Terapie innovative

Michela Casanova

Fondazione IRCCS Istituto Nazionale dei Tumori

Bologna, 4 ottobre 2023

XLVIII CONGRESSO NAZIONALE AIEOP

Bologna
2-4 Ottobre 2023

la sottoscritta Michela Casanova

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

dichiara

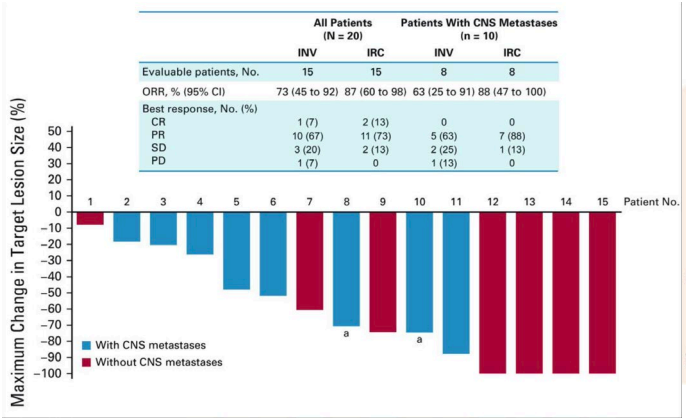
che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

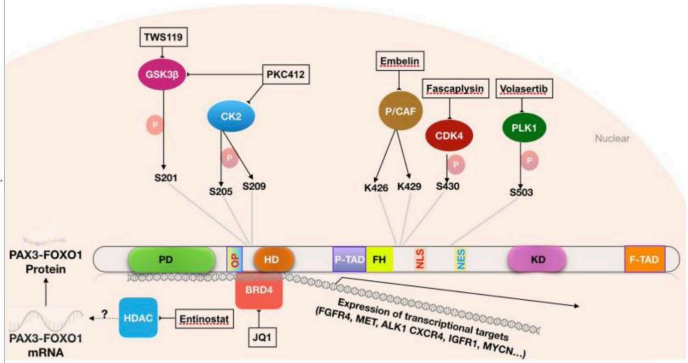
- *Astra-Zeneca*
- *Bayer*
- *Pfizer*

Innovative therapies for paediatric soft tissue sarcomas

Novel targets for therapy?

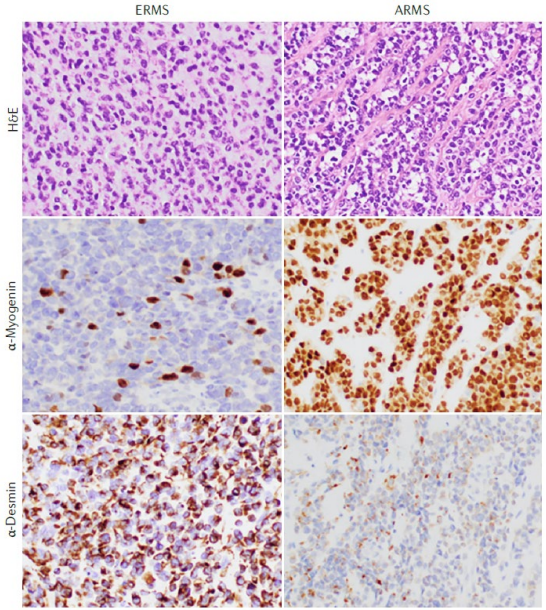
	All Patients (N = 20)		Patients With CNS Metastases (n = 10)	
	INV	IRC	INV	IRC
Evaluable patients, No.	15	15	8	8
ORR, % (95% CI)	73 (45 to 92)	87 (60 to 98)	63 (25 to 91)	88 (47 to 100)
Best response, No. (%)				
CR	1 (7)	2 (13)	0	0
PR	10 (67)	11 (73)	5 (63)	7 (88)
SD	3 (20)	2 (13)	2 (25)	1 (13)
PD	1 (7)	0	1 (13)	0

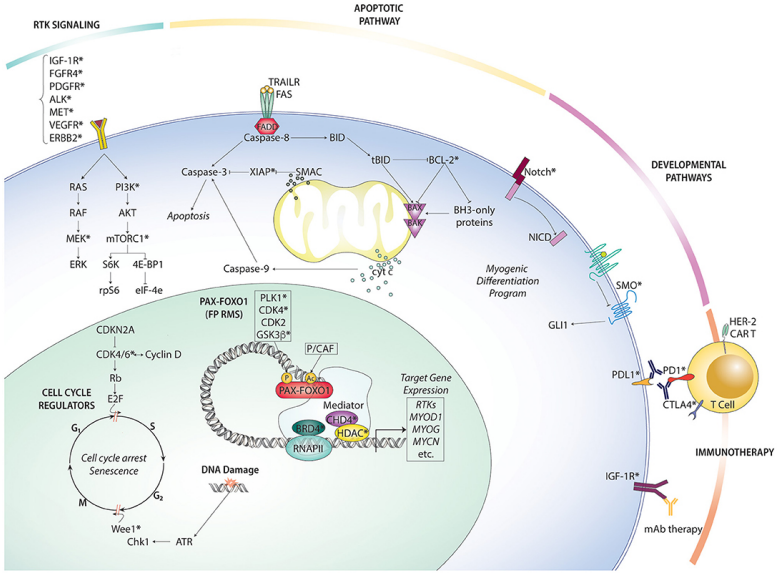




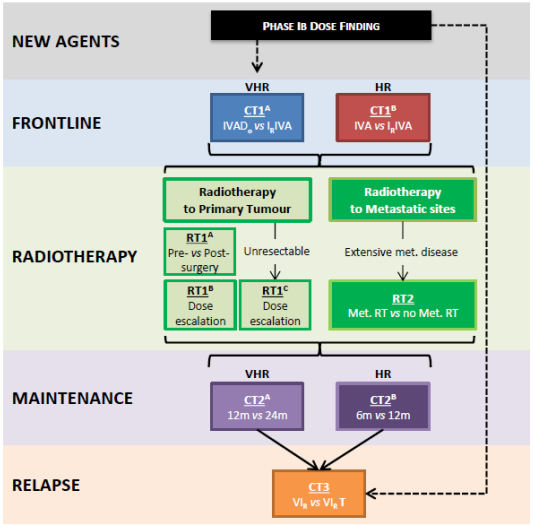
Simple vs complex drivers of disease
=
Simple vs complex (combination) therapy

Rhabdomyosarcoma (RMS)





FaR-RMS

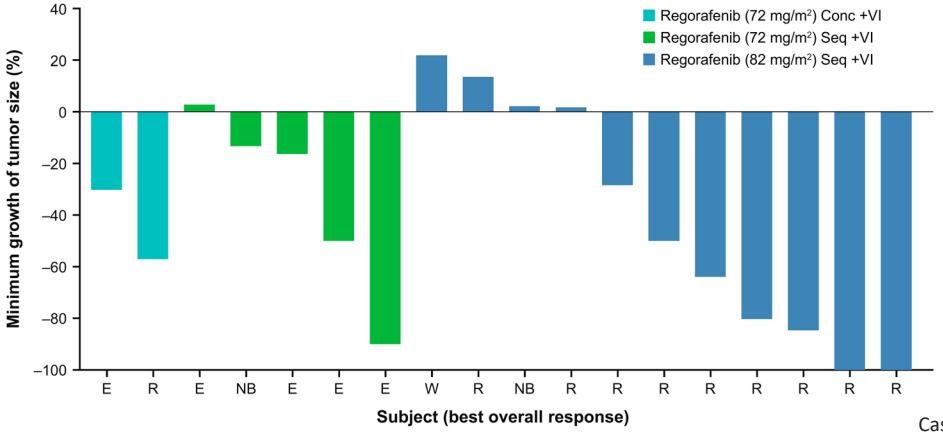


Studying novel agents in the FaR-RMS study can be part of a PIP

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

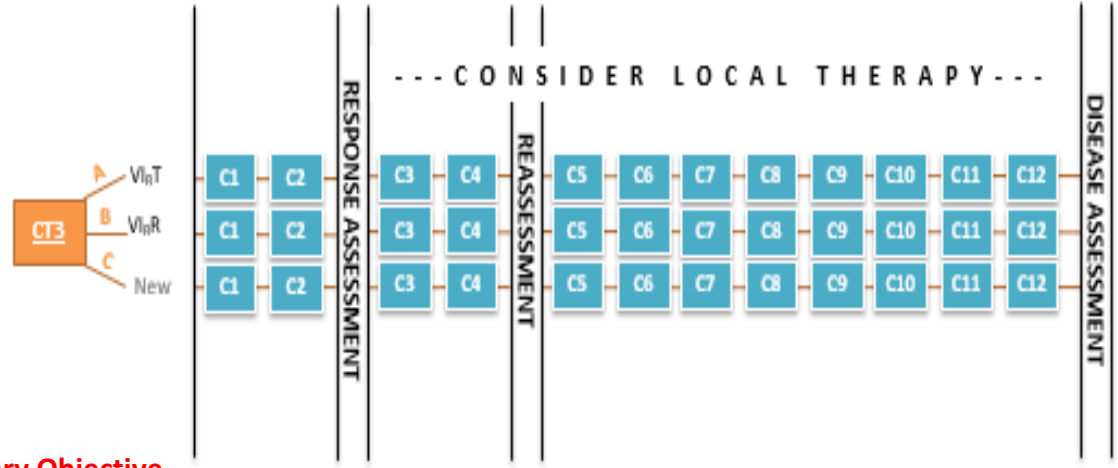
Regorafenib plus Vincristine and Irinotecan in Pediatric Patients with Recurrent/Refractory Solid Tumors: An Innovative Therapy for Children with Cancer Study

Michela Casanova[1], Francisco Bautista[2], Quentin Campbell-Hewson[3], Guy Makin[4], Lynley V. Marshall[5], Arnauld C. Verschuur[6], Adela Cañete Nieto[7], Nadège Corradini[8], Bart A. Ploeger[9], Barbara J. Brennan[9], Udo Mueller[10], Hong Zebger-Gong[11], John W. Chung[12], and Birgit Geoerger[13]



Casanova M, et al. Clin Cancer Res 2023:CCR-23-0257

FaR-RMS Relapse: VI_R + Rego



Primary Objective

- **To determine whether new systemic therapy regimens improve event-free survival (EFS)**
- **The first new regimen to be tested is regorafenib added to vincristine and irinotecan**

Biomarker Analysis

- **Imaging biomarkers**
  DWI MRI

- **Molecular biomarkers work from FFPE tissue**
  mRNA seq: signature and customized analysis of genes of interest
  WES for mutation analysis (panel 500 if insufficient DNA)
  RNA fusion panel for fusion detection
  Germline WES from whole blood

- **Molecular biomarkers work from plasma**
  including breakpoint analysis from FFPE DNA
  ct DNA analysis

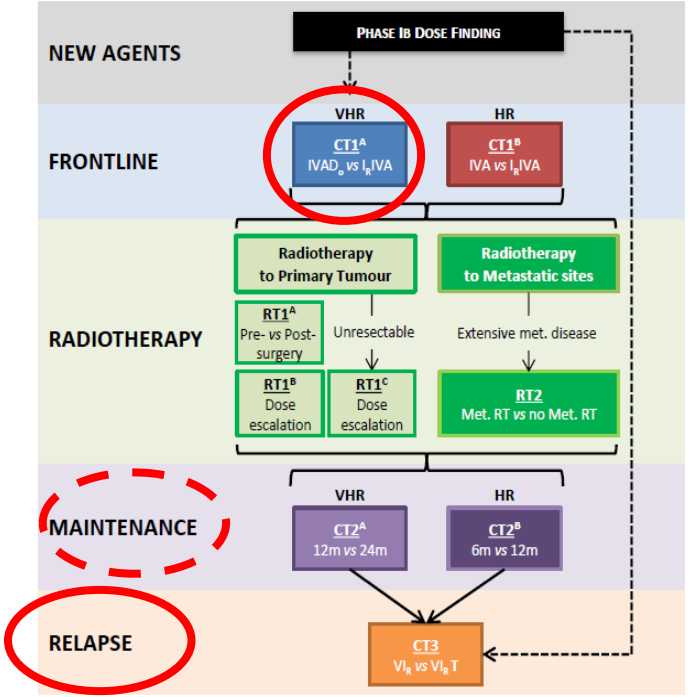
FaR-RMS

FaR-RMS platform trial is a great opportunity to introduce new drugs and ask new questions – biology alongside will be essential

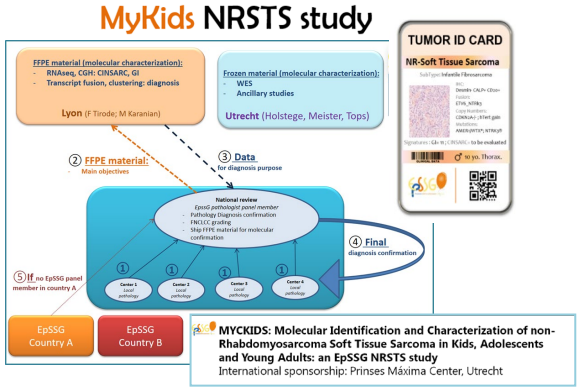
- **Key priority:**

New arm for metastatic patients (Very high risk RMS) in the upfront setting

- Other possibilities (can be developed in parallel):
  - 1st relapse (Phase II/III)
  - Subsequent relapse (Phase Ib)
  - Maintenance



Molecular characterisation possibilities for NRSTS tumours



Other molecular characterisation initiatives at frontline

GEL (NHS)
MICADO (France)
ACCELERATE CRUK grant (adult STS)
etc

REACH

(**RE**gorafenib in young adults, **A**dolescents and **C**hildren with **H**igh-risk non-rhabdomyosarcoma soft tissue sarcoma)

REACH-NRST

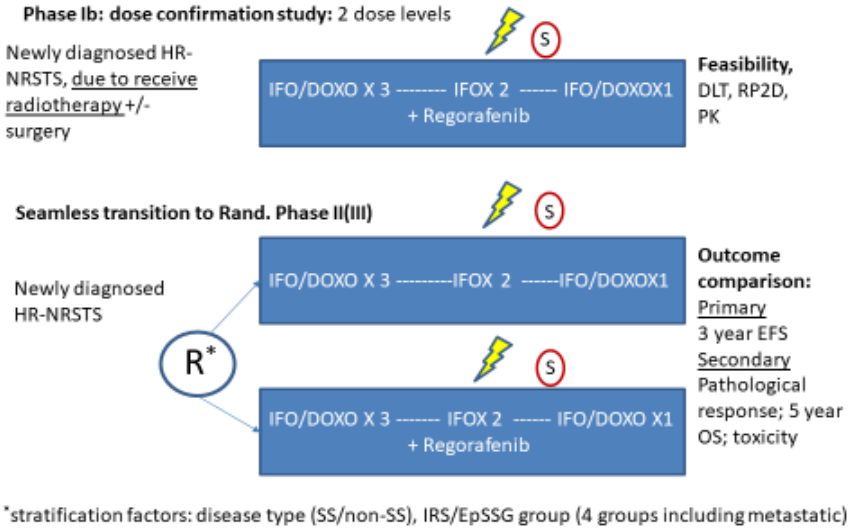
(**RE**gorafenib in young adults, **A**dolescents and **C**hildren with **H**igh-risk non-rhabdomyosarcoma soft tissue sarcoma)

Design (preliminary)

- Overarching design: seamless design from phase I-II (III)
- Upper age limit < 25 years (or consider adults with selected histotypes?)
- Eligibility:
  - Phase I only patients receiving RT
  - Phase II/III, also IRS I > 5cm SS/ any adult type not receiving RT
- Number of cycles: depending on risk group, 4 cycles, 6 cycles or 7 cycles

- **Comprehensive biomarker package planned**

Dose level (DL)	Chemotherapy, 1 cycle 3 weeks	Regorafenib (2 out of 3 weeks not overlapping with chemotherapy)
DL1	100%	82 mg/m2
DL0	100%	72 mg/m2



Fusion-driven Pediatric Sarcomas

- Fusion oncoproteins common in pediatric sarcomas:
  early molecular alterations at a clonal level (generally observed in cancers with low mutation burden)

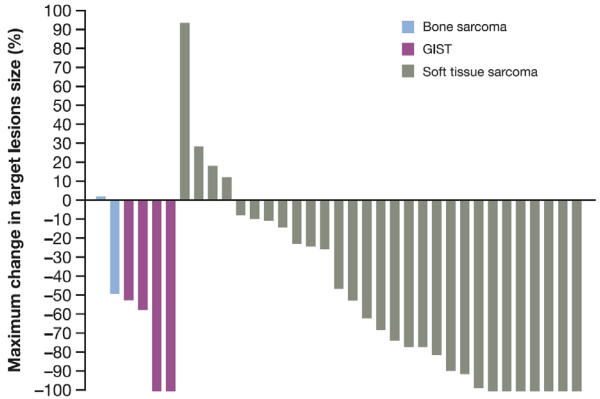
- Fusion is initiating event and is required for tumor maintenance

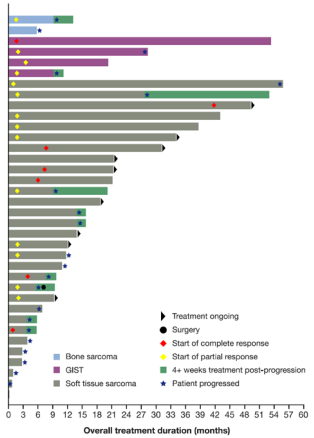
- Fusion can involve a kinase (ALK, NTRK, RET, ROS1), transcription factor (EWS/FLI, PAX/FOXO1) or chromatin regulator (BRD4/NUT, BCOR/CCNB3)

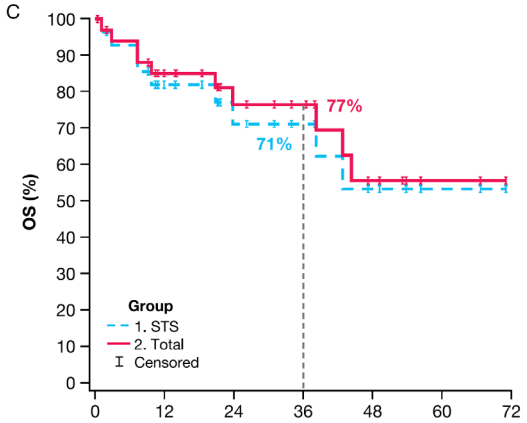
ORIGINAL ARTICLE

Larotrectinib efficacy and safety in adult patients with tropomyosin receptor kinase fusion sarcomas

Shivaani Kummar MD, FACP[1] | Lin Shen MD[2] | David S. Hong MD[3] | Ray McDermott MD, PhD[4] | Vicki L. Keedy MD[5] | Michela Casanova MD[6] | George D. Demetri MD[7] | Afshin Dowlati MD[8] | Soledad Gallego Melcón MD, PhD[9] |







Kummar S, et al Cancer 2023 Sep 28. doi: 10.1002/cncr.35036

2023 ASCO ANNUAL MEETING

Phase 2 study of larotrectinib in children with newly diagnosed infantile fibrosarcoma: COG ADVL1823 cohort A

Theodore W Laetsch, Kathleen Ludwig, David Hall, Donald A Barkauskas, Stephan Voss, Steven G. DuBois, Joan Ronan, Erin R. Rudzinski, Amanda Memken, Krystal Robinson, Joel Sorger, Joel M. Reid, Teena Bhatla, Brian Crompton, Alanna Church, Elizabeth Fox, and Brenda J. Weigel

CHILDREN'S ONCOLOGY GROUP

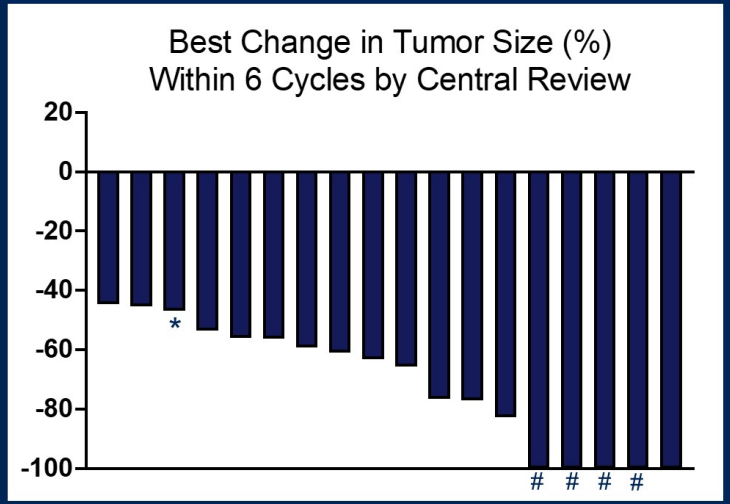
Presented by: Theodore W Laetsch, MD
Children's Hospital of Philadelphia

94% Overall Response Rate within First 6 Cycles

Confirmed Response By Central Review	N=18
Overall Response Rate	17 (94%)
Complete Response	1 (6%)
Partial Response	16 (89%)
Non-responder*	1 (6%)
Progressive Disease	0

* Patient with 47% tumor reduction after cycle 2 by central review (79% by investigator), but no confirmatory scan obtained within 6 cycles

Partial responder (complete response was not confirmed within 6 cycles)

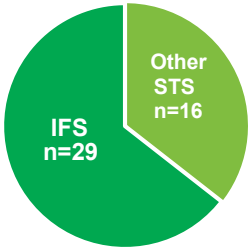


Discontinuation of larotrectinib prior to disease progression in pediatric sarcoma: Updated analysis from SCOUT trial

Pediatric phase 1/2 trial (SCOUT, NCT02637687)
- Aged ≤21 years
- Advanced solid tumors

Post-hoc analysis
- TRK fusion sarcoma
- Discontinued larotrectinib for at least 28 days in the absence of on-treatment PD
- TRK fusion status determined primarily by local CLIA-accredited (or similar) laboratories

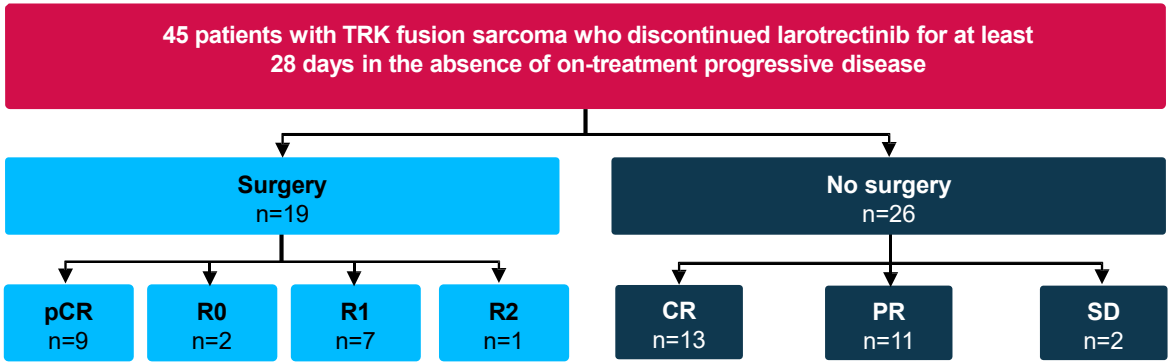
N=45



Laetsch TW, et al. Oral presentation at CTOS 2022: Abstract 25

Tumor status at time of discontinuation

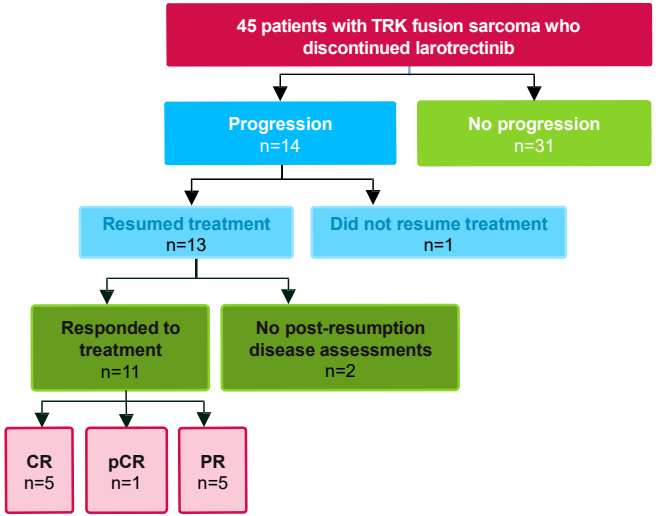
- Median time (range) to larotrectinib discontinuation was 10.3 months (3.0–28.6) in all patients and 16.8 months (4.4–28.6) in patients with no surgery
- In patients with IFS (n=29) and STS (n=16), median time (range) to discontinuation was 11.1 months (3.7–28.6) and 8.6 months (3.0–25.6), respectively



Laetsch TW, et al. Oral presentation at CTOS 2022: Abstract 25

Conclusions on discontinuation

- **14 of the 45 patients (31%) with TRK fusion sarcoma who discontinued larotrectinib without evidence of disease progression had subsequent progression**
- **Objective responses were achieved by all patients with post-resumption disease assessments (n=11)**
- **Treatment discontinuation may be feasible in carefully selected patients**
- **Longer follow-up is necessary to track the durability of the progression-free interval, and additional patients are needed to confirm these findings**

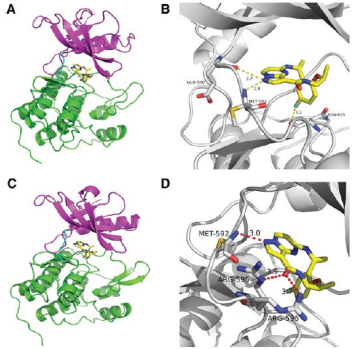


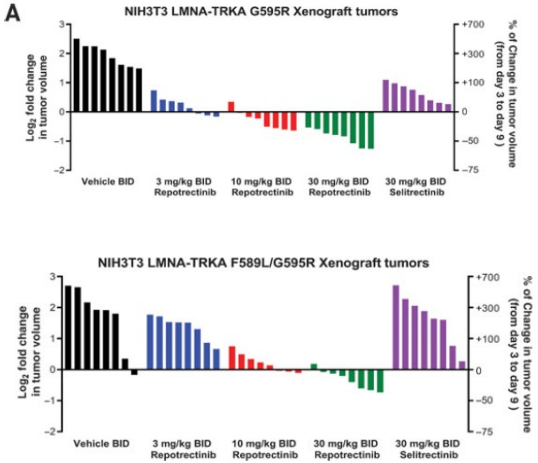
Laetsch TW, et al. Oral presentation at CTOS 2022: Abstract 25

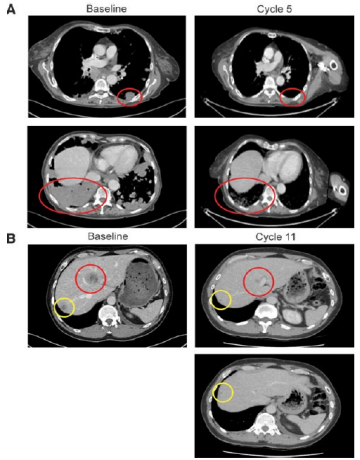
MOLECULAR CANCER THERAPEUTICS | SMALL MOLECULE THERAPEUTICS

Molecular Characteristics of Repotrectinib That Enable Potent Inhibition of TRK Fusion Proteins and Resistant Mutations

Brion W. Murray[1], Evan Rogers[1], Dayong Zhai[1], Wei Deng[1], Xi Chen[2], Paul A. Sprengeler[1], Xin Zhang[1], Armin Graber[1], Siegfried H. Reich[1], Shanna Stopatschinskaja[1], Benjamin Solomon[3], Benjamin Besse[4], and Alexander Drilon[5]



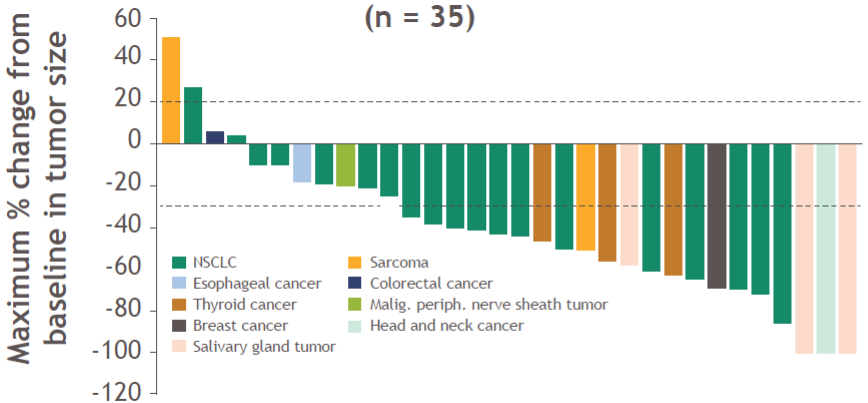


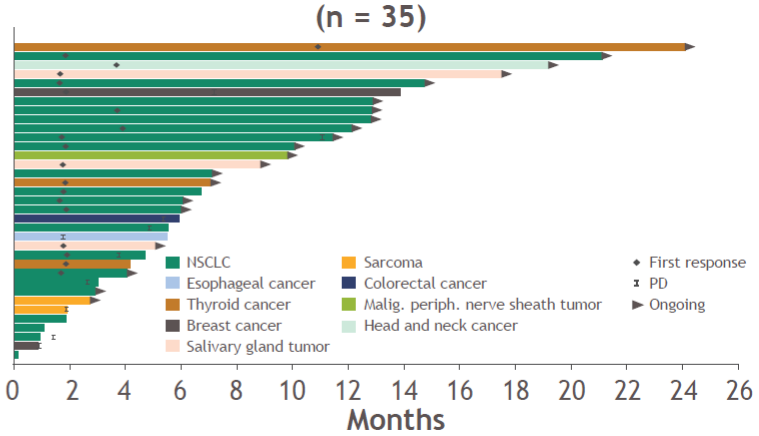


Repotrectinib Efficacy (TRK TKI-naive)

TRK TKI-naive (n = 35)	
ORR per investigator[a,b], % (95% CI) CR, n (%) PR, n (%)	54 (36.6–71.2) 2 (5.7) 17 (48.6)
CBR per investigator[c], % (95% CI)	82.9 (66.4–93.4)
Duration of response, range, mo	1.87-17.64+
Median time to response, mo (range)	1.8 (1.6–10.9)

TRK TKI-naive (n = 35)	
Median duration of treatment, mo (range)	6.1 (0.1–24.1+)
Patients remaining on treatment, n (%)	21 (60)



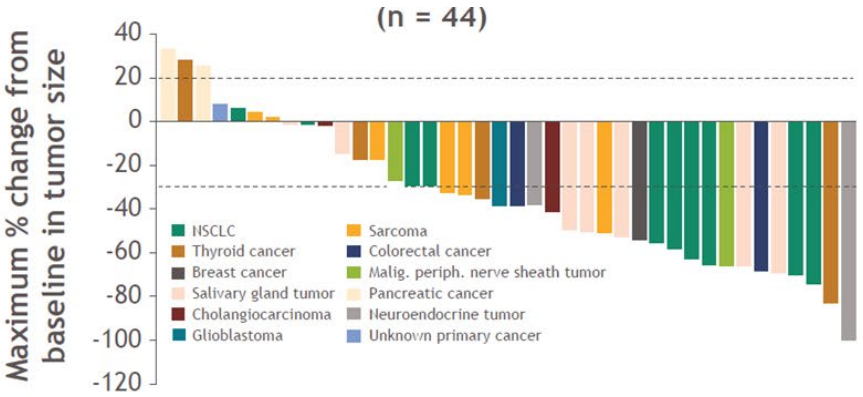


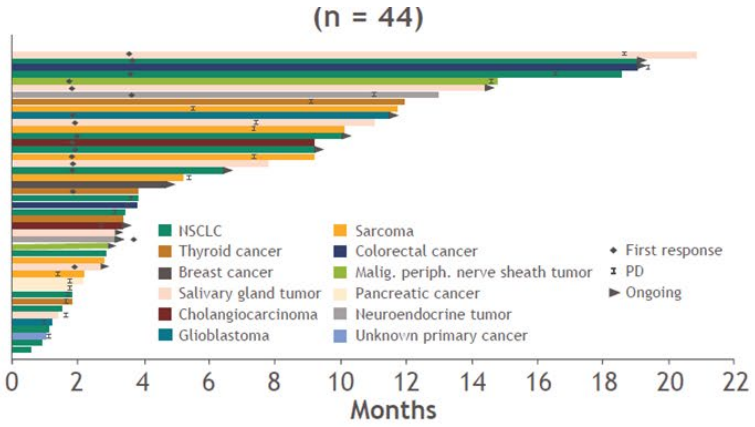
Besse B et al. Poster presentation at the EORTC-NCI-AACR (ENA) Symposium; October 26–28, 2022; Barcelona, Spain. Abstract 209.

Repotrectinib Efficacy (TKI-pretreated)

TRK TKI-pretreated (n = 44)	
ORR per investigator[a,b], % (95% CI) CR, n (%) PR, n (%)	43.2 (28.3–59.0) 1 (2.3) 18 (40.9)
CBR per investigator[c], % (95% CI)	75 (59.7–86.8)
Duration of response, range, mo	1.05+-17.54
Median time to response, mo (range)	1.87 (1.7–3.7)

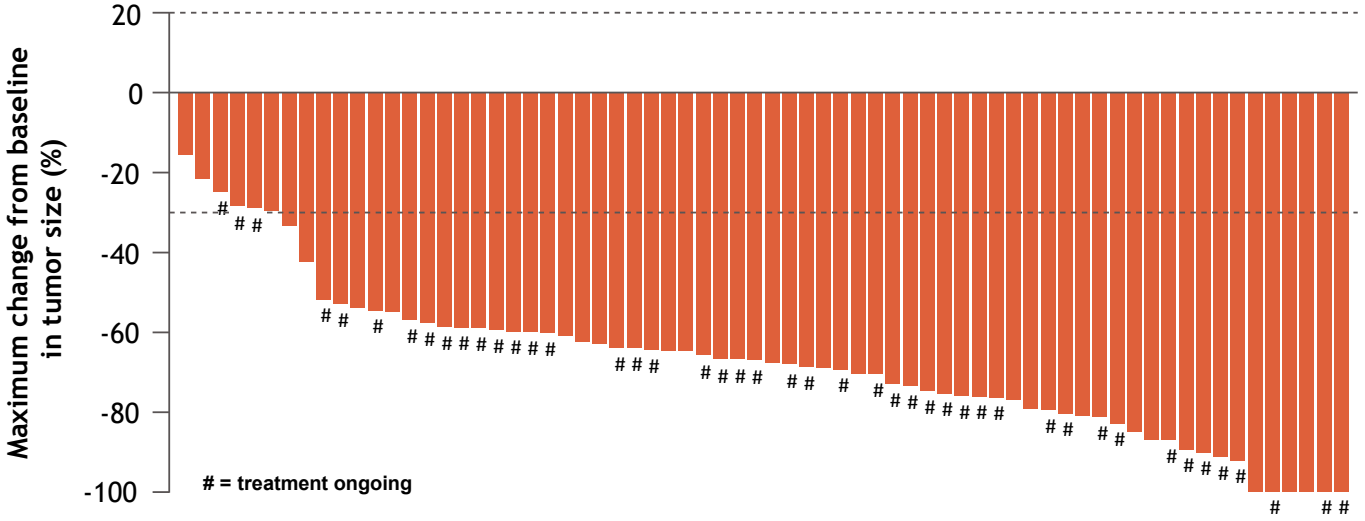
TRK TKI-pretreated (n = 44)	
Median duration of treatment, mo (range)	3.8 (0.6-20.8)
Patients remaining on treatment, n (%)	13 (30)





Besse B et al. Poster presentation at the EORTC-NCI-AACR (ENA) Symposium; October 26–28, 2022; Barcelona, Spain. Abstract 209.

Change in tumor burden, ORR, CBR, and duration of treatment (ROS1 TKI-naive)



ROS1 TKI-naive (n = 71)	
ORR[b,c], % (95% CI)	78.9 (67.6–87.7)
CR, n (%)	4 (5.6)
PR, n (%)	52 (73.2)
CBR[b,d], % (95% CI)	94.4 (86.2–98.4)

Adapted with permission.

- For all treated patients (n = 71), median duration of treatment (range) was 13.3 (0.80-60.6+) months; 63% of patients remained on treatment
- Of all patients with confirmed response (n = 56), median duration of treatment (range) was 15.5 (3.1-60.6+) months; 75% of patients remained on treatment

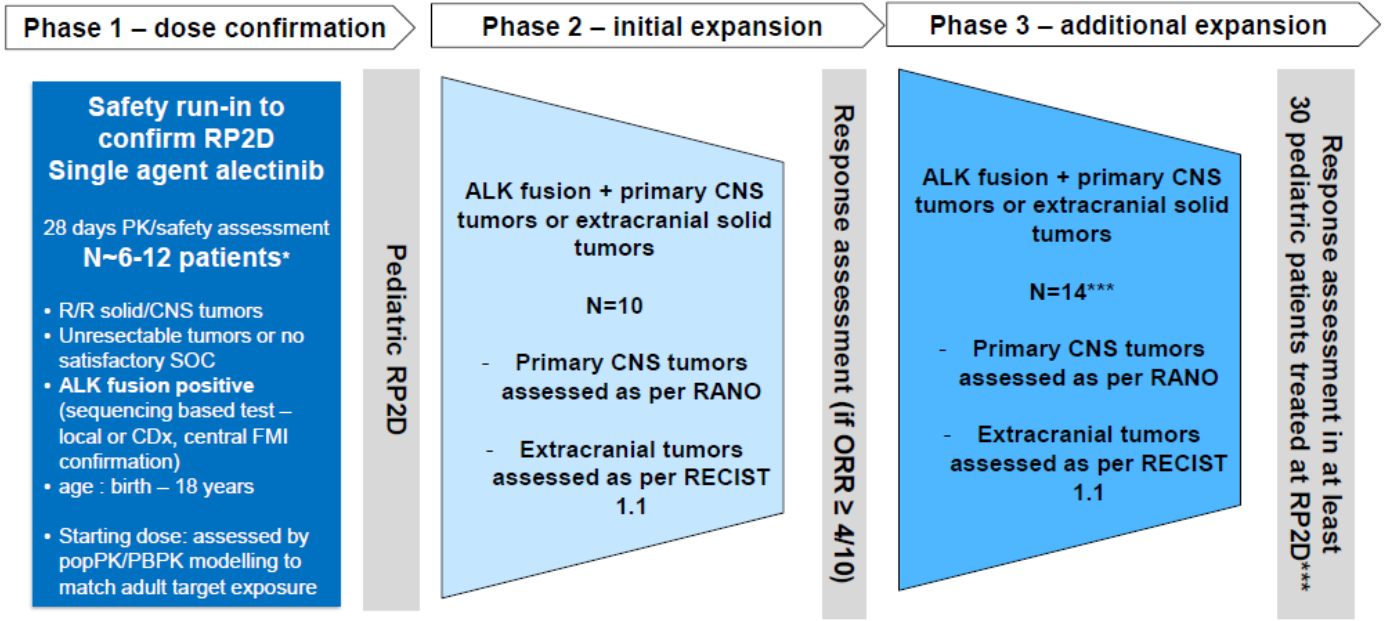
Cho BC et al. Oral presentation at the EORTC-NCI-AACR (ENA) Symposium; October 26–28, 2022; Barcelona, Spain. Abstract 2LBA.

Innovative Therapies for Children with Cancer ITCC European Consortium

iMatrix Alectinib Study Design

"All-in one study" - basket trial from phase 1 to confirmation of signal

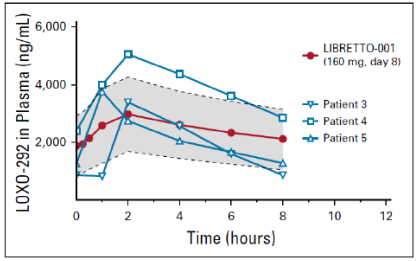
Roche



* 3 patients between 2-6 years of age need to be dosed before enrolling patients < 2 years of age. in each of the age category (0-2, 2-12 and >12 years), patients > 35kg will receive adult recommended dose 600mg BID ***pediatric patients treated at RP2D in phase 1 are considered evaluable for initial efficacy assessment

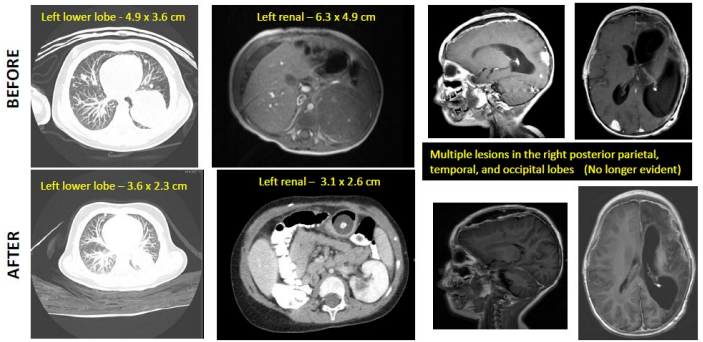
Activity of the Highly Specific RET Inhibitor Selpercatinib (LOXO-292) in Pediatric Patients With Tumors Harboring *RET* Gene Alterations

Michael V. Ortiz, MD[1]; Ulrike Gerdemann, MD[2]; Sandya Govinda Raju, MBBS, PhD[3]; Dahlia Henry, BA[3]; Steve Smith, BS[4]; S. Michael Rothenberg, MD, PhD[3]; Michael C. Cox, MHS, BCOP, PharmD[4]; Stéphanie Proust, MD[5]; Julia Glade Bender, MD[1]; A. Lindsay Frazier, MD[2]; Peter Anderson, MD, PhD[6]; and Alberto S. Pappo, MD[7]



A Study of Oral LOXO-292 in Pediatric Patients With Advanced Solid or Primary Central Nervous System Tumors (LIBRETTO-121; NCT03899792)

SPECC1- RET driven fibrosarcoma 21days after Selpercatinib



ESMART – Overview + New arms (Amendment #9)

Protocol v1.0 Approved 25/05/2016 → **Protocol v2.0 Approved 28/02/2018** → **Protocol v4.0 Approved September 2020**

ARM	Target	Treatment
Arm A	CDK4/6	Ribociclib + TOTEM
Arm B		Ribociclib + Everolimus
Arm C	WEE1	Adavosertib (AZD1775) + Carboplatin
Arm D	PARP	Olaparib + Irinotecan
Arm E	mTORC1/T	Vistusertib
Arm F	ORC2	Vistusertib + TOTEM
Arm G	PD1	Nivolumab + Cyclophosphamide +/-RT

AstraZeneca NOVARTIS Bristol-Myers Squibb

ARM	Target	Treatment
Arm H	MEK + mTOR	Selumetinib + Vistusertib
Arm I	IDH2	Enasidenib
Arm J	PD1 + KIR	Nivolumab + Lirilumab

Celgene

Protocole v3.0 (20/03/2019)

→ Harmonisation Européenne

Amendment #10

Protocol v5.0 12/2021

ARM	Target	Treatment
Arm K	CDK2/9	Fadraciclib (CYC065) + Temozolomide
Arm L		Fadraciclib (CYC065) + Cytarabine
Arm M	CDK4/6 + mTOR	Ribociclib + Everolimus
Arm N	ATR + PARP	Ceralasertib (AZD6738) + Olaparib
Arm O	pan-FGFR	Futibatinib (TAS-120)

AstraZeneca CYCLACEL TAIHO NOVARTIS

ARM	Target	Treatment
Arm P	MET + mTOR	Capmatinib + Everolimus

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA
XLVIII CONGRESSO NAZIONALE AIEOP
Bologna
2-4 Ottobre 2023

Patients with relapsed or refractory hematologic or solid tumor malignancy with extensive molecular analysis

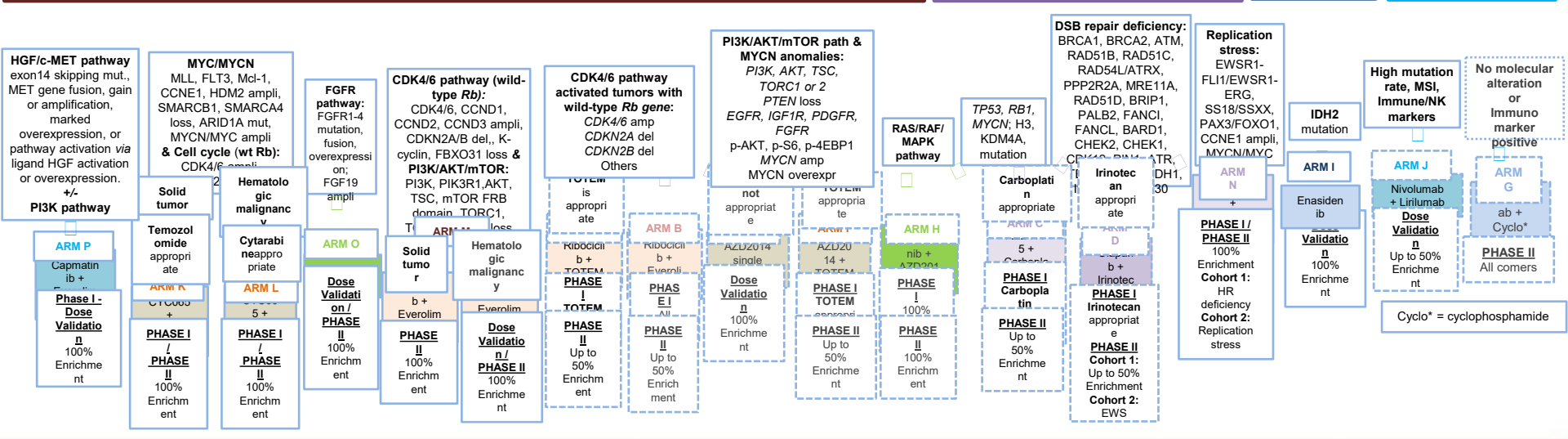
e★smart
European proof of concept therapeutic stratification trial of molecular anomalies in relapsed or refractory tumors in children

Patients whose tumor present

Key Inclusion criteria

- Age < 18 years at inclusion
- Evaluable/measurable disease
- Lansky/Karnofsky ≥70%
- Adequate organ function
- Absence of ≥ G2 toxicities
- Adequate "wash-out" of previous therapies

Alterations in cell cycle and signaling | **Alterations in DNA repair** | **Metabolic** | **Immune therapy**

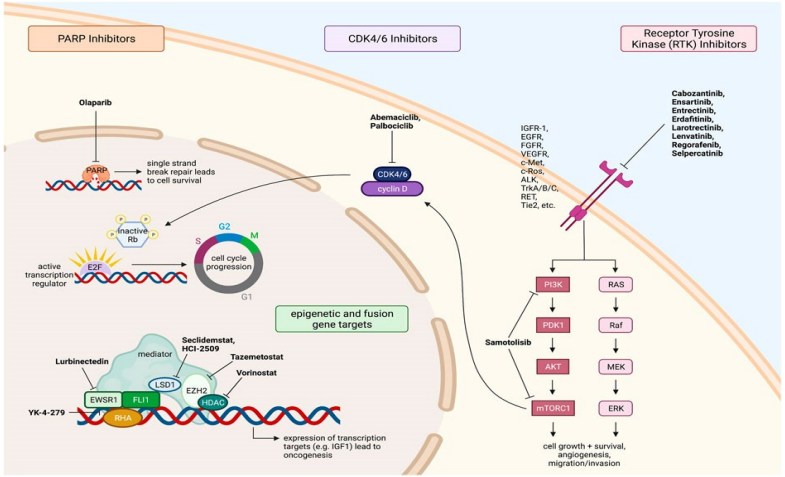


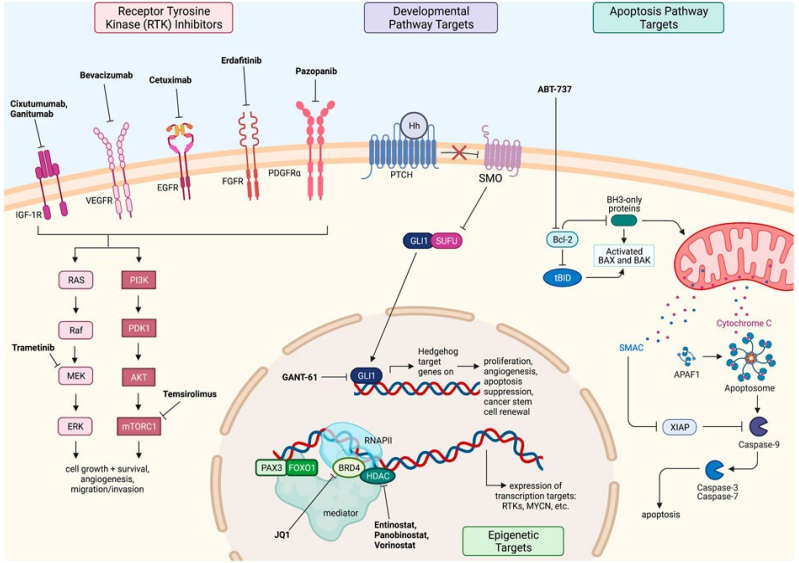
Gantt Chart AcSe-ESMART

		2016				2017				2018				2019				2020				2021				2022			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Arm A	Ribociclib + TOTEM																					J Clin Oncol							
Arm B	Ribociclib + Everolimus																					J Clin Oncol							
Arm C	Adavosertib + Carboplatin																									to be submitted			
Arm D	Olaparib + Irinotecan																												to be submitted
Arm E	Vistusertib																					Eur J Cancer							
Arm F	Vistusertib + TOTEM																					Eur J Cancer							
Arm G	Nivolumab + Cyclophosphamide																					Eur J Cancer							
Arm H	Vistusertib + Selumetinib																					Eur J Cancer							
Arm I	Enasidenib																									Case report to be submittted			
Arm J	Nivolumab + Lirilumab																									to be submitted			
Arm K	Fadraciclib + Temozolomide																												
Arm L	Fadraciclib + Cytarabine																												
Arm M	Ribociclib + Everolimus +/- dexa																												
Arm N	Olaparib + Ceralasertib																												
Arm O	Futibatinib																												
Arm P	Capmatinib + Everolimus																												

- **7 arms open to enrolment (I, K, L, M, N, O, P)**
- **6 arms with already published results**
- **3 arms with ongoing analyses**

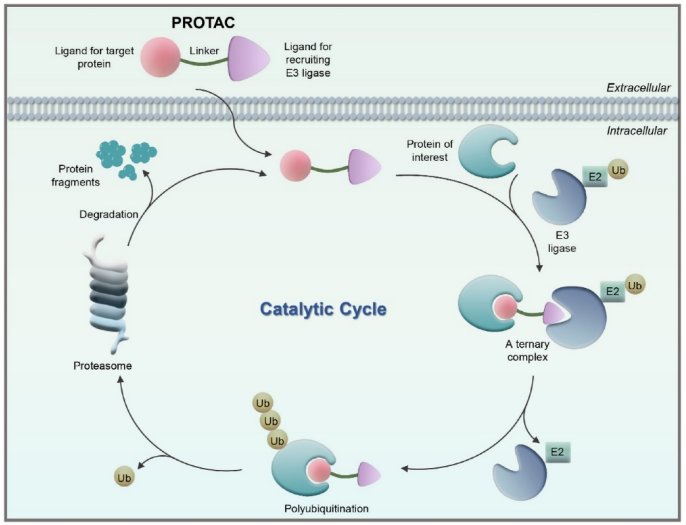
Targeting fusion-driven pediatric sarcomas





Chang WI, et al. Front Pharmacol 2022

Rethinking direct targeting of transcription factor fusions



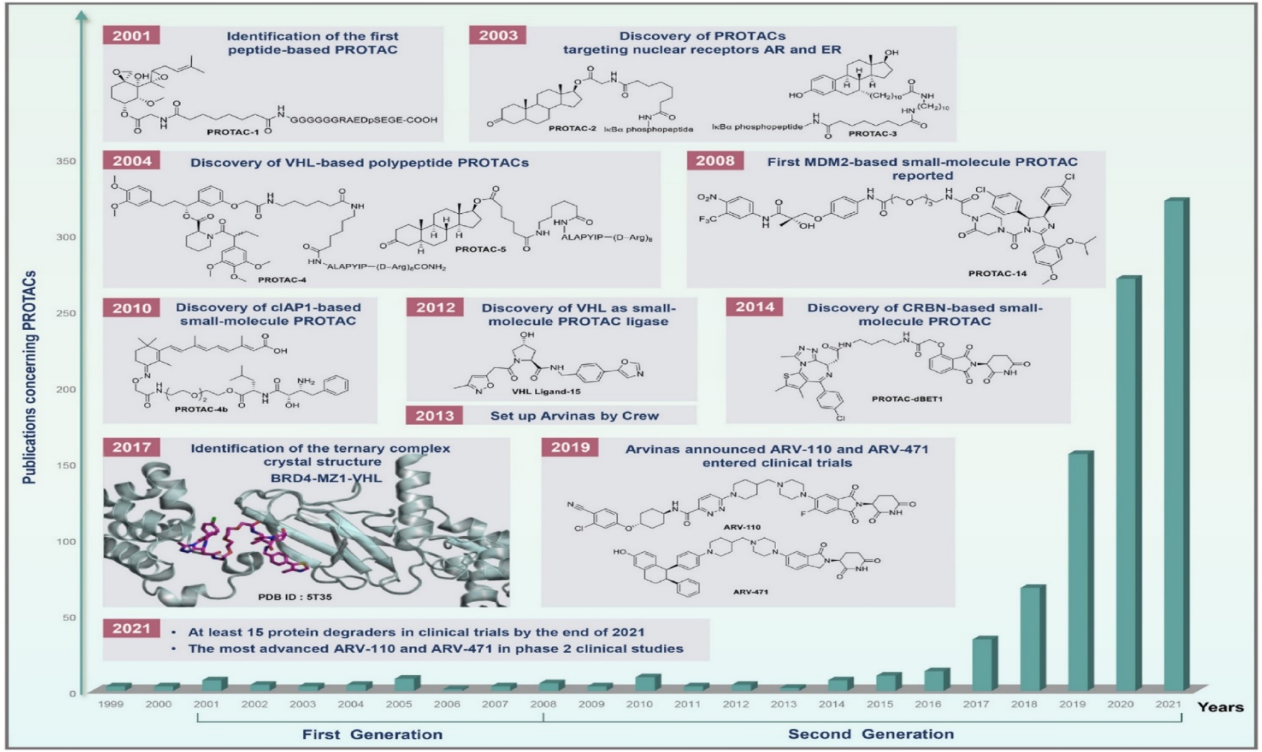
New enabling chemistry

Targeted protein degradation is an emerging direction in the field of drug discovery

PROTACs, SNIPERs, molecular glues, etc

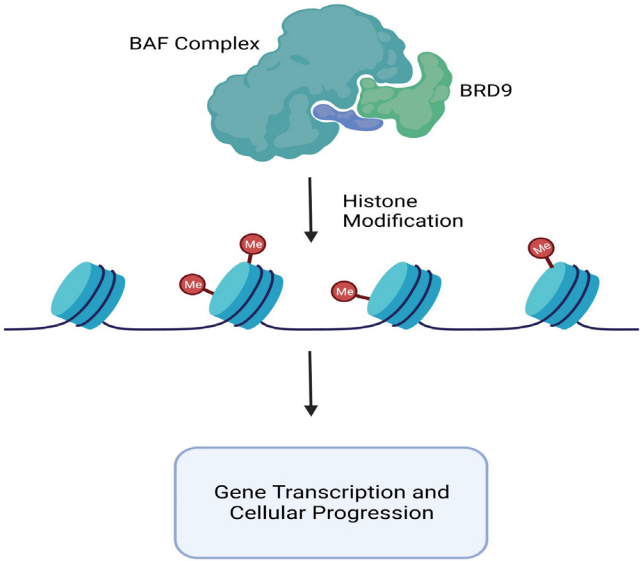
Zhong Y, Eur J Med Chem 2022

The “degradation” revolution

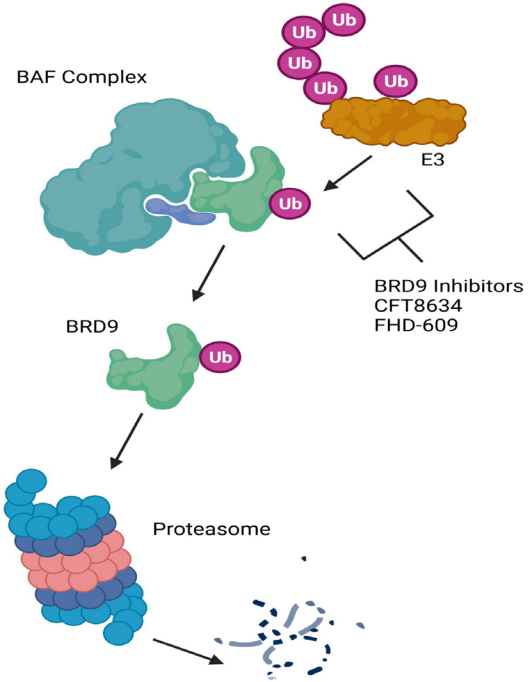


Zhong Y, Eur J Med Chem 2022

Synovial sacrcoma BAF dysregulation



BRD9 degraders



Antibody-drug conjugates (ADC)

Improving the therapeutic index of cytotoxic drugs

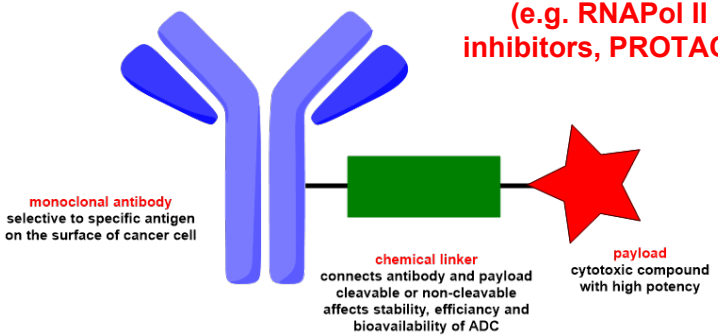
Tumor penetration

Target copy number

Potency of payload

Unconventional payloads in develoment (e.g. RNAPol II inhibitors, PROTACs)

Maximize concentration of free payload in tumor cells



ADC internalization
ADC degradation
Drug-antibody ratio (DAR)

DsS8201a
(trastuzumab deructecan)

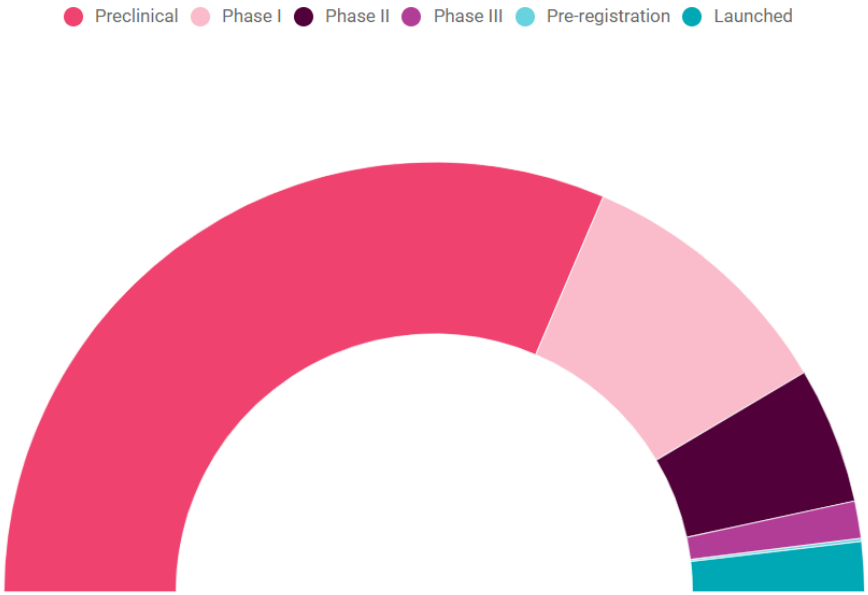
TRASTUZUMAB (ENHERTZ®)
(Anti-HER2 antibody)
Topoisomerase I (DXd)
DAR = 8

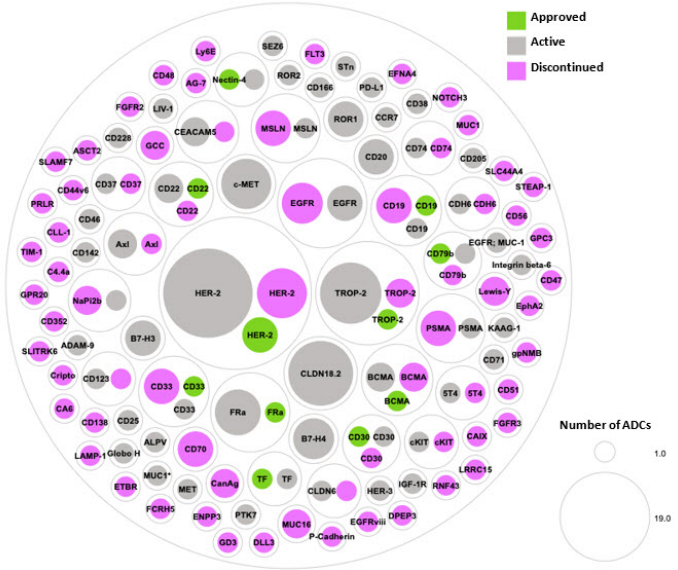
EMA/FDA approved (HER2+ breast cancer, gastric/ gastrooesophageal cancer)

Conilh et al, J Hematol Oncol, 2023
Sheyi et al, Pharmaceutics, 2022

ADC Pipeline By Development Stage

According to data from Pharmaprojects, there are 428 ADC drugs in the pipeline. The majority of assets are in preclinical development.





From: ADCs Coming Of Age: Deals, Targets And Catalysts
invivo.pharmaintelligence.informa.com

T-cell receptor-based therapy in synovial sarcoma

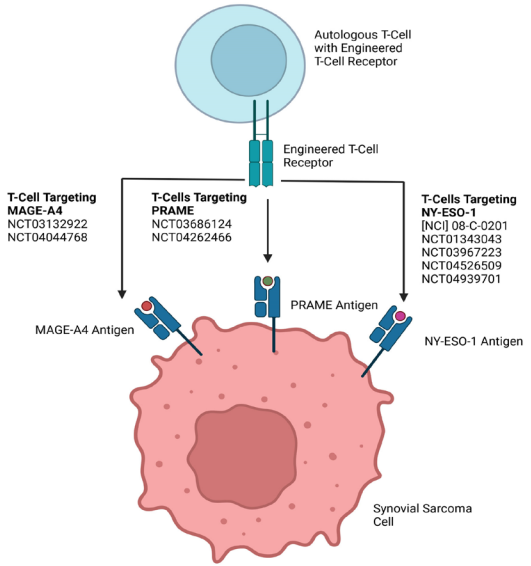
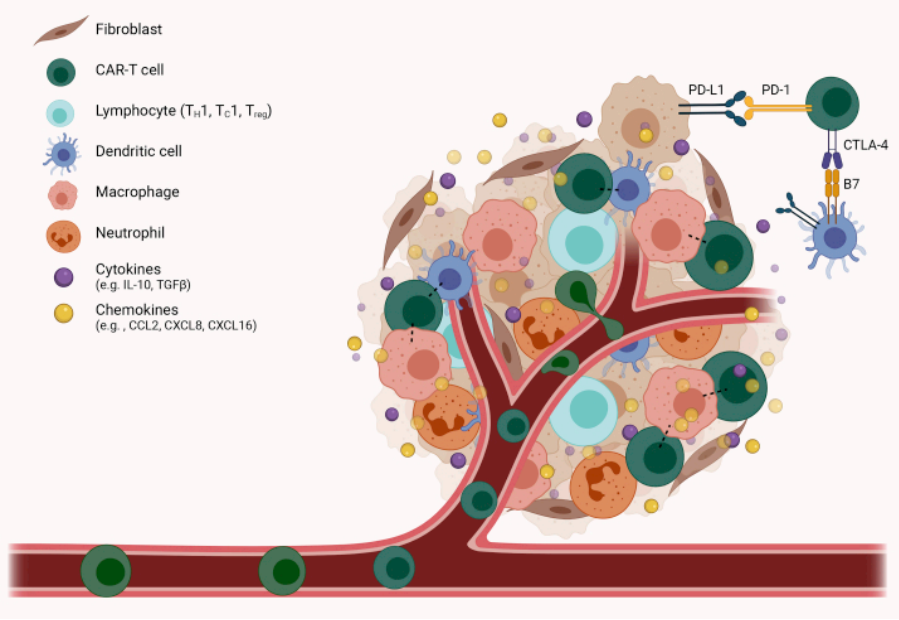


Table 1. Main clinical trials, based on adoptive transfer of engineered immune cells, including SyS patients in their cohorts.

Target Antigen	Trial Number	Study Description	Main Results and References
NY-ESO-1	NCT00670748	Pilot phase I study: NY-ESO-1 TCR-T-cells plus IL2 in heavily pretreated metastatic HLA-A*02-positive SyS patients with >50% expression of NY-ESO-1	ORR 61% objective clinical responses in 11/18 SyS patients [66]
	NCT01343043	Pilot phase I study: NY-ESO-1 TCR-T-cells plus IL2 in heavily pretreated metastatic HLA-A*02-positive SyS patients among four cohorts allocated between different levels of NY-ESO-1 expression and lympho-depletion regimens	ORR 20–50% [68,69,70,80]
	NCT03967223	Phase II study: First generation of NY-ESO-1 TCR-T-cells as a first line treatment in advanced metastatic, previously untreated HLA-A*02-positive patients with NY-ESO-1-positive SyS or MRCLS and as a second line treatment after first line anthracycline-based chemotherapy	Active, not recruiting [70]
	NCT04526509	Phase I master protocol of three different next generation NY-ESO-1 TCR-T-cell co-expressing CD8 alpha cell surface receptor, or co-expressing the dominant-negative TGF-beta receptor type II, or engineered using the epigenetically reprogrammed (Epi-R) manufacturing process	Active, not recruiting [70]
	NCT04939701	Phase I/II trial: Human artificial adjuvant vector cells (aAVC) loaded with the CD1d ligand alpha-galactosylceramide and modified to express NY-ESO-1 in combination with pembrolizumab for SyS, MRCLS, ovarian carcinoma, non-small cell lung cancer, and esophageal squamous cell carcinoma	Active, not recruiting [45]
MAGE-A4	NCT03132922	Phase I multi-tumor trial: Afami-cel (carrying TCR specific for a MAGE-A4230−239 peptide, GVYDGREHTV, presented by HLA-A*02) in HLA-A*02+ patients with advanced metastatic MAGE-A4-expressing solid tumors, across nine tumor types including SyS	ORR 44% for SyS and 9% for all other tumors [74]
	NCT04044768	Phase II SPEARHEAD-1 trial: A single arm open-label clinical trial on ADP-A2M4 SPEAR™ T-Cells in HLA-A*02 eligible and MAGE-A4 positive subjects with metastatic or inoperable SyS or MRCLS	ORR 40.7% in SyS [75,76]
PRAME	NCT03686124	The ACTENGINE IMA203/IMA203CD8 trial: TCR-T-cells directed against an HLA-A*02-restricted peptide derived from PRAME after lymphodepletion, with or without nivolumab in patients with advanced solid tumors	ORR 60% in SyS Objective clinical responses in 3/5 SyS patients [79]

The trafficking of CAR-T cells into tumors is considered one of the first challenges in developing effective CAR-T cell therapy against solid cancers



Successful CAR-T cell therapy against solid tumors requires numerous challenges to be met:

identification of a suitable target antigen

Physical barriers, aberrant vasculature, and mismatched migratory signals prevent spatial recognition of tumors by CAR-T cells and block their infiltration into the parenchyma

Macrophages and dendritic cells may also sequester CAR-T cells in the tumor-associated stroma….

CAR-T cell clinical trials in pediatric sarcoma

Trial Number	Target Antigen	Sarcoma Subtype	Phase	Age (Years)	Dose	Lymphodepletion	Status
NCT00902044	HER2	All sarcoma	I/II	All	1×10^4–1×10^8/m^2	Fludarabine, Cyclophosphamide	Completed, with results
NCT00889954	HER2	All cancers	I	3+	1×10^4–1×10^8/m^2	No	Completed
NCT01343043	NY-ESO-1	Synovial	I	4+	>40 kg: 1×10^9–6×10^9 <40 kg: 0.025×10^9 cells/kg	Fludarabine, Cyclophosphamide	Completed, with results
NCT03638206	NY-ESO-1	All cancers	I/II	4–70	Not specified	Cyclophosphamide or Fludarabine	Recruiting
NCT02107963	GD2	All	I	<36	1×10^5–1×10^7 cells/kg	Cyclophosphamide	Completed
NCT1953900	GD2	Osteosarcoma	I		1×10^6–1×10^9	Fludarabine, Cyclophosphamide	Active
NCT03635632	GD2	All	I	1–74	1×10^7–1×10^8	Fludarabine, Cyclophosphamide	Recruiting
NCT04539366	GD2	Osteosarcoma	I	<36	Not specified	Fludarabine, Cyclophosphamide	Not yet recruiting
NCT03721068	GD2	Osteosarcoma	I	1.5–18	0.5×10^6–1.5×10^6	Fludarabine, Cyclophosphamide	Recruiting
NCT04483778	B7-H3	All	I	0–27	Not specified	Not specified	Recruiting
NCT04897321	B7-H3	All	I	0–21	Not specified	Fludarabine, Cyclophosphamide	Not yet recruiting
NCT04864821	B7-H3	All	I	1–70	Not specified	Not specified	Not yet recruiting
NCT03618381	EGFR	All	I	1–26	Not specified	Not specified	Recruiting
NCT04377932	GPC3	All	I	1–21	3×10^7–3×10^8/m^2	Fludarabine, Cyclophosphamide	Not yet recruiting
NCT04715191	GPC3	All	I	1–21	1×10^8–1×10^9/m^2	Fludarabine, Cyclophosphamide	Not yet recruiting