New Opinion in the treatment of Childhood Rhabdomyosarcoma

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Background and epidemiology

- from primitive mesenchymal cells committed to skeletal muscle lineage
- found virtually anywhere
- including those sites where striated muscles are normally not found
- the most common soft tissue sarcoma in children and young adults
- 4 - 5 % of all childhood malignancies

Etiology

- remains unknown
- genetic factors may play an important role
- association between RMS and several germ-line genetic disorders such as
  - Li Fraumeni syndrome,
  - congenital anomalies (involving the genitourinary and central nervous system) and
  - other genetic conditions, including neurofibromatosis type 1 and DICER1 tumour predisposition syndrome

Classification

- Old:
- Since the first classification of RMS in 1958 by Horn and Enterline, multiple modifications to their classification have been made.
- There are four main subtypes of RMS, distinguished by histopathology: embryonal subtype (which accounts for approximately 80% of all RMS), alveolar subtype (15 - 20% of RMS) and the rarer pleomorphic and sclerosing/spindle cell RMS.

Classification

- historically classified based on histopathologic features:
  - embryonal RMS (ERMS)
  - alveolar RMS (ARMS)
  - pleomorphic
  - spindle cell and sclerosing RMS (ssRMS)
- ERMS represents most cases and is associated with a favorable prognosis,
- ARMS is more clinically aggressive due to a propensity for metastasis and recurrence

Classification

- Eighty percentage of ERMS tumors are characterized by a loss of heterozygosity at the 11p15 locus.
- spindle cell and sclerosing RMS is
  - a rare variant of RMS characterized by
  - recurring fusions of VGLL2 or NOCA2 and
  - has a favorable prognosis,
  - so, it is treated without the aggressive multimodal regimens used to treat ARMS and ERMS

Classification

- New: Three main classes have been identified:
- 1) Superior prognosis: including botryoid RMS and spindle cell or leiomyomatous RMS;
- 2) Intermediate prognosis: represented by embryonal RMS (eRMS);
- 3) Poor prognosis: including alveolar RMS (aRMS) and its variant solid alveolar.
- This classification system does not include the pleomorphic category, as this is very rarely seen in children, and requires a different approach

Classification

- The majority of ARMS ➔ a recurrent chromosomal translocation, t(2;13)(q35;q14) or t(1;13)(p36;q14).
- The 2;13 and 1;14 translocations encode for a chimeric transcription factor (TF), consisting of the N-terminal DNA binding domain of PAX3 or PAX7 fused to the C-terminal transactivation domain of FOXO1 Of all ARMS patients,
- ≈ 60% express PAX3-FOXO1, 20% express PAX7-FOXO1, 20% are fusion Neg.
- PAX7-FOXO1 has superior overall survival (82%) compared to with PAX3-FOXO1 (61%)
- The remaining 20% of fusion-negative ARMS tumors present a similar molecular profile and clinical outcome to the ERMS subtype.

Classification

- sub classification of RMS (presence or absence of a PAX3/7-FOXO1 fusion): Fusion-positive and fusion-negative RMS.
- the t(2;13) or t(1;13) translocation has a prognostic value with alveolar RMS fusion positive having a worse prognosis in comparison with those fusion negative.
- still not clear if the t(1;13) might be more favorable than the t(2;13).
- fusion status has a stronger impact on prognosis than histology.
- Therefore, in current treatment stratification fusion status replaces histology.
- Where fusion status is unknown, histology can be used

Classification

- The size of the tumor has a prognostic impact similar to that of other soft tissue sarcomas.
- More recently the patient’s age at diagnosis has been recognized as a predictor of survival, with the older children (> 10 years old) having the worse outcome.

Risk Groups

- Biology and pathology:
- We recommend patients to be stratified according to the fusion status, but if this would not be available then histology (favourable* vs unfavourable*) should be used
- Favourable = PAX3 or 7/FOXO1 negative
- Unfavourable = PAX3 or 7/FOXO1 positive
- *Favourable = all embryonal, spindle cells (not MYOD1 mutated), botryoid RMS
- *Unfavourable = all alveolar tumours (including the solid-alveolar variant)

Classification

- **Post-surgical stage:**
- According to the IRS grouping.
- Group I = primary complete resection
- Group II = microscopic residual or primary complete resection but node involvement (N1);
- Group III = macroscopic residual

Classification

- Site:
  - Favourable = orbit, GU non bladder prostate (i.e. paratesticular and vagina/uterus), GU Bladder prostate and head & neck non PM, biliary tract
  - Unfavourable = parameningeal, extremities, and “other site”

- Node stage
  - According to the TNM classification
  - N0 = no clinical or pathological node involvement
  - N1 = clinical or pathological nodal involvement

Classification

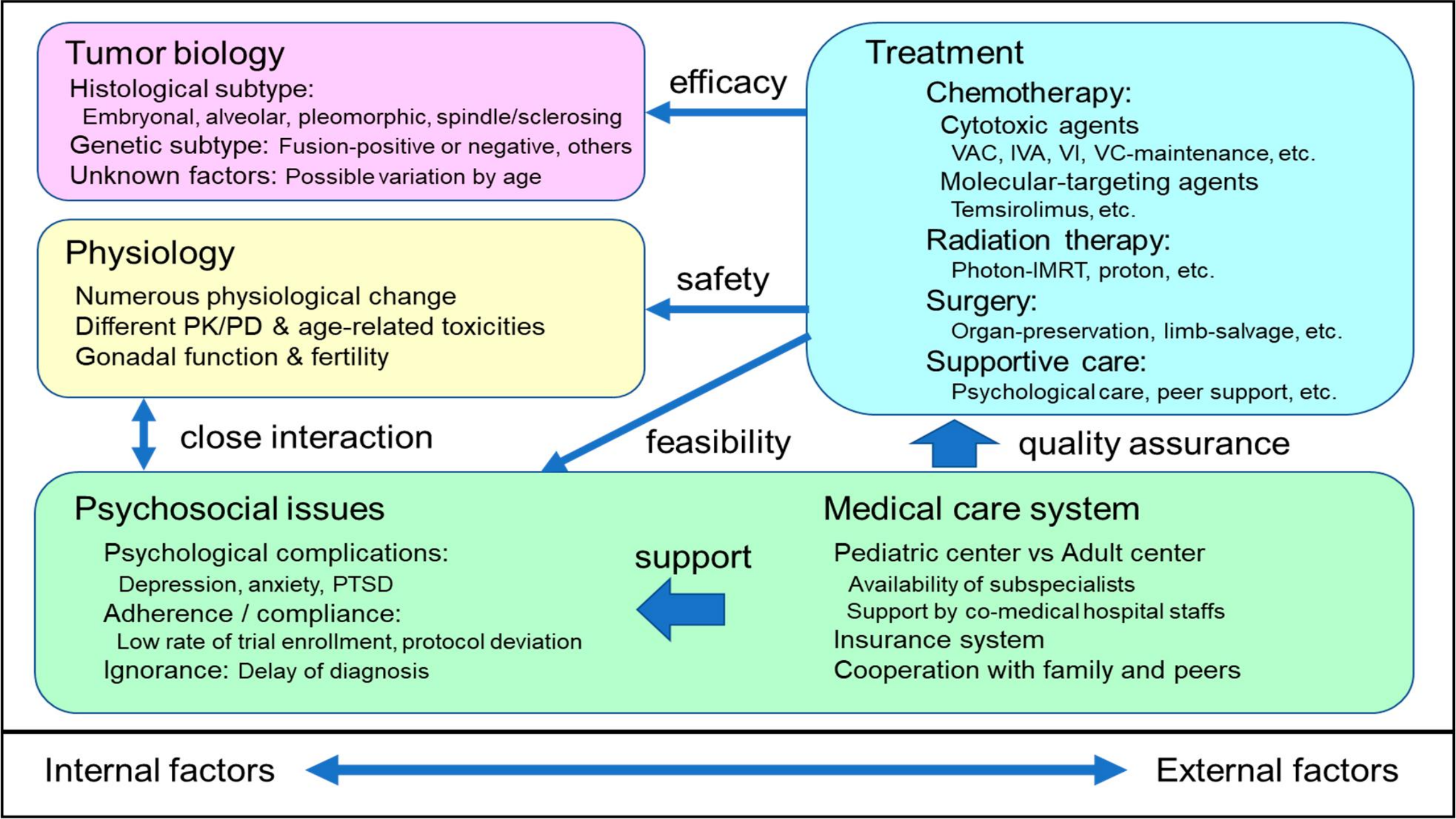
- Size & Age:
- Favourable = Tumour size (maximum dimension) <5 cm AND age < 10 years
- Unfavourable = all others (i.e. Size >5 cm OR age ≥ 10 years)
- **Note:** patients with malignant effusion (i.e. tumour cell in peritoneal or pleural fluid) or cells in the spinal fluid should be treated according to the protocol for metastatic RMS

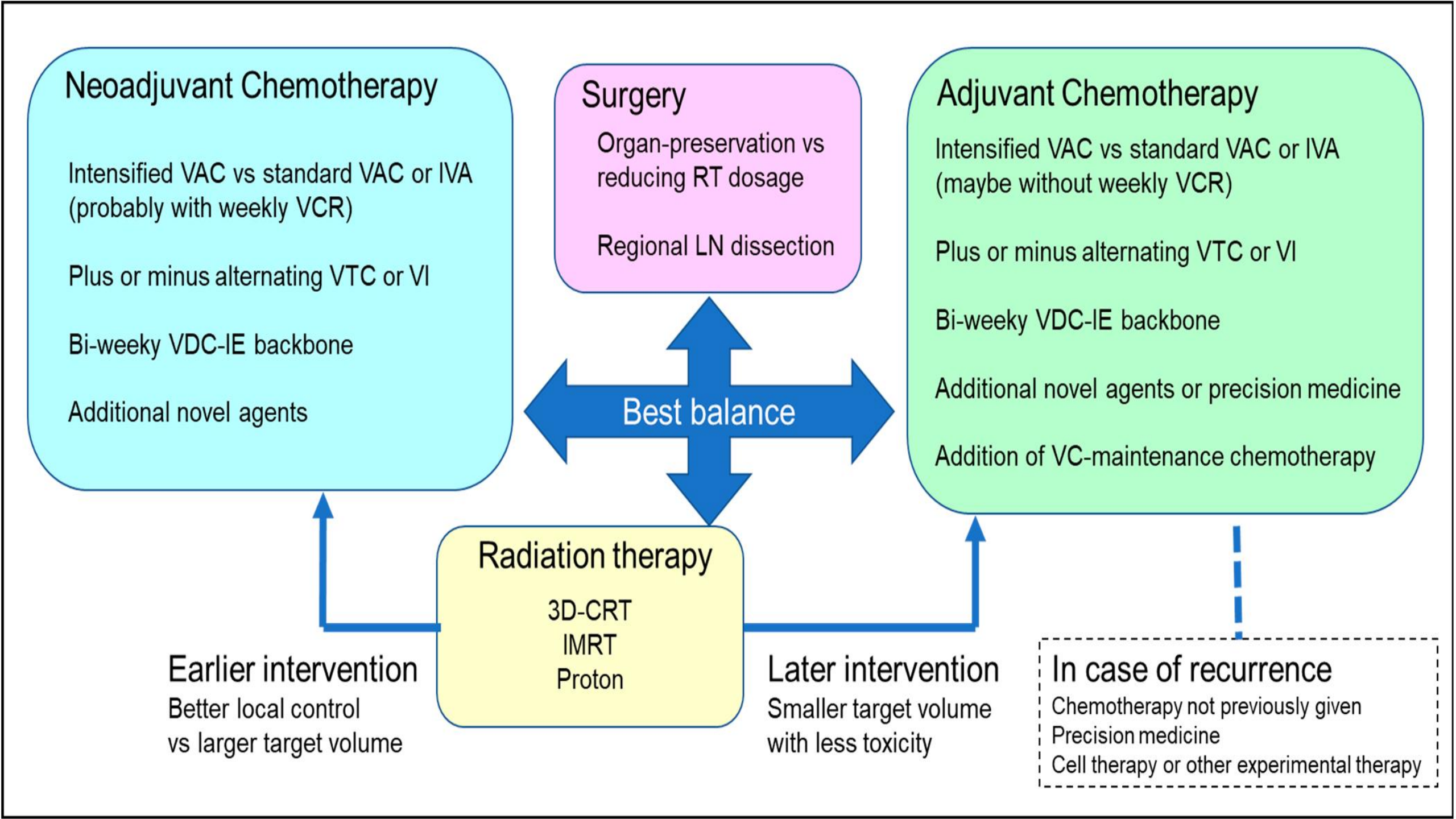
Risk Stratification for RMS

Risk Group	Subgroup	Fusion Status	IRS Group	Site	Node Stage	Size or Age
Low Risk	***A***	Negative	I	Any	N0	Both Favourable
Standard Risk	***B***	Negative	I	Any	N0	One or both Unfavourable
	C	Negative	II, III	Favourable	N0	Any
High Risk	***D***	Negative	II, III	Unfavourable	N0	Any
	E	Negative	II, III	Any	N1	Any
	F	Positive	I, II, III	Any	N0	Any
Very High Risk	***G***	Positive	II, III	Any	N1	Any
	H	Any	IV	Any	Any	Any

Treatment

- The current frontline treatment for all risk-groups of RMS is a multi-modal approach, comprising chemotherapy, surgical resection, and/or radiation therapy


Tumor biology
Histological subtype:
Embryonal, alveolar, pleomorphic, spindle/sclerosing
Genetic subtype: Fusion-positive or negative, others
Unknown factors: Possible variation by age
efficacy
Treatment
Chemotherapy:
Cytotoxic agents
VAC, IVA, VI, VC-maintenance, etc.
Molecular-targeting agents
Temsirolimus, etc.
Radiation therapy:
Photon-IMRT, proton, etc.
Surgery:
Organ-preservation, limb-salvage, etc.
Supportive care:
Psychological care, peer support, etc.
Physiology
Numerous physiological change
Different PK/PD & age-related toxicities
Gonadal function & fertility
safety
close interaction
feasibility
quality assurance
Psychosocial issues
Psychological complications:
Depression, anxiety, PTSD
Adherence / compliance:
Low rate of trial enrollment, protocol deviation
Ignorance: Delay of diagnosis
support
Medical care system
Pediatric center vs Adult center
Availability of subspecialists
Support by co-medical hospital staffs
Insurance system
Cooperation with family and peers
Internal factors
External factors


Neoadjuvant Chemotherapy
Intensified VAC vs standard VAC or IVA (probably with weekly VCR)
Plus or minus alternating VTC or VI
Bi-weeky VDC-IE backbone
Additional novel agents
Surgery
Organ-preservation vs reducing RT dosage
Regional LN dissection
Adjuvant Chemotherapy
Intensified VAC vs standard VAC or IVA (maybe without weekly VCR)
Plus or minus alternating VTC or VI
Bi-weeky VDC-IE backbone
Additional novel agents or precision medicine
Addition of VC-maintenance chemotherapy
Best balance
Radiation therapy
3D-CRT
IMRT
Proton
Earlier intervention
Better local control
vs larger target volume
Later intervention
Smaller target volume
with less toxicity
In case of recurrence
Chemotherapy not previously given
Precision medicine
Cell therapy or other experimental therapy

Chemotherapy regimens available for newly diagnosed RMS.

Regimen	Trial	Dosage (mg/m^2) and Schedule
VAC	IRS-IV	VCR 1.5 on days 1, 8, 15; ACD 0.015/kg on days 1–5; CPA 2200 on day1; every 3 weeks
VAC	D9802/ D9803	VCR 1.5 on days 1, 8, 15; ACD 1.5 on day 1; CPA 2200 on day1; every 3 weeks
VAC	ARST0531	VCR 1.5 on days 1, 8, 15; ACD 1.5 on day 1; CPA 1200 on day 1; every 3 weeks
VIE	IRS-IV	VCR 1.5 on days 1, 8, 15; IFM 1800 on days 1–5; ETP 100 on days 1–5; every 3 weeks
VAI	IRS-IV	VCR 1.5 on days 1, 8, 15; ACD 1.5 on day 1; IFM 1800 on days 1–5; every 3 weeks
VTC	D9803	VCR 1.5 on days 1, 8, 15; Topo 250 on days 1–5; CPA 250 on days 1–5; every 3 weeks
VI	ARST0431/ ARST0531	VCR 1.5 on days 1, 8, 15; IRI 50 on days 1–5; every 3 weeks
VDC	ARST0431	VCR 1.5 on days 1, 8, 15; DXR 37.5 on days 1, 2; CPA 1200 on day 1; every 2 weeks alternating with IE
IE	ARST0431	IFM 1800 on days 1–5; ETP 100 on days 1–5; every 2 weeks alternating with VDC
IVA	RMS2005	IFM 3000 on days 1–2; VCR 1.5 on days 1, 8, 15; ACD 1.5 on day 1; every 3 weeks
VC maintenance	RMS2005	VNR 25 on days 1, 8, 15; CPA (po) 25 daily; for 4 weeks cycles × 6 cycles

TREATMENT DETAILS-CHEMOTHERAPY

- **Low Risk Group (A)**
- Chemotherapy: VA x 8
- The total duration of chemotherapy is 22 weeks.
- After the initial complete resection, no further local treatment procedure should be required.
- If there is any doubt whatsoever about the completeness of resection, the patient should be allocated and treated in the Standard Risk Group.

Standard Risk

- subgroup B
  - 4 cycles of IVA followed by 5 courses VA
  - The total duration of chemotherapy is 25 weeks.
  - These patients are in complete remission after initial surgery therefore they will not receive further local treatment (no RT or second look surgery).
  - If there is any doubt whatsoever about the completeness of resection, and the tumour is at a favourable site, the patient should be allocated and treated in the Standard Risk Subgroup C;
  - if the tumour is at an unfavourable site, patient should be treated according to subgroup D.

Standard risk Subgroup C treatment

- Chemotherapy regimen depends on whether radiotherapy is given:
- 5 courses of Ifosfamide, Vincristine and Actinomycin (IVA) and 4 courses of Vincristine and Actinomycin (VA) + Ifosfamide when combined with radiotherapy.
- Local treatment will be administered at week 13

High risk patients (groups D, E and F)

- Chemotherapy:
  - Regimen: IVA
  - Duration: 22 wks
  - Maintenance: Vinorelbine / cyclophosphamide
  - Duration: 6 months

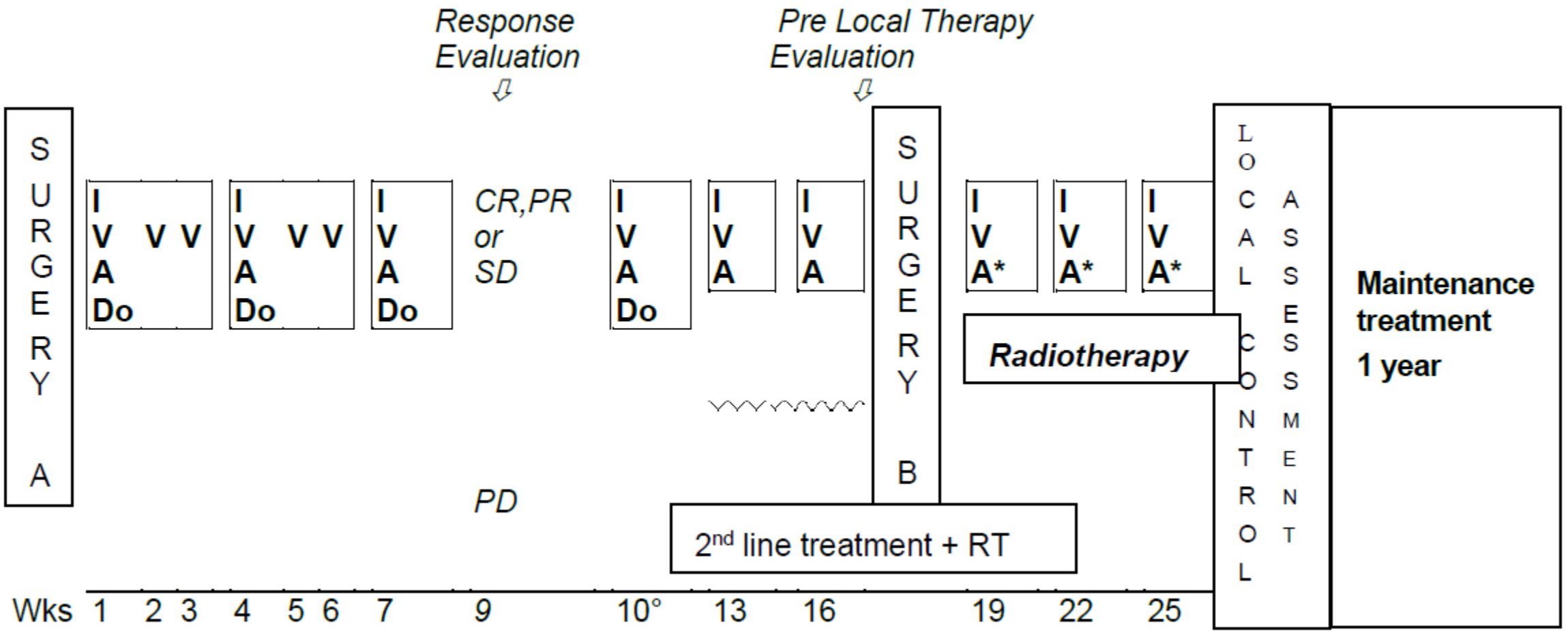
Very High-Risk Fusion positive/node positive patients (Subgroup G)

- Chemotherapy:
  - Regimen: IVADx4 + IVAx5
  - Duration: 25 wks
  - Maintenance: Vinorelbine / cyclophosphamide
  - Duration: 1 yr

Radiotherapy

- Indications:
- Radiotherapy to the site of the primary tumor is indicated for the HR and VHR Groups; and the majority of Standard Risk Subgroup C patients.
- Key exceptions which do not require radiotherapy are:
  - Localized fusion negative rhabdomyosarcoma with initial R0 resection (IRS Group I) i.e., subgroups A and B
  - Localized fusion negative rhabdomyosarcoma of the vagina achieving complete remission with induction chemotherapy
  - A highly selected group of patients with IRS Group III Standard Risk Subgroup C fusion negative RMS, arising at a favorable site, where secondary surgery achieves an R0 resection.

Metastatic RMS



Second line drugs for R/R RMS

- Liposomal Doxorubicin
- HD Ifosfamide
- Gemcitabine
- Temozolomide
- Irinotecan
- Topotecan
- Etoposide
- Docetaxel
- Ixabepilone
- Oxaliplatin
- Pemetrexed
- Trabectedin
- Vinorelbine
- Cyclophosphamide
- Amifostine
- Decitabine
- ICE
- Temsirolimus

Results

Three-year event-free survival (EFS) was 18,1% and predominantly determined by disease relapse. Survival depended on response to pre-transplant therapy (3y-EFS of patients in complete or very good partial response: 36,4%).

However, no patient with metastatic relapse could be rescued.

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Haploidentical hematopoietic stem cell transplantation as individual treatment option in pediatric patients with very high-risk sarcomas

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Targeted Therapy

- Targeted therapy for rhabdomyosarcoma (RMS) involves drugs that identify and attack specific cancer cells, aiming to reduce harm to healthy cells and improve treatment outcomes compared to chemotherapy alone.
- While still largely investigational, current research explores various targets, including those related to the IGF-1R pathway, mTOR inhibitors, Tyrosine Kinase Inhibitors, KDM4-blocking drugs, and ATR inhibitors. The most promising approach appears to be combination therapies, where targeted drugs are paired with each other or with chemotherapy to overcome resistance and enhance efficacy.

TARGETED THERAPY

- PAX-FOXO1
- Receptor Tyrosine Kinases
- Developmental Pathways
- Cell Cycle Regulators
- DNA Damage Response (DDR) Pathway
- Apoptosis Pathway

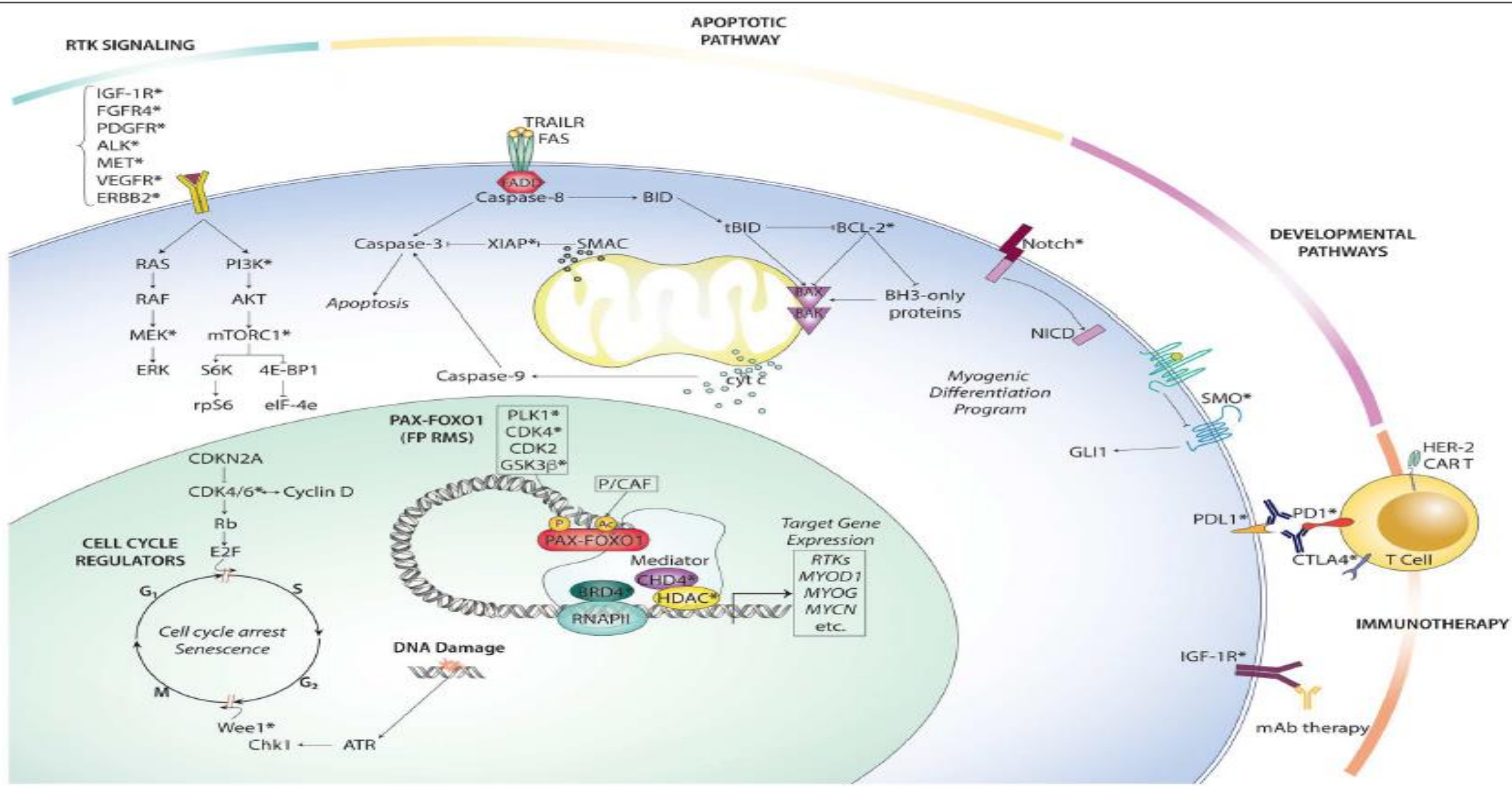


FIGURE 2 | Overview of rhabdomyosarcoma targeted therapies organized by pathway. Therapeutically actionable targets (at least one existing small molecule inhibitor or antibody) are indicated with an asterisk (*).

Current and Investigational Targets

- **Insulin-like Growth Factor 1 Receptor (IGF-1R) Inhibitors**:
  - One of the few single-agent targeted therapies with demonstrated clinical activity in RMS, although clinical effects are often short-lived and limited to a subset of patients.
- **mTOR Inhibitors**:
  - These drugs block a protein that helps cancer cells divide and survive; Sirolimus is an example being studied for recurrent RMS.
- **Tyrosine Kinase Inhibitors (TKIs)**:
  - These inhibitors block signaling pathways necessary for cancer cell growth, with examples like MK-1775, cabozantinib-s-malate, and palbociclib being investigated.

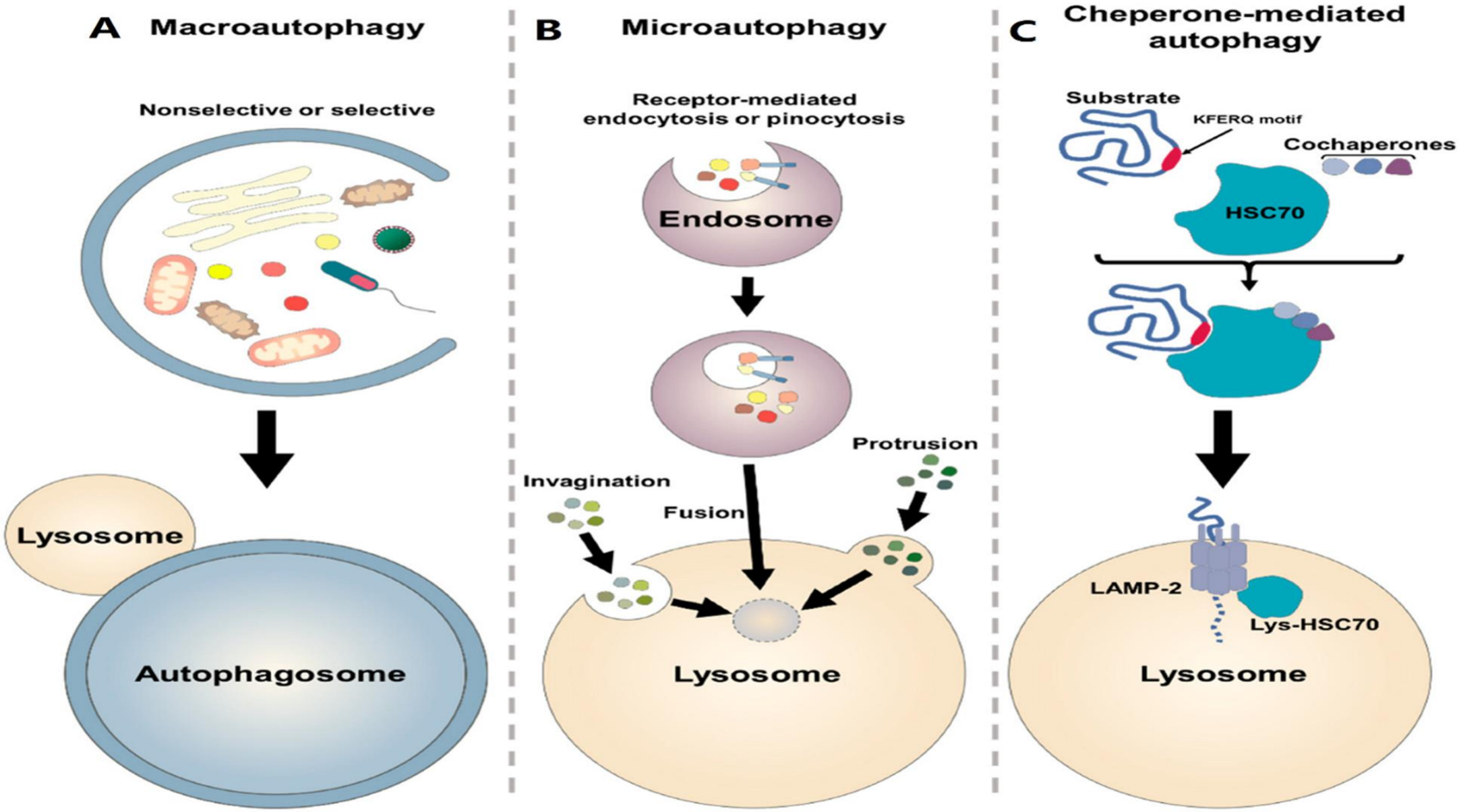
Current and Investigational Targets

- **KDM4-Blocking Drugs**:
  - Targeting the KDM4 enzyme has shown potential in preclinical models, with one drug, QC6352, being studied for its ability to suppress cancer growth.
- **ATR Inhibitors**:
  - Drugs like AZD6738 inhibit the ATR pathway, which is involved in DNA damage repair, and have demonstrated activity in rhabdomyosarcoma cell lines.

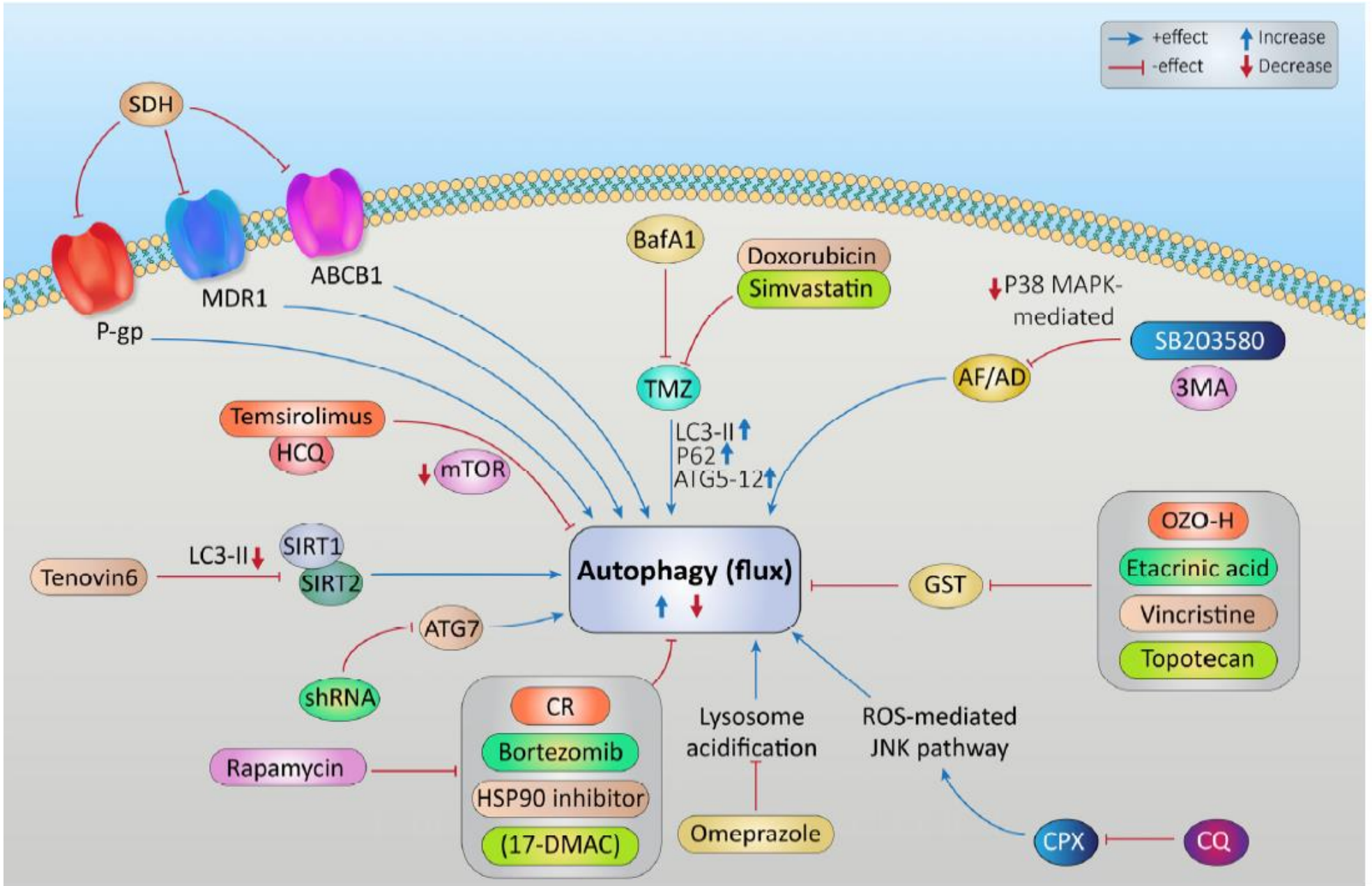
RMS targeted therapies and their clinical trial status

Treatment	Clinical Trial Phase
Pazopanib	II
Pazopanib or placebo	III
Sorafenib	II
Sorafenib	II
Crizotinib	II
Temsirolimus	II
Cixutumumab	II
Cixutumumab	II

Targeting Autophagy to Increase the Effectiveness of Chemotherapy in RMS



Autophagy targeting related to RMS



IMMUNOTHERAPY

- Targeting PAX-FOXO1 as a Tumor Antigen
- Monoclonal Antibodies
- CAR T-Cells
- EGFR-CAR NK cells
- Immune Checkpoint inhibitors

checkpoint inhibitors in rhabdomyosarcoma

- ipilimumab (anti-CTLA-4)
- Nivolumab (anti-PD-1) with or without ipilimumab (anti-CTLA-4)
- Atezolizumab (anti-PD-1) in combination with chemotherapy
- niraparib and dostarlimab (anti-PD-1)

antibody-based therapies in RMS

- Temozolomide, cixutumumab, and combination chemotherapy in treating patients with metastatic rhabdomyosarcoma
  - Neither agent improved outcome compared with the same chemotherapy
- Vinorelbine tartrate and cyclophosphamide in combination with bevacizumab or temsirolimus in treating patients with recurrent or refractory rhabdomyosarcoma
  - Patients who received temsirolimus had a superior EFS compared with bevacizumab. Temsirolimus has been selected for additional investigation in newly diagnosed patients with intermediate-risk RMS
- Enoblituzumab (MGA271) in children with B7-H3-expressing solid tumors
- CAB-AXL-ADC safety and efficacy study in adult and adolescent patients with sarcoma

adoptive NK cell therapy in RMS

- Phase II STIR Trial: Haploidentical transplant and donor natural killer cells for solid tumors (STIR)
- HLA-haploidentical bone marrow transplant preceded by reduced-intensity chemotherapy and radiation therapy, followed by donor NK cells on day +7 after transplant
- Overall survival of 64% and 40% at 1 and 2 years respectively

Clinical trials testing adoptive CAR-T cell therapy in RMS

- HER2 chimeric antigen receptor expressing T Cells in advanced sarcoma
  - Results:
  - One patient with metastatic RMS had CR
  - two other patients had SD
  - and three had PD
- HER2 chimeric antigen receptor (CAR) T cells in combination with checkpoint blockade in patients with advanced sarcoma (HEROS 3.0)
  - Result: No result posted

CAR-cytokine-induced killer (CIK) cells

- CAR CIK cells efficiently and specifically killed ERBB2-positive tumor cells.
- Recruiting study

Other novel trial study

- targeted thermosensitive liposomes therapy in RMS
- nanoparticles therapy in rhabdomyosarcoma

Conclusion

- Modern risk grouping according to Fusion status must use for management.
- New opinion in childhood rhabdomyosarcoma treatment focuses on
- reducing toxicity by modifying existing chemotherapy regimens
- and conserving radiotherapy for lower-risk patients
- maintenance treatment with vinorelbine and low-dose oral cyclophosphamide has improved overall survival
- It appears that Targeted / immunotherapy can be improved outcome in the future.


Thank you for your attention