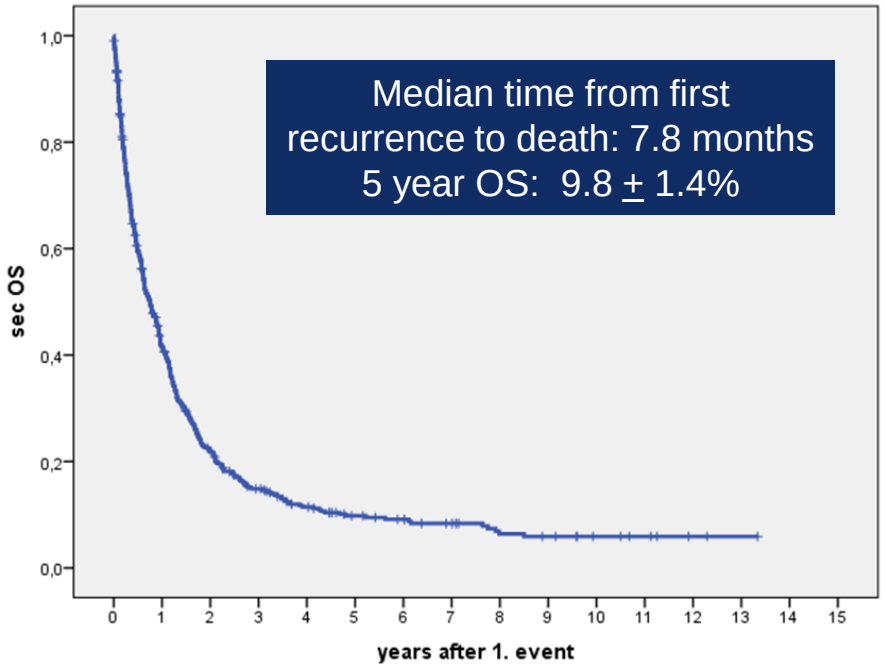
Relapse of stage 4 neuroblastoma carries a particular poor prognosis

Age >18 months at diagnosis, first recurrence (n=522)

Secondary progression free survival

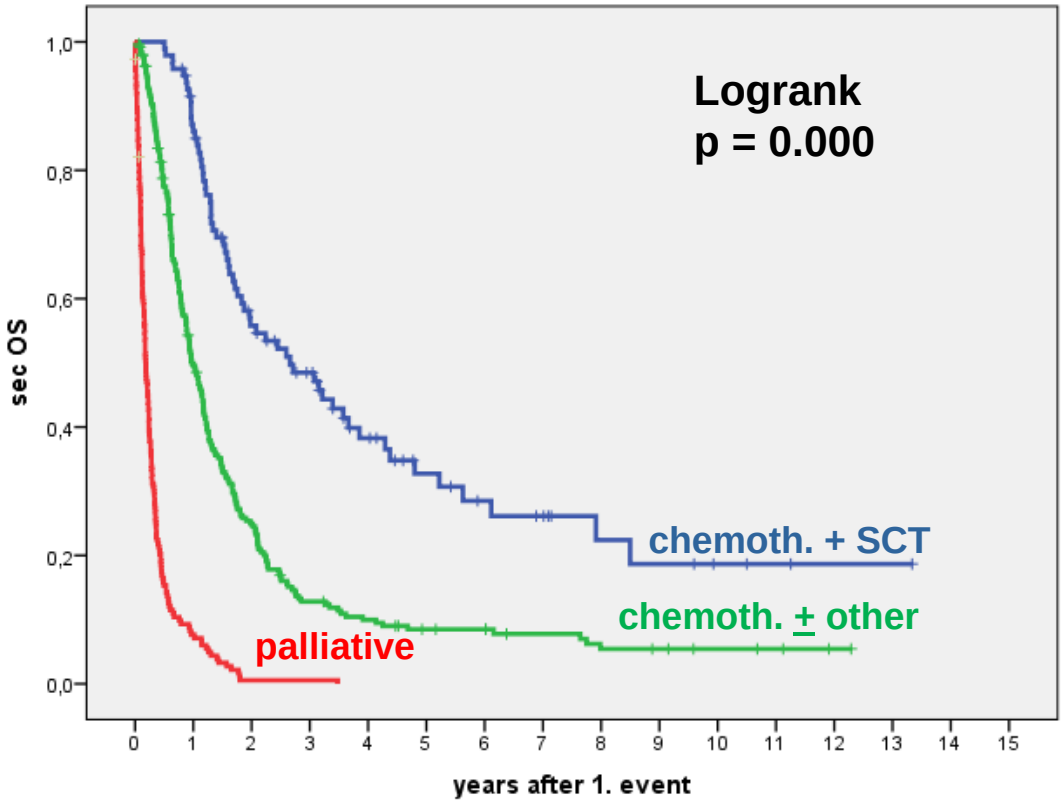


Secondary overall survival



PFS, progression-free survival; OS, overall survival
Data unpublished

Secondary OS of 521 patients with stage 4 neuroblastoma by treatment approach



chemotherapy and SCT n=95 **chemotherapy ± other therapy n= 242** **palliative therapy n=185**

Conclusions

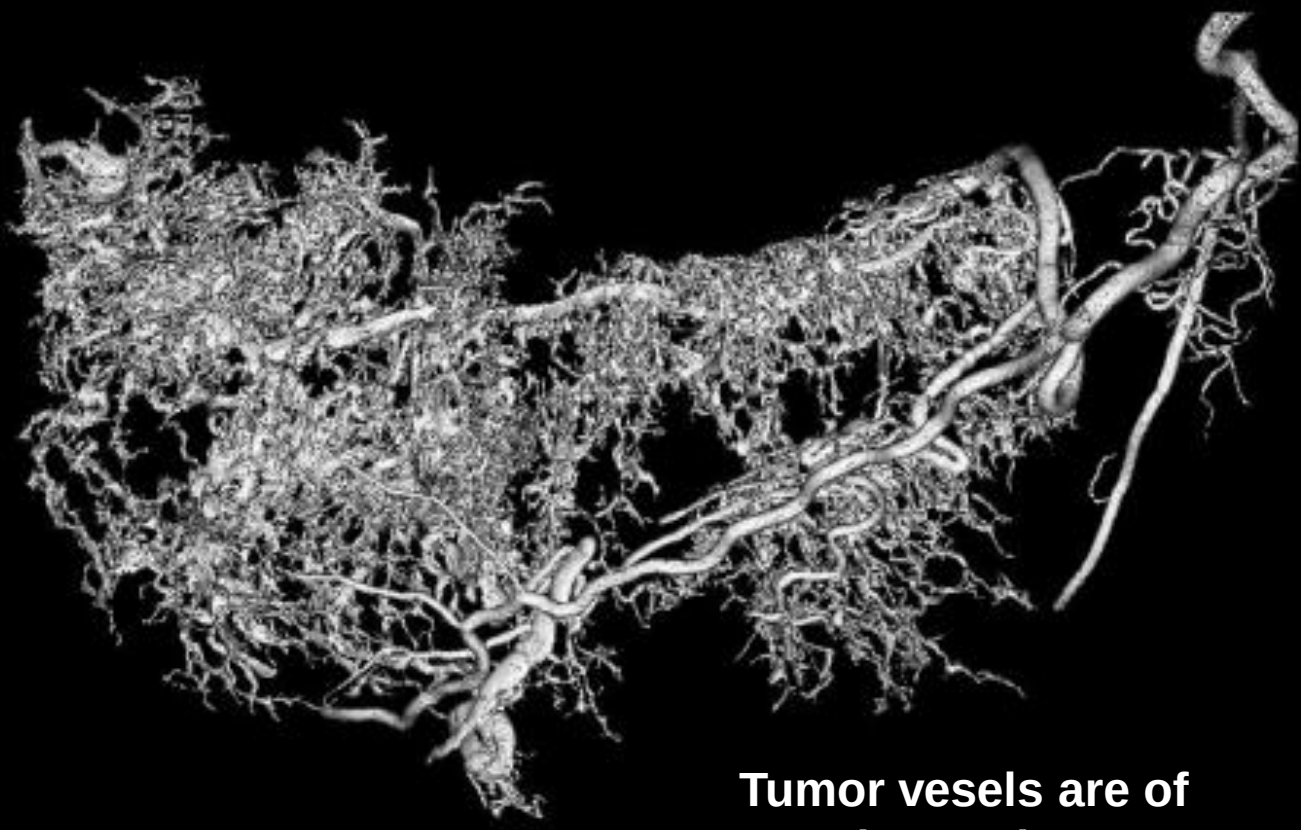
- 1/3 of patients received palliative care only
- Significant survival chances only for the minority of patients responding to second line chemotherapy and undergoing ASC

Vasculature of normal kidney

Kidney vesels are fractal
and pruned

Courtesy of Gianulla Klement, Tufts Medical Center

Vasculature of neuroblastoma

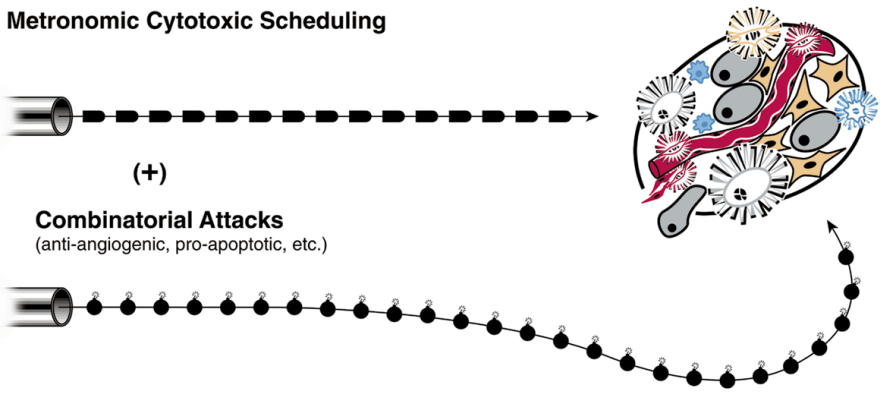


Tumor vesels are of embryonal type

Courtesy of Gianulla Klement

METRO-NB 2012: Metronomic treatment

- Defined by frequent and continuous use of low doses of conventional chemotherapeutics
- Combination with antiinflammatory and/or antiangiogenic drugs
- Targets: angiogenesis and anti-cancer immunity



Hanahan, D., G. Bergers, et al. (2000)

Drugs used

Celecoxib (anti-neuroblastic, effect on microenvironment)

2 x 200 mg/m²xd d1-365 oral

Cyclophosphamide (anti-neuroblastic, anti-angiogenetic)

1 x 25 mg/m²xd d1-365 oral

Etoposide (anti-neuroblastic, anti-angiogenetic)

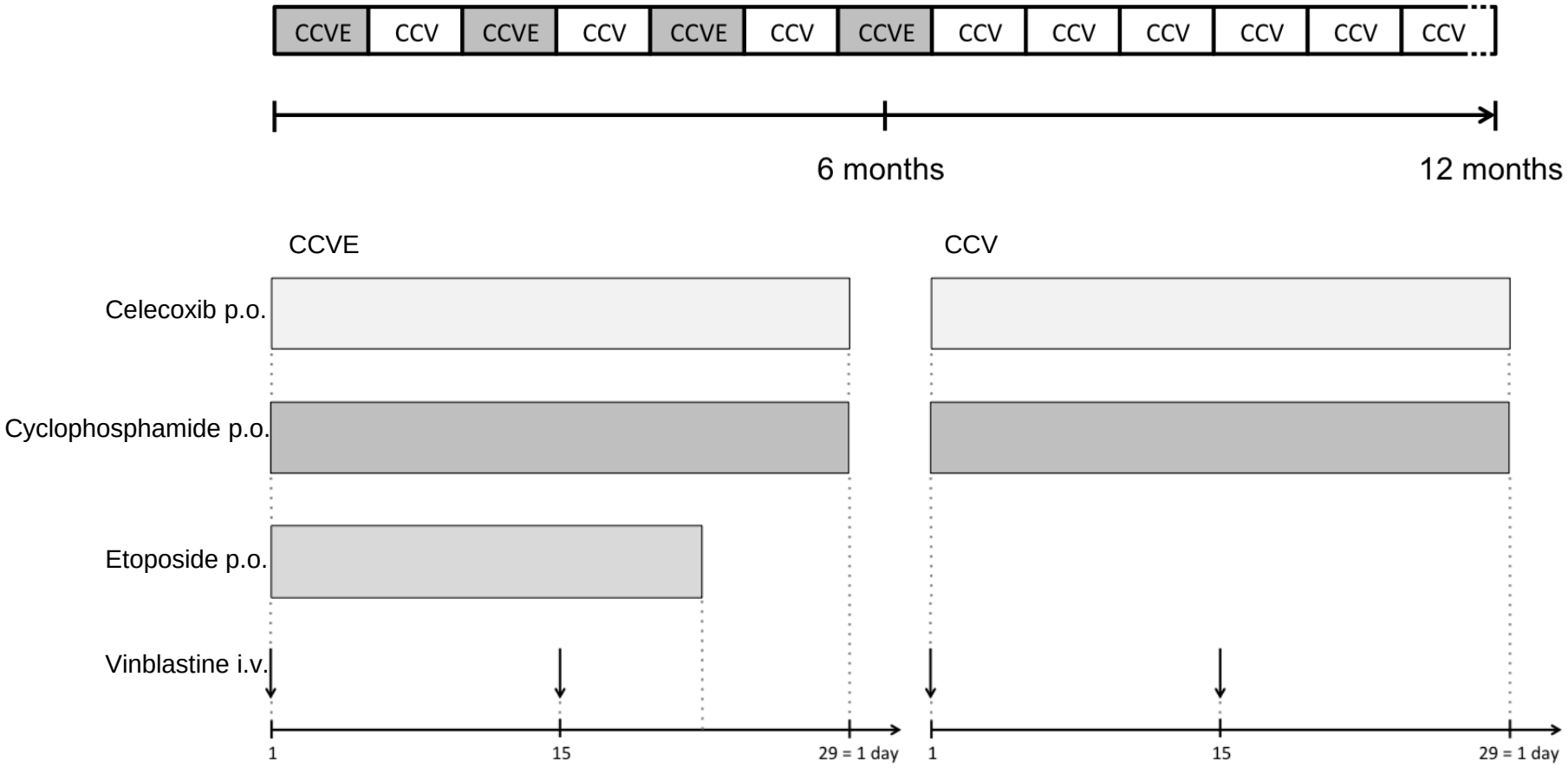
1 x 25 mg/m²xd d1-21 for 4 cycles oral

Vinblastin (anti-neuroblastic, anti-angiogenetic)

1x 3 mg/m²xd every 14 days

Duration of treatment: until event, if no event up to 24 months

METRO-NB 2012 Treatment overview



Results (1) in 20 pilot patients

international collaboration: St. Petersburg, Minsk, Brno, Cologne

Number of recurrences before metronomic therapy:

1 recurrence: 1 patient

2-4 recurrences: 19 patients

Number of recurrent sites:

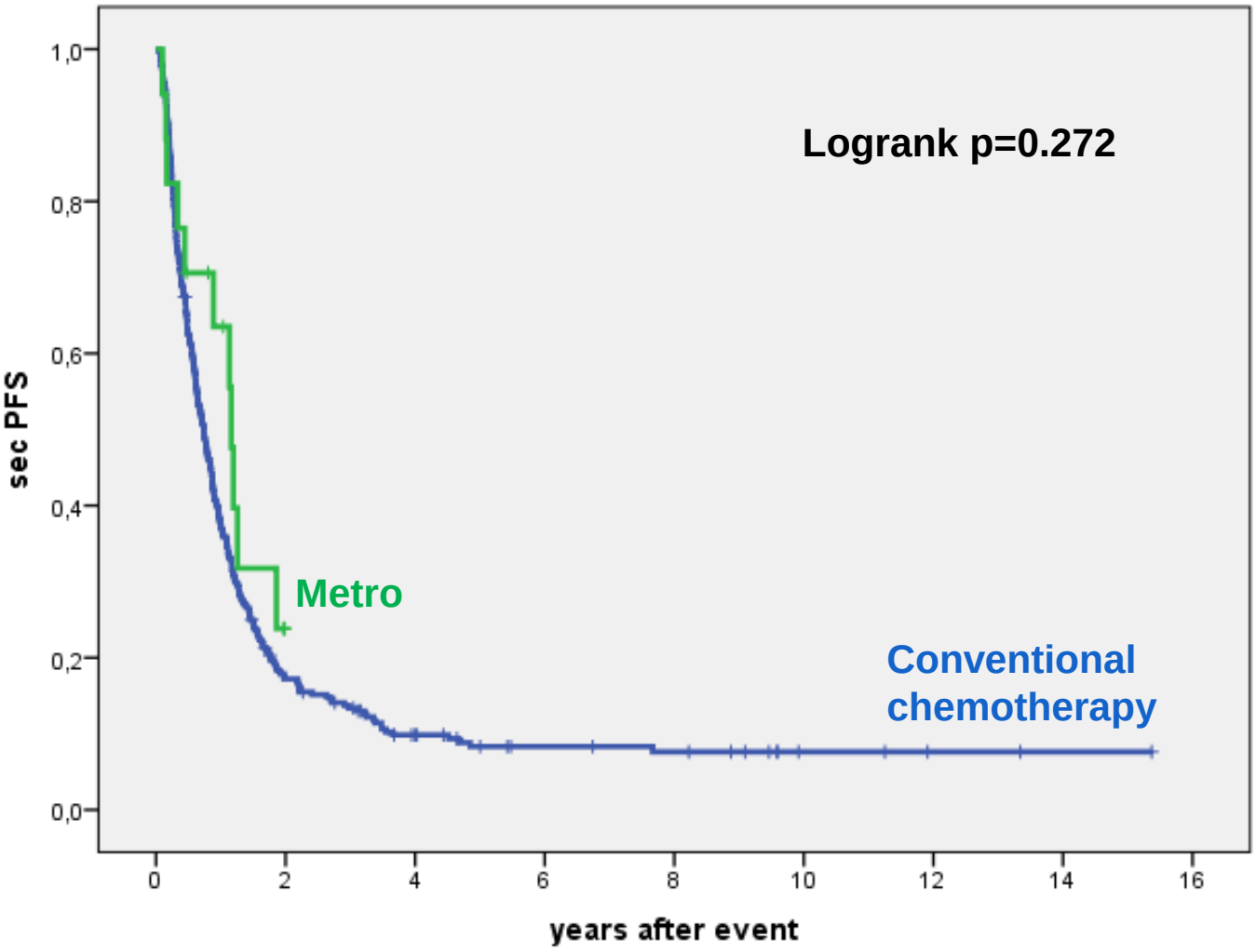
1 site: 5 patients

2 sites: 11 patients

3 sites: 1 patient

Sites of recurrences:

Primary tumor:	**12 patients**
Osteomedullary recurrences:	**12 patients**
CNS recurrence:	**3 patients**
Liver	**1 patient**
lymph nodes:	**1 patient**

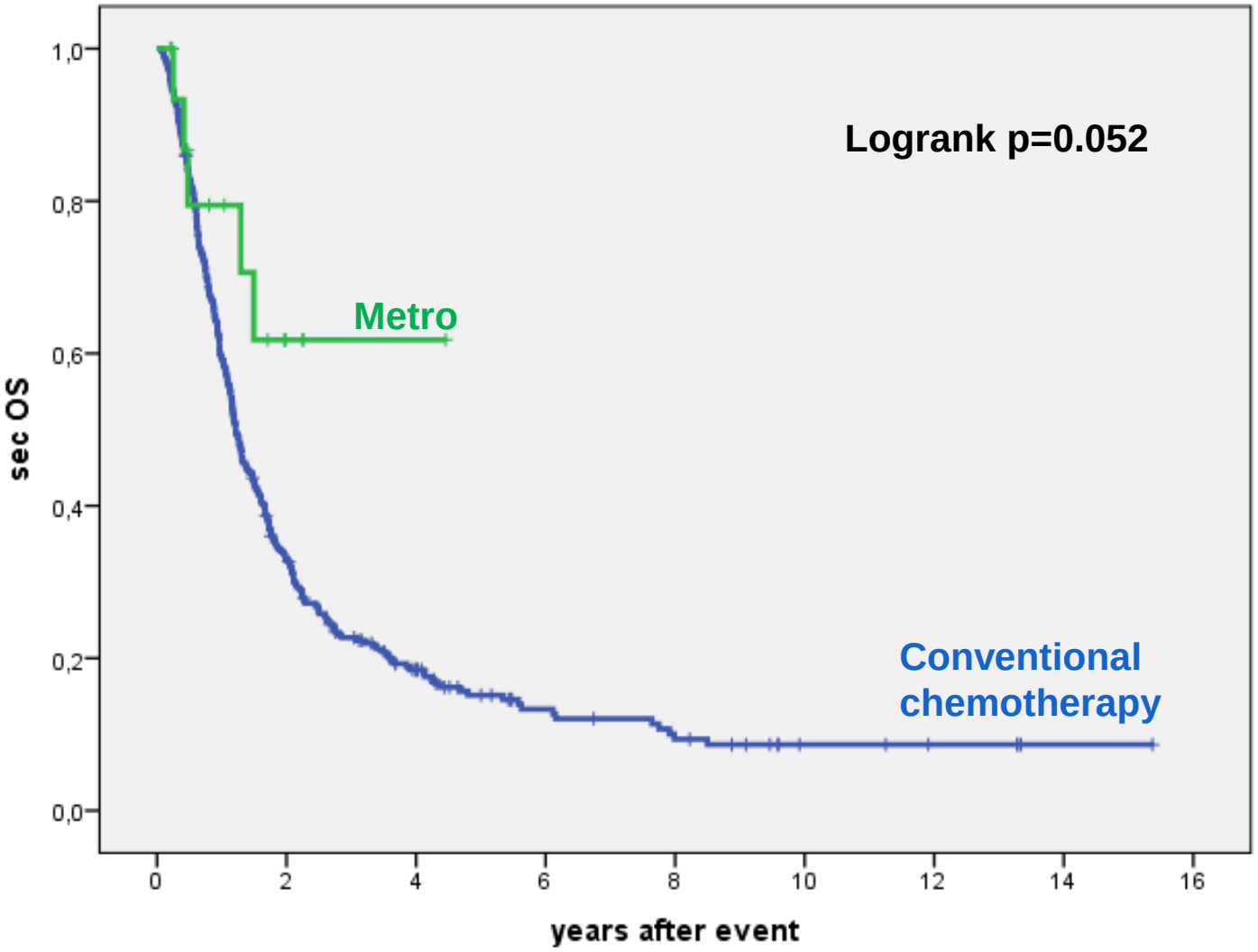


Secondary progression free survival of patients with recurrent HR-neuroblastoma by type of chemotherapy

Control group weighted for number of recurrence sites (1 vs. >1) and time from first dx to 1. recurrence (<vs.>18 mo.)

Metronomic therapy (n=17) median sec. PFS 16.2 months

Conventional chemotherapy (n= 307) median sec. PFS 8.8 months



Secondary overall survival of patients with recurrent HR-neuroblastoma by type of chemotherapy

Control group weighted for number of recurrence sites (1 vs. >1) and time from first dx to 1. recurrence (<vs.>18 mo.)

Metronomic therapy (n=17)

Conventional chemotherapy (n= 307) **median sec. OS 14.6 months**

Results (2) in 20 pilot patients

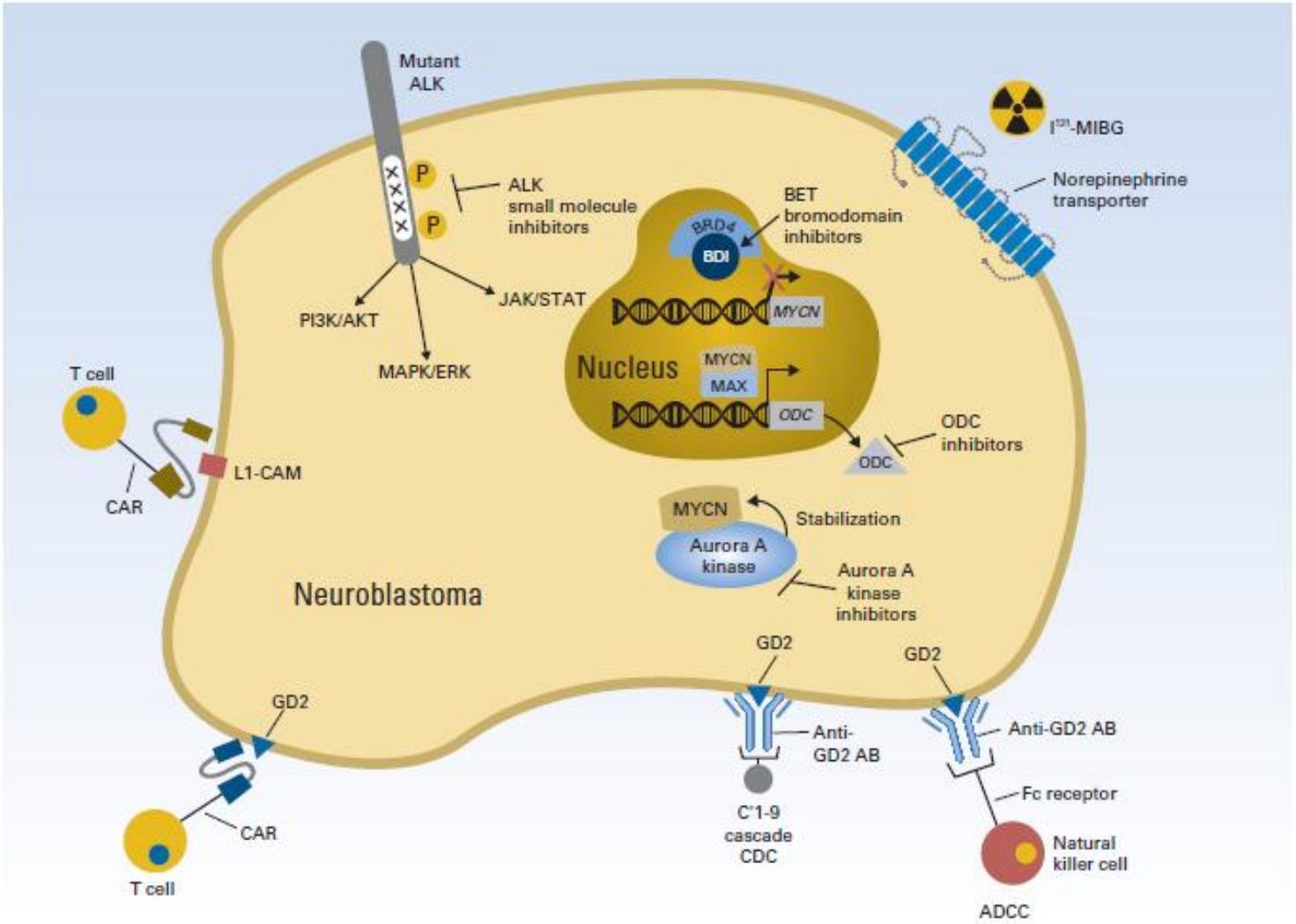
Toxicity

Minimal except grade 2 – 3 thrombocytopenia / leukocytopenis / anemia

(all patients heavily pretreated)

Outpatient setting

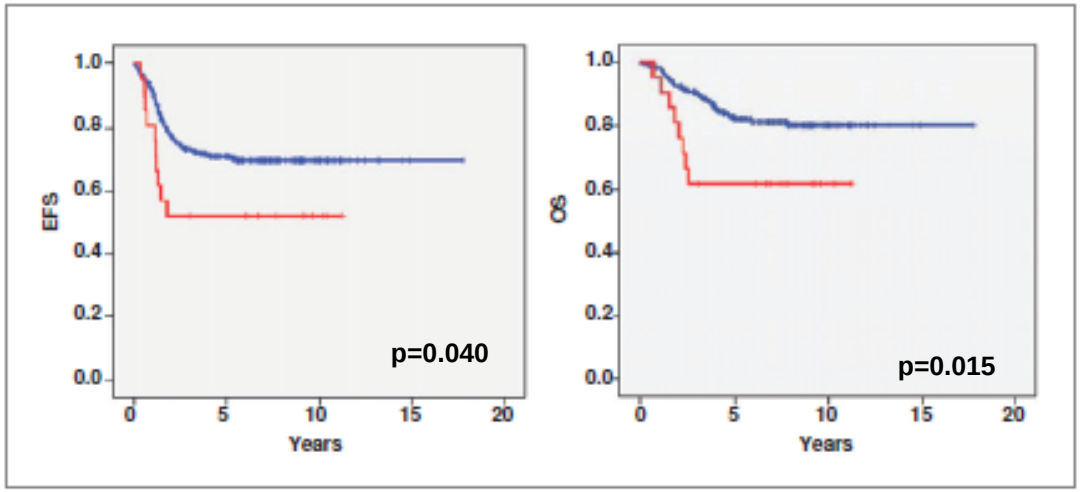
Current clinical approaches in targeting neuroblastoma.



Pinto NR et al. 2015; J Clin Oncol 33 Doi:10.1200/JCO.2014.59.4648

Prevalence of ALK mutations in neuroblastoma subtypes

- **Mutation frequency in neuroblastoma:**
  ~8% non-synonymous nucleotide substitution, ~1% focal amplification
- **Association of ALK mutations with clinical variables:**
  significant correlation with *MYCN* amplification
- **Slight association of ALK mutations with poor outcome:**



Blue – ALK-WT

Red – ALK mutated

Schulte JH, … and Fischer M, Clin Cancer Res 2011
De Brouwer et al., Clin Cancer Res 2010

Treatment of ALK^{mut} neuroblastoma patients with ALK inhibitors

***Lancet Oncol* 2013; 14: 472–80:**

Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study

Yael P Mossé, Megan S Lim, Stephan D Voss, Keith Wilner, Katherine Ruffner, Julie Laliberte, Delphine Rolland, Frank M Balis, John M Maris, Brenda J Weigel, Ashish M Ingle, Charlotte Ahern, Peter C Adamson, Susan M Blaney

- **11 neuroblastoma patients with ALK mutations; 1 CR, 3 SD**
- **23 neuroblastoma patients with unknown ALK status; 1 CR, 5 SD**

- **Specific mutations (such as F1174L) confer crizotinib resistance to ALK mutated malignancies**
- **Second generation ALK inhibitors with greater preclinical antitumor potency, such as LDK378, may overcome crizotinib resistance**

Mossé YP et al., Lancet Oncol 2013

Treatment of ALK^{mut} neuroblastoma patients with ALK inhibitors

A Phase I, open-label, dose escalation study of LDK378 in pediatriac patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK)

Daily oral treatment

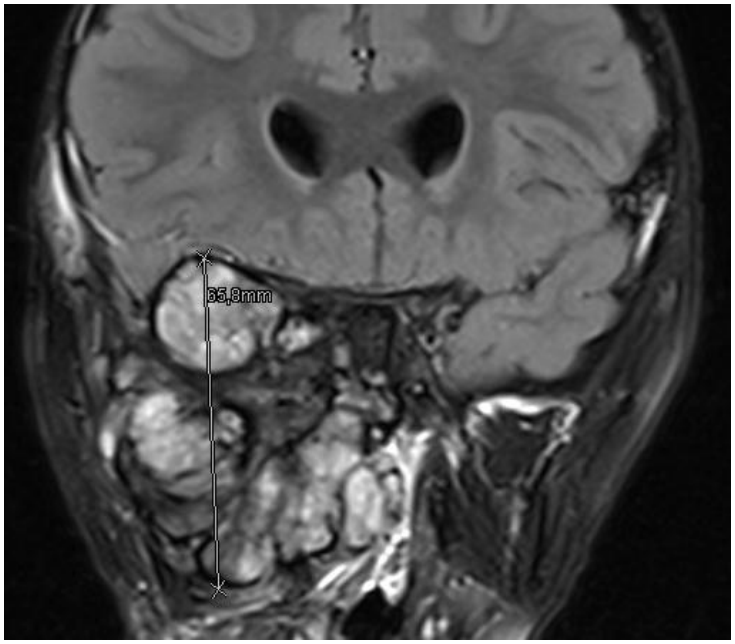
Age: ≥1 - ≤ 17 years, progressive disease, Karnowsky ≥ 60

Pre-treatment with crizotinib allowed

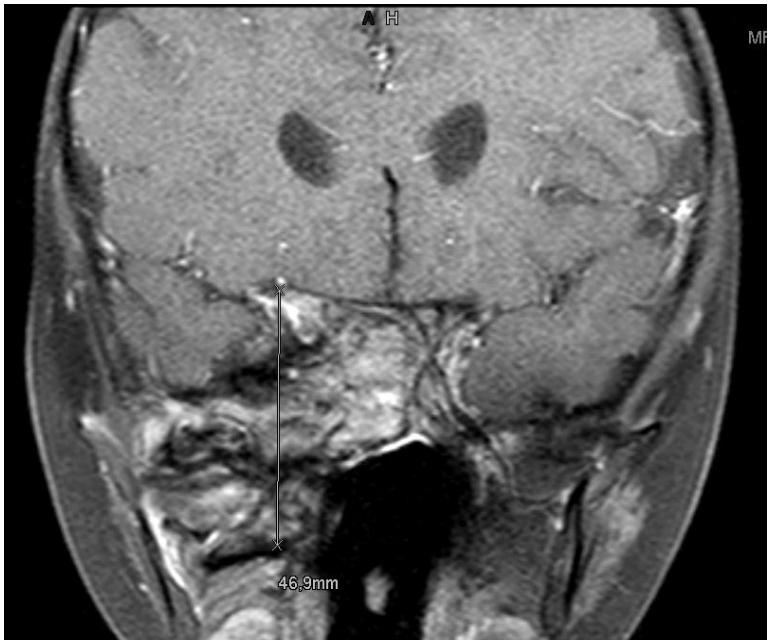
Treatment of ALK^{mut} neuroblastoma patients with ALK inhibitors

- **4-year old girl, 3. relapse of stage 4 neuroblastoma at skull base, ALK F1245V mutation**
- **LDK378 treatment July-November 2014**

17.06.2014



15.08.2014



November 2014:metastatic progress (BM, bones, lung, local. NSE 635 µg/L)
June 2015: death of tumor progression

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Boris De Carolis, Maike Reisberg, Nina Hindrichs
Martina Breuer, Monika Schmitz

Parents & Patients

> 80 participating Hospitals

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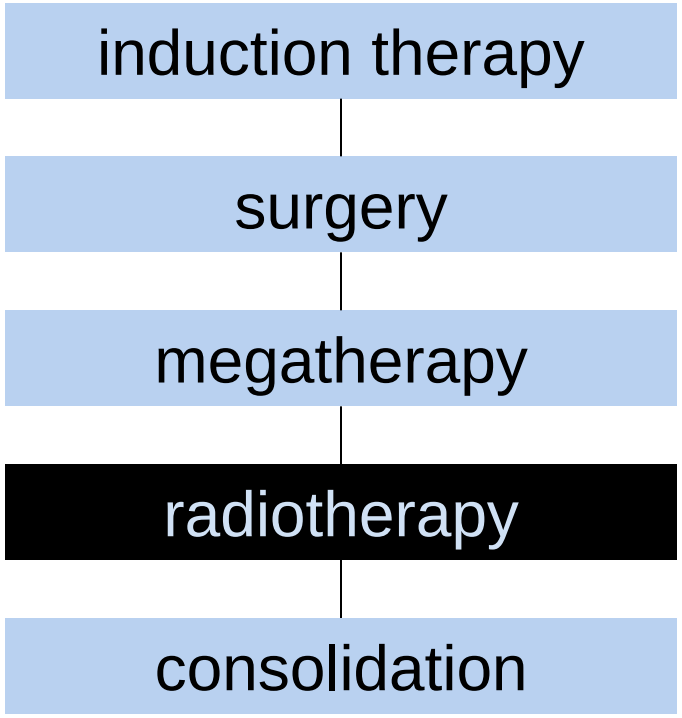
Therapy in High Risk Neuroblastoma



Radiotherapy

- experimental studies: radiosensitivity of neuroblastoma
- clinical experience in palliative care (bone pain)
- GPOH trial NB90
  - no effect for the whole cohort
  - useful in patients with residual primary ?
  - dose (30 Gy) not sufficient?

→ Trial NB97: radiotherapy of residual primary,

→ 36 – 40 Gy

Radiation therapy to the primary and postinduction mIBG-avid sites in HR neuroblastoma*

30 HR patients, single center experience (Houston)

RT to the primary site 24-30 Gy + to mIBG avid mets 24 Gy

5 year local control at primary site: 84%

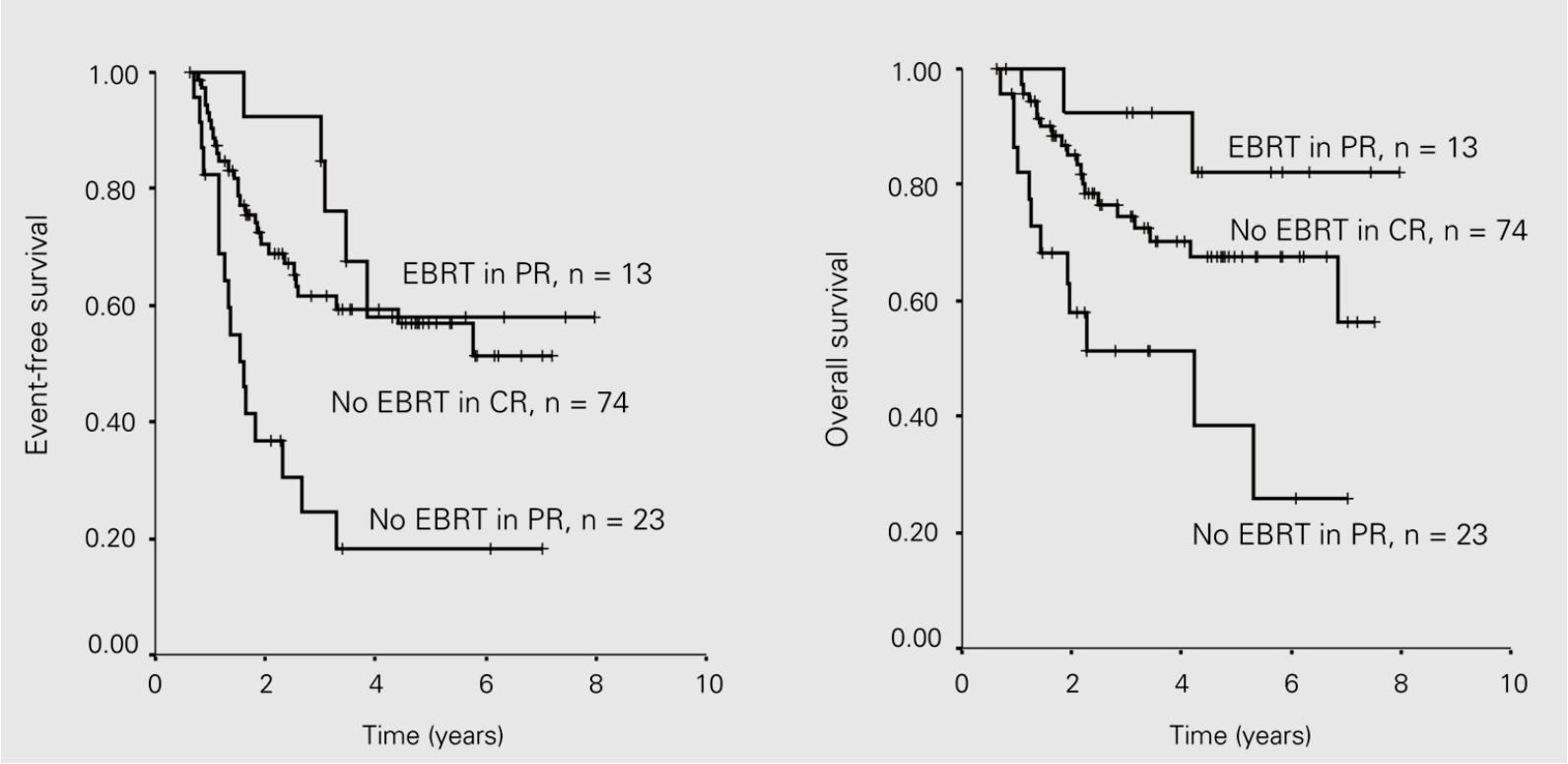
metastatic sites: 74%

5 y PFS: 48% **5 y OS 59%**

5 y PFS rates for patients with 0, 1,2, >3 sites were 66%, 57%, 20%, 0%

***Mazloom A et al. 2014; Int J Radiation Oncol Biol Physics 90:858-62**

NB97: Radiotherapy in High Risk Neuroblastoma



Simon T et al., Strahlenther Onkol 2006;7: 389-94

radiotherapy in HR neuroblastoma

Indication (NB2004-HR):

- **after induction chemotherapy still active, non-resectable primary tumor**
- **36-40 Gy**

data suggest:

irradiation may compensate surgical non-resectabilty

Metaanalysis on mIBG radiotherapy*

Study:

30 studies, no randomized controlled trials

1987-2012

979 patients (range 10-164)

Induction: 57 patients

Consolidation 11 patients

Relapsed and refractory pat. 911 patients

Results:

Mean tumor response rate: 32% (0-75%)

Large heterogeneity between the studies

RCT urgently needed

***Wilson JS et al. (2014) Eur J Cancer 50:801-15**

Long term results stage 4 retinoic acid maintenance therapy (COG)*

Regimen	5 year EFS %*	5 year OS %*
	*from the time of second randomization	
Retinoic acid + (n=130)	42 ± 5	50 ± 5
Retinoic acid - (n=128)	31 ± 5	39 ± 5
P	0.12	0.19

→ **no statistical difference,**

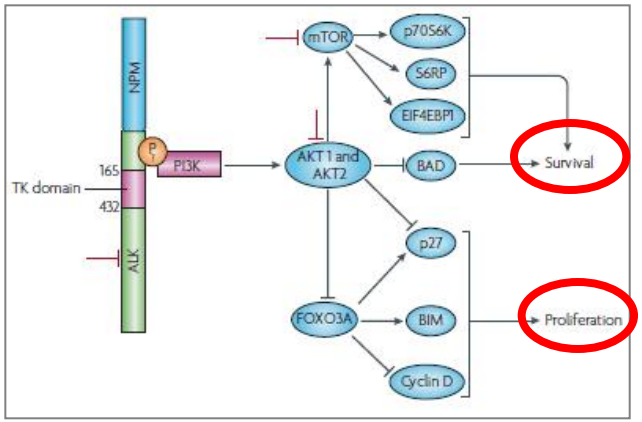
evidence for RA use is uncertain

*Matthay KK et al. J Clin Oncol (2009) 27:1007-13 and June 10th 2014:1862-63

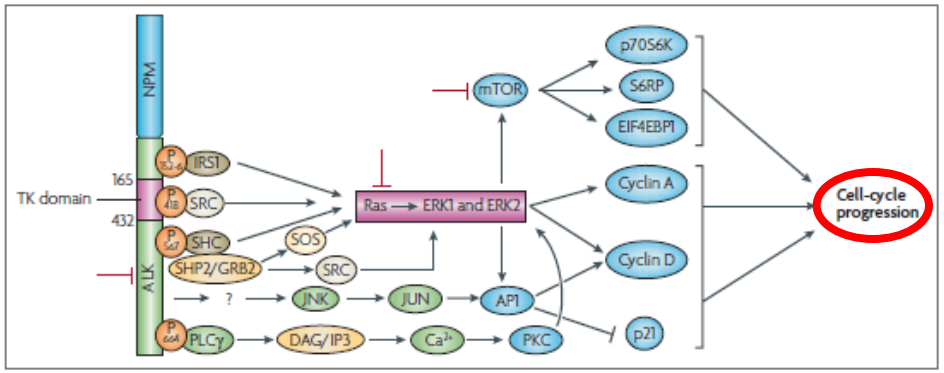
Peinemann F et al The Cochrane Database of Systematic Reviews 2015; DOI10.1002/14651858

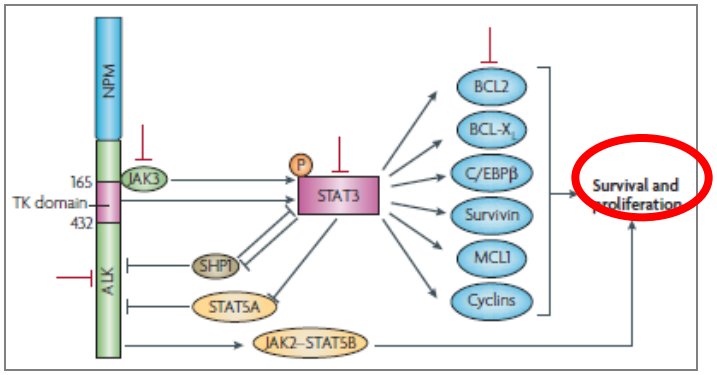
ALK signaling in cancer

- **Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase**
- **function of the full-length ALK receptor is still poorly characterized; ALK is involved in neuronal cell differentiation and regeneration, synapse formation and muscle cell migration**
- **activating ALK mutations (fusion genes, amplification, nucleotide substitution) occur in several cancer entities (ALCL, NSCLC, IMT, NB)**



- **ALK signalling in cancer:**





Chiarle et al., Nat Rev Cancer 2008

Conclusion and perspectives of targeted therapie

Example ALK

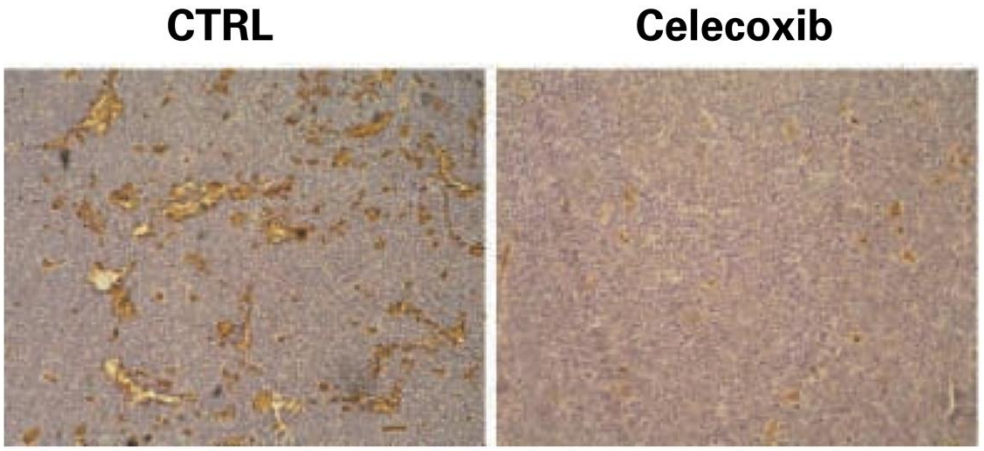
- ***ALK* is a bona fide cancer gene in neuroblastoma**
- **promising therapeutic strategy for the treatment of high-risk patients with *ALK* mutated neuroblastoma.**
- **A phase I clinical trial of the ALK inhibitor LDK378 in pediatric patients currently ongoing (Novartis trial-no. LDK378X2103).**

General strategy

- **Therapies targeting specific pathways/mutations will rather complement existing treatment regimens than lead to their replacement**
- **The added complexity of the cancer will need to screen patients for biomarkers and other response predictors**

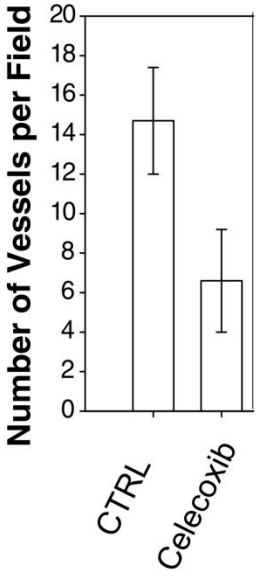
Identification of molecular targets for high-risk neuroblastoma treatment

Celecoxib - COX-2 Inhibition



Ponthan 2007

Rats carrying SH-SY5Y xenografts; BS-1 staining endothelial cells



- **antiangiogenic**
- **anti tumorpromoting activities of tumor-associated macrophages**

  gene expression↑ in metastatic > locoregional NB (Asghardzadeh 2012)
- **synergism with cytostatic drugs:** tumor growth↓; Bax,BCL-2, VEGF, caspases↓

  Kaneko 2009, Redova 2010
- **NB cells express high levels of COX-2:** growth↓, apoptosis↑ (Johnson 2004)