Tumore atipico teratoide rabdoide

Angela Mastronuzzi
Ospedale Pediatrico Bambino Gesù

Bologna, 3 ottobre 2023

XLVIII CONGRESSO NAZIONALE AIEOP
Bologna
2-4 Ottobre 2023

Il sottoscritto Angela Mastronuzzi

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

Atypical teratoid rhabdoid tumor: general overview

Location

- Supratentorial tumors, more common with increasing age, often located in the cerebral hemispheres, less frequently in the ventricular system, suprasellar region, or pineal gland.
- Infratentorial tumors can arise in the cerebellar hemispheres, cerebellopontine angle, and brainstem.
- Spinal cord localization is rare.
- Rare AT/RTs affecting adults tend to occur in the cerebral hemispheres and sellar region.
- Seeding of AT/RT via CSF pathways is common and found in approximately one-third of all patients at presentation.

Epidemiology

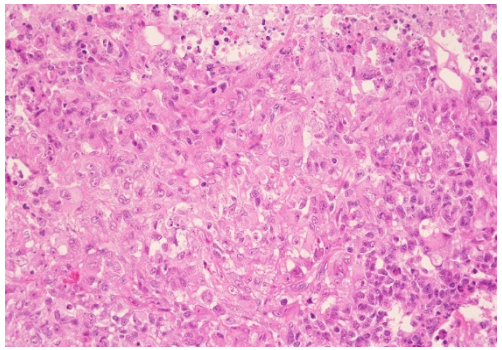
1.6% of all pediatric CNS tumors and 10.1% of CNS tumors in children aged < 1 year, with an M:F ratio of 1.2:1.
The majority of patients are aged < 2 years, with 33% aged ≤ 1 year at diagnosis. Occurrence in adults is rare.
(CBTRUS data)

Prognosis

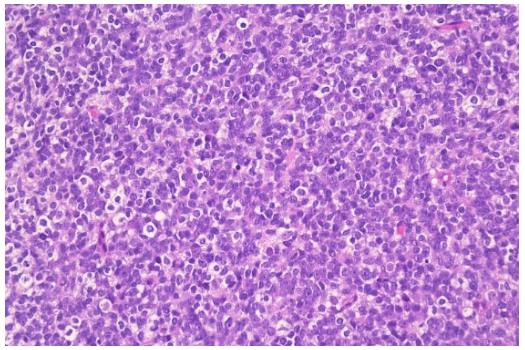
Poor although data from retrospective studies and clinical trials have shown that AT/RTs do not always have a dismal outcome:

- COG: 4-year EFS rate of 37% and an OS rate of 43%.
- HIT: 3-year OS rate of 22% and an EFS rate of 13%, but also identified a subset of patients (14%) who were long-term event-free survivors.
- Canadian Brain Tumour Consortium: 2-year OS rate of 60% ± 12.6%.
- EU-RHAB: 5-year OS and EFS rates of 34.7% and 30.5%, respectively.

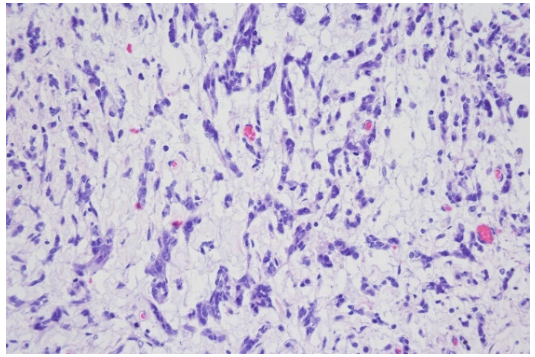
Atypical teratoid rhabdoid tumor: histological point of view



Rhabdoid cells of varying size with vesicular nuclei, prominent nucleoli, and pale eosinophilic cytoplasm.



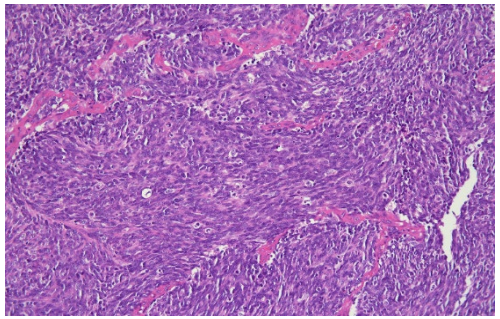
Lesions composed of small embryonal cells without typical rhabdoid cells raise the diagnostic possibility of other CNS embryonal tumors.



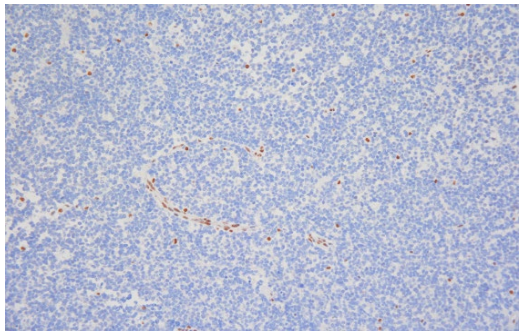
Mesenchymal area composed of loosely arranged elongated cells.

Histopathological patterns are related to molecular subgroups

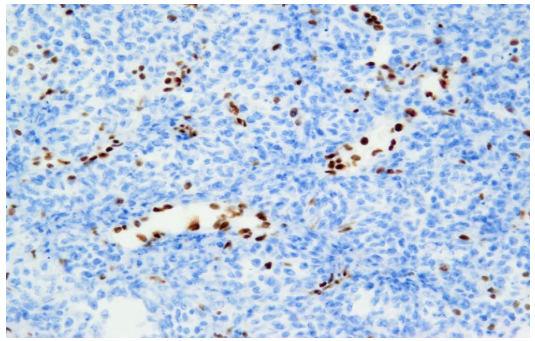
Zin F et al. Brain Pathology 2021:31:e12967



Compact area with fascicular growth pattern



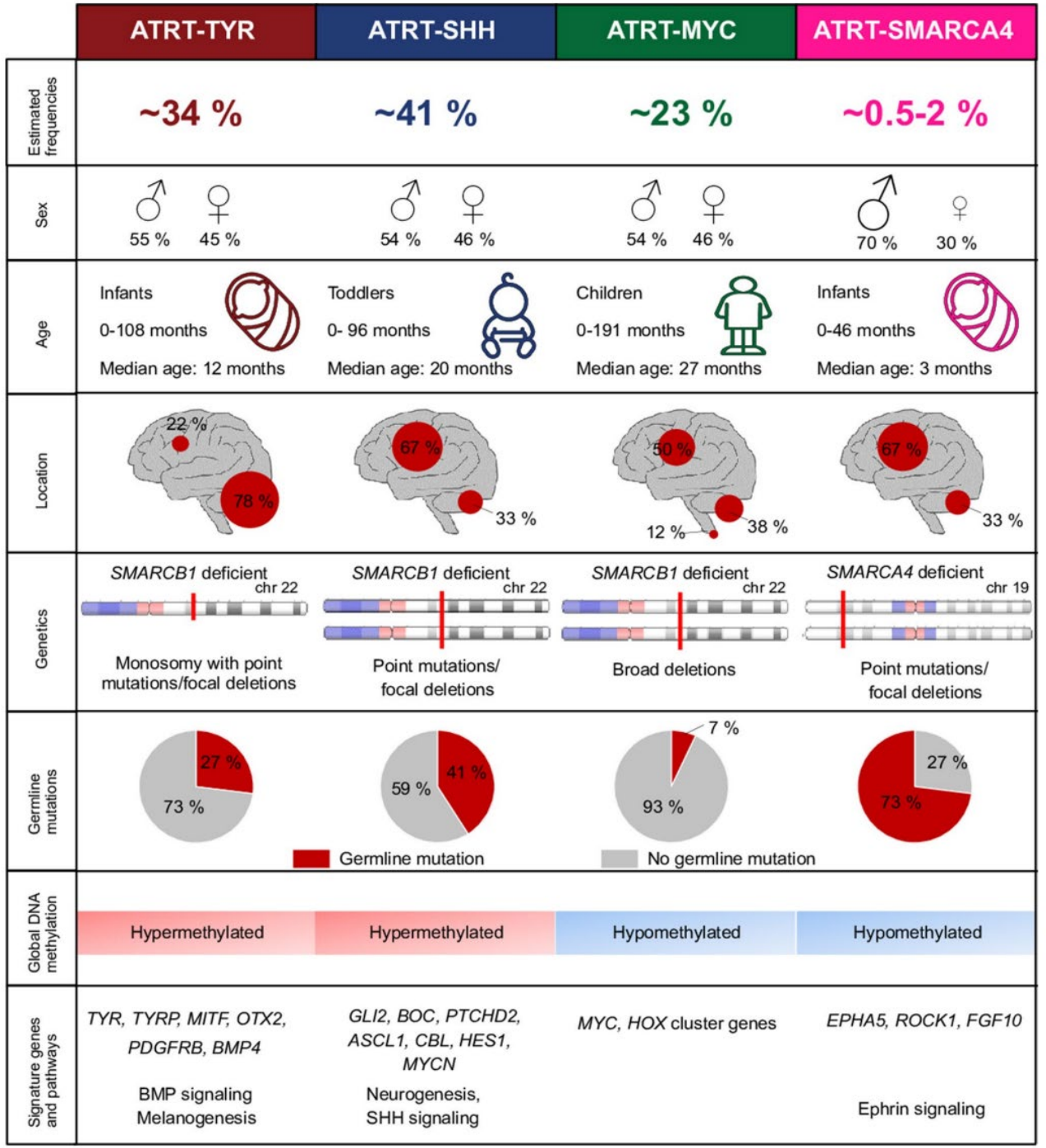
Loss of nuclear immunoreactivity for SMARCB1 in tumour cells, with retained expression in endothelial cells.



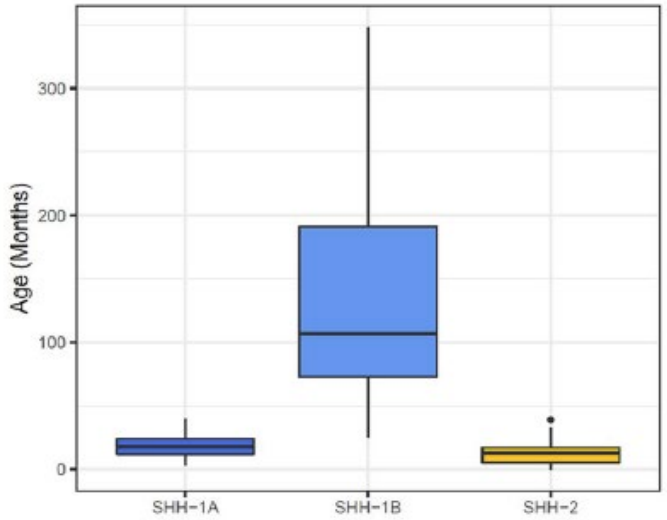
Rare cases manifest loss of SMARCA4 (BRG1) immunoreactivity, as illustrated here, but retain expression of SMARCB1 (INI1).

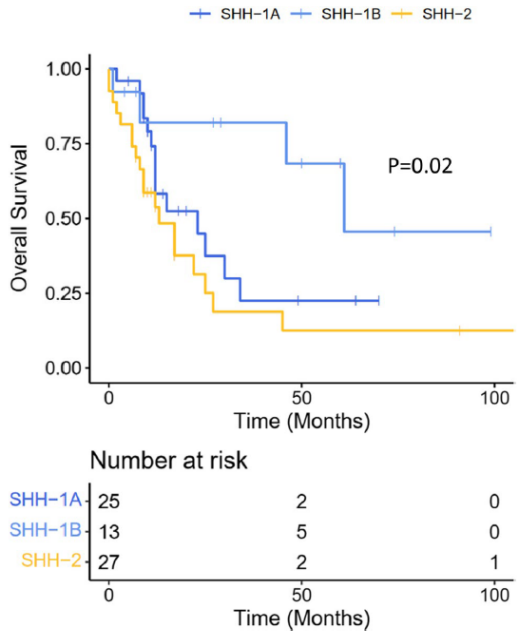
https://tumourclassification.iarc.who.int/chaptercontent/44/110

Atypical teratoid rhabdoid tumor: molecular point of view

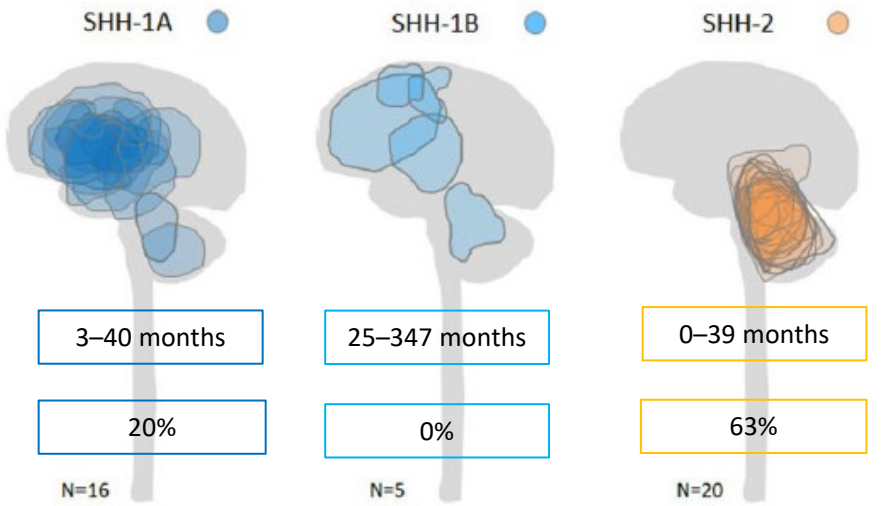


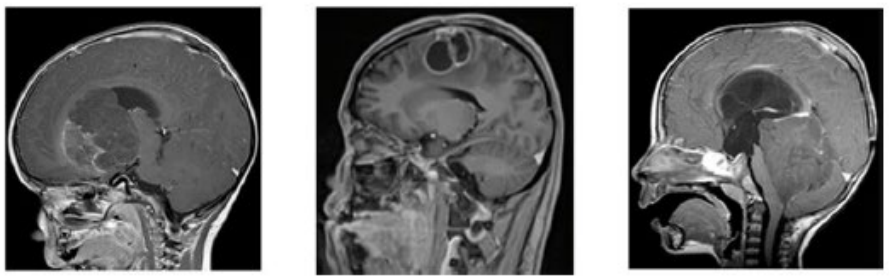
Acta Neuropathologica (2021) 141: 291-301





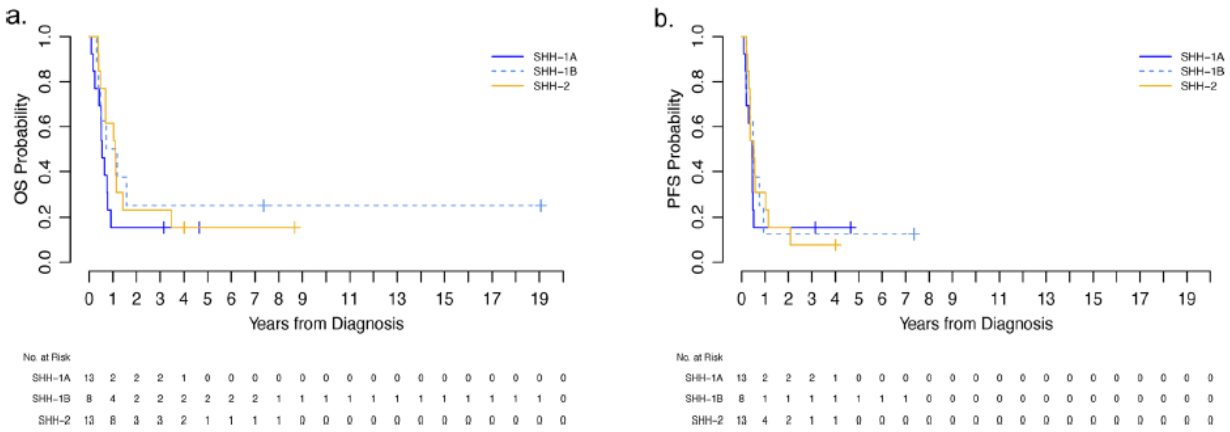
Federico A et al, Acta Neuropathol 143, 697–711 (2022)





Age at onset

SMARCB1 germline



Tran QT et al Acta Neuropathol 146, 543–545 (2023)

Atypical teratoid rhabdoid tumor: Rhabdoid tumor predisposition syndromes

Common Characteristics

- Autosomal dominant
- More than 70% of individuals with RTPS present before age 12 months with synchronous tumors
- Potentially have a worse prognosis than those with a sporadic rhabdoid tumor, although long-term survival has been reported in some individuals
- 2/3 de novo

SMARCB1 (RTPS1)

- The vast majority of individuals with *SMARCB1*-related RTPS have a *de novo* disease-causing *SMARCB1* germline variant
- Proportion of RTPS Attributed to Disease-Causing Variants in Gene: 85%-95%
- Penetrance of *SMARCB1*-related RTPS may be extremely high (>90% by age 5 years)
- The risk of germline mutations is reported to be between 26% and 41% in *SMARCB1*-deficient tumours

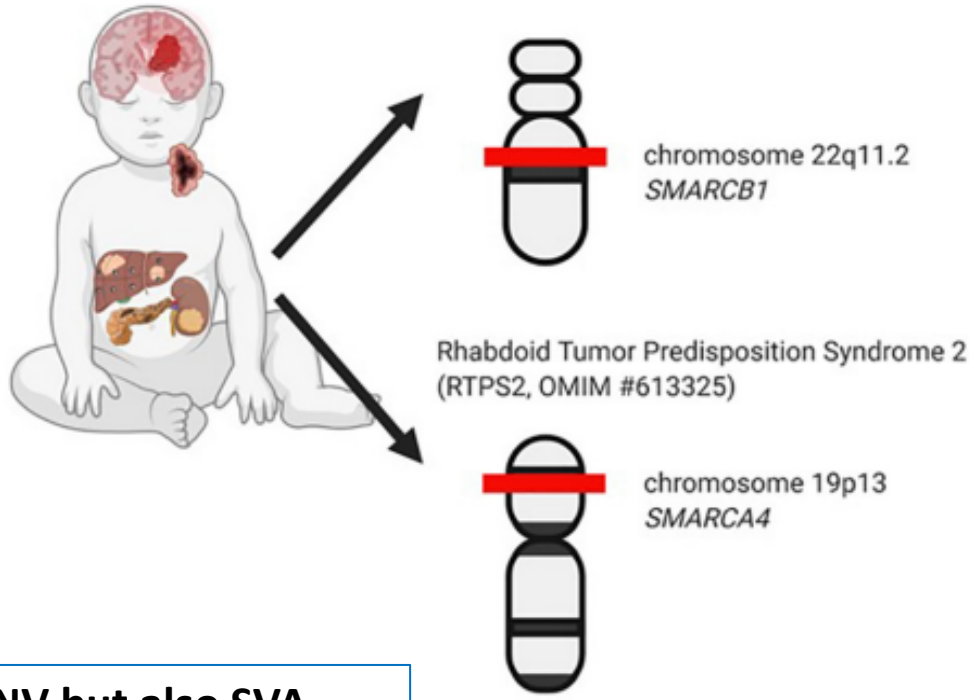
SMARCA4 (RTPS2)

- Most reported individuals diagnosed with *SMARCA4*-related RTPS inherited a disease-causing variant from a parent without a history of a rhabdoid tumor or SCCOHT
- Proportion of RTPS Attributed to Disease-Causing Variants in Gene: 5%-15%
- Less is know. The penetrance of *SMARCA4*-related RTPS appears to be incomplete
- May be substantially higher in *SMARCA4*-deficient tumours

Del Baldo et al, Front. Oncol. 11:586288 (2021)

The diagnosis of **RTPS** should be considered in patients with:
1) **rhabdoid tumors**;
2) especially if they have **multiple primary tumors**;
3) and/or in individuals with a **family history**

Other features suggesting RTPS: SCCOHT or other malignant entities such as cribriform neuroepithelial tumor, malignant peripheral nerve sheath tumor, and non-malignant schwannoma or meningioma



CNV but also SVA

Warning

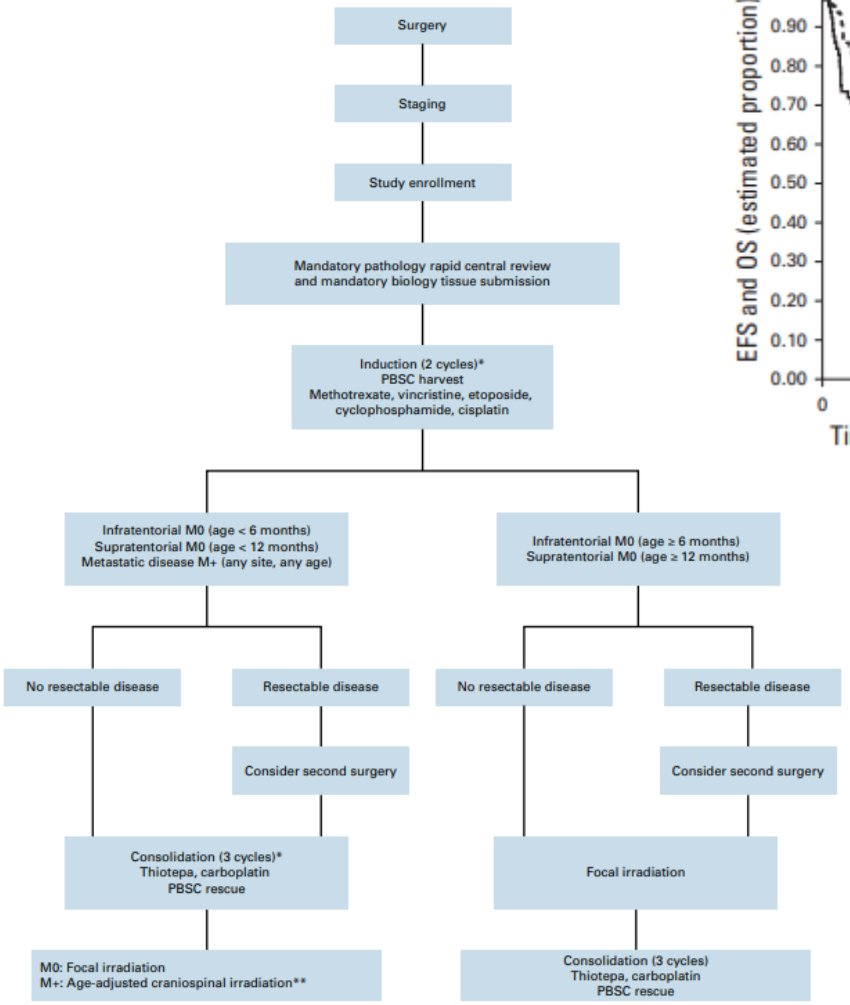
Unaffected adult carriers and gonadal mosaicism have been reported: if the *SMARCB1* or *SMARCA4* disease-causing variant identified in the proband cannot be detected in the constitutional DNA of either parent, **the recurrence risk to sibs is still greater** than that of the general population because of the possibility of parental germline mosaicism. Germline mosaicism may account for up to half of the families with sibs affected by RTPS.

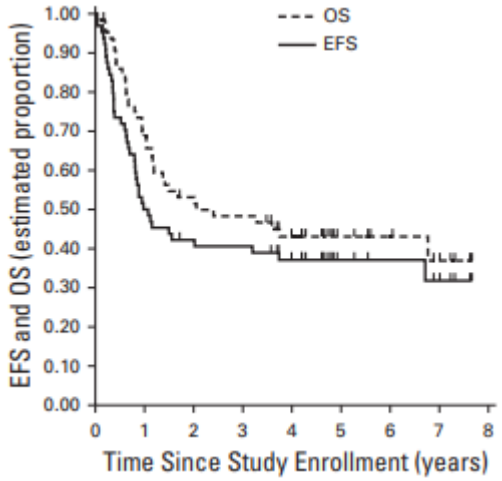
Pay attention to p53 somatic mutation according to variant allele frequency

TABLE 1. Patient Characteristics

Case No.	Sex	Age (y)	Tumor Location	SMARCB1	SMARCA4	TP53 Mutation	VAF (Tumor)
1	Male	17	Temporo-occipital	Loss/retained	Retained	TP53:NM_000546.6: c.586C > T (p.Arg196*)	0.87
2	Male	5	Parietotemporal	Loss	Retained	TP53:NM_000546.6:c.783-2A > G	0.98
3	Male	19	Frontotemporal	Retained	Loss	TP53:NM_000546.6:c.1024C > T (p.Arg342*)	0.97

Efficacy of High-Dose Chemotherapy and Three-Dimensional Conformal Radiation for Atypical Teratoid/Rhabdoid Tumor: A Report From the Children's Oncology Group Trial ACNS0333

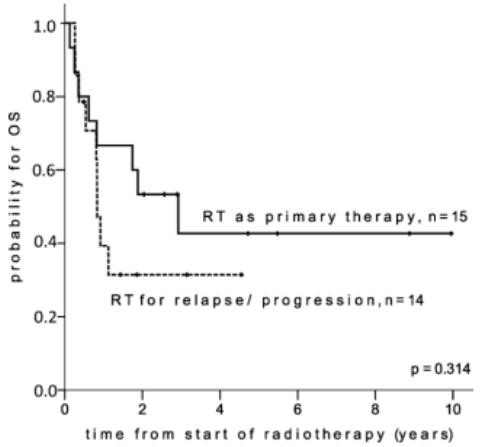




J Clin Oncol 38:1175-1185. © 2020

Pediatr Blood Cancer 2011;57:978–985

Frequency, Risk-Factors and Survival of Children With Atypical Teratoid Rhabdoid Tumors (AT/RT) of the CNS Diagnosed between 1988 and 2004, and Registered to the German HIT Database



Central nervous system atypical teratoid rhabdoid tumours: The Canadian Paediatric Brain Tumour Consortium experience

EUROPEAN JOURNAL OF CANCER 48 (2012) 353 – 359

Results: There were 50 patients (31 males; median age at diagnosis of 16.7 months). Twelve patients were >36 months. Infratentorial location accounted for 52% of all cases. Nineteen patients (38%) had metastatic disease. Fifteen (30%) underwent gross total resection (GTR). Ten patients (20%) underwent palliation. Among the 40 remaining patients, 22 received conventional chemotherapy and 18 received high dose chemotherapy regimens (HDC); nine received intrathecal chemotherapy and 15 received adjuvant radiation.

Thirty of the 40 treated patients relapsed/progressed at a median time of 5.5 months (0–32). The median survival time of the entire cohort was 13.5 months (1–117.5 months).

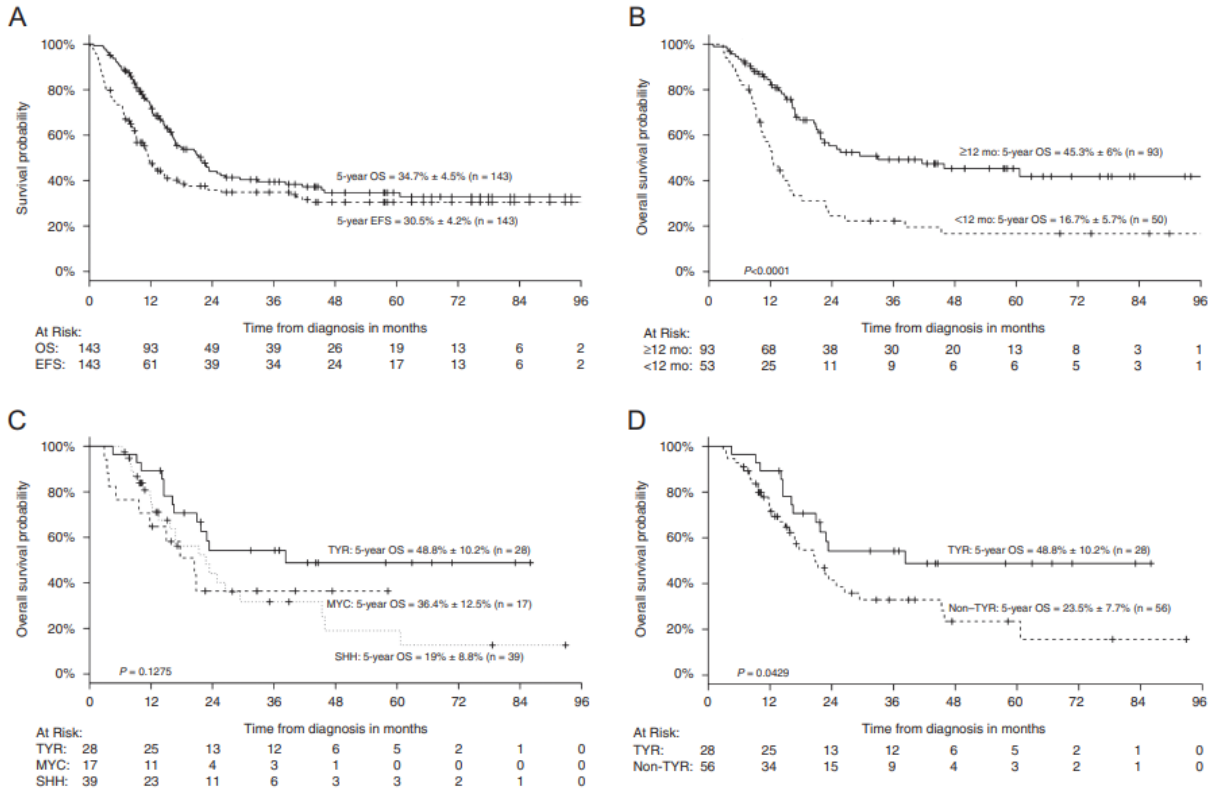
1006

Neuro-Oncology

22(7), 1006–1017, 2020 | doi:10.1093/neuonc/noz244 | Advance Access date 28 December 2019

Age and DNA methylation subgroup as potential independent risk factors for treatment stratification in children with atypical teratoid/rhabdoid tumors

Therapy consisted of surgery, anthracycline-based induction, and either radiotherapy or high-dose chemotherapy following a consensus among European experts



Atypical teratoid rhabdoid tumor

- Estensive surgery is related with better outcomes
- Radiation therapy improved survival
- Patients treated with high-dose chemotherapy versus conventional chemotherapy benefit from better survival *in some studies*

- Aggressive neurosurgical interventions may lead to neurological deficits
- Irradiation in very young children results in long-term neurological sequelae
- High-dose chemotherapy is burdened by high rate of toxicities

SIOPe ATRT 01

First randomized trial for ATRT in European countries

An international prospective umbrella trial for children with atypical teratoid/rhabdoid tumours (ATRT)

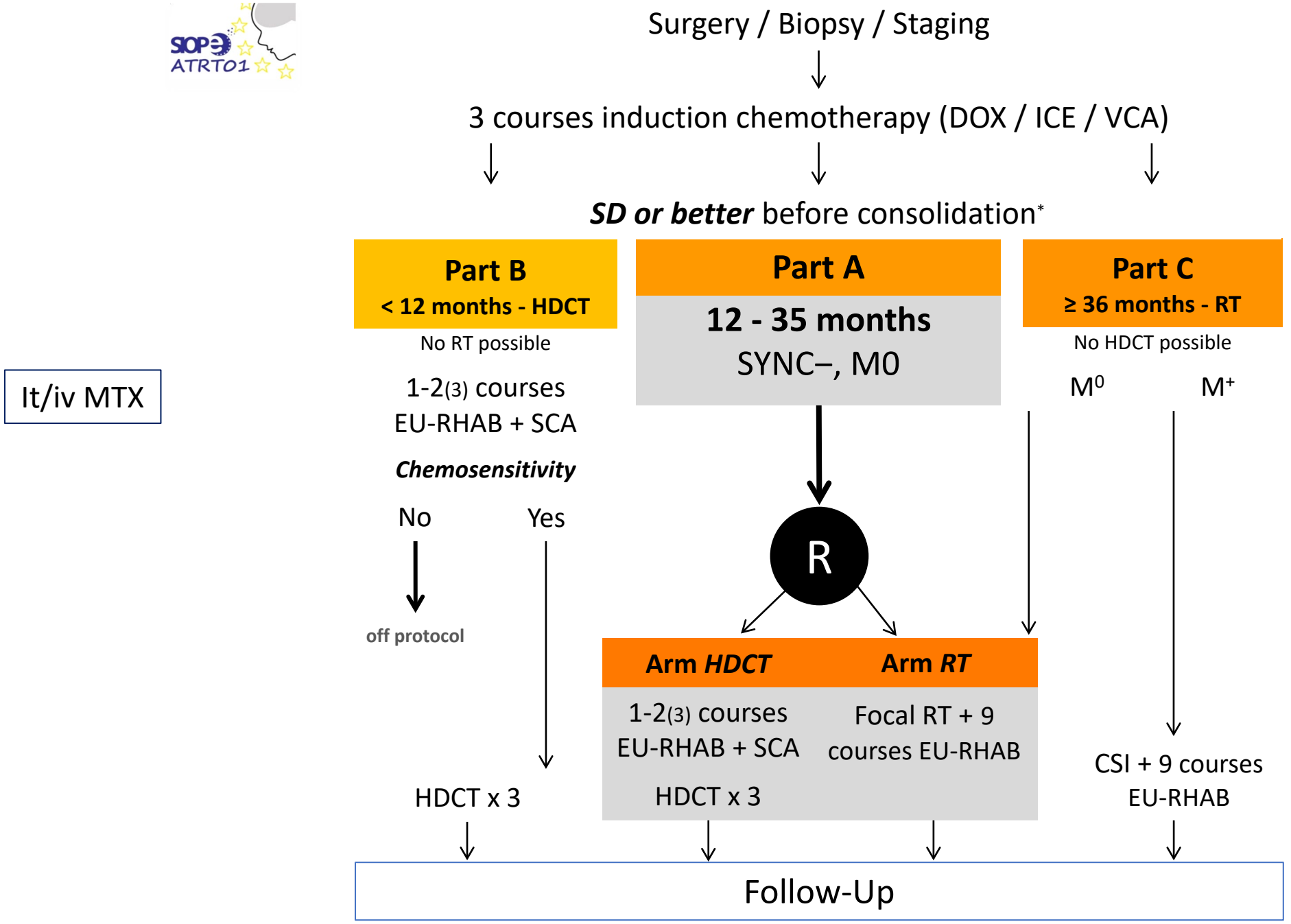
including

A randomized phase III study evaluating the non-inferiority of three courses of high-dose chemotherapy (HDCT) compared to focal radiotherapy as consolidation therapy

SIOPe ATRT 01

Surgery

- Complete surgical resection is often difficult because of the invasive nature of the tumor
- GTR is associated with improved outcomes over those with significant residual disease
- Second-look surgery may be indicated in the following situations:
  - Total or partial resection of primary tumor, post-operative (residual) tumor or recurrent tumor can lead to increased overall survival.
  - Total or partial resection prior to radiotherapy may lead to a smaller radiation field.
  - Total or partial resection prior to chemotherapy may enhance the effects of post-operative chemotherapy.

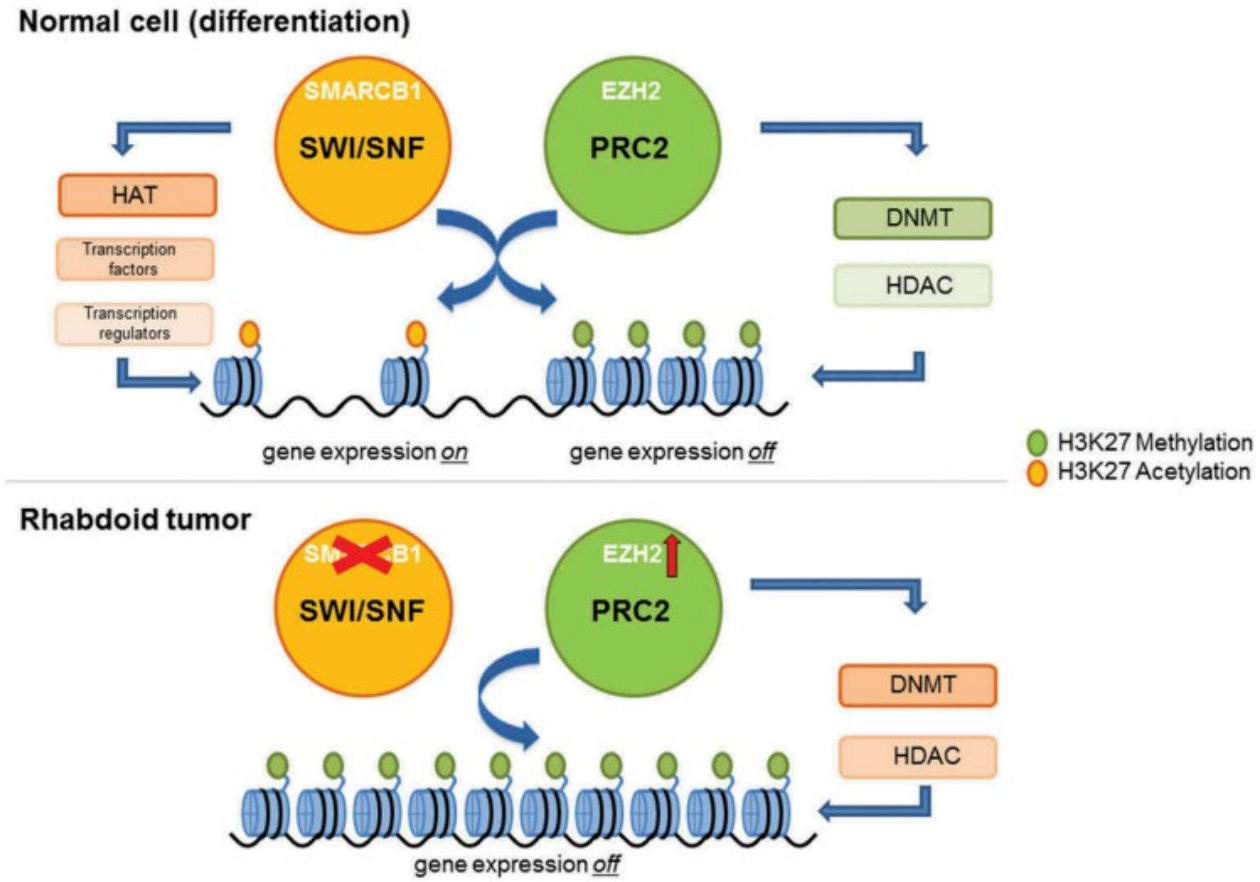

Surgery / Biopsy / Staging
3 courses induction chemotherapy (DOX / ICE / VCA)
SD or better before consolidation*
Part B
< 12 months - HDCT
No RT possible
1-2(3) courses
EU-RHAB + SCA
Chemosensitivity
No
Yes
off protocol
HDCT x 3
Part A
12 - 35 months
SYNC–, M0
R
Arm HDCT
1-2(3) courses
EU-RHAB + SCA
HDCT x 3
Arm RT
Focal RT + 9
courses EU-RHAB
Part C
≥ 36 months - RT
No HDCT possible
M0
M+
CSI + 9 courses
EU-RHAB
Follow-Up
PD/M+/SYNC+: contact trial office

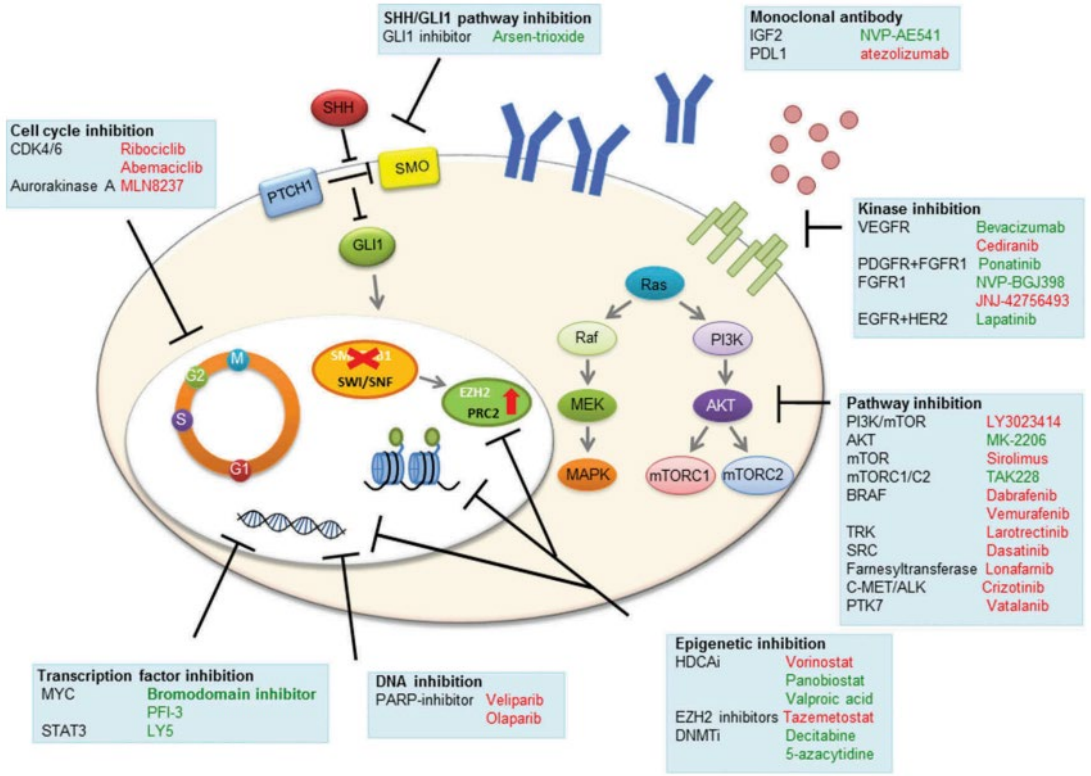
It/iv MTX

SIOPe ATRT 01:
Radiotherapy

< 12 months	**No RT (all stages)**
12 months to ≤ 35 months *ARM RT of Part A*	**Tumour bed only (all stages)**
	No residue: 54.0Gy, 1.8Gy/fraction
	With residue (MR2 or MR3): ± boost of 5.4Gy, 1.8Gy/fraction (cum. 59.4Gy)
	Craniospinal axis (all stages)
	Not done
>35 months	**Tumour bed (in M0 only)**
	No residue: 54.0Gy, 1.8Gy/fraction
	With residue (MR2 or MR3; optional): ± boost of 5.4Gy, 1.8Gy/fraction (cum. 59.4Gy)
	Craniospinal axis (in M1-3 only)
	36.0 Gy, 1.8 Gy /Fraction to CSA + tumour bed RT for the primary 18 Gy, 1.8Gy/fraction (cum 54 Gy) ± boost to primary residuum (optional; MR2 or MR3) 5.4Gy 1.8Gy/fraction (cum 59.4 Gy) ± boost to bulky residual mets (spine/cranial) up to 9-14.4 Gy, 1.8 Gy/fraction (cum. 45-50.4 Gy)

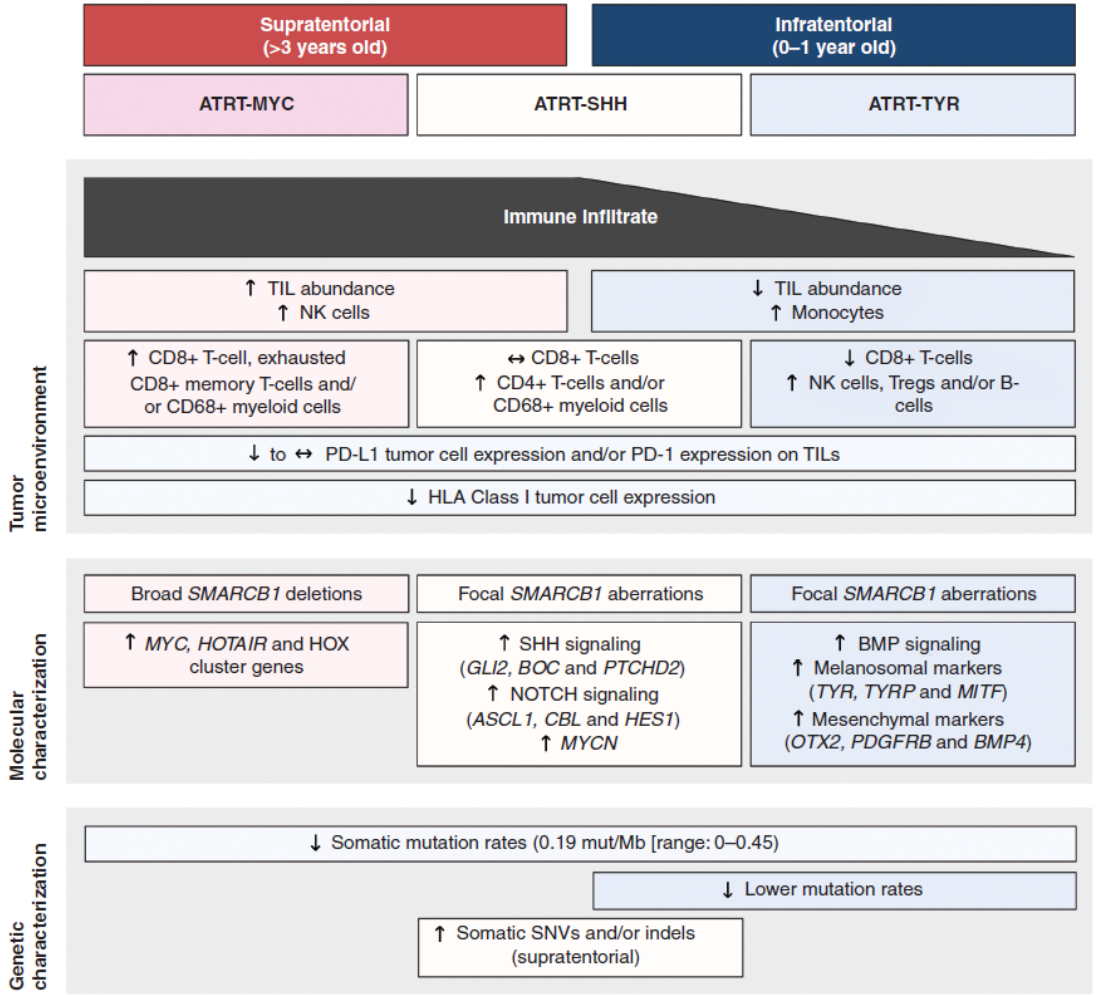
New perspectives: Epigenetic Dysregulation in ATRT





EXPERT OPINION ON THERAPEUTIC TARGETS, 2018
VOL. 22, NO. 4, 365–379

Immunologic Dysregulation in ATRT



322

Neuro-Oncology

10(4), 322–334, 2023 | https://doi.org/10.1093/nop/npad005 | Advance Access date 28 January 2023

Current advances in immunotherapy for atypical teratoid rhabdoid tumor (ATRT)

Conclusions

- Every day, we flip a new page and uncover thrilling twists and turns in AT/RT biology and genetics.
- ATRT is the Pandora's box of pediatric oncology. When we open it, we find not only challenges but also opportunities to rewrite the ending of this story.
- The more we study ATRT, the more we realize that it's a puzzle with missing pieces. But the map is far from complete, and the adventure continues.
- ATRT leaves us eagerly awaiting the next chapter in its story.

Thanks for your Attention

angela.mastronuzzi@opbg.net