



XLIX
CONGRESSO
NAZIONALE
AIEOP

Sarcoma di Ewing

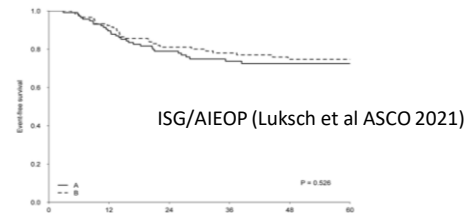
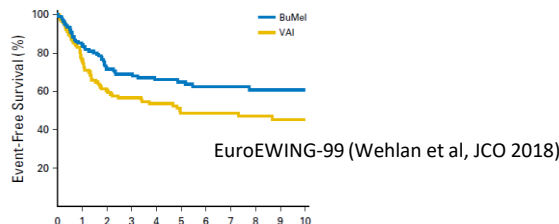
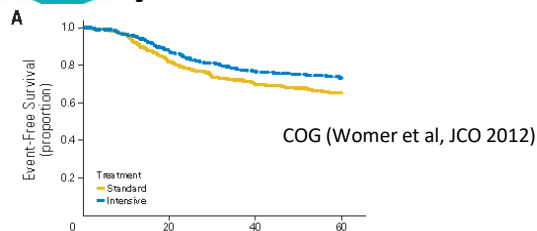
Malattia recidivata dopo prima linea di trattamento

Sebastian D. Asaftei

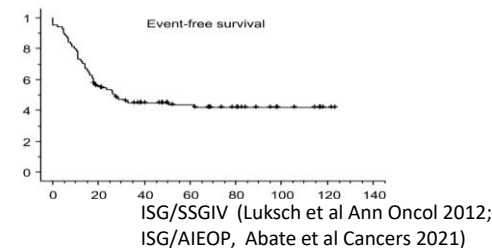
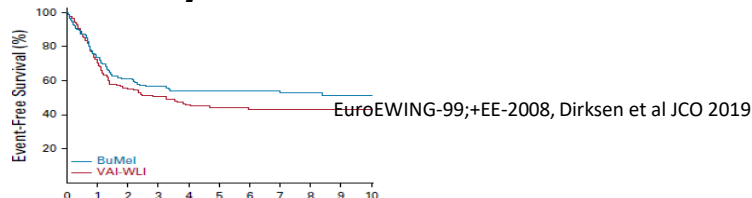
S.C Oncoematologia OIRM Torino

Bologna, 01 ottobre 2024

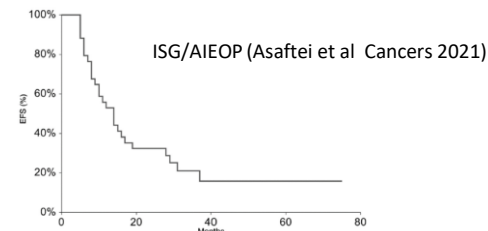
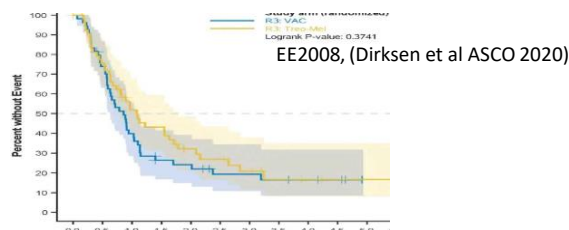
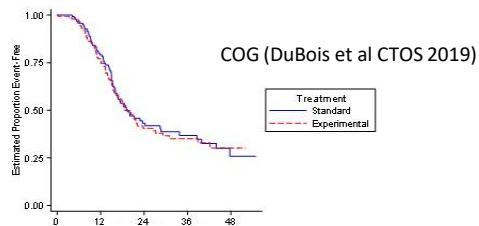
- **localizzati: 5-yrs EFS ~ 70%**

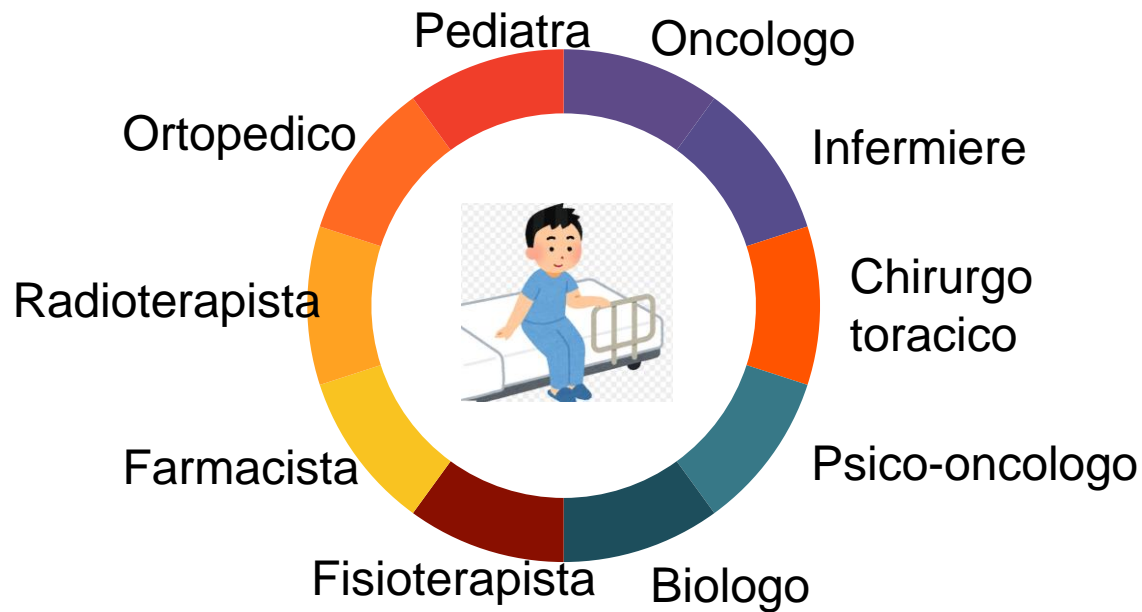


- **metastasi a pleura/polmoni 5-yrs EFS ~45%**



- **metastasi extrapolmonari 5-yrs EFS < 15%**





MULTIDISCIPLINARE



rEECCur

International Randomised Controlled Trial of
Chemotherapy for the Treatment of Recurrent
and Primary Refractory Ewing Sarcoma

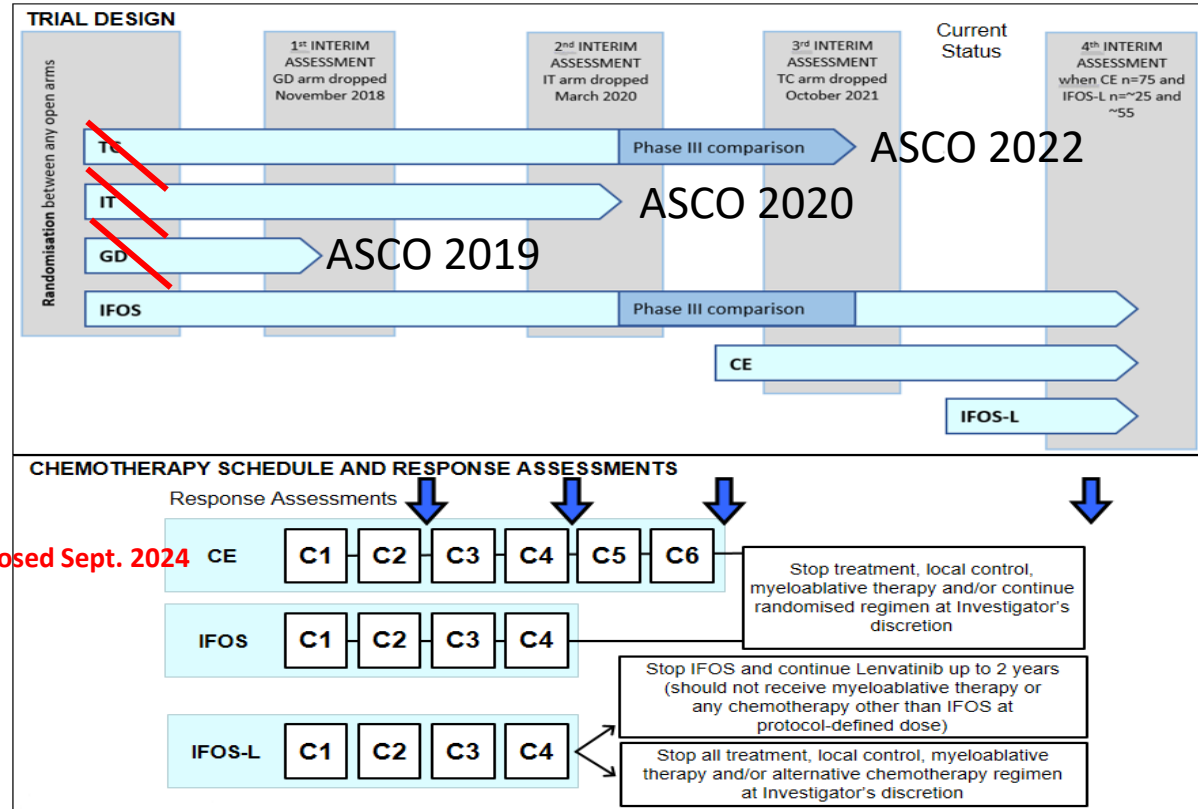
• Site	• Number of Patients enrolled
• IOR	• 38
• OPBG	• 15
• INT ped	• 14
• OIRM	• 10
• Meyer	• 3
• IFO	• 2
• Padova	• 2
• Santobono Pausillipon	• 2
• INT adults	• 1
• Total	• 87

• Country	• Number of Patients
• United Kingdom	• 167
• Spain	• 128
• Italy	• 87
• France	• 77
• Germany	• 40
• Australia	• 24
• Denmark	• 11
• Hungary	• 8
• Czech Republic	• 7
• Netherlands	• 6
• Switzerland	• 6
• Norway	• 5
• Belgium	• 4
• Finland	• 4
• New Zealand	• 2
• Poland	• 1
• Austria	• 1
• Total	• 578

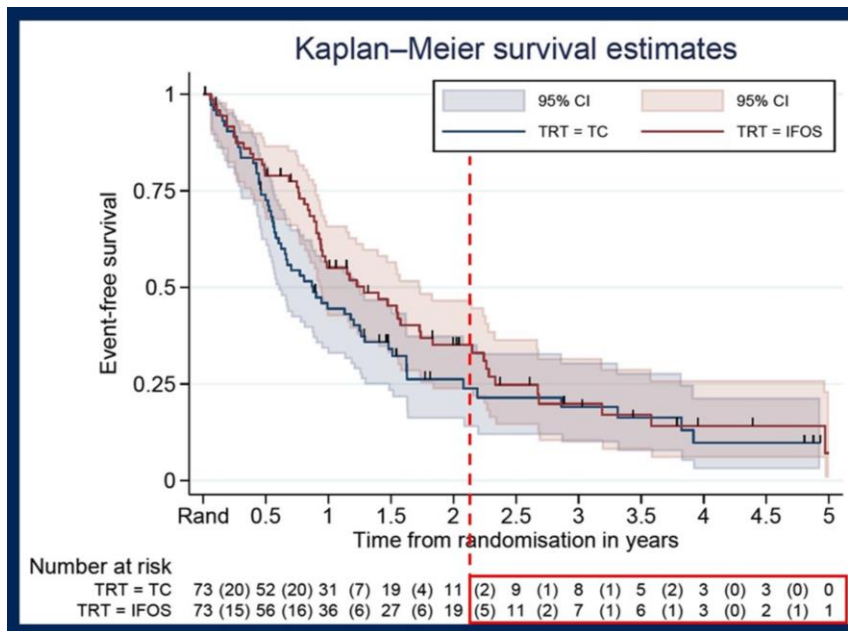


rEEC_{ur}

International Randomised Controlled Trial of
Chemotherapy for the Treatment of Recurrent
and Primary Refractory Ewing Sarcoma



rEECur trial – EFS by treatment group



Vital status	TC	IFOS	Overall
Alive	16 (22%)	20 (27%)	36 (25%)
Dead	57 (78%)	53 (73%)	110 (75%)
Total	73	73	146

Again, note small numbers beyond ~2 years

Median survival:

TC: 10.5 months (95% CI 7.2, 15.0)

IFOS: 15.4 months (95% CI 11.3, 20.9)

1-year OS:

TC: 45% (95% CI 33%, 56%)

IFOS: 55% (95% CI 43%, 66%)



Targeted therapy

Immune therapies

Combined therapies

Chemotherapy



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DOI: 10.1002/cam4.3712

ORIGINAL RESEARCH

Cancer Medicine WILEY

Systematic review of phase-I/II trials enrolling refractory and recurrent Ewing sarcoma: Actual knowledge and future directions to optimize the research

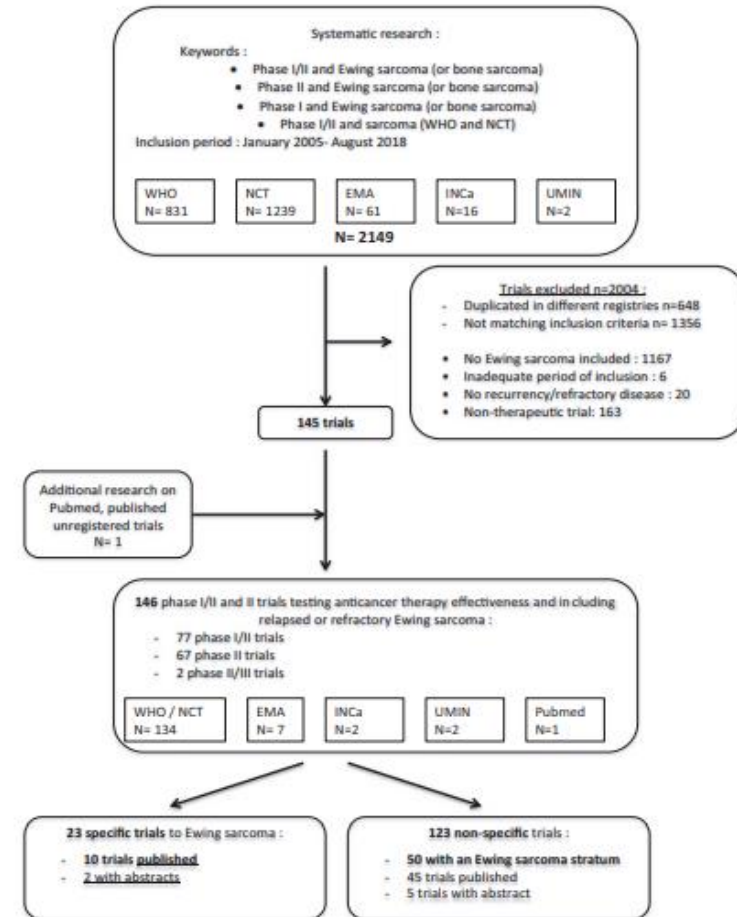
Arthur Felix¹ | Pablo Berlanga¹ | Maud Toulmonde² | Judith Landman-Parker³ | Sarah Dumont⁴ | Gilles Vassal¹ | Marie-Cécile Le Deley⁵ | Nathalie Gaspar¹

62 published trials enrolled 827 ES patients

targeted therapy (34%), chemo- (23%), immune therapies (19%), or combined therapies (24%)

10% RR (15 CR=1.7%, 68 PR=8.3%). Stable disease was the best response for 186 patients (25%)

Median PFS/OS was of 1.9 (range 1.3–14.7) and 7.6 months (5–30), respectively





Chemotherapy

Table 1. rEECur: pairwise comparisons of chemotherapy combinations in recurrent and refractory Ewing sarcoma^a

Chemotherapy comparison	Number in comparison	Number receiving each regimen	Hazard ratio for EFS (95% CrI)	Confidence	Comparison favours	Median EFS ^b
IT/TC	230	115/115	1.12 (0.84–1.48)	78%	TC	
IFOS/TC	146	73/73	0.69 (0.48–0.99)	98%	IFOS	IFOS 5.7 months (95% CI 3.8–6.9 months) vs. TC 3.5 months (95% CI 2.1–5.1 months)
GD/TC	125	65/60	1.60 (1.08 – 2.36)	>99%	TC	
GD/IT	117	58/59	1.40 (0.93–2.10)	95%	IT	
IFOS/IT	80	38/42	1.00 (0.61–1.63)	50%	–	
IFOS/GD	47	22/25	0.55 (0.28–1.07)	96%	IFOS	

Consensus recommendations for systemic therapies in the management of relapsed Ewing sarcoma: A report from the National Ewing Sarcoma Tumor Board

Chemotherapy

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Regimen	Agents	Schedule	Cycle length	GOCS ^a	Toxicity profile	Reference(s)	Design	No.	ORR	Partial response	Complete response	6-month PFS	TTP, months
IT/VIT 5 day	Irinotecan 50 mg/m ² /day IV	Days 1-5	21 days	No	N/V/D, less alopecia (unless vincristine used)	Raciborska 2013, ²³ Palmerini 2018 ²⁴	Retrospective, Retrospective	22, 51	55%, 34%	32%, 24%	23%, 10%	NR, 49%	3.0, 3.9
	or Irinotecan 90 mg/m ² /day PO												
	Temozolomide 100-150 PO mg/m ² /day	Days 1-5											
	Vincristine 1.5 mg/m ² /day IV	Day 1											
IT/VIT 10 day	Irinotecan 10-20 mg/m ² /day IV	Days 1-5, days 8-12	21 days	No	N/V/D, less alopecia (unless vincristine used)	Van Winkle 2005, ²⁵ Casey 2009 ²⁶	Prospective RCT, Retrospective	22, 20	55%, 63%	50%, 37%	5%, 26%	41%, ^a NR	4.3, 8.3
	or Irinotecan 35 mg/m ² /day PO (Wagner 2010 ²⁷)												
	Temozolomide 100-150 PO mg/m ² /day	Days 1-5											
	Vincristine 1.5 mg/m ² /day IV	Days 1, 8											
TC	Topotecan 0.75 mg/m ² /day	Days 1-5	21 days	Yes	Bone marrow suppression, N/V, alopecia	Hunold 2006 ²⁸	Retrospective	54	33%	33%	0%	NR	NR
	Cyclophosphamide 250 mg/m ² /day	Days 1-5											
IFOS	Ifosfamide 3 g/m ² /day IV	Days 1-5	21 days	Yes	Bone marrow suppression, N/V, alopecia, renal insufficiency	Ferrari 2009 ²⁹	Prospective single arm	35	34%	29%	6%	NR	NR
	Mesna 3 g/m ² /day IV	Days 1-5											
GD	Gemcitabine 675-900 mg/m ² /day IV	Days 1, 8	21 days	Yes	Bone marrow suppression, N/V, alopecia, neuropathy, edema	McCabe 2019 ³⁰	Prospective RCT	66	11.5%	NR	NR	NR	3
	Docetaxel 75-80 mg/m ² /day IV	Day 8											
	Dexamethasone 3 mg/m ² /day (up to 8 mg) PO/IV	Days 7-9											
ICE	Ifosfamide 1.8 g/m ² /day IV	Days 1-5	21 days	Yes	Bone marrow suppression, N/V, alopecia, renal insufficiency, ototoxicity	Van Winkle 2005 ²⁵	Prospective single-arm strata	22	48%	22%	29%	NR	NR
	Carboplatin 400 mg/m ² /day IV	Days 1, 2											
	Etoposide 100 mg/m ² /day IV	Days 1-5											



REVIEW

Targeted therapy



Emerging therapies in Ewing sarcoma

Sandra J. Strauss^a, Pablo Berlanga^b and Martin G. McCabe^c

Table 2. Single agent tyrosine kinase inhibitor trials in recurrent, relapsed, Ewing sarcoma

Tyrosine kinase inhibitor	Trial name	Age inclusion (years)	No. patients ^a	Media age, years (range)	RECIST 1.1 ORR, % (95% CI)	Median PFS, months (95% CI)
Cabozantinib	CABONE	>12	39	36 (23-45)	26 (13-42)	4.4 (3.7-5.6)
Regorafenib	REGOBONE	≥18	23	32 (18-59)	13 (NR) [placebo, 7 (NR)]	2.6 (1.1-5.3) [placebo 0.9 (0.8-1.7)]
Regorafenib	SARC024	≥18	30	32 (19-65)	10 (NR)	3.45 (1.7-3.7)



Targeted therapy

- Single agent tyrosine kinase inhibitors have demonstrated efficacy in relapsed Ewing sarcoma
- Needs assessment as combination and maintenance therapies

European Journal of Cancer 173 (2022) 71–90



Review

Paediatric Strategy Forum for medicinal product development of multi-targeted kinase inhibitors in bone sarcomas

ACCELERATE in collaboration with the European Medicines Agency with participation of the Food and Drug Administration

Andrew DJ. Pearson ^{a,*}, Nathalie Gaspar ^{b,1}, Katherine Janeway ^{c,1}, Quentin Campbell-Hewson ^{d,1}, Elizabeth R. Lawlor ^{e,f,1}, Chris Copland ^{a,g}, Dominik Karres ^h, Koen Norga ^{i,j,k}, Fawzi Benzaghoul ^l, Susan Weiner ^m, Brenda Weigel ⁿ, Aaron R. Weiss ^o, Sandra J. Strauss ^p, Malcolm Smith ^q, Bhuvana A. Setty ^r, Nita Seibel ^q, Nicole Scobie ^s, Alberto Pappo ^t,

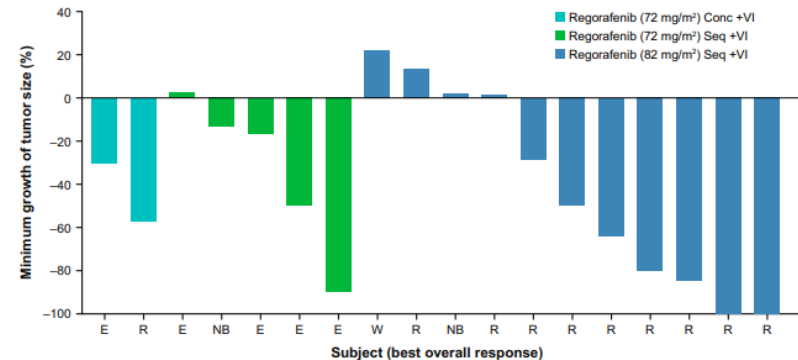
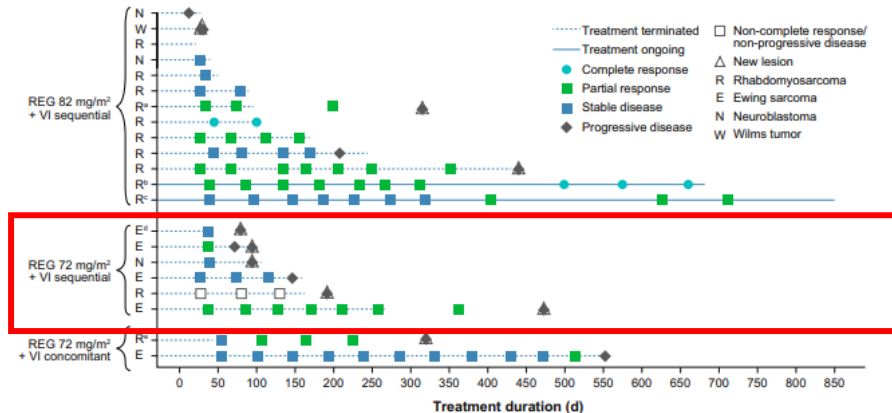
Product	pcKinases inhibited	PIP	WR	Planned paediatric clinical development in bone sarcoma
Aykavit [®] , avapritinib, Blueprint medicines	KIT/PDGFRα (highly selective and potent)	+	–	Phase 1/2, solid tumours dependent on KIT or PDGFRα signalling
Cabometyx [®] /Cometriq [®] , cabozantinib, Ipsen pharma/Exelixis	VEGFR2, MET and AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT3 and TIE-2	+	–	Monotherapy, combination and planned in front-line in osteosarcoma (COG)
Dovitinib, Oncoheroes/Allarity	FGFR, VEGFR, PDGFR and other RTKs.	–	=	Phase 1B-2 osteosarcoma (DRP [®] biomarker-driven)
Lenvima [®] /Kisplyx [®] , lenvatinib, Eisai GmbH	VEGFR1, VEGFR2, VEGFR3 and FGFR1, 2, 3 and 4, PDGFRα, KIT and RET	+	+	Monotherapy, combination (with chemotherapy and other targeted therapy) and randomised phase 2 (OLIE)
Nexavar [®] , sorafenib, Bayer	CRAF, BRAF and mutant BRAF and KIT, FLT-3, RET, RET/PTC, VEGFR1, VEGFR2, VEGFR3, PDGFR-β.	–	–	Phase 1 and 2 – limited activity in paediatric phase 1 and combinations studies which included osteosarcoma and Ewing (Completed)
Surufatinib, HUTCHMED	VEGFR1, 2, 3, FGFR1 and CSF-1	–	–	Phase 1/2 in osteosarcoma, Ewing, and soft tissue sarcoma in combination with gemcitabine
Stivarga [®] , regorafenib, Bayer	RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-α, PDGFR-β, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, Abl, and CSF-1	–+	–	Monotherapy, combination and planned in front-line in Ewing sarcoma (INTER EWING-1)
Votrient [®] , pazopanib, Novartis ^a	VEGFR1, VEGFR2, VEGFR3, PDGFRα and PDGFRβ; and c-K	+	–	Phase 2 single agent closed early due to lack of sufficient signal in Ewing and osteosarcoma [87]

Combined therapies

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Regorafenib plus Vincristine and Irinotecan in Pediatric Patients with Recurrent/Refractory Solid Tumors: An Innovative Therapy for Children with Cancer Study

Michela Casanova¹, Francisco Bautista², Quentin Campbell-Hewson³, Guy Makin⁴, Lynley V. Marshall⁵, Arnaud C. Verschuur⁶, Adela Cañete Nieto⁷, Nadège Corradini⁸, Bart A. Ploeger⁹, Barbara J. Brennan⁹, Udo Mueller¹⁰, Hong Zebger-Gong¹¹, John W. Chung¹², and Birgit Georger¹³





Combined therapies

DOI: 10.1002/pbc.30681

RESEARCH ARTICLE

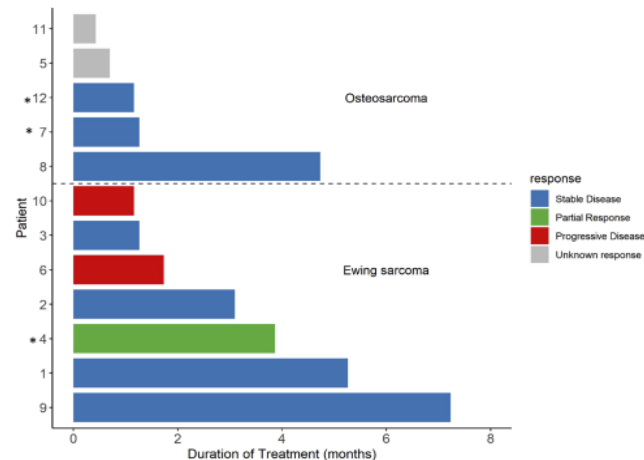
Pediatric
Blood &
Cancer

aspho
The American Society of
Pediatric Hematology/Oncology

WILEY

Phase 1 study of cabozantinib in combination with topotecan–cyclophosphamide for patients with relapsed Ewing sarcoma or osteosarcoma

Kevin Campbell¹ | Andrew Posner¹ | Nan Chen¹ | Kerri Cavanaugh¹ |
Ketki Bhushan¹ | Katherine A. Janeway¹ | David S. Shulman¹ | Suzanne George² |
Kelly Klega¹ | Brian Crompton¹ | Wendy B. London¹ | Steven G. DuBois¹





Combined therapies

REVIEW

Chemotherapy

Targeted therapy



Emerging therapies in Ewing sarcoma

Sandra J. Strauss^a, Pablo Berlanga^b and Martin G. McCabe^c

Tyrosine kinase inhibitors (TKIs)

Lenvatinib	ISRCTN36453794	rEECur – International Randomised Controlled Trial of Chemotherapy for the Treatment of Recurrent and Primary Refractory Ewing Sarcoma
Regorafenib	NCT05830084	Phase Ib Regorafenib With Conventional Chemotherapy/Newly Diagnosed Patients/Multimetastatic Ewing Sarcoma
Regorafenib	NCT04698785	Efficacy of Regorafenib Combined With Best Supportive Care as Maintenance Treatment in High Grade Bone Sarcomas Patients
Regorafenib	NCT04055220	Efficacy and Safety of Regorafenib as Maintenance Therapy After First-line Treatment in Patients With Bone Sarcomas.
Cabozantinib	NCT05182164	Combination of Pembrolizumab and Cabozantinib in Patients With Advanced Sarcomas (PEMBROCABOSARC)
Cabozantinib	NCT06156410	Cabozantinib With Ifosfamide in Ewing's Sarcoma and Osteosarcoma



Immunotherapy

CAR T-cell therapy trials

GD2 CART	NCT03635632	C7R-GD2.CART Cells for Patients With Relapsed or Refractory neuroblastoma and Other GD2 Positive Cancers (GAIL-N)
EGFR CAR T	NCT03618381	EGFR806 CAR T Cell Immunotherapy for Recurrent/Refractory Solid Tumors in Children and Young Adults
GD2 CAR T	NCT03373097	Anti-GD2 CAR T Cells in Pediatric Patients Affected by High Risk and/or Relapsed/Refractory Neuroblastoma or Other GD2-positive Solid Tumors

Role of immunotherapy in Ewing sarcoma

Immunotherapy

Erin Morales,¹ Michael Olson,² Fiorella Iglesias,¹ Saurabh Dahiya,³
Tim Luetkens,^{1,2,3,4} Djordje Atanackovic^{2,3,4}

Table 1 Clinical vaccination studies in Ewing sarcoma

Status	Phase	Type of vaccine	Antigen	Trial number
R	III	TC transfected with rhGM-CSF/RNAi bi-shRNAfurin+temozolimide	Autologous tumor cells	NCT03495921
C	I	DC+adjuvant	NY-ESO-1, MAGEA1, MAGEA3	NCT01241162
C	III	DC+autologous T cells	EWS/FLI-1	NCT00001566
C	I	TC transfected with rhGM-CSF/RNAi bi-shRNAfurin	Autologous tumor cells	NCT01061840
C	I	Antigen presenting cells (APC)+IL-2±autologous T cells	EWS/FLI-1	NCT00001564
C	I/II	DC+IL-7+autologous T cells	Tumor cell lysate	NCT00923351
C	I	DC+decitabine	NY-ESO-1, MAGEA1 and MAGEA3	NCT01241162
C	II	TC transfected with rhGM-CSF/RNAi bi-shRNAfurin+temozolimide	Autologous tumor cells	NCT01241162
C	I	Racotumomab anti-idiotypic antibody	–	NCT01598454
C	I	Peptide+adjuvant	MAGEA12	NCT00020267

C, completed; DC, dendritic cells; IL, interleukin; R, recruiting; rhGM-CSF, recombinant human granulocyte macrophage-colony stimulating factor; TC, tumor cells.

Peter Anderson et al,
Clin Cancer Res 2023



DNA damage, cell cycle and apoptosis

PARP +ATR inhibitor	NCT02813135	European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (ESMART): Arm N: Olaparib and Ceralasertib
CDK4/6	NCT03709680	Study of Palbociclib Combined With Chemotherapy in Pediatric Patients With Recurrent/Refractory Solid Tumors
CDK4/6	NCT05440786	CAMPFIRE: A Study of Abemaciclib (LY2835219) in Participants With Ewing's Sarcoma
DR5 agonist	NCT03715933	The Tetravalent Death Receptor 5 Agonist Inhibrox-109 combined with chemotherapy in Ewing sarcoma



Take home message

- the need to develop the international randomized phase I-II-III trials
 - early dialogue between academia, industry, regulators, and patient advocates is essential
 - evaluating feasibility of combination strategies and then undertaking a randomised trial in the same protocol accelerates drug development
 - biological differences – impacting management
 - chemotherapy – tolerance and response
- } across all age ranges



Ciao Massimo!



GRAZIE!!!

Dott. S. D. Asaftei

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