

SFP Novembre 2018
Les cancers de l'Enfant

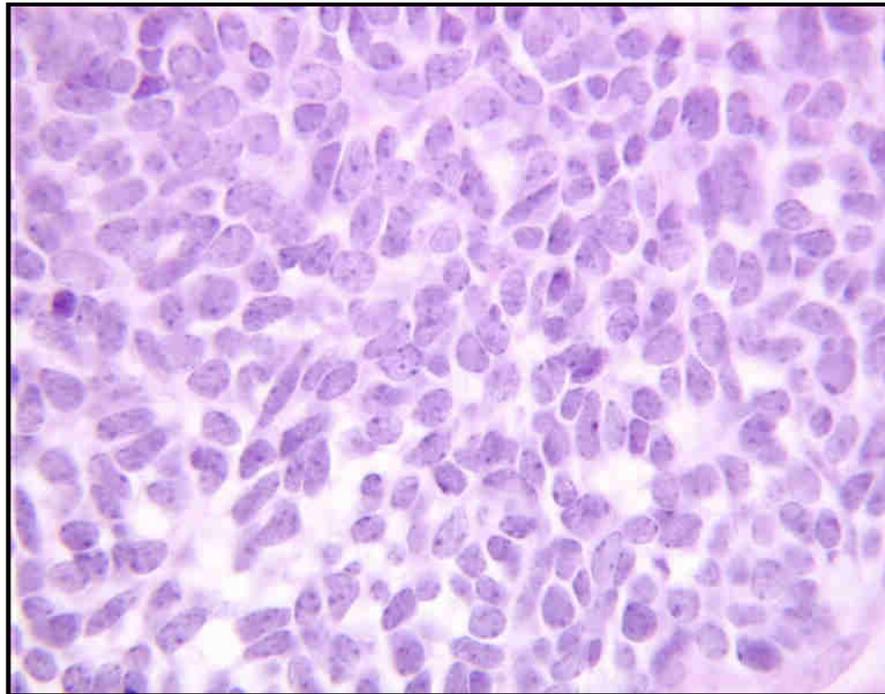
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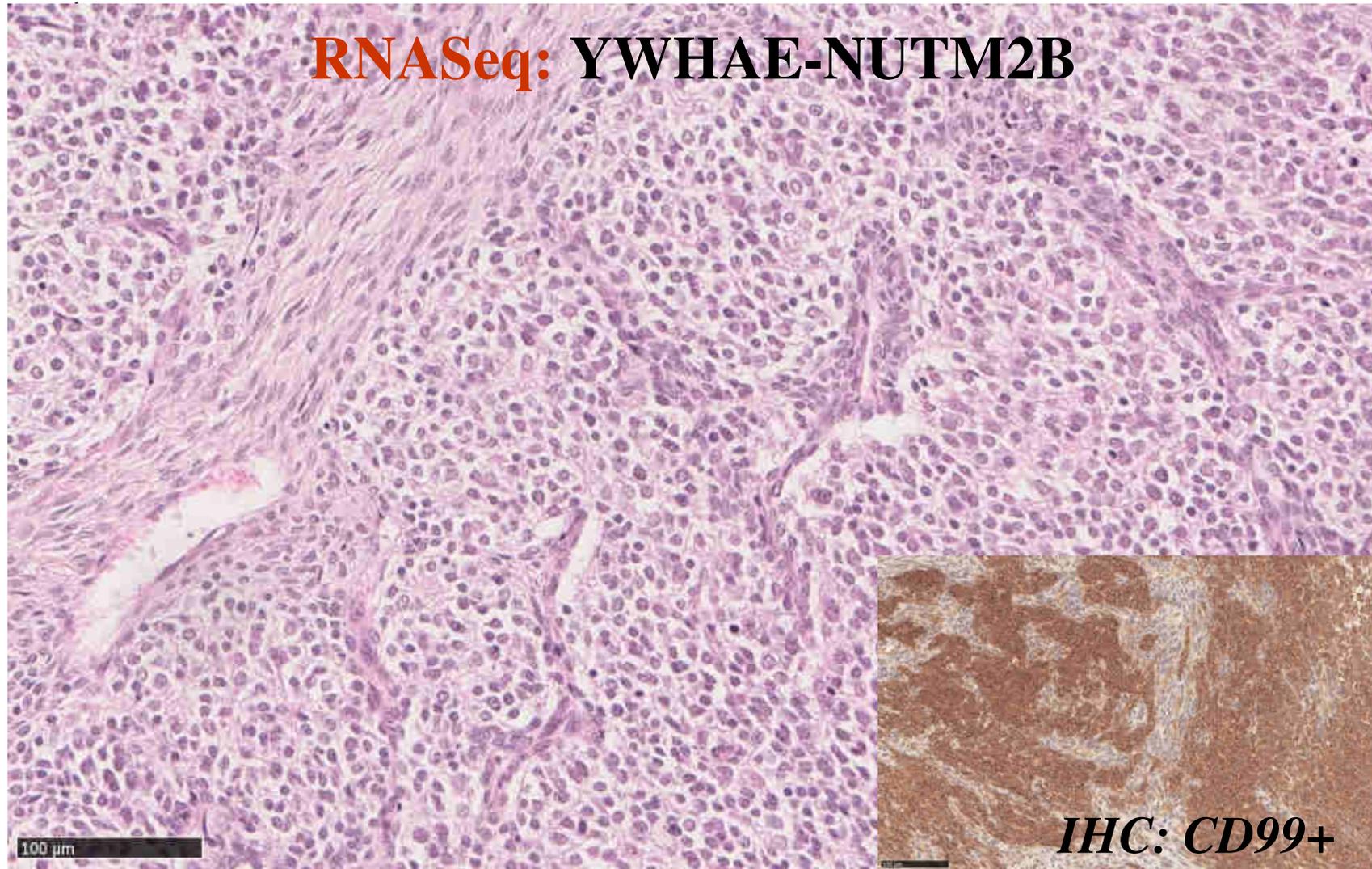
- *Le diagnostic: tumeurs de blastème
tumeur à (petites) cellules rondes*



Ewing	EWS / FLI-1 ou ERG ou ETV1 ou E1AF ou FEV
Rhabdomyosarcome alvéolaire	PAX3 ou PAX7 / FKHR

Groupes diagnostiques selon l'ICCC	N
I. Leucémies, syndromes myéloprolifératifs et myélodysplasiques	5 895
II. Lymphomes et néoplasmes réticulo-endothéliaux	2 387
III. Tumeurs du système nerveux central et diverses tumeurs intracrâniennes et spinales	5 031
IV. Tumeurs du système nerveux sympathique	1 704
V. Rétinoblastomes	590
VI. Tumeurs rénales	1 173
VII. Tumeurs hépatiques	203
VIII. Tumeurs malignes osseuses	975
IX. Sarcomes des tissus mous et extraosseux	1 334
X. Tumeurs germinales, trophoblastiques et gonadiques	788
XI. Mélanomes malins et autres tumeurs malignes épithéliales	650
XII. Autres tumeurs malignes	41
Total	20 771

Sous-groupes de Sarcomes indifférenciés à petites
cellules rondes
transcriptome



0-14 ans

[Tableau 5] Incidence des cancers de l'enfant en France métropolitaine, par tranche d'âge et répartition en fréquence [2007-2011]

Groupes diagnostiques selon l'ICCC	Effectif moyen annuel	En %	Incidence (par million)				
			< 1 an	1-4 ans	5-9 ans	10-14 ans	0-14 ans
I. Leucémies, syndromes myéloprolifératifs et myélodysplasiques	497	28,3%	39,0	70,6	38,2	27,3	43,2
II. Lymphomes et néoplasmes réticulo-endothéliaux	196	11,2%	4,7	8,7	15,5	27,7	17,1
III. Tumeurs du système nerveux central et diverses tumeurs intracrâniennes et spinales	438	24,9%	39,3	45,8	38	32	38,1
IV. Tumeurs du système nerveux sympathique	143	8,1%	69,2	22,5	4,1	1,3	12,4
V. Neuroblastomes	143	2,8%	27,8	8,5	0,3	0,8	4,2
VI. Tumeurs rénales	102	5,8%	19,8	20,2	5,7	0,9	8,9
VII. Tumeurs hépatiques	18	1,0%	5,2	2,9	0,4	0,8	1,5
VIII. Tumeurs malignes osseuses	81	4,6%	0,3	1,6	6,3	13,6	7,1
IX. Sarcomes des tissus mous et extraosseux	113	6,5%	15,1	11,1	9,1	8,6	9,9
X. Tumeurs germinales, trophoblastiques et gonadiques	63	3,6%	19,5	3,7	2,5	6,9	5,5
XI. Mélanomes malins et autres tumeurs malignes épithéliales	53	3,0%	1,0	1,8	2,7	9,4	4,6
XII. Autres tumeurs malignes	4	0,2%	0,8	0,8	0,2	0,1	0,3
Total	1 757	100,0%	241,5	197,9	120,5	131,2	152,8

Source : Registre national des hémopathies malignes de l'enfant et Registre national des tumeurs solides de l'enfant, 2007-2011.
 ICC: International classification of childhood cancer.

15-18 ans

[Tableau 8] Distribution des différents types de cancers chez l'adolescent (15-17 ans) en France métropolitaine (2011)

Groupes diagnostiques selon l'ICCC	Effectif	En %
I. Leucémies, syndromes myéloprolifératifs et myélodysplasiques	60	15,8%
II. Lymphomes et néoplasmes réticulo-endothéliaux	103	27,2%
III. Tumeurs du système nerveux central et diverses tumeurs intracrâniennes et spinales	65	17,2%
IV. Tumeurs du système nerveux sympathique	5	1,3%
V. Rétinoblastomes	0	0,0%
VI. Tumeurs rénales	2	0,5%
VII. Tumeurs hépatiques	4	1,1%
VIII. Tumeurs malignes osseuses	36	9,5%
IX. Sarcomes des tissus mous et extraosseux	28	7,4%
X. Tumeurs germinales, trophoblastiques et gonadiques	33	8,7%
XI. Mélanomes malins et autres tumeurs malignes épithéliales	42	11,1%
XII. Autres tumeurs malignes	1	0,3%
Total	379	100,0%

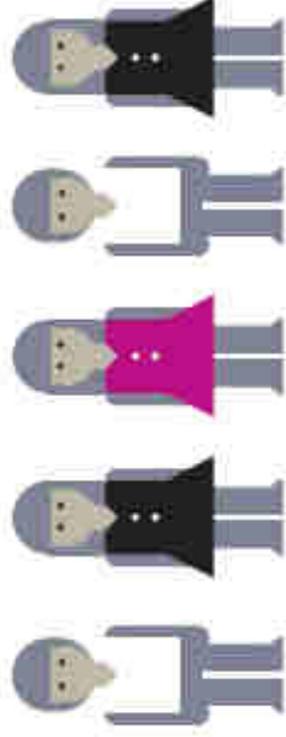
Source: Registre national des hémopathies malignes de l'enfant et Registre national des tumeurs solides de l'enfant, 2011 (France métropolitaine).
ICCC: International classification of childhood cancer.

[Tableau 7] Taux de survie à 5 ans des enfants atteints d'un cancer sur la période 2000-2011 par tranche d'âge

Groupes diagnostiques selon l'ICCC	N	Survie à 5 ans [%]				
		< 1 an	1-4 ans	5-9 ans	10-14 ans	0-14 ans
I. Leucémies, syndromes myéloprolifératifs et myélodysplasiques	5 895	58,3 [52,3-63,5]	89,1 [87,8-90,2]	88,1 [86,4-89,6]	78,8 [76,3-81,1]	84,8 [83,8-85,7]
II. Lymphomes et neoplasmes réticulo-endothéliaux	2 387	89,8 [77,2-95,6]	91,8 [88,1-94,5]	93,9 [91,8-95,5]	93,6 [92,1-94,9]	93,4 [92,3-94,4]
III. Tumeurs du système nerveux central et diverses tumeurs intracrâniennes et spinales	5 031	60,5 [55,1-65,5]	69,8 [67,4-72,0]	71,9 [69,6-74,1]	80,3 [78,0-82,3]	72,7 [71,4-74,0]
IV. Tumeurs du système nerveux sympathique	1 704	89,7 [87,3-91,8]	66,4 [62,9-69,7]	60,4 [52,5-67,4]	60,9 [45,3-73,0]	74,6 [72,4-76,7]
V. Tumeurs blastomes	590	99,2 [96,9-99,8]	98,6 [96,3-99,5]	100 [-.]	100 [-.]	98,9 [97,6-99,5]
VI. Tumeurs rénales	1 173	88,8 [82,9-92,7]	94,4 [92,4-95,9]	93,2 [88,9-95,8]	84,1 [69,4-92,1]	92,9 [91,3-94,3]
VII. Tumeurs hépatiques	203	89,9 [77,5-95,7]	89,0 [81,0-93,8]	73,7 [47,9-88,1]	52,0 [31,6-69,1]	82,4 [76,1-87,1]
VIII. Tumeurs malignes osseuses	975	66,7 [5,4-94,5]	67,9 [53,3-78,7]	77,1 [71,6-81,6]	74,8 [70,9-78,2]	75,1 [72,1-77,8]
IX. Sarcomes des tissus mous et extraosseux	1 334	70,2 [61,6-77,2]	74,1 [69,4-78,3]	73,3 [68,2-77,8]	67,4 [62,3-72,0]	71,5 [68,8-73,9]
X. Tumeurs germinales, trophoblastiques et gonadiques	788	90,0 [84,8-93,5]	95,2 [90,2-97,7]	96,1 [89,9-98,5]	92,6 [88,9-95,1]	93,0 [90,9-94,6]
XI. Mélanomes malins et autres tumeurs malignes épithéliales	650	95,7 [72,9-99,4]	87,1 [74,7-93,6]	92,5 [86,4-95,9]	93,1 [90,1-95,3]	92,6 [90,2-94,4]
XII. Autres tumeurs malignes	41	100 [-.]	71,4 [47,2-86,0]	83,3 [27,3-97,5]	60,0 [19,5-85,2]	75,0 [58,4-85,7]
Total	20 771	80,4 [78,7-82,0]	82,3 [81,4-83,2]	81,7 [80,6-82,8]	82,7 [81,6-83,7]	82,1 [81,1-82,6]

Source: Registre national des hémopathies malignes de l'enfant et Registre national des tumeurs solides de l'enfant, 2000-2011.
 ICC: International classification of childhood cancer, N: nombre de cas de 0-14 ans. Date de point au 30/06/2013

- développement et conduite d'essais thérapeutiques, spécialement pour optimiser les traitements et tester les doses, afin de réduire les effets secondaires des traitements;
- accélération et augmentation des inclusions d'enfants et d'adolescents dans les essais cliniques;
- participation au développement des essais cliniques multi-organes, aux projets de médecine de précision organisés par l'INCa;
- développement et soumission de projets de recherche translationnelle aux appels à projets de l'INCa;
- contribution à la structuration de la recherche initiée et pilotée par l'INCa, notamment en aidant à mobiliser les chercheurs en cancérologie pédiatrique dans les programmes pluridisciplinaires, comme le prochain programme de recherche pluridisciplinaire en oncopédiatrie.



LE PLAN CANCER 2014-2019 FIXE COMME OBJECTIF D'OFFRIR AUX ENFANTS, AUX ADOLESCENTS ET AUX JEUNES ADULTES DES SOINS APPROPRIÉS EN FONCTION DE LEURS TYPES DE CANCER

L'INSTAURATION DU DROIT À L'OUBLI CHEZ LES ENFANTS DE MOINS DE 18 ANS

Avec environ 1 750 cas par an, les cancers de l'enfant (survenant entre 0 et 15 ans) sont rares. Bien qu'ils puissent toucher les enfants à tout âge, ils sont plus fréquents au cours des premières années de la vie (Tableau 1).

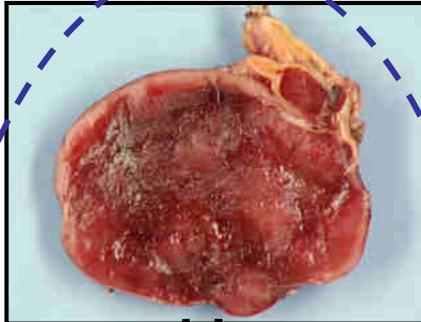
Les cancers de l'enfant sont généralement de bon pronostic, avec des taux de survie à 5 ans pouvant atteindre plus de 90 % en fonction du type de cancer et de l'âge au diagnostic (Tableau 2). Les données observées par les registres pédiatriques des cancers (registre des tumeurs solides de l'enfant et registre national des hémopathies) sont confirmées par les données observées dans d'autres pays, dont celles du Programme Seer³ aux États-Unis. Face à ce constat, et selon une volonté de ne pas imposer une « double peine » aux jeunes générations ayant eu un cancer au cours des 18 premières années de la vie, le législateur et les signataires de la convention Aeras ont instauré un véritable droit à l'oubli, c'est-à-dire une absence de déclaration cinq ans après la fin des traitements actifs.

tumeurs de blastème

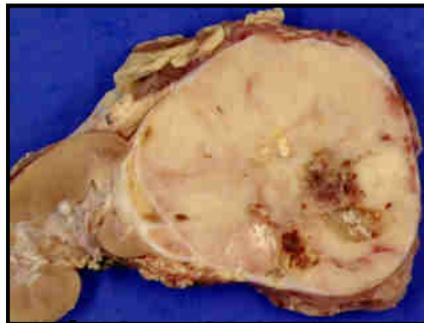
préfixe: nom de l'organe

suffixe: -blastome

fréquentes



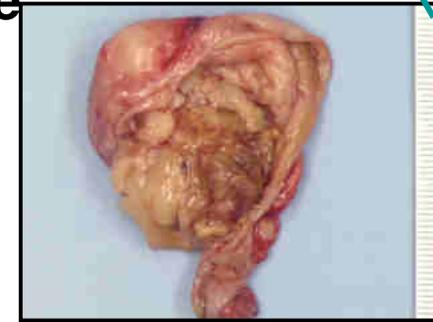
neuroblastome



néphroblastome

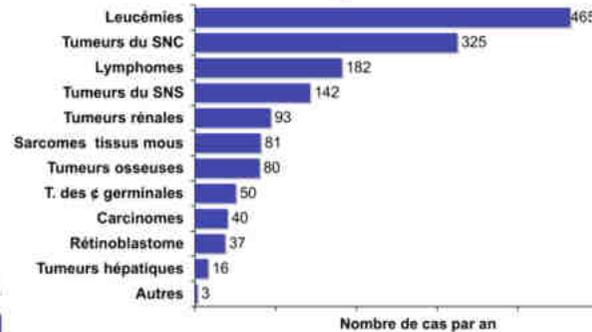


hépatoblastome



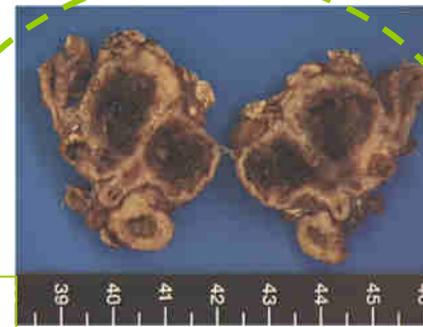
pneumoblastome

Rares
(très...)



700 nouveaux cas par an

exceptionnelles



sialoblastome

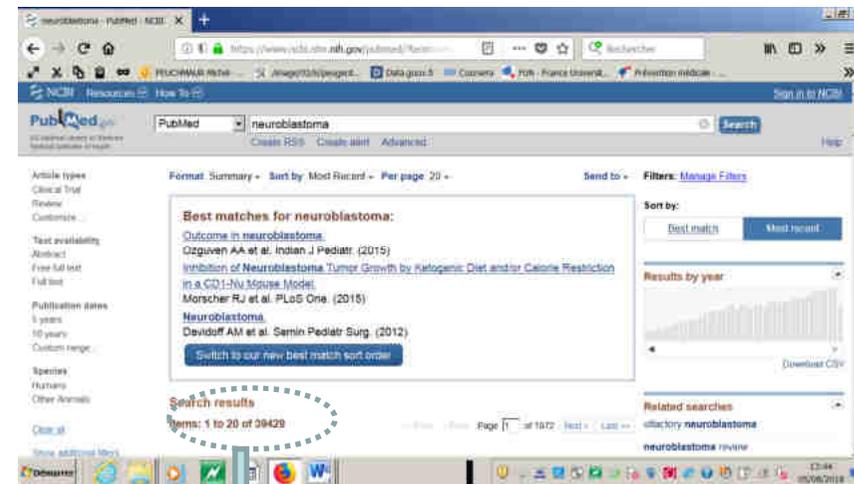


Author, Year (Reference)	Technique	Recurrent mutations/ structural rearrangements
Molenaar et al 2012 (45)	WGS	ALK (6% m, 2% sr) ATRX (5.7%) ODZ3 (5.7%) PTPRD (5.7%) TIAM1 (3.4%) FANCM/FAN1 Rac/Rho regulators
Sausen et al 2012 (47)	WGS WGS WES	ALK (9%) ARID1B, ARID1A VANGL ZHX2 LIN28B
Cheung et al 2012 (46)	WGS	ATRX (enrichment in older children)
Pugh et al 2013 (48)	WES WGS	ALK (9.2% m) ATRX (2.5% m/7.1% sr) PTPN11 (2.9%) OR5T1 (1.25%) PDE6G (0.8%) MYCN (1.7%) NRAS (0.8%)
Boeva V et al 2013 (49)	WGS	FHIT ODZ4 NBAS ALK PTPRD

neuroblastome



Somatic genetic alterations in Neuroblastoma determined by NGS techniques



Pubmed: 40 000 publications



Disruption of the normal program of neuroblast differentiation and growth control.

Neuroblastoma is a genetic disease with few somatic mutations.

1/Association of a peculiar germline genotype with somatic genomic aberrations:

amplifications: **MYCN**, others rare (**ALK**)

translocations : rare, more frequent in relapses (**ALK**, others)

mutations: rare compared to adult tumors, most commonly concern **ALK**, telomeres (**TERT**), chromatin remodeling (**ATRX**, leading to the **ALT**, ARID 1A/1B), others.

Responsible for blocking the processes of differentiation and driving proliferation

2/Familial neuroblastoma (1% neuroblastomas): **ALK** mutation, **PHOX2B** mutation (congenital central hypoventilation syndrom, Hirschsprung disease, neuroblastoma, particularly if bilateral, could be associated).

3/Sporadic neuroblastoma predisposition: between 10 and 15 genomic loci found associated with neuroblastoma predisposition;

Germline genotypes could dictate clinical and pathological phenotypes.



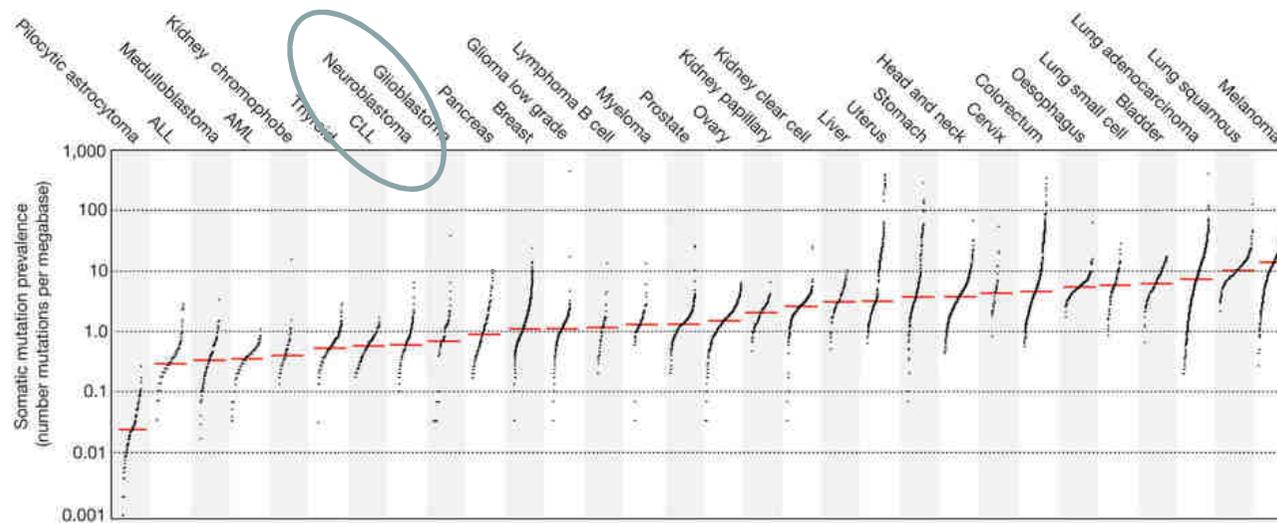
Genes involved in cell cycle, proliferation

- **MYCN amplification**: heterodimers MYCN / MAX, activate the transcription of downstream target genes (proliferation genes)
 - 20% of all cases and **40%** of high risk neuroblastomas.
- **MYC** focal amplification of distal enhancers or enhancer hijacking: potent oncogene in a distinct subset of high risk neuroblastoma cases

low frequency of recurrent mutations in neuroblastomas compared with high number disclosed in adult cancers.

Children

Low



Adult

High

Alexandrov LB et al, Signatures of mutational processes in human cancer. Nature. 2013;500:415-21.

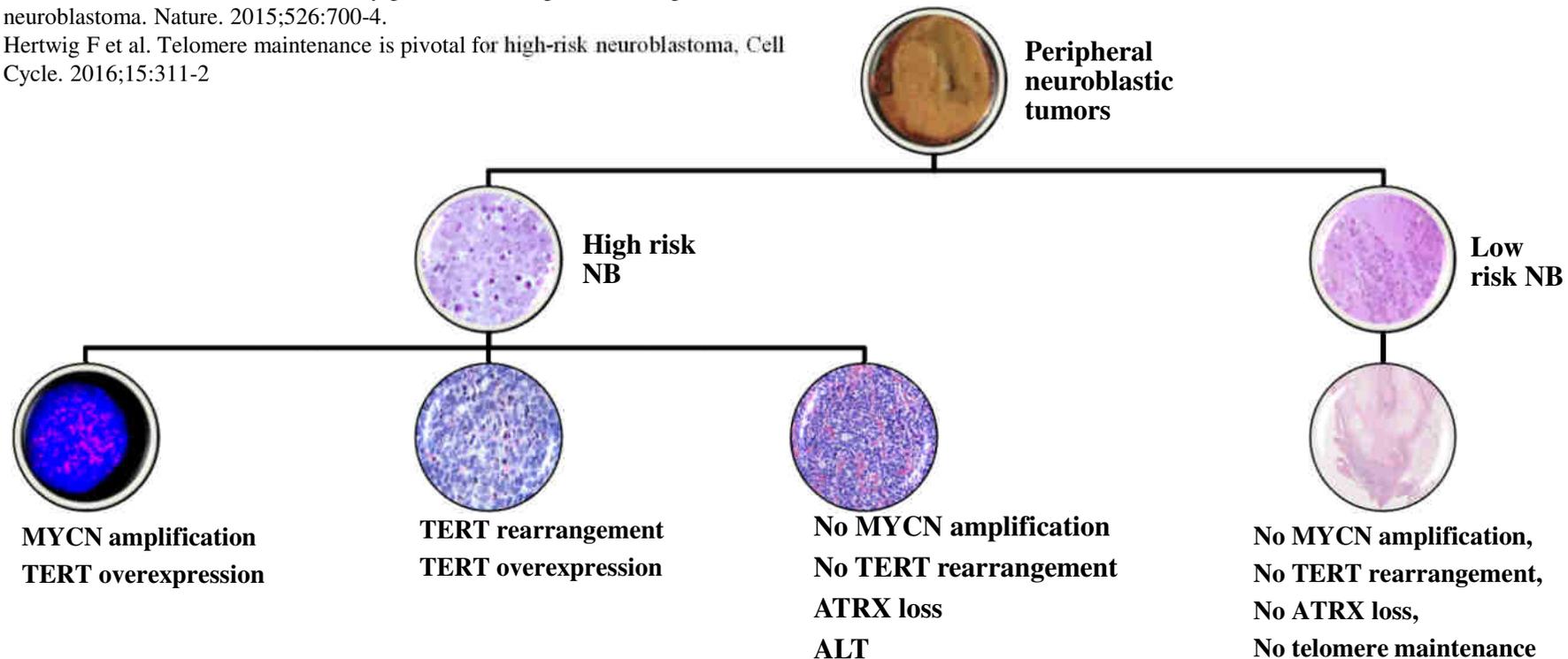


Genes involved in cell cycle, proliferation

- Rearrangements of **TERT** (telomerase reverse transcriptase) in cases with poor outcome (15% of high risk neuroblastoma), mutually exclusive of **MYCN** amplifications.
- Either **MYCN** amplification and **TERT** rearrangements lead to **TERT** overexpression.
- (Alpha-thalassemia/mental retardation syndrome-X linked) **ATRX** loss undergo telomerase-independent telomere maintenance mechanism (**ALT**: alternative lengthening of telomeres).

Peifer M et al. Telomerase activation by genomic rearrangements in high-risk neuroblastoma. Nature. 2015;526:700-4.

Hertwig F et al. Telomere maintenance is pivotal for high-risk neuroblastoma, Cell Cycle. 2016;15:311-2

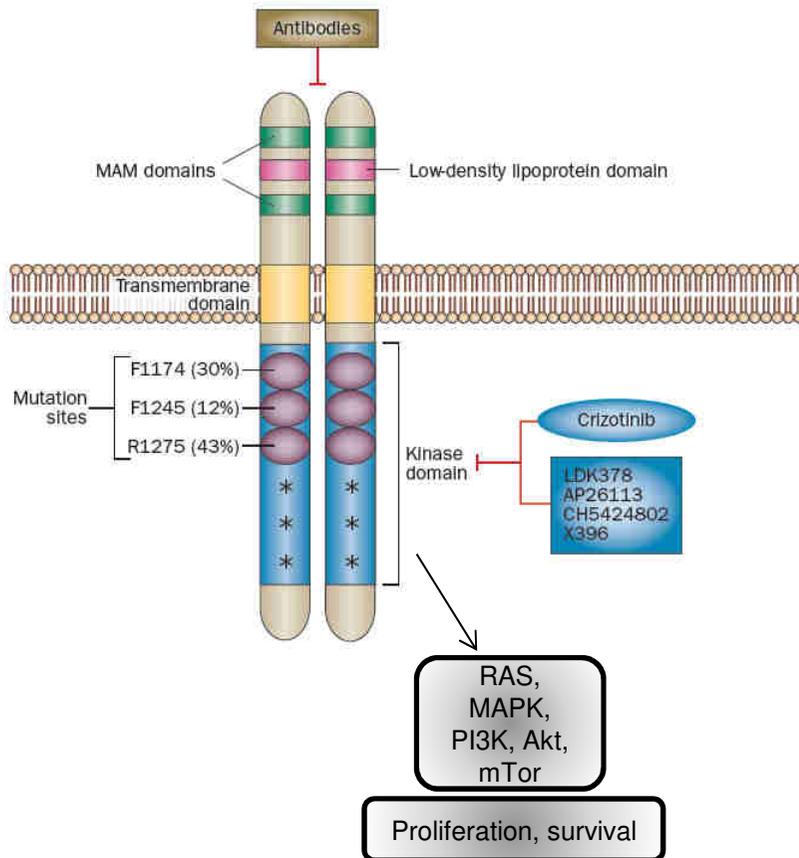


activation of telomere lengthening mechanisms : proliferation

regression

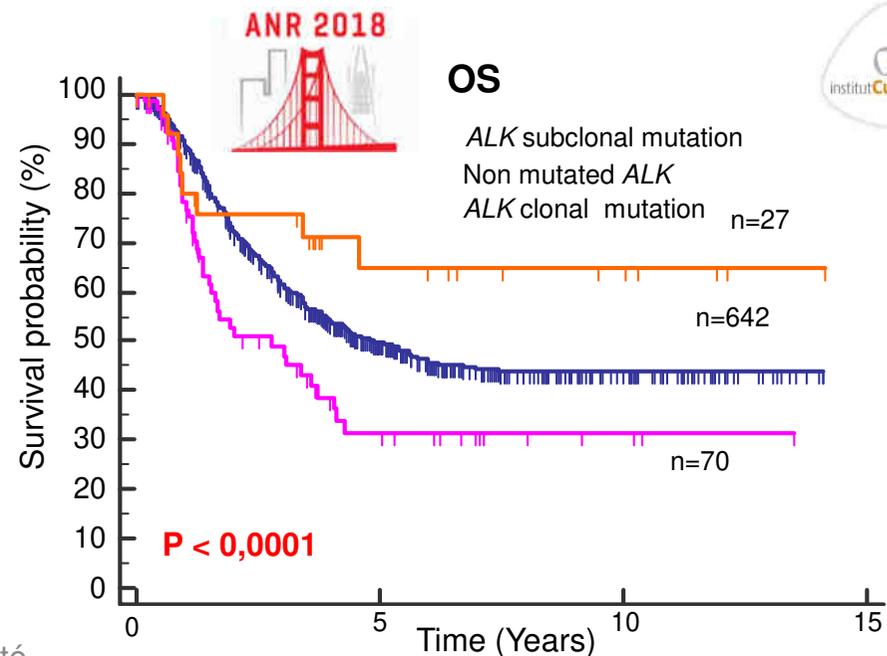
Gene involved in cell cycle, proliferation / apoptosis

ALK (anaplastic lymphoma kinase)



Carpenter EL et al. Targeting ALK in neuroblastoma—preclinical and clinical advancements. *Nat Rev Clin Oncol.* 2012 May 15; 9(7): 391–399.

1. **Sporadic NB** : activating mutations in 8 – 10%, amplification
2. **Familial NB**: activating mutations (mutation R1275)
3. **Therapeutic target**: Crizotinib (phase 1/2 (COG) (Mosse et al 2013)





Gene involved in Cell lineage Bourdeaut F., et al. J Pathol. 2009;219:463-472.

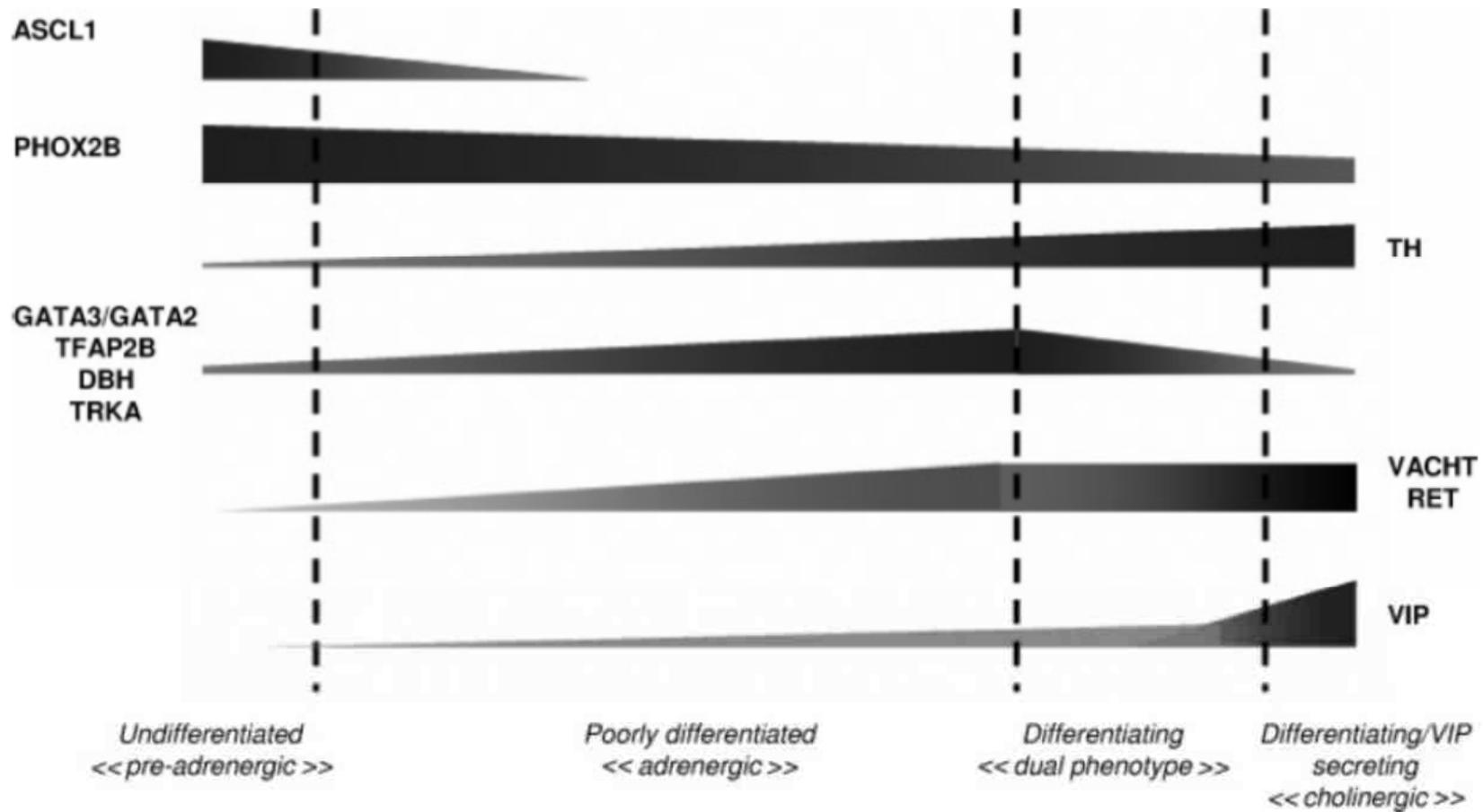


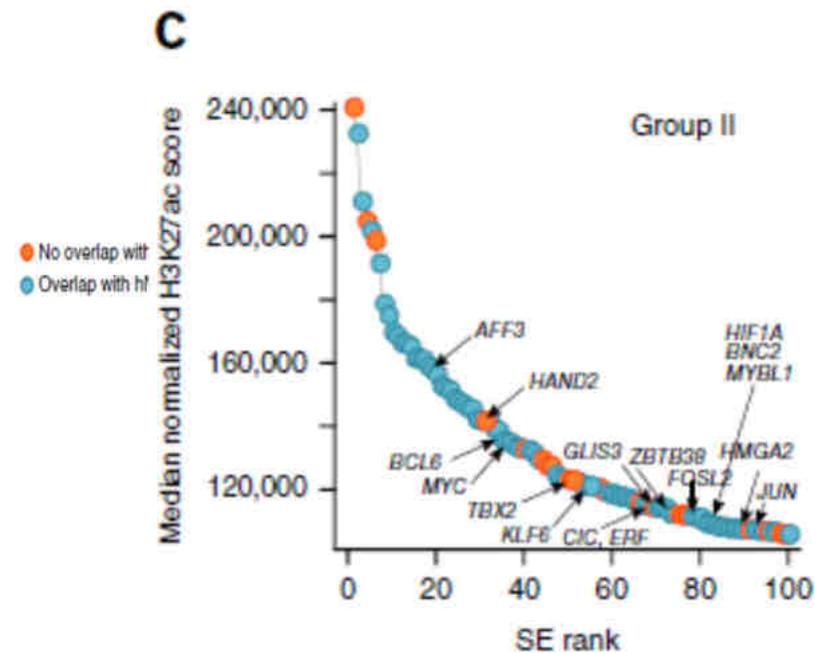
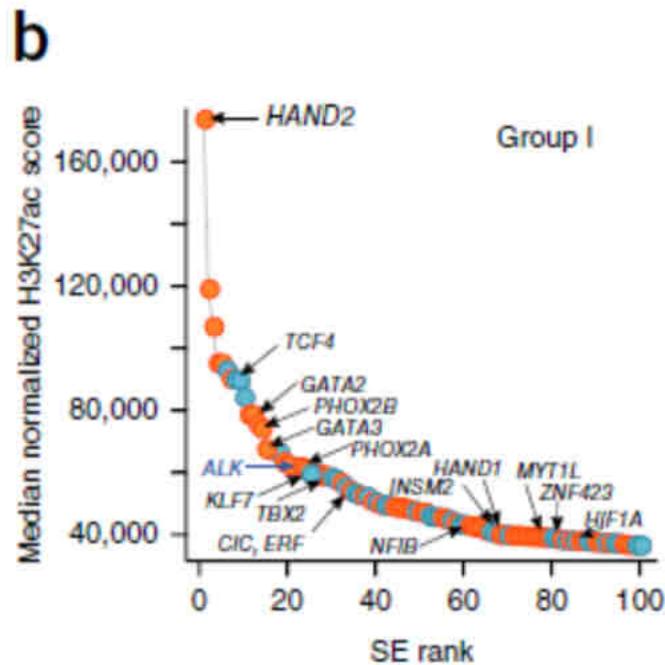
Figure 5. Neuroblastoma subcategories according to their molecular pattern of differentiation

Gene involved in Cell lineage

two distinct cell types were identified by different core regulatory circuitries defined by super-enhancers (SE) cell identities: noradrenergic and mesenchymal neural crest cell-like

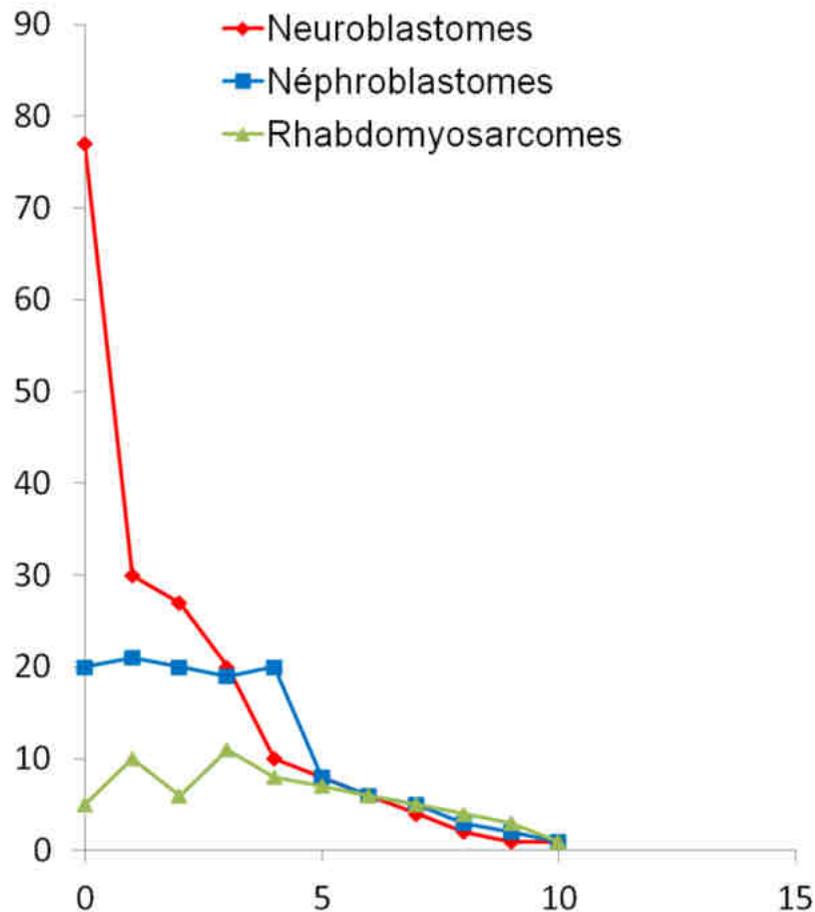
Adrenergic identity: super-enhancer comprise a set of TF loci including HAND2, PHOX2B, GATA2/3, and ALK. These gene control normal sympathetic neuron differentiation

NCC-like identity: super-enhancer of group II identity overlap with those of neural crest cells.





Neuroblastoma is the most common extracranial solid tumor of childhood



- Most common solid tumors of children.
- 1 child / 10000 births.
- Adrenal glands, paraspinal ganglia
- Mean age: 18 - 20 months old.
- Clinical outcome variable:
 - 5-year survival rates 75%
 - 1/2 regression
 - 1/2 metastasis, relapses, death.
 - 15% of all cancer related death in children

Registre national des hémopathies de l'enfant (RNHE) et des tumeurs solides de l'enfant (RNTSE) (Prs. J. Clavel et B. Lacour)

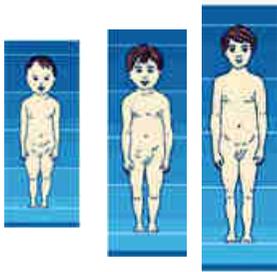


INRG: International Neuroblastoma Risk Grouping

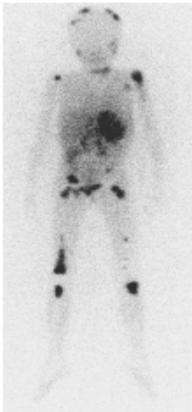
Cohn S et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. *JCO*. 2009;27:289-97.

INRG Stage	Age (months)	Histologic Category	Grade of Tumor Differentiation	<i>MYCN</i>	11q Aberration	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	< 18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥ 18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
		Poorly differentiated or undifferentiated	NA				
				Amp			N High
M	< 18			NA		Hyperdiploid	F Low
	< 12			NA		Diploid	I Intermediate
	12 to < 18			NA		Diploid	J Intermediate
	< 18			Amp			O High
	≥ 18						P High
MS	< 18			NA	No		C Very low
					Yes		Q High
					Amp		R High

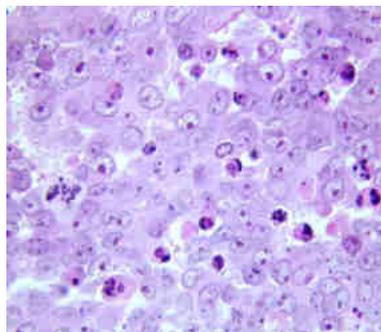
Neuroblastoma / Prognostic markers:



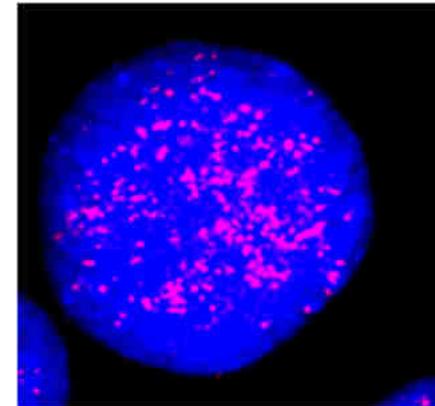
Age: 18 months



Stage: Localized
vs Metastatic

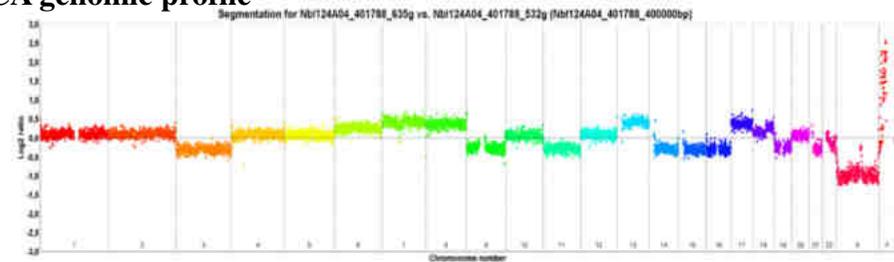


Pathology:
Favorable vs
Unfavorable

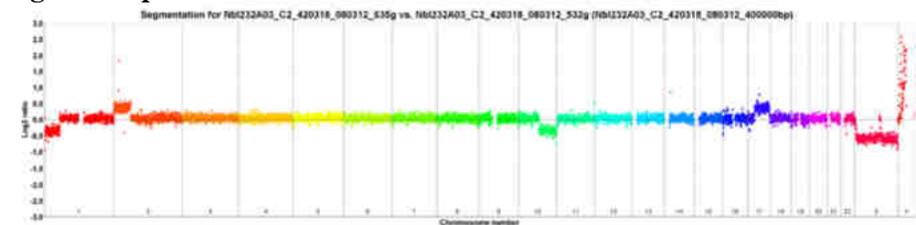


MYCN: amplified or non amplified

NCA genomic profile



SCA genomic profile



Janoueix-Lerosey I et al. Overall genomic pattern is a predictor of outcome in neuroblastoma. *J Clin Oncol* 2009;27:1026-33



INPC: international neuroblastoma pathology classification, *Peripheral Neuroblastic Tumors*

<u>categories</u>	<u>stroma</u>	<u>grade</u>	<u>MKI</u>
neuroblastoma	stroma poor	undifferentiated poorly differentiated differentiating	MKI L, i, H
ganglioneuroblastoma	stroma mixed rich and poor, nodular	in nodule(s)	in nodule(s)
ganglioneuroblastoma	stroma rich, intermixed		
ganglioneuroma	stroma dominant		

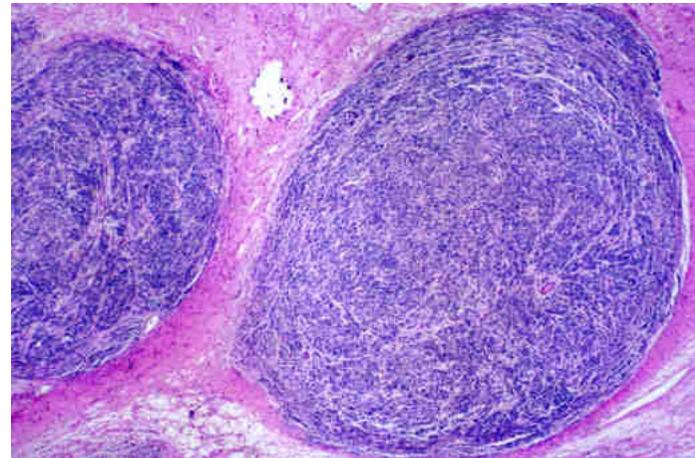
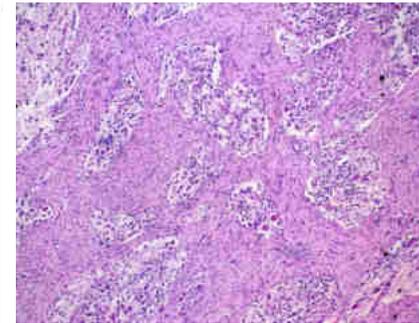
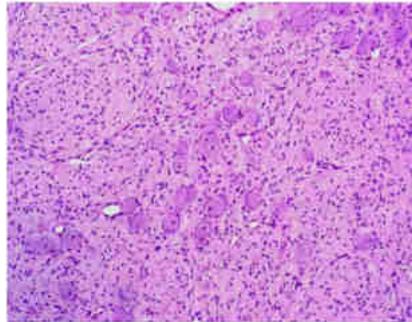
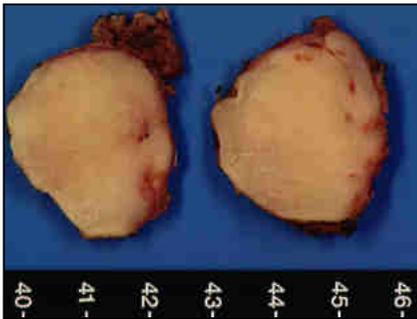
Shimada H, et al. The International Neuroblastoma Pathology Classification. *Cancer*. 1999;86:364-72.

Shimada H, et al. Terminology and morphologic criteria of neuroblastic tumors: recommendations by the International Neuroblastoma Pathology Committee. *Cancer*.1999;86:349-63.

Peuchmaur M, et al. Revision of the International Neuroblastoma Pathology Classification: confirmation of favorable and unfavorable prognostic subsets in ganglioneuroblastoma, nodular. *Cancer*. 2003;98:2274-81.

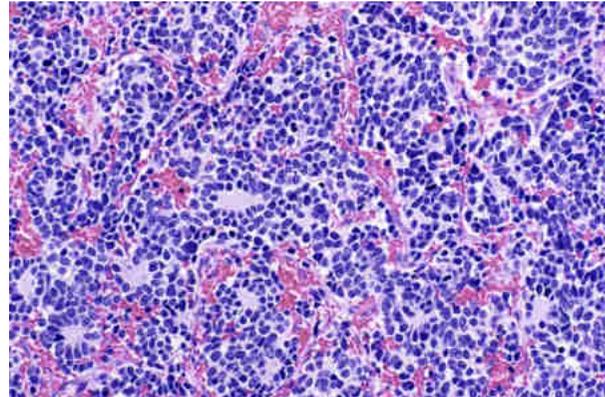
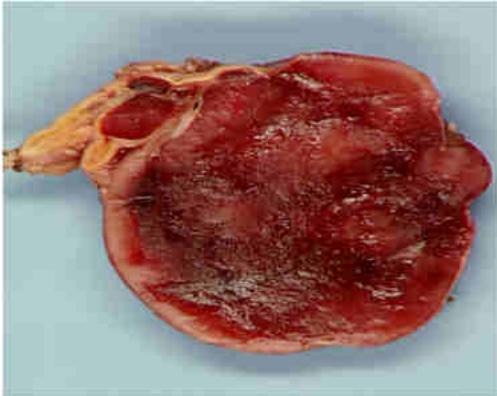


Ganglioneuroma, stroma rich
Ganglioneuroblastoma, stroma rich, intermixed
Ganglioneuroblastoma, stroma mixed rich and poor, nodular

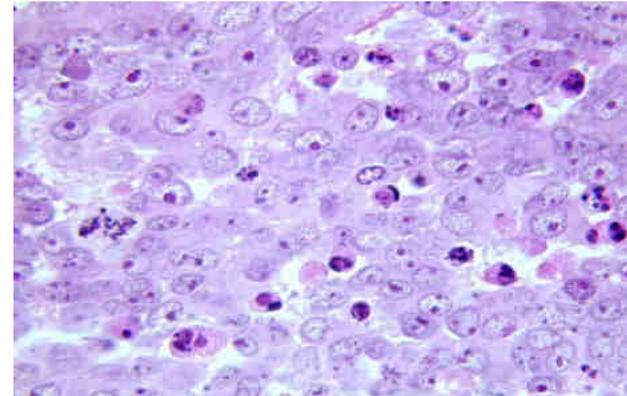


Neuroblastoma, stoma poor

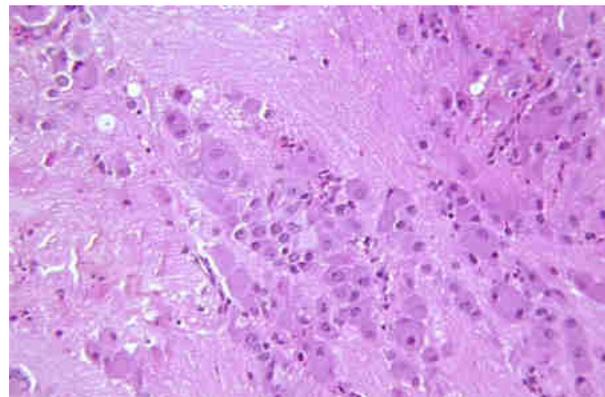
a: poorly differentiated, b: undifferentiated, c: differentiating



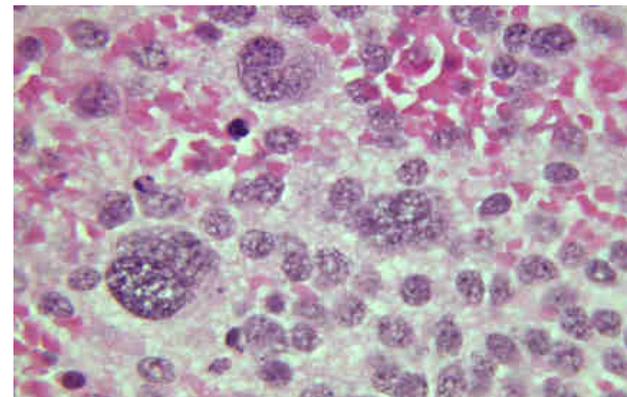
a: poorly differentiated



b: undifferentiated (nucleoli +)



c: differentiating



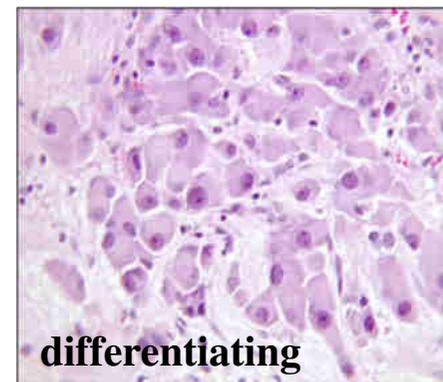
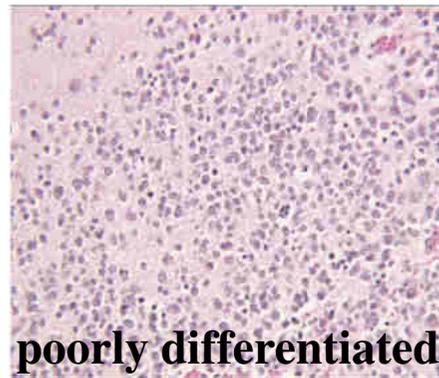
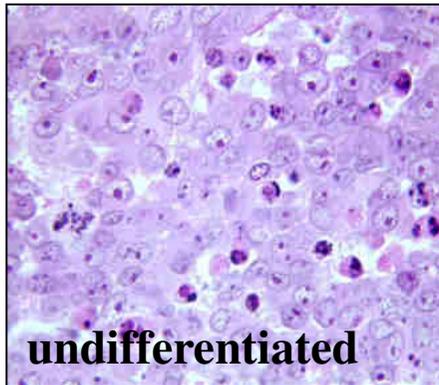
Polymorphic nuclei



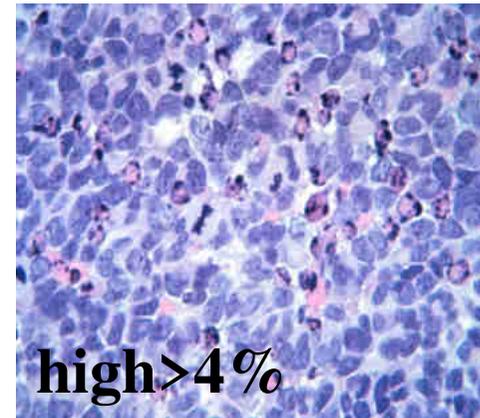
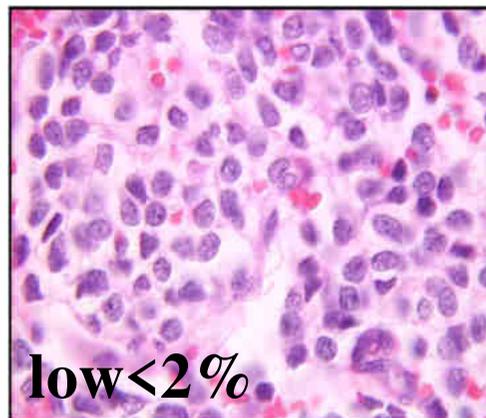
histoprognosis

age : <1.5 year, [1.5-5], >5 years

grade:



MKI: low(<2%), intermediate [2%-4%], high>4%





	Undifferentiated	Poorly differentiated	Differentiating
Low MKI	U	F	F
Intermediate MKI	U	F	F
High MKI	U	U	U

Prognostic categorization of neuroblastomas and nodular ganglioneuroblastomas (classic and variants, prognosis determined by the nodule)

U and red: unfavorable.

F and green: favorable

Age < 18 months

	Undifferentiated	Poorly differentiated	Differentiating
Low MKI	U	U	F
Intermediate MKI	U	U	U
High MKI	U	U	U

Age 18-60 months

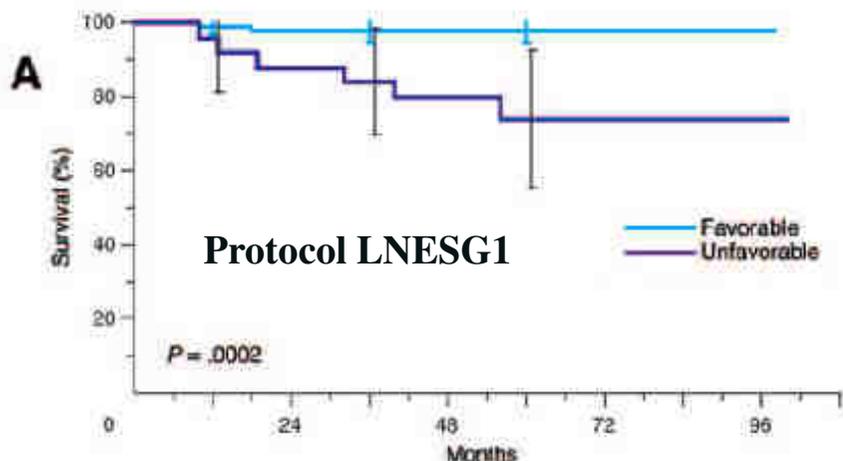
	Undifferentiated	Poorly differentiated	Differentiating
Low MKI	U	U	U
Intermediate MKI	U	U	U
High MKI	U	U	U

Age > 18 months



Prognostic categorization of ganglioneuroblastomas, intermixed and ganglioneuromas.

Any age

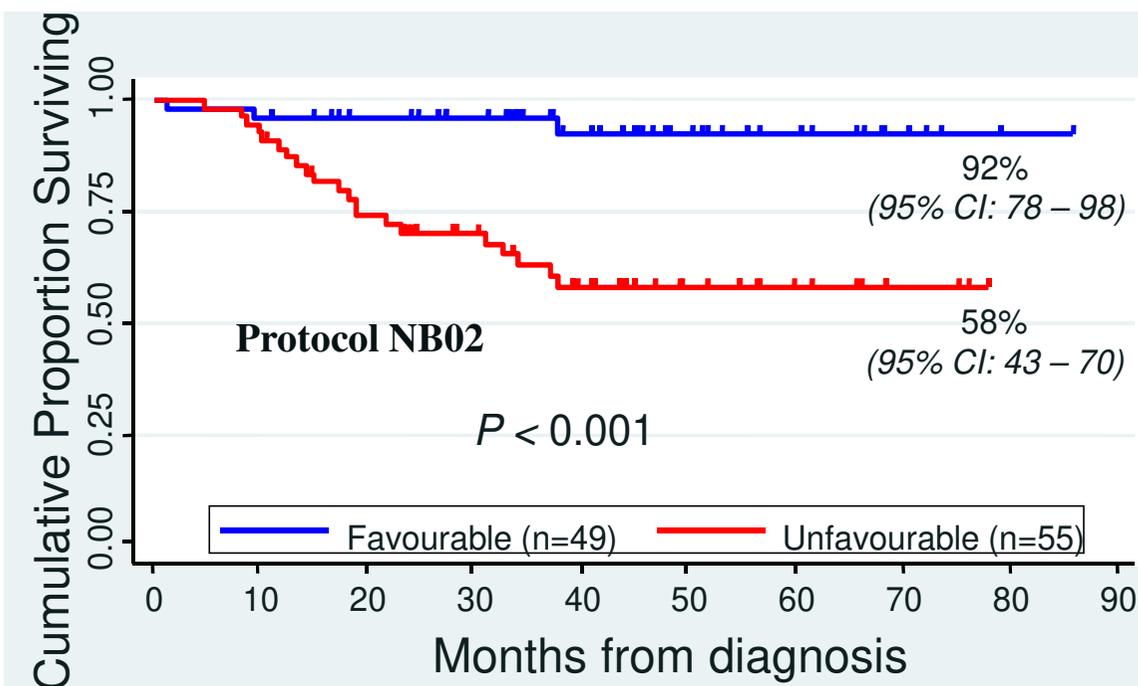


Patients at risk:

Favorable	90	88	85	84	73	48	30	11	1
Unfavorable	25	24	22	21	19	10	5	2	1

inter-observer reliability of agreement for histoprognosis

Navarro S, Peuchmaur M. Prognostic value of International Neuroblastoma Pathology Classification in localized resectable peripheral neuroblastic tumors: a histopathologic study of localized neuroblastoma European Study Group 94.01 Trial and Protocol. J Clin Oncol. 2006;24:695-9





Core needle biopsies

PHRC IC200709 (prospective french protocol): CGHa- pathology correlation

Eve Lapouble et al, ANR2018

2 Genomic Profiles

Cohort = 512 Patients

 Median age = 23,15 months

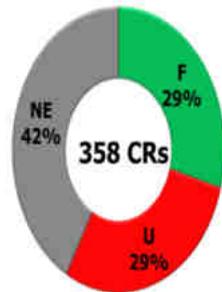
 <18 months (63%), <5 years (85%)



A **strong correlation** between INPC histoprognosis classification and genomic profiles was documented

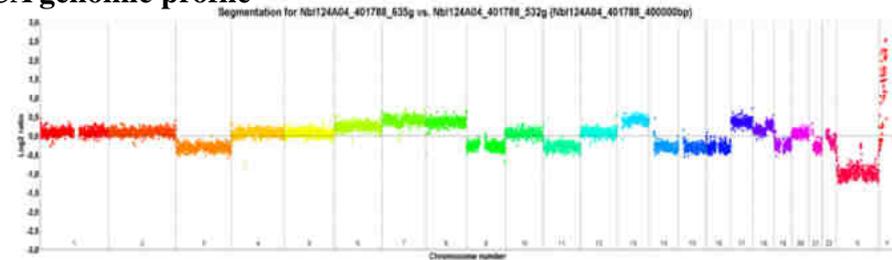
Classification X	INPC		
Classification Y	PG		
PG	INPC		
	F	U	
MNA	1	16	17 (10,6%)
NC	7	6	13 (8,1%)
NCA	43	13	56 (34,8%)
SCA	26	49	75 (46,6%)
	77 (47,8%)	84 (52,2%)	161

3 HistoPathological Review

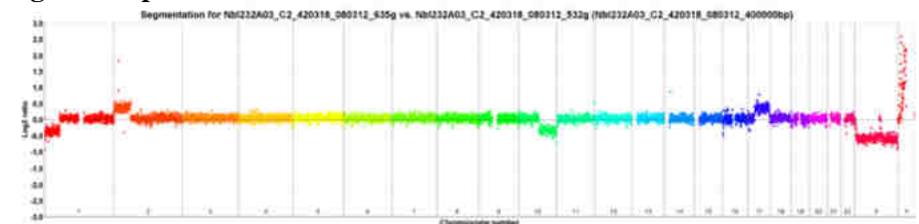


Histopathological review was obtained for 358 cases (INPC favorable n=105, unfavorable n=103, non-evaluable n=150), with GP data available in 281 cases.

NCA genomic profile



SCA genomic profile



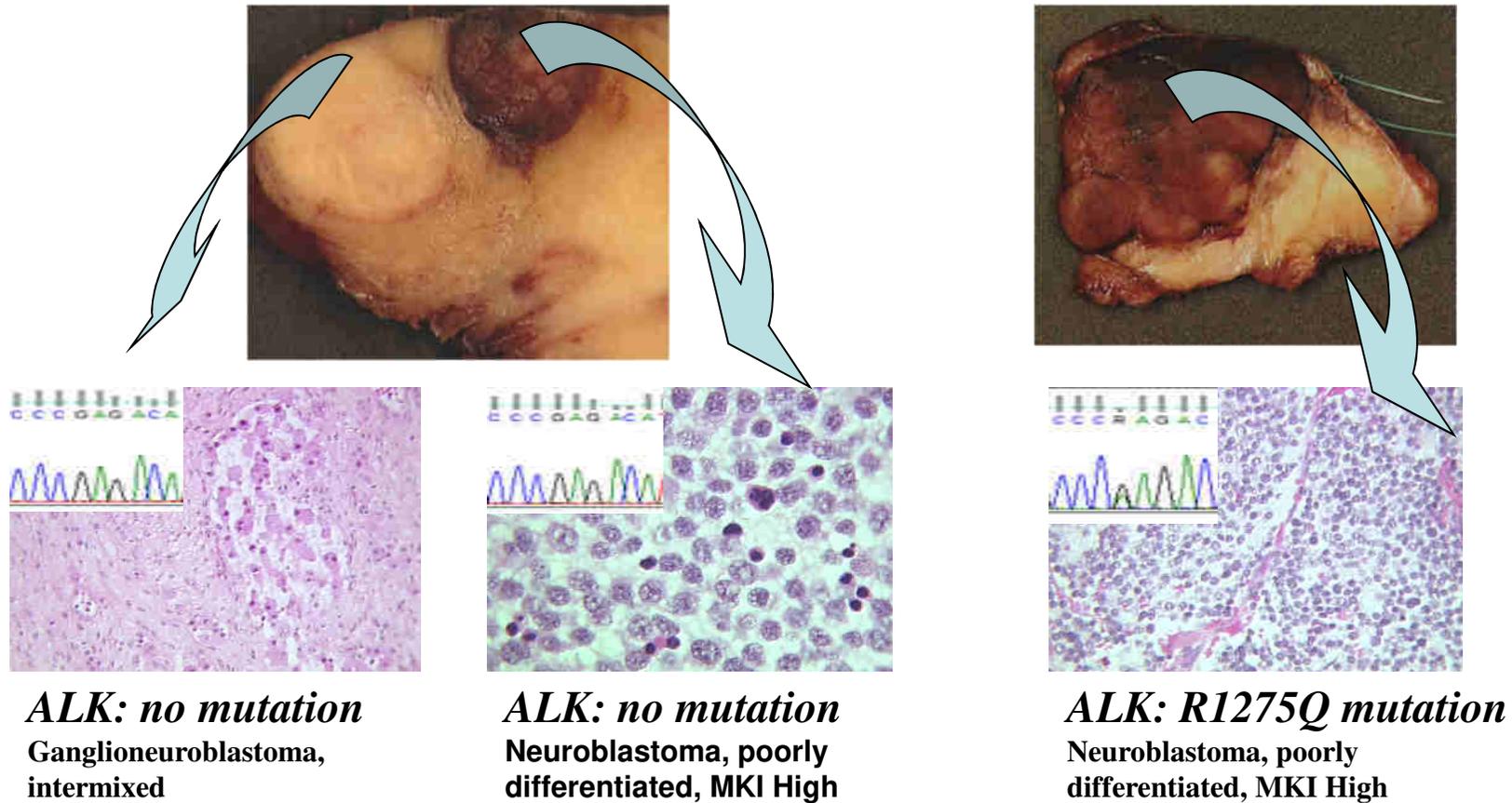


Heterogeneity of pNT : ALK somatic mutations at relapse

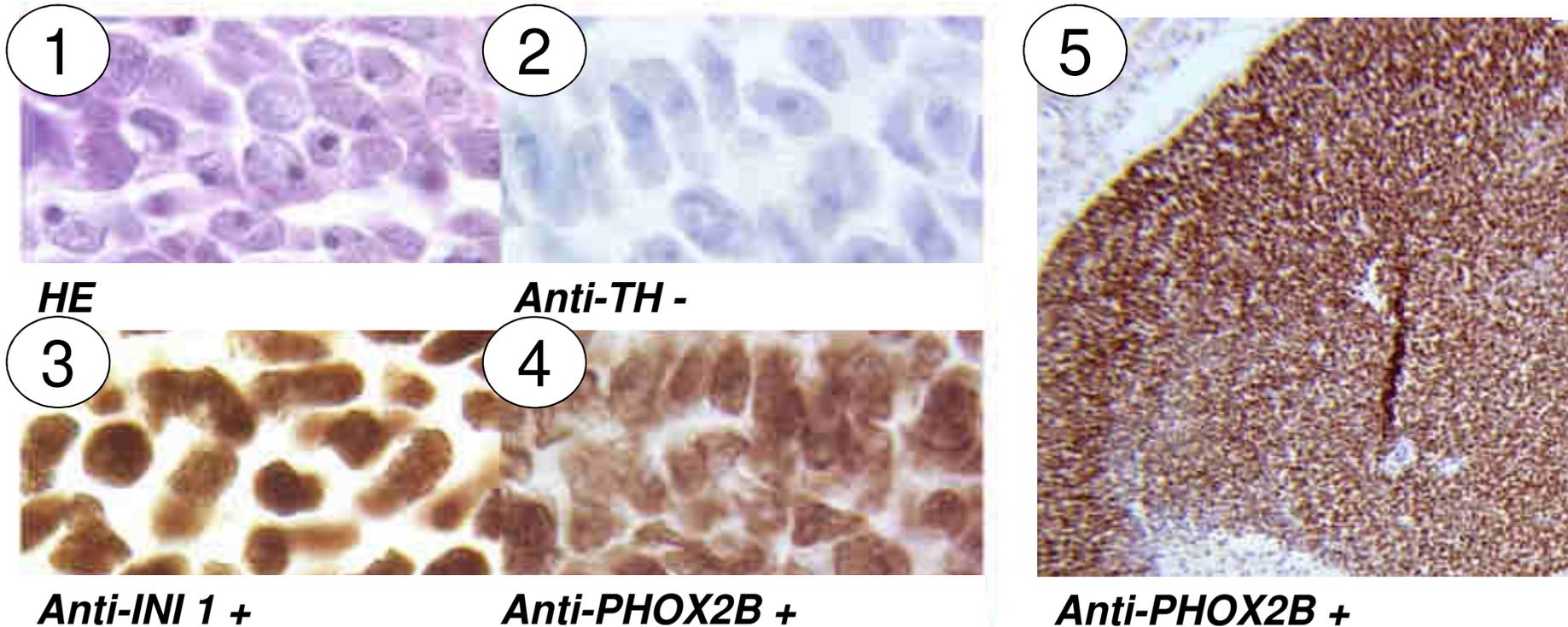
Schleiermacher G. Emergence of new ALK mutations at relapse of neuroblastoma.

JCO 2014;32:2727-34

new tumoral tissue banking from surgical specimens obtained at relapse



Neuroblastoma, undifferentiated



1 primitive tumor

2,3,4 immunohistochemistry

5 Metastasis

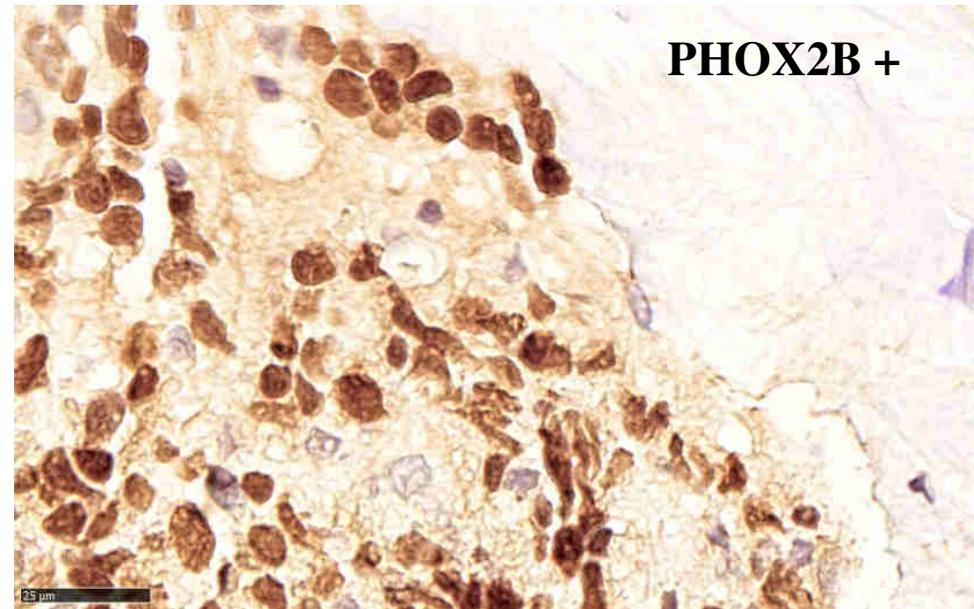
F. Bielle et al. **PHOX2B Immunolabeling**: A Novel Tool for the Diagnosis of Undifferentiated Neuroblastomas Among Childhood Small-, Round-, Blue-cell Tumors. *Am J Surg Pathol* 2012, 36:1141-9

Anti-PHOX2B: the gold standard for the diagnosis of undifferentiated neuroblastoma and for the detection of neuroblastoma tumor cells in bone marrow biopsies

Warren M et al. Utility of **PHOX2b** immunohistochemical stain in neural crest tumours and non-neural crest tumours in paediatric patients. *Histopathology*. **2018;72:685-696**.

Hung YP et al. **PHOX2B** reliably distinguishes neuroblastoma among small round blue cell tumours. *Histopathology*. **2017;71:786-794**.

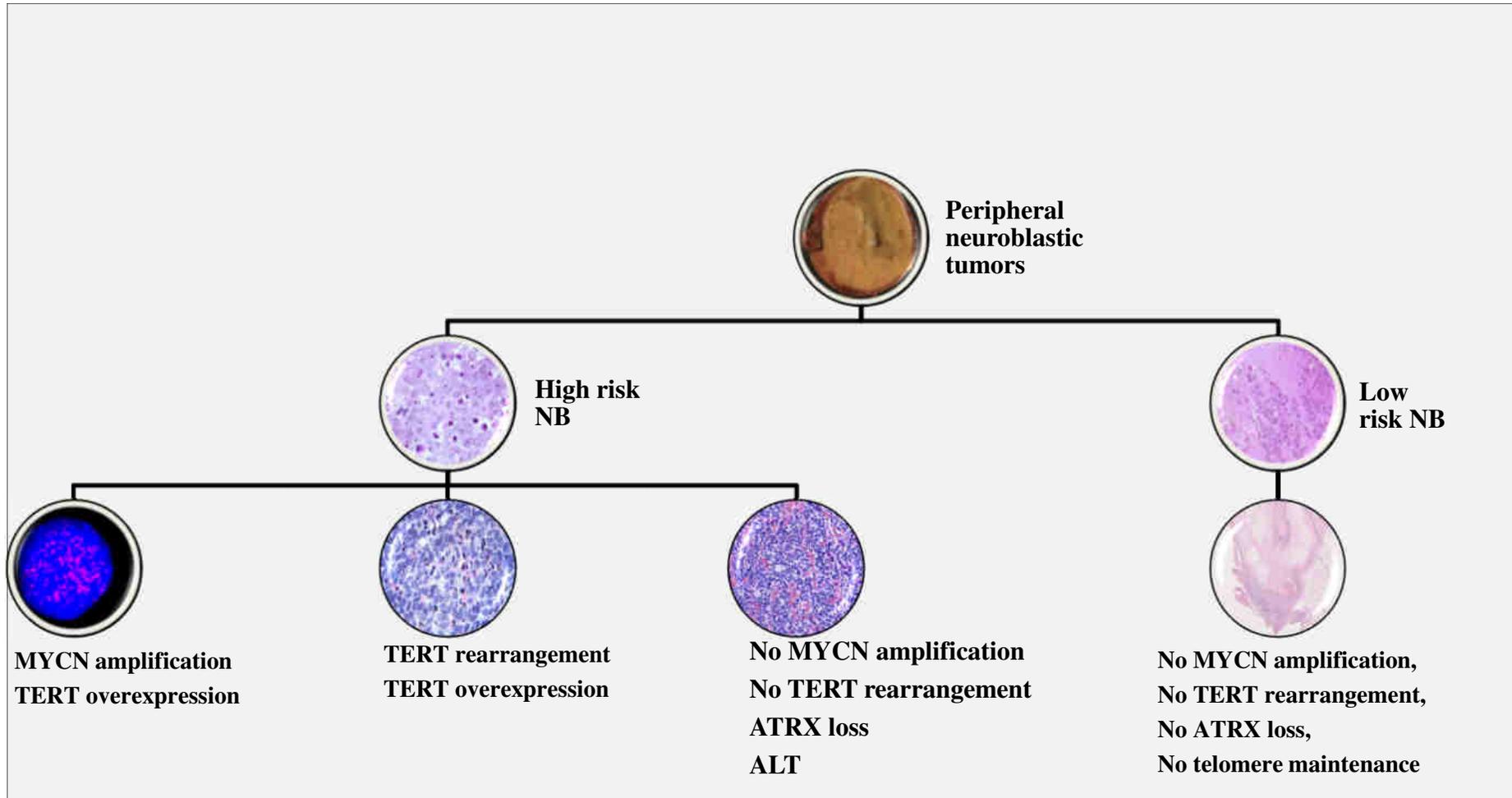
Burchill SA et al. Recommendations for the standardization of bone marrow disease assessment and reporting in children with neuroblastoma on behalf of the **International Neuroblastoma Response Criteria Bone Marrow Working Group**. *Cancer*. **2017;123:1095-1105**.



Bone marrow biopsy, x80

Pathology and Gene products.
For histoprognosis purpose:

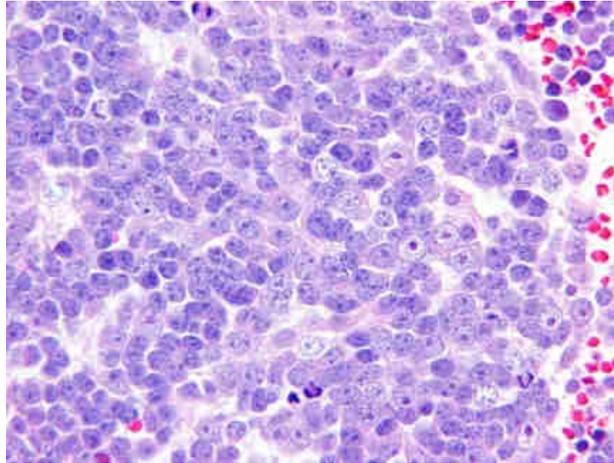
Genes involved in cell cycle/proliferation-apoptosis: **MYCN, MYC, TERT, ATRX and ALT, ALK.**



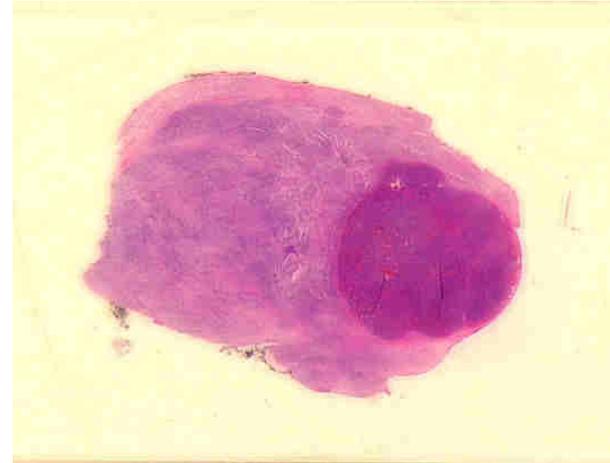


Next revision of the INPC?

Nucleoli



Composite neuroblastoma



Proteins of interest: MYCN/MYC, TERT, ATRX /ALT, ALK, ...

Potentially actionable genomic alterations in Neuroblastoma:

- ALK: **ALK** inhibition
- **RAS-MAPK pathway**: MEK inhibition (PTPN11, RAS family, ...)
- Cell cycle control: **TERT**, CDK4/6 inhibition
- Chromatin modification (**ATRX**, ARID1A/1B, ...)

(Bosse KR and Marris JM. Cancer. 2016;122:20-33)

Conclusion

Pathologie des tumeurs pédiatriques: réseaux et dialogue

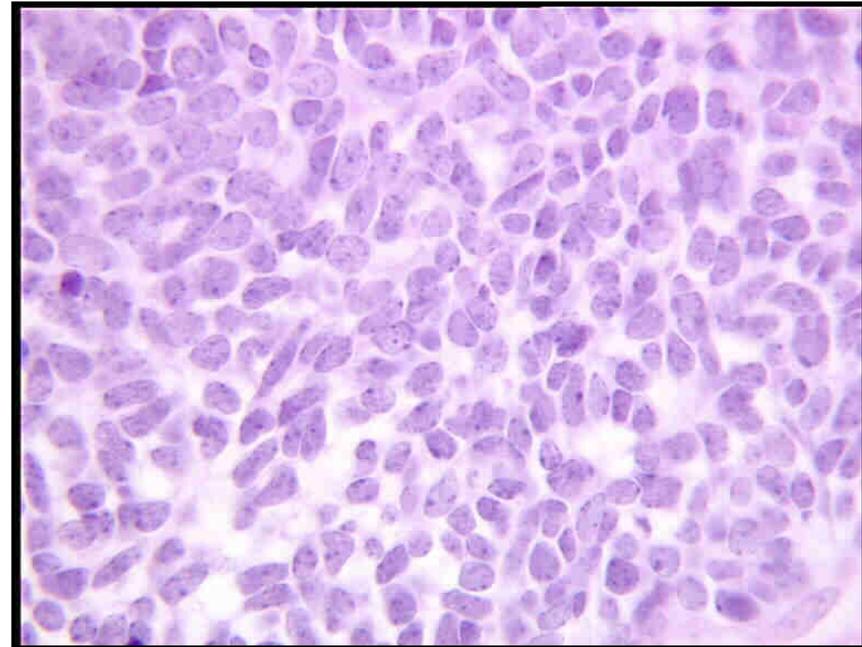
- ▶ **Rareté, localisation et âge**
- ▶ **Diagnostic, histopronostic et banque tissulaire**
- ▶ **Réseaux et collaborations***
- ▶ **Pronostic bon mais varié**
- ▶ **Adapter le traitement: groupes de différents risques**

*Pinto NR et al. Advances in Risk Classification and Treatment Strategies for Neuroblastoma. JCO, 2015, 33, 3008-3017.

Coopération internationale:

- 1/Progrès dans la biologie des tumeurs
- 2/Amélioration de la classification des risques
- 3/Amélioration des stratégies thérapeutiques
- 4/Majeure pour évaluer les traitements pour les petites cohortes de patients avec des formes rares

**tumeurs de blastème
(embryonnaires): classification
internationale**





Acknowledgments

SIOPEN Pathology committee:

- Amann G, Österreich
- Beiske K, Norge
- Cullinane C, UK
- D'Amore E, Italia
- Navarro S, España
- Sementa A, Italia
- Peuchmaur M., France

*Past-members: Ambros I, Gambini C,
Roald B.*

INPC members:

- USA: Shimada H, Jarzembowski J,
Wang LL.
- UE: Amann G, Beiske K, Cullinane
C, D'Amore E, Navarro S, Sementa
A, Tornóczyki T and Peuchmaur M.
- Japan *H. Okita*

*Past-members: Ambros I, Gambini C,
Hata J, Joshi V, Leuschner I (in
memoriam), Roald B.*

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- Hôpital Universitaire Robert
Debré/APHP-Université Diderot P7
- Institut Curie
- Gustave Roussy Cancer Campus
- The Pathologists participating in
the protocols.